## *Aim and Scope*

Archives of Breast Cancer (ABC) is an open access, peer-reviewed journal that publishes articles on all aspects of breast cancer research, including the pathophysiology, prevention, early detection, diagnosis, treatment, molecular and cellular biology, genetics, epidemiology, psychological issues, rehabilitation and quality of life. Although the main focus of the journal is breast cancer, some important topics among benign breast diseases and breast health such as breastfeeding will be considered for publication.


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ARCHIVES OF BREAST CANCER

**Dear colleagues,**

We are proud to announce the publication of 2018 year book of Archives of Breast Cancer. This year book includes papers from diverse as well as relevant areas including surgical aspects, medical ethics, chemoprevention, genetics, neoadjuvants, pathology, risk assessment, nano-medicine, quality of life, patient satisfaction, medical decision making, legal aspects and prognosis. All these papers have valuable messages to share in one direction: contributing to optimum prevention, diagnosis, treatment and rehabilitation of breast cancer. In 2019, we intend to expand this diversity not only in the contents but also in our audience around the world. Moreover, we are going to endorse the COPE (Committee on Publication Ethics) guidelines; therefore, all researchers are kindly requested to consult these guidelines to avoid cases of suspected research orpublication misconduct (e.g. falsification, fabrication, plagiarism, inappropriate image manipulation, and redundant publication). For more information about COPE, please visit http://www.publicationethics.org.

Thank you in advance for being with us in 2019 and sharing your valuable research work with ABC. Your feedback on this year book would encourage us to work with more passion and determination in Archives of Breast cancer.

**Best Regards,**
**Mojgan Karbakhsh, MD**
**Managing Editor, Archives of Breast Cancer**

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Letter to Editor Open Access

Archives Of Breast Cancer

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# Privacy Is an Important Issue for Women With Breast Cancer

Ahmad Kalateh Sadati*[a]

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Breast cancer is one of the most common form of cancer that threatens women and needs more attention ethically. Your valuable editorial titled "ABC of Medical Ethics and Professionalism in the Breast Clinic" was published in the recent issue.[1] Because of my interest in medical ethics, and in line with your claim, I would like to contribute the results of my PhD dissertation in this area. The study was conducted in a public hospital in Iran based on critical ethnography and included 156 recorded clinical consultations, 920 hours of participant observation, and six focus groups consisting of patients and their families.[2] The theme that was explored *was violation of patients' privacy*. This theme was about the concerns of female patients of urology and breast cancer clinics. Their main concern was about being visited by male physicians. Exposure during examination, operation, and changing dressing were their main concerns. One of my participants who was very upset was a 52-year-old woman with breast cancer who had mastectomy. Despite the success of the operation, she was very upset that her breasts had to be examined in the presence of 6 or 7 male medical students at operation room. She said this was one of the worst experiences she ever had. She believed that although her physician was quite expert at his job, he did not acknowledge her privacy concerns. That seems to be a problem in medical departments of breast cancer. Other evidence also confirms that privacy is a major issue. Mamdouh *et al* showed that 71.4% of Egyptian women complained about the lack of privacy as a barrier to participation in breast cancer screening.[3] Also, Brown *et al* found that a small percentage (3%) of women were dissatisfied with privacy arrangements in screening units; however, when privacy was discussed in an ethical context, the percentage increased significantly.[4]

I believe that this problem lies in doctor-patient interaction (DPI). Study showed that, in the context of Iranian health system, DPI has unequal, unprofessional, instrumental, and non-cooperative characteristics, which can lead to "patient's distrust, patient's dissatisfaction, lack of mutual understanding, patient suppression, and patient deception."[5] Theoretically, it is due to doctor-centeredness that doctors determine everything and do not pay attention to patients' lifeworld. If physicians want to become great physicians, they must strengthen their human dimensions and communication skills alongside their medical skills. In this view, doctors look at the patients from a holistic point of view, treating them while taking into consideration every dimension of their problems. As for women with breast cancer, as you observed, breast is a feminine organ and is considered a private organ for many women;[1] and paying attention to all concerns of these people is the first principle of medical ethics. Thus, all physicians, specialists, and nurses who provide care for these people should appreciate the fact that privacy is an important issue for women with breast cancer. It is the women's right as well as an ethical obligation that their privacy not be violated in the clinic, operation room, recovery room, and ward. Finally, based on our Islamic views, patient privacy is a main responsibility of the medical team in all situations, which should be considered for women with breast cancer.

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## Conflict of Interest

None to declare.

## References

1. Kaviani A, Karbakhsh M, Tehrani SS, Jamei K.

ABC of medical ethics and professionalism in the breast clinic. Archives of Breast Cancer. 2017;4(3):75-80
2. Sadati AK, Iman MT, Lankarani KB, Derakhshan S. A critical ethnography of doctor–patient interaction in southern Iran. Indian J Med Ethics. 2016; 1(3):147-55
3. Mamdouh HM, El-Mansy H, Kharboush IF, Ismail HM, Tawfik MM, El-Baky MA, *et al*. Barriers to breast cancer screening among a sample of Egyptian females. Journal of family & community medicine. 2014;21(2):119.
4. Brown M, Caswell B, Heath M, editors. Between four walls: what level of privacy do women want? Breast Cancer Res. 2000; 2(Suppl 2): A49.
5. Sadati AK, Tabei SZ, Ebrahimzade N, Zohri M, Argasi H, Lankarani KB. The paradigm model of distorted doctor-patient relationship in Southern Iran: a grounded theory study. J Med Ethics Hist Med. 2016;9:2.

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# Breast Cancer Treatment and Cardiovascular Considerations

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ABSTRACT

**Background:** Breast cancer is the most frequently occurring cause of cancer-related mortality in women all around the world. However, the risk of cardiovascular diseases increases in parallel with dramatic improvements in target-specific treatment for breast cancer. The aim of this review was to show the importance of cardiovascular involvement in patients with breast cancer.

**Methods:** Published literature, regarding breast cancer and cardiovascular involvements, as well as cardiovascular complications of current treatments for breast cancer, including chemotherapy and radiotherapy, was reviewed.

**Results:** Review of our data revealed that there are extensive direct and indirect impacts of breast cancer on the cardiovascular system. Cardiovascular complications of breast cancer are common and range from cardiomyopathy, pericardial involvement, venous thromboembolism, and arterial thrombosis to some uncommon problems.

**Conclusion:** Early detection of cardiovascular damages from breast cancer is strongly recommended. Considering the significant cardiovascular complications of both breast cancer and its treatment, early recognition, prevention, and management of these complications, even the minor ones, improve prognosis and survival of patients with breast cancer.

## Introduction

Breast cancer is the most frequently occurring cause of cancer mortality in women all around the world (in developed countries as well as low- and middle-income countries).[1] Most of the newly diagnosed cases, as well as the largest number of breast cancer deaths, happen in less developed areas of the world,[2] which is mostly due to economic and financial situations. Therefore, the development of effective but less expensive therapies is necessary.[3] After lung cancer, it is the second leading cause of cancer death in women.[4] On the one hand, screening for breast cancer has led to mortality reduction, but on the other, breast cancer incidence has increased.[4] Globally, it is estimated that 1.4 million women are diagnosed with breast cancer each year, and 458 000 die as the result of the disease.[5] Finally, mortality reduction in breast cancer after screening mammography was remarkably due to diagnosis in earlier stages and improving in systemic therapy.[6]

The risk of cardiovascular diseases increases in parallel with the dramatic improvement in target-specific treatment of breast cancer. This susceptibility to cardiovascular complications is potentially due to the fact that these therapies include radiotherapy and chemotherapy drugs.[7,8] This risk is aggravated remarkably after 65 years of age.[7,9,10]

Consequently, considering the cardiovascular complications in breast cancer survivors, recognition, prevention, and management of this critical event is a very important clinical issue. We will discuss these cardiovascular issues in this review. We will look at cardiovascular complications

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of breast cancer irrespective of chemotherapy or radiotherapy. In the second section, we will talk about cardiovascular complications of radiotherapy or chemotherapy in patients treated for breast cancer.

**Methods**

A literature search was performed for the years 1989 through 2017. We searched PubMed, Elsevier, MEDLINE, and Google Scholar. We considered scientific publications relevant to breast cancer for inclusion in our work.

First of all, we searched with "breast cancer," and again with the "breast cancer and cardiovascular." Then we select some of the articles obtained from the first search strategy, but most of them were related to the second search strategy.

Published literature regarding breast cancer and cardiovascular involvements, as well as cardiovascular complications of the current treatments for breast cancer, including chemotherapy and radiotherapy, were reviewed.

We used review articles (n = 22), cohort studies (n = 5), cross-sectional studies (n = 27), population-based case-control studies (n = 1), case reports (n = 6), guidelines (n = 2), case-control studies (n = 2), experimental studies (n = 3), and RCTs (n = 5).

Papers without full text, presented at conferences, or published in languages other than English were excluded.

**Results**

*Cardiovascular complications of metastatic breast cancer*

Cardiovascular complications of breast cancer included metastasis to the heart, superior vena cava syndrome, pericardial involvement, vascular problems, and cardiac function deterioration in a background of paraneoplastic syndrome.

*Cardiac metastases*

Cardiac metastases are detected in 6–20% of autopsies of patients with malignant neoplasms such as lung cancer, mediastinal tumors, breast cancer, melanoma, and esophageal cancer.[11] Although intracavitary growth of secondary heart tumors is rare, the important point is that symptomatic heart metastasis can occur even many years after diagnosis.[12] According to Bussani *et al.*, cardiac metastasis (more commonly pericardial metastasis, and rarely direct myocardial and endocardial metastasis) could be as high as 15.5% in patients with breast cancer.[12]

From pathophysiological viewpoint, multiple mechanisms have been proposed for breast cancers that are able to induce heart metastasis. For instance, breast-tumor cells in brain and heart metastases express high levels of endoglin, a cell-surface disulfide-linked homodimeric glycoprotein which binds to integrins and is a co-receptor for TGF-β.[13,14] These ligands and mediators participate in heart metastasis. Two-dimensional transthoracic and transesophageal echocardiography are easy, quick, and sensitive techniques for detection of cardiac metastasis. Computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose integrated with computed tomography (18F-FDG PET/CT), and PET-MRI as confirming methods could be helpful when there is any suspicion as to excluding cardiac involvement during clinical follow-up of these patients.[15-17]

*Superior vena cava syndrome (SVCS)*

Approximately 87% to 97% of SVCS cases are caused by primary intrathoracic malignancies. Breast cancer is one of the solid tumors causing SVCS, but not as much as other tumors like non-Hodgkin lymphoma, lung, or testicular cancer.[18] The most common nonmalignant cause of SVCS in cancer patients is thrombosis associated with venous access devices, especially patients with breast cancer who have long term central venous port catheter. There are some noninvasive therapeutic measures for SVCS, but endovascular revascularization of complete occlusion of the SVC is considered the therapy of choice.[19,20]

*Pericardial involvement*

Breast cancer could cause significant pericardial effusion or tamponade. This kind of pericardial involvements impairs quality of life. Recurrent pericardial effusion along with the development of dyspnea or tachycardia may necessitate repetitive hospitalization. Percutaneous pericardiocentesis with extended catheter drainage can be safely and effectively implemented as the primary treatment for pericardial effusion in cancer patients, including in those with thrombocytopenia.[21]

*Venous thromboembolism (VTE)*

Cancer patients constitute about 20% of all cases of VTE, and are also 4- to 7-fold more likely to develop VTE compared with patients without cancer.[22-24] Patients with cancer often show abnormalities in each component of Virchow's triad, leading to hypercoagulability.[23] Breast cancer is not a common cause of primary VTE per se, but patients with multiple metastasis or immobile ones, or who are under hormone therapy with tamoxifen or aromatase inhibitors, have higher risk for VTE and should receive VTE prophylaxis.[24]

*Arterial thrombosis*

Arterial thrombosis and its resultant clinical syndromes, such as cerebrovascular events or peripheral ischemia, could happen in cancer patients, and the most common reported malignancy in this setting is metastatic breast cancer.[25]

Thrombosis may be related to cancer itself or its treatment. The paraneoplastic process leads to hypercoagulability with changes in levels of factor VII and proteins C and S. Tissue factor and cancer procoagulant levels may rise. Thrombocytosis, increased fibrinogen levels and reduced fibrinolysis, endothelial damage, and stasis may also contribute to thrombosis. Premenopausal breast cancer patients who receive both chemotherapy and tamoxifen are more likely to present with arterial thrombosis compared with those who receive chemotherapy alone.[26,27]

Heart failure (HF) or cardiac function deterioration also occurs in a background of paraneoplastic syndrome of breast cancer.[28]

*Complications of therapy for breast cancer*

Here we explain more about anti-human epidermal growth factor receptor 2 (HER2) agents, especially trastuzumab.

*Novel chemotherapy agents and related cardiac toxicity*

The overexpression of HER2 in breast cancer is associated with more aggressive disease with a poor prognosis.[2,9,30] Trastuzumab, pertuzumab, and other anti-HER2 agents are monoclonal antibodies against the extracellular domain of HER2 that have been shown to be effective in metastatic breast cancer as monotherapy or combining with other chemotherapy agents.[31,32] These agents have proved to be effective in both metastatic and early-stage breast cancers when combined with chemotherapy, and reduce relapse rates by 50% irrespective of age and other relevant prognostic factors.[33,34]

As mentioned by the American Society of Clinical Oncology, in contrast to anthracycline-related cardiac toxicity (type 2/irreversible), trastuzumab does not result in myocyte loss. In trastuzumab-induced cardiac dysfunction, myocytes appear normal histologically and alterations may be noticed only by using electron microscopy.[35]

In a study by Swain *et al*., the addition of pertuzumab to trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer significantly increased the median overall survival to 56.5 months—an improvement of 15.7 months over survival in the control group.[30]

As mentioned before, these novel biologic therapies improve disease-free and overall survival, but increase the risk of cardiotoxicity,[36] as has been shown in many studies.[29,34] The cardiotoxicity of these agents could involve any part of the heart's structure, and the ongoing studies are assessing these damages to heart using various methods and parameters.

Recently, we compared cardiomyopathy-related findings before and after trastuzumab therapy in patients with breast cancer and found that diastolic function was significantly impaired after treatment (25.9% versus 43.6 %).[37] After the therapy, left ventricular ejection fraction (LVEF) was reduced significantly, and troponin levels were increased remarkably (0% versus 6.7 %); however, no significant differences were observed for CRP and NT-pro-BNP levels. This study showed the importance of troponin for trastuzumab-induced cardiomyopathy.

In a study by Rossner and colleagues[38] in 28 female patients with metastatic HER2-positive breast cancer, blood samples were drawn before and 30 min after intravenous trastuzumab infusion, and EF and NT-pro-BNP levels before and after the initiation of trastuzumab were compared. According to higher median 3-month mortality in cases with elevated levels of NT-pro-BNP, this marker could be considered as a prognostic factor in these patients.

In one study by Cardinale *et al.*,[39] the incidence rate of trastuzumab-induced cardiotoxicity (TIC) in breast cancer patients was reported to be 17%, and TIC was significantly associated with elevated levels of troponin I (TNI) (62% in TNI+ vs 5%; $P < .001$). They suggested that increased TNI levels can identify trastuzumab-treated patients who are at risk for cardiotoxicity and who are unlikely to recover from cardiac dysfunction despite HF therapy.

In another study by Goel *et al.*, serum troponin I and NT-pro-BNP were assayed immediately before and 24 hours after trastuzumab infusion in patients with breast cancer. A significant proportion of the patients with normal LVEF who received trastuzumab experienced elevated levels of NT-pro-BNP , but that was not the case for troponin I levels.[40]

Lamot *et al.* reported evaluated trastuzumab treatment-induced cardiac toxicity in 30 breast cancer patients.[41] Cardiac toxicity was assessed based on LV function. LVEF showed a significant decrease after trastuzumab adjuvant therapy.

In a large cohort study by Chavez-MacGregor *et al.*,[42] 2203 older breast cancer patients under trastuzumab therapy were evaluated. They observed a chronic heart failure rate of 29.4% among trastuzumab users, compared with 18.9% in non-trastuzumab users ($P < 0.001$).

In addition to ejection fraction (EF) and cardiac biomarkers, a few studies have also shown adverse effect of this drug on left atrium. A recently published observational study revealed changes in atrial diameter and geometry during the early periods of trastuzumab treatment.[43] Ongoing studies are evaluating precisely the effect of these monoclonal antibodies on atrial structure and function.

Finally, regarding the research on cardiotoxicity of trastuzumab, most recent and valuable studies some of which have been mentioned above, have demonstrated the adverse effect of newer biologic therapies on heart system, but their cardiotoxicity is significantly lower than the older agents such as

anthracyclines.[4]

*Contemporary radiotherapy and related cardiac toxicity*

Like chemotherapy, radiation causes mainly a series of toxic effects and hemodynamic and structural damages to the cardiovascular system, affecting the long-term survival.[44, 45] Radiation to the chest can damage the pericardium, myocardium, heart valves, and coronary vessels.[46, 47] According to available evidence, the damage to the cardiovascular system is directly related to the dose of radiation and the volume of heart irradiated, especially if combined with chemotherapy.[48] The extent of damage will be doubled in patients with preexisting cardiac diseases. In radiation-induced vascular damage, endothelial dysfunction is the first sign.[49] After starting radiation therapy, , large myocardial perfusion defects were detected in single-photon emission computerized tomography scans (even in 55% of asymptomatic patients),[50,51] and radiotherapy has even been accompanied by HF in these patients; overall, however, HF is not common in patients undergoing radiation therapy and is usually a late effect of radiation therapy. The mechanism responsible for radiation-induced injury to heart could be myocardial fibrosis resulting from collagen disruption.[52] Radiation can cause injury to the intima of the coronary arteries and initiate a cascade of atherosclerotic events. The left anterior descending and the right coronary arteries are most often involved in patients undergoing mediastinal radiation for Hodgkin's disease.[53]

Progressive fibrosis following radiation-induced myocardial collagen synthesis results in valvular heart disease by increasing the valvular thickness, and in left ventricular dysfunction by increasing ventricular wall thickness.[54] Ongoing studies are evaluating radiotherapy-induced LV dysfunction by new imaging methods and parameters like (18F-FDG PET/CT) and PET-MRI, as mentioned.

In spite of all the mentioned complications, the absolute risk of radiation therapy is small and seems to be cancelled out by the advantages for patients receiving radiation therapy.

## Discussion

*Approach to cardiac toxicity of chemotherapeutic agents in patients with breast cancer*

*Risk factors of trastuzumab-induced cardiomyopathy*

Epidemiologic evidence indicates that, even without a clear LVEF at the time of treatment, early treatment of breast cancer with trastuzumab presents a substantial long-term risk of HF, especially for women older than 65 years.[55]

*Diagnosis of trastuzumab-induced cardiomyopathy*

Echocardiographic evolution of EF using Simpson's method is recommended for assessment of left ventricular function.[56-58] Abnormalities of right ventricular contractility, ventricular dilation, and abnormal left ventricular contractility are the earliest presentations of myocardial damage diagnosed by echocardiography.

Strain rate imaging (SRI) is a new echocardiographic modality that enables accurate measurement of regional myocardial function and is recommended especially for chemotherapy- and radiotherapy-induced cardiotoxicity in breast cancer patients.[59]

There are some recommendations by experts and in reported articles from tertiary centers, and almost all of them agree that treatment with trastuzumab must be stopped if clinical symptoms of HF are present.[35,60,61]

In the event of an asymptomatic decrease in LVEF by 15% or more, discontinuation of trastuzumab therapy is mandatory.[62, 63] Patients receiving chemotherapy may be considered to be at elevated risk of developing cardiac dysfunction —Stage A heart failure in ACC/AHA guidelines.[64]

Baseline cardiac evaluation through history taking, physical examination, and electrocardiography should be done for all patients before they are given trastuzumab.[61] Five main randomized trials have demonstrated the survival advantages of adjuvant trastuzumab in early breast cancer patients.[35,60] Recently, guidelines were developed for cardiac monitoring of metastatic breast cancers receiving trastuzumab treatment.[61] Since trastuzumab-associated cardiac toxicity is a great concern in making all the adjuvant trials, strict cardiac evaluation is necessary in these trials prior designing and monitoring at regular intervals during therapy. In National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31, trastuzumab-induced symptoms were monitored and patients who developed clinically significant cardiac symptoms while receiving anthracycline treatment were excluded from subsequent trastuzumab therapy. The initiation or continuation of trastuzumab treatment in asymptomatic patients required an LVEF equal to or exceeding the lower limit of normal range.[65] In North Central Cancer Treatment Group (NCCTG) N9831, pooled with NSABP B-31, 6.7% of the enrolled patients were not allowed to start trastuzumab treatment because their LVEF had declined to a subnormal level or had been decreased by ≥ 16% from baseline after completion of anthracycline treatment.[65, 66] Jones *et al.*, published cardiology assessment and monitoring methods in *British Journal of Cancer*,[35] and Saad *et al.* presented the second recommendations and their related demonstrations.[60]

The newest accepted guidelines are developed by the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[61]

**Table 1.** Assessment of LVEF and cardiac toxicity criteria in adjuvant trials of Trastuzumab

| Trial | Method of LVEF assessment |
|---|---|
| NSABP B31 | MUGA scanning |
| NCCTG N9831 | MUGA scanning or echocardiography |
| HERA67 | MUGA scanning or echocardiography |
| FinHer 68 | MUGA scanning or echocardiography |

*LVEF = left ventricular ejection fraction; MUGA = multigated acquisition; NCI–CTC = National Cancer Institute–Common Toxicity Criteria; NYHA = New York Heart Association*

Baseline evaluation of LVEF by 2D or 3D echocardiography, global longitudinal strain (GLS), and troponin I should be determined at the initiation of any regimen potentially associated with type 1 toxicity.

At the initiation of trastuzumab, baseline evaluation of LVEF should be done by 2D or 3D echocardiography, GLS, and troponin I assessment. If LVEF is less than 53%, GLS is near the lower limit of normal, and troponin test is positive, cardiology consultation should be recommended, and if these three parameters are in normal range, follow-up by measurement of LVEF, GLS, and troponin every 3 months is recommended.

At the initiation of trastuzumab after a regimen associated with type I toxicity, such as anthracycline (cell apoptosis and irreversible cell damage) the assessment is similar to above guidelines.[61] Follow-up by measurement of LVEF, GLS, and troponin every 3 months during therapy, and 6 months after therapy, is recommended. As in trastuzumab monitoring, if parameters are abnormal, cardiology consultation would be necessary; and if parameters are within normal range, follow-up at the completion of therapy and 6 months later should be considered. For early detection of subclinical LV dysfunction GLS is the optimal parameter: a relative percentage reduction of < 8% from baseline is not significant, but those >15% are probably abnormal.

Today, cardiovascular magnetic resonance (CMR) imaging is widely used in patients with breast cancer for detecting both the acute and chronic complications of cardiotoxic chemotherapeutic agents. CMR is recommended when the quality of the echocardiogram is suboptimal. With the introduction of late gadolinium enhancement (LGE), CMR is considered the gold standard for myocardial viability imaging accompanied by positron emission tomography.[61]

Aerobic training (AT) is a non-pharmacological strategy to attenuate or even counteract acute and chronic cardiovascular abnormalities in the context of early breast cancer. It can improve systolic and diastolic function and reduce pathologic cardiac remodeling.[69, 70] This may lead to enhanced exercise tolerance and resistance to fatigue during exertion in patients with known cardiovascular disease.[71] Cardioprotective properties of AT in the context of early breast cancer has been well explained in an important study by Scott *et al.*[72] They proposed an exercise paradigm based on the principles of AT to facilitate a personalized medicine approach that may optimize prevention or attenuation of breast cancer therapy-associated cardiovascular disease.

Echocardiography can be utilized as a routine method for monitoring cardiac side effects. It helps in assessment of parameters for systolic and diastolic function and anatomical cardiac dimensions as well.

The remarkable improvements in screening and adjuvant therapy for breast cancer, combined with close surveillance of cancer survivors, have led to a significant decrease in recurrence rate. Currently, cardiovascular disease is one of the leading causes of death in many patients who have been treated for breast cancer.

We recommend screening and surveillance for early detection of subclinical cardiovascular complications of breast cancer itself, or cardiotoxicity associated with its treatment. Early detection and treatment of even the smallest cardiac damages will improve prognosis and life expectancy of patients with breast cancer.

**Conflict of Interest**

None to declare.

**References**


1. Lauby-Secretan B, Scoccianti C, Loomis D, Benbrahim-Tallaa L, Bouvard V, Bianchini F, *et al.* Breast-cancer screening—viewpoint of the IARC Working Group. New England Journal of Medicine. 2015;372(24):2353-8.
2. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, *et al.* GLOBOCAN 2012 v 1.0, Cancer Incidence and Mortality Worldwide. 2013. Lyon, International Agency for Research on Cancer IARC CancerBase. 2015(11).
3. Coates A. PG 0.1 Evolution of the St. Gallen Consensus process for the optimal treatment of women with breast cancer. The Breast. 2015;24:S1.
4. Ban KA, Godellas CV. Epidemiology of breast cancer. Surgical oncology clinics of North America. 2014;23(3):409-22.
5. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer. 2010;127(12):

2893-917.
6. Welch HG, Prorok PC, O'Malley AJ, Kramer BS. Breast-cancer tumor size, overdiagnosis, andmammography screening effectiveness. New England Journal of Medicine. 2016;375(15): 1438-47.
7. Anthony FY, Jones LW. Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. Cardio-Oncology. 2016;2(1):1.
8. Abdel-Qadir H, Austin PC, Lee DS, Amir E, Tu JV, Thavendiranathan P, *et al.* A population-based study of cardiovascular mortality following early-stage breast cancer. JAMA cardiology. 2017;2(1):88-93.
9. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Research. 2011;13(3):R64.
10. Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, Rouzier R, Broglio KR, Hortobagyi GN, *et al.* Overall survival and cause-specific mortality of patients with stage T1a, bN0M0 breast carcinoma. J Clin Oncol. 2007;25(31):4952-60.
11. Cheruvu B, Cheruvu P, Boyars M. An unusual case of metastasis to the left side of the heart: a case report. J Med Case Rep. 2011;5:23.
12. Katalinic D, Stern-Padovan R, Ivanac I, Aleric I, Tentor D, Nikolac N, *et al.* Symptomatic cardiac metastases of breast cancer 27 years after mastectomy: a case report with literature review-pathophysiology of molecular mechanisms and metastatic pathways, clinical aspects, diagnostic procedures and treatment modalities. World J Surg Oncol. 2013;11(1):1.
13. Oxmann D, Held-Feindt J, Stark A, Hattermann K, Yoneda T, Mentlein R. Endoglin expression in metastatic breast cancer cells enhances their invasive phenotype. Oncogene. 2008;27(25): 3567-75.
14. Hancox RA, Allen MD, Holliday DL, Edwards DR, Pennington CJ, Guttery DS, *et al.* Tumour-associated tenascin-C isoforms promote breast cancer cell invasion and growth by matrix metalloproteinase-dependent and independent mechanisms. Breast Cancer Res. 2009; 11(2):R24.
15. Johnson TR, Becker CR, Wintersperger BJ, Herzog P, Lenhard MS, Reiser MF. Detection of Cardiac Metastasis by Positron-Emission Tomography–Computed Tomography. Circulation. 2005;112(4):e61-e2.
16. Houck RC, Cooke JE, Gill EA. Live 3D echocardiography: a replacement for traditional 2D echocardiography? American Journal of Roentgenology. 2006;187(4):1092-106.
17. Ohnishi M, Niwayama H, Miyazawa Y, Kondo N, Imai H, Nishimoto Y, *et al*. [Echocardiography in patients with malignant metastatic neoplasms of the heart and great vessels]. J Cardiol. 1989;20(2):377-84.
18. Escalante CP, Manzullo E, Weiss M, Bonin S. Oncologic emergencies and paraneoplastic syndromes. Cancer Management: A Multidisciplinary Approach, Ninth Edition Melville, NY: The Oncology Group, FA Davis Company. 2005:982-6.
19. Dağdelen S. Superior vena cava syndrome arising from subclavian vein port catheter implantation and paraneoplastic syndrome. Turk Kardiyol Dern Ars. 2009;37:125-7.
20. Tonak J, Fetscher S, Barkhausen J, Goltz J. Endovascular recanalization of a port catheter-associated superior vena cava syndrome. J Vasc Access. 2015;16(5):434-6.
21. El Haddad D, Iliescu C, Yusuf SW, William WN, Khair TH, Song J, *et al.* Outcomes of cancer patients undergoing percutaneous pericardiocentesis for pericardial effusion. Journal of the American College of Cardiology. 2015;66(10):1119-28.
22. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Archives of Internal Medicine. 2000;160(6):809-15.
23. Blann AD, Dunmore S. Arterial and venous thrombosis in cancer patients. Cardiol Res Pract. 2011;2011:394740.
24. Connolly GC, Francis CW. Cancer-associated thrombosis. ASH Education Program Book. 2013;2013(1):684-91.
25. Du Toit JM. Upper limb ischaemia: a twelve year experience: University of Cape Town; 2014.
26. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005;293(6):715-22.
27. Kwaan HC, Parmar S, Wang J, editors. Pathogenesis of increased risk of thrombosis in cancer. Seminars in thrombosis and hemostasis; 2003.
28. Pelosof LC, Gerber DE, editors. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clin Proc. 2010:85(9), 838-854.
29. Ross JS, Slodkowska EA, Symmans WF, Pusztai L, Ravdin PM, Hortobagyi GN. The HER-2 receptor and breast cancer: ten years of targeted anti–HER-2 therapy and personalized medicine. The oncologist. 2009;14(4):320-68.
30. Swain SM, Baselga J, Kim S-B, Ro J, Semiglazov V, Campone M, *et al.* Pertuzumab, trastuzumab, and docetaxel in HER2-positive

metastatic breast cancer. New England Journal of Medicine. 2015;372(8):724-34.
31. Valabrega G, Montemurro F, Aglietta M. Trastuzumab: mechanism of action, resistance and future perspectives in HER2-overexpressing breast cancer. Annals of oncology. 2007;18(6):977-84.
32. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, *et al.* Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. New England Journal of Medicine. 2005;353(16):1659-72.
33. Marty M, Cognetti F, Maraninchi D, Snyder R, Mauriac L, Tubiana-Hulin M, *et al.* Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol. 2005;23(19):4265-74.
34. Adamo V, Ricciardi GRR, Adamo B, Ferraro G, Franchina T, Rossello R, *et al.* The risk of toxicities from trastuzumab, alone or in combination, in an elderly breast cancer population. Oncology. 2013;86(1):16-21.
35. Jones A, Barlow M, Barrett-Lee P, Canney PA, Gilmour I, Robb S, *et al.* Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. British journal of cancer. 2009; 100(5):684-92.
36. Chen J, Long JB, Hurria A, Owusu C, Steingart RM, Gross CP. Incidence of heart failure or cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. Journal of the American College of Cardiology. 2012;60(24): 2504-12.
37. Mehrpooya M, Emadi SH, Sattarzadeh-Badkoobeh R, Shahi F, Parsa AFZ, Mohagheghi A, *et al.* Trastuzumab-Induced Cardiomyopathy Evaluation by Combined Echocardiography and Biomarkers in Patients with Breast Cancer. Iranian Heart Journal 201531-26 : (4)15 ؛.
38. Rossner D, Knobloch K, Lichtinghagen R, Lichtenberg A, Kuehnle H, Lueck H, editors. NT-pro-BNP and CA 125 as potential markers of mortality during long-term immunetherapy with trastuzumab in HER-2-positive metastatic breast cancer. ASCO Annual Meeting Proceedings; 2004.
39. Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, *et al.* Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. Journal of clinical oncology. 2010;28(25):3910-6.
40. Goel S,Simes RJ, Beith JM. Exploratory analysis of cardiac biomarkers in women with normal cardiac function receiving trastuzumab for breast cancer. Asia-Pacific Journal of Clinical Oncology. 2011;7(3):276-80.
41. Lamot C, Rottey S, De Backer T, Van Bortel L, Robays H, Van Belle S, *et al.* Cardiac toxicity of trastuzumab: experience at the Ghent University Hospital, Belgium. Acta Clinica Belgica. 2010;65(5):300-4.
42. Chavez-MacGregor M, Zhang N, Buchholz TA, Zhang Y, Niu J, Elting L, *et al.* Trastuzumab-related cardiotoxicity among older patients with breast cancer. J Clin Oncol. 2013;31(33):4222-8.
43. Chang C-M, Cheng FT-F, Yang T-L, Wen W-C. Cardiotoxicity Associated with Trastuzumab Therapy in Taiwan: A Single Medical Center's 5-Year Experience. Journal of Cancer Research and Practice. 2015;2(2):139-50.
44. Group EBCTC. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2006;366(9503):2087-106.
45. Højris I,Overgaard M, Christensen JJ, Overgaard J. Morbidity and mortality of ischaemic heart disease in high-risk breast-cancer patients after adjuvant postmastectomy systemic treatment with or without radiotherapy: analysis of DBCG 82b and 82c randomised trials. The Lancet. 1999;354(9188):1425-30.
46. Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, *et al.* Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. Journal of the National Cancer Institute. 2007;99(5):365-75.
47. Correa CR,Litt HI, Hwang W-T, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. Journal of clinical oncology. 2007;25(21):3031-7.
48. Prosnitz RG, Chen YH, Marks LB, editors. Cardiac toxicity following thoracic radiation. Semin Oncol. 2005;32(2 Suppl 3):S71-80.
49. Landau D, Adams EJ, Webb S, Ross G. Cardiac avoidance in breast radiotherapy: a comparison of simple shielding techniques with intensity-modulated radiotherapy. Radiotherapy and Oncology. 2001;60(3):247-55.
50. Hatoum OA, Otterson MF, Kopelman D, Miura H, Sukhotnik I, Larsen BT, *et al.* Radiation induces endothelial dysfunction in murine intestinal arterioles via enhanced production of reactive oxygen species. Arteriosclerosis, thrombosis, and vascular biology. 2006;26(2): 287-94.
51. Seddon B, Cook A, Gothard L, Salmon E, Latus K, Underwood SR, *et al.* Detection of defects in myocardial perfusion imaging in patients with early breast cancer treated with radiotherapy. Radiotherapy and Oncology. 2002;64(1):53-63.
52. Paris F, Fuks Z, Kang A, Capodieci P, Juan G, Ehleiter D, *et al.* Endothelial apoptosis as the

primary lesion initiating intestinal radiation damage in mice. Science. 2001;293(5528):293-7.
53. Group EBCTC. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. The Lancet. 2005;366(9503):2087-106.
54. Darby SC, Cutter DJ, Boerma M, Constine LS, Fajardo LF, Kodama K, *et al.* Radiation-related heart disease: current knowledge and future prospects. International journal of radiation oncology, biology, physics. 2010;76(3):656.
55. Doyle JJ, Neugut AI, Jacobson JS, Grann VR, Hershman DL. Chemotherapy and cardiotoxicity in older breast cancer patients: a population-based study. J Clin Oncol. 2005;23(34):8597-605.
56. Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK, editors. Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. Mayo Clin Proc. 2008;83(2):197-203.
57. Fox K. The evaluation of left ventricular function for patients being considered for, or receiving Trastuzumab (Herceptin) therapy. British journal of cancer. 2006;95(10):1454.
58. Stoodley PW, Richards DA, Meikle SR, Clarke J, Hui R, Thomas L. The potential role of echocardiographic strain imaging for evaluating cardiotoxicity due to cancer therapy. Heart, Lung and Circulation. 2011;20(1):3-9.
59. Erven K, Florian A, Slagmolen P, Sweldens C, Jurcut R, Wildiers H, *et al.* Subclinical cardiotoxicity detected by strain rate imaging up to 14 months after breast radiation therapy. Int J Radiat Oncol Biol Phys. 2013;85(5):1172-8.
60. Saad A, Abraha J. Trastuzumab and cardiac toxicity: monitoring in the adjuvant setting. Community Oncology. 2007;4(12):739-44.
61. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, *et al.* Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography. 2014;27(9):911-39.
62. Duchnowska R, Szmit S, Szczylik C, Opolski G. [Difficulties in echocardiographic monitoring of trastuzumab therapy in breast cancer patients: case report and review of recommendations]. Kardiol Pol. 2008;66(8):895-8.
63. Huszno J, Les D, Sarzyczny-Slota D, Nowara E. Cardiac side effects of trastuzumab in breast cancer patients-single centere experiences. Współczesna Onkologia. 2013;17(2):190.
64. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, *et al.* 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Journal of the American College of Cardiology. 2013;62(16):e147-e239.
65. Tan-Chiu E, Yothers G, Romond E, Geyer CE, Ewer M, Keefe D, *et al.* Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2–overexpressing breast cancer: NSABP B-31. J Clin Oncol. 2005;23(31):7811-9.
66. Romond EH, Perez EA, Bryant J, Suman VJ, Geyer Jr CE, Davidson NE, *et al.* Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. New England Journal of Medicine. 2005;353(16):1673-84.
67. De Azambuja E, Procter MJ, Van Veldhuisen DJ, Agbor-Tarh D, Metzger-Filho O, Steinseifer J, *et al.* Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin Adjuvant trial (BIG 1-01). Journal of clinical oncology. 2014:JCO. 2013.53. 9288.
68. Joensuu H, Kellokumpu-Lehtinen P-L, Bono P, Alanko T, Kataja V, Asola R, *et al.* Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. New England Journal of Medicine. 2006;354(8):809-20.
69. Duquaine D, Hirsch GA, Chakrabarti A, Han Z, Kehrer C, Brook R, *et al.* Rapid-onset endothelial dysfunction with adriamycin: evidence for a dysfunctional nitric oxide synthase. Vascular Medicine. 2003;8(2):101-7.
70. Kotamraju S, Konorev EA, Joseph J, Kalyanaraman B. Doxorubicin-induced apoptosis in endothelial cells and cardiomyocytes is ameliorated by nitrone spin traps and ebselen role of reactive oxygen and nitrogen species. Journal of Biological Chemistry. 2000;275(43): 33585-92.
71. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. Canadian medical association journal. 2006;174(6):801-9.
72. Scott JM, Koelwyn GJ, Khouri MG, Douglas PS, Jones LW. Preventing Cardiovascular Complications of Breast Cancer Treatment: The Utility of Effective Exercise Prescription. Current Cardiovascular Risk Reports. 2013;7(4):275-82.

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# A Comparative Study of Multilayer Neural Network and C4.5 Decision Tree Models for Predicting the Risk of Breast Cancer

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ABSTRACT

**Background:** Diagnosing breast cancer at an early stage can have a great impact on cancer mortality. One of the fundamental problems in cancer treatment is the lack of a proper method for early detection, which may lead to diagnostic errors. Using data analysis techniques can significantly help in early diagnosis of the disease. The purpose of this study was to evaluate and compare the efficacy of two data mining techniques, i.e., multilayer neural network and C4.5, in early diagnosis of breast cancer.

**Methods:** A data set from Motamed Cancer Institute's breast cancer research clinic, Tehran, containing 2860 records related to breast cancer risk factors were used. Of the records, 1141 (40%) were related to malignant changes and breast cancer and 1719 (60%) to benign tumors. The data set was analyzed using perceptron neural network and decision tree algorithms, and was split into two a training data set (70%) and a testing data set (30%) using Rapid Miner 5.2.

**Results:** For neural networks, accuracy was 80.52%, precision 88.91%, and sensitivity 90.88%; and for decision tree, accuracy was 80.98%, precision 80.97%, and sensitivity 89.32%. Results indicated that both algorithms have acceptable capabilities for analyzing breast cancer data.

**Conclusion:** Although both models provided good results, neural network showed more reliable diagnosis for positive cases. Data set type and analysis method affect results. On the other hand, information about more powerful risk factors of breast cancer, such as genetic mutations, can provide models with high coverage.

## Introduction

Breast cancer is a disease in which malignant cells originate from breast tissue and proliferate irregularly and increasingly while passing immune system without causing any defensive and aggressive immune response.[1,2] The disease usually initiates as a solid mass in superior lateral region of breast and may expand to axillary lymph nodes and then to the whole body.[3] Although cancer is the result of a combination of genetic and environmental factors, the main cause of breast cancer is not clear. A number of risk factors are known for breast cancer,[4,5] including genetic and racial factors, diet, obesity, hormones, radiation, menopause (after age 50), oral contraceptives use, hormone therapy, family history, and alcohol consumption.[5,6] Thus, identification of all breast cancer risk factors along with taking right actions to increase public awareness about those factors can help in the prevention and early detection of the disease. Using artificial intelligence and soft calculations are among the methods which can facilitate diagnosis, identification, and decision making in cancers, especially breast cancer.[7,8]

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Researchers have been interested in artificial intelligence for developing prediction models in various scientific fields such as medical engineering. Medical prediction models help physicians in overcoming health care problems and decreasing medical errors.[9] Furthermore, data analysis models may result in better and more accurate diagnosis of conditions in clinical settings by detecting hidden patterns. Classification is one of the main functions of data analysis. Neural networks are the most applicable models of artificial intelligence in medicine because they provide accurate responses and decision trees and the process is simple to follow.[10] Since the classification of medical problems is inherently non-linear, prediction models based on linear statistical methods would not be precise. Furthermore, conventional statistical techniques are not suitable for analyzing large data sets.[11] Data analysis and its techniques, if used properly, can be more efficient in this regard. Considering that the use of modern technologies and software knowledge have increased in medicine during the last two decades, and given the fact that early diagnosis has a significant role in decreasing cancer mortality, applying data analysis techniques to breast cancer data sets and extracting useful results for improvement of accuracy in medical diagnosis is crucial.[11]

Given the importance of breast cancer and its early diagnosis as well as understanding the effective role of different data analysis methods in development of prediction models, it seems essential that the accuracy of these techniques be evaluated practically in various sites and the most efficient and effective models be identified. Thus, the objective of the present study was to compare the accuracy of two different models, namely, neural network data analysis and decision tree, in predicting the risk of breast cancer.

**Methods**

In this retrospective study, a data set from Breast Cancer Research Center of Motamed Cancer Institute, Tehran, Iran, were used, which contained information related to patients admitted to ACECR breast diseases clinic in Tehran from March 2007 to September 2015. Every record consisted of 14 fields of information on breast cancer risk factors and 1 field on the type of main tumor (malignant or benign). The data set consisted of 2860 records, of which 1141 (40%) were related to breast cancer patients and 1719 (60%) to benign breast tumors. Table 1 presents the evaluated risk factors.

In preprocessing stage, columns unrelated to disease risk factors or related to patients' demographic information were omitted. Then, for the purpose of increasing validity, efforts were made to omit records with more than 20% missed information and records having irrelevant information, although no such record was identified. Finally, missing values were replaced by the mean of that variable for 25 adjacent cases in SPSS 21 so that the number of the remaining records were 2860 (unchanged). Then, by random sampling, 70% and 30% of the data set were used for model training and model testing, respectively. In order to design a multilayer perceptron neural network with Rapid Miner 5.2, the number of nodes was considered 14 with a learning rate of 0.3 and 1 hidden layer. The number of nodes in hidden layer was 10, and the number of iteration was considered 1000. To design the tree with Rapid Miner 5.2, data productivity criteria, minimum branch size of 4, minimum leaf size of 2, minimum productivity of 0.1, and confidence of 0.25 were used, and models were evaluated using 70% of the training data and 30% of the test data.

**Table .** Breast cancer risk factors considered in the study

| Risk factor | Type |
|---|---|
| 1.The age at the time of diagnosis | Quantitative – discrete |
| 2.The age of the first menstruation | Quantitative – discrete |
| 3.Menopausal age | Quantitative – discrete |
| 4.The age of the first pregnancy | Quantitative – discrete |
| 5.History of breastfeeding | Qualitative – classified |
| 6.History of taking OCP | Qualitative – classified |
| 7.History of hormone therapy after menopause | Qualitative – classified |
| 8.History of breast cancer | Qualitative – classified |
| 9.Family history of breast cancer | Qualitative – classified |
| 10.History of infertility | Qualitative – classified |
| 11.Tobacco use | Qualitative – classified |
| 12.Marital status | Qualitative – classified |
| 13.Education | Qualitative – classified |
| 14.Traumatic events in life | Qualitative – classified |
| 15.Type of disease (malignant or benign) | Qualitative – classified |

For investigation of the success rate and efficacy of these models, we used confusion matrix and ROC diagram as common techniques in diagnosis classification models.[12] For interpretation of classification and diagnosis of diseases and breast cancer patients using confusion matrix, there exists four states including true positive, true negative, false positive, and false negative, with each one having a special meaning in confusion matrix as follows:

True Positive (TP): the number of records that are positive and the algorithm has truly identified their class.

False Positive (FP): the number of records that are negative but the algorithm has falsely identified their class as positive.

True Negative (TN): the number of records that are negative and the algorithm has truly identified their class.

False Negative (FN): the number of records that are positive but the algorithm has falsely identified their class as positive.[13]

In this paper, the function of confusion matrix was developed using concepts above, and, for analyzing their functions, three main criteria of sensitivity, specificity, and accuracy in classification were used. Definitions and characteristics of these indices have been described in all resources for data analysis.[13]

As mentioned earlier, after being entered in Rapid Miner software, the data set was split into two sets (70% for training and 30% for testing models), and the multi-layer perceptron neural network (MLP) and the decision tree (C4.5) were trained and tested using those data sets. Results were provided by three criteria of accuracy, sensitivity and specificity.

**Results**

As described in previous section, after training and testing the models, the software reported results by three indices of sensitivity, specificity, and accuracy. Table 2 presents the results of the evaluation of models.

It can be seen from the table that there was no significant difference between sensitivity and accuracy indices. However, regarding specificity, neural network is significantly effective than decision tree.

**Discussion**

In this study, we analyzed a data set from ACECR Breast Cancer Research Center for diagnosis of breast cancer using multilayer perceptron neural network and decision tree algorithms. In comparison, the neural network was significantly effective in diagnosing negative cases. Early diagnosis of breast cancer is important from different aspects and can improve patients' survival. Considering the importance of the risk factors in breast cancer incidence, the efficacy of data analysis techniques in development of effective models for prediction and diagnosis is undeniable.[9] It is worth mentioning that the use of the general terms "neural network" and "decision tree" do not seem appropriate for other algorithms like C4.5 and multilayer neural networks. In other words, "neural network" and "decision tree" are general terms for techniques which contain various algorithms.

Researchers have used neural network and decision tree algorithms with other breast cancer data sets, and the results are different from the present study. For instance, in a work by Senturk and Kara using neural network and decision tree algorithms for analysis of Wisconsin sampling data set, the accuracy of both models was greater than that of the present study. The reason for this difference can be attributed to the difference in databases, methods, and missing data management.[14]

In another work, Rajesh and Anand used C4.5 algorithm for analysis of SEER data set for diagnosing breast cancer, which displayed greater accuracy compared with the present study. Again, the difference can be attributed to differences in data sets, data selection, and data classification methods.[15] In a work by Lakshmi *et al* evaluating the efficacy of data analysis algorithms, Wisconsin sampling data set was analyzed using C4.5 algorithm. The accuracy of this model was significantly higher than our study because of the difference in the evaluation method. Therefore, differences in data sets can produce different results in data analysis.[16] Kiani and Atashi used decision tree algorithm for prediction of breast cancer recurrence. Similarities of these two studies are using decision tree, using a real sample of patients, and using similar outcomes for evaluation of the models. The researchers showed 75% accuracy for decision tree model, which is lower than that for our study. The most important reason for this difference may be that Kiani and Atashi used a lower number of records and different set of dependent variables.[17] Also, it is possible that increasing the amount of training data to a specific level may improve model accuracy.[10] Furthermore, Tolooi *et al* used C5 decision tree for analysis of the same data set used in this study and obtained an accuracy of 95%.

**Table 2 .** The results of model testing by sensitivity, specificity, and accuracy of models

| Model | Sensitivity | Specificity | Accuracy |
|---|---|---|---|
| Multilayer perceptron neural network | 90.88% | 88.91% | 80.52% |
| C4.5 decision tree | 89.32% | 80.97% | 80.98% |

This shows that significant differences in data modeling can be found among decision tree algorithms.

Among limitation of this study, we can mention the missing data. Because of independency among variables and the lack of specific order in them, missing data were estimated using replacement methods, which may have affected the results. Another limitation was the use of only one of the various available methods in neural network and decision tree, so it was not possible to identify the most effective algorithm among these algorithms. However, the main strength of this study was using a real-world data set of patients consisting of a large number of records, which improves system training and is relatively better than other regional studies in this context.

Considering one of the main purposes of medical data analysis, which is to produce the best algorithm for data description, the results of analyses of data sets are unique based on the method applied in every study, so the results are only valid for that specific method. On the other hand, a more complete list of risk factors can provide a model with more extensive coverage. Moreover, results of the models may be affected by data preprocessing and missing data handling, and the method used for data evaluation. Researchers can use the results of the present study for future analyses of breast cancer risk factor data sets to generate models with higher efficacy and accuracy. It is suggested that future studies compare separate modeling results in decision tree with different numbers of iterations, investigate results with different neural network indices, and compare more algorithms-specially SVM, due to its promising results in medicine.

**Conflict of Interest**

The authors have none to declare.

**References**


1. Rezvani B. The relationship between TRU9I polymorphism in vitamin D receptor (VDR) gene and breast cancer. MSc thesis: Islamic Azad University, Damghan branch; 2013.
2. Setayeshi S, Akbari ME, Darghahi R, Haghighat khah HR. Breast Cancer and Technical Analysis of its Diagnostics. Tehran: Bitarafan; 2011.
3. American Cancer Society. Breast cancer facts & figures 2009 [Available from: https://www.cancer.org/ research/cancer-facts-statistics/breast-cancer-facts-figures.html.]
4. National Breast Cancer Foundation. Early Detection 2012 [Available from: http://www.nationalbreastcancer.org/ earlydetection-of-breast-cancer]
5. Khoury-Collado F, Bombard AT. Hereditary breast and ovarian cancer: what the primary care physician should know. Obstetrical & gynecological survey. 2004;59(7):537-42.
6. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer Implications for risk prediction. Cancer. 1994; 73:643- 651.
7. Shell J, Gregory WD. Efficient Cancer Detection Using Multiple Neural Networks. IEEE journal of translational engineering in health and medicine. 2017;5:1-7.
8. Udayakumar E, Santhi S, Vetrivelan P. An investigation of Bayes algorithm and neural networks for identifying the breast cancer. Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical & Paediatric Oncology. 2017;38(3):340.
9. Azimian F, Tadaion-T GH, Jalali M. Breast Cancer Detection Using Data Mining Techniques. 4th Iranian Data Mining Conference2010.
10. Grzymala-Busse JW, Hu M. A comparison of several approaches to missing attribute values in data mining. InInternational Conference on Rough Sets and Current Trends in Computing 2000: 378-385. Springer, Berlin, Heidelberg.
11. Hota H. Diagnosis of breast cancer using intelligent techniques. International Journal of Emerging Science and Engineering (IJESE). 2013;1(3):45-53.
12. Fielding A. Cluster and classification techniques for the biosciences. 2007.
13. Larose DT. Data mining methods & models: John Wiley & Sons; 2006.
14. Senturk ZK, Kara R. Breast cancer diagnosis via data mining: performance analysis of seven different algorithms. Computer Science & Engineering. 2014;4(1):35.
15. Rajesh K, Anand S. Analysis of SEER dataset for breast cancer diagnosis using C4. 5 classification algorithm. International Journal of Advanced Research in Computer and Communication Engineering. 2012;1(2):2278-1021.
16. Lakshmi K, Krishna MV, Kumar SP. Performance comparison of data mining techniques for prediction and diagnosis of breast cancer disease survivability. Asian Journal of Computer Science & Information Technology. 2013;3(5):81 - 87.
17. Kiani B, Atashi A. A prognostic model based on data mining techniques to predict breast cancer recurrence. Journal of Health and Biomedical Informatics. 2014;1(1):26-31.

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# Clinicians' Practice and Perception of Disclosure Model for Breaking Bad News to Breast Cancer Patients

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ABSTRACT

**Background:** Physicians' beliefs about disclosure manner and their ethical attitude for telling the truth is an important issue in patient-physician interaction. The aim of this study was to examine clinicians' practice and perception of disclosure models for giving bad news to breast cancer patients.

**Methods:** Participants (n = 207, age 21–61 years, mean work experience = 4.03 ± 6 years) working in different medical centers in Tehran, Iran, were recruited by purposive sampling method. They completed clinicians' attitude and practice of Breaking Bad News (BBN) scales. Psychometric properties (reliability and validity) of these scales were approved.

**Results:** Clinicians' practice differed significantly by their perception of disclosure model for giving bad news. Furthermore, difference in clinicians' practice and perception of disclosure model for BBN was observed for age, gender, medical work experience in oncology setting, and receiving special training. Finally, clinicians' perception of disclosure model for BBN (Adj. R2 = 0.32), age (Adj. R2 = 0.17), gender (Adj. R2 = 0.11), and receiving special training for giving bad news (Adj. R2 = 0.09) positively predicted their practice of BBN.

**Conclusion:** Findings of the study point to the importance of the clinicians' perception of disclosure model for giving bad news and transcultural variables as factors affecting their practice. Therefore, it seems necessary to incorporate special BBN trainings and protocols culturally adapted to the Iranian society in educational curricula of medical specialties and medical ethics in breast cancer setting.

## Introduction

The recent Greek *New Code of Medical Ethics and Deontology* declared that according to the principle of patients' autonomy, physicians should provide the patients with the appropriate information about their health status.[1] Based on the International Code of Medical Ethics, physicians must respect patient's right to select different methods of treatment and inform patients about their decisions.[2]

Informing patients about the diagnosis of a serious health-threatening disease or failure in treatment is called a clinically bad news.[3, 4] In other words, "bad news" is any information that negatively impacts one's expectations for the future.[5] Breaking bad news (BBN) has been studied widely in oncology setting.[6-8] Disclosing the diagnosis of cancer or its prognosis is a stressful task for doctors.[9] Oncologists may have to break bad news to patients with an average of 20000 times over the course of their career.[10]

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Breast cancer is the most prevalent cancer among women worldwide.[11] Disclosure of breast cancer to the patients is of utmost importance and affects all aspects of the patients' life as well as their decisions on different types of treatment.[3] It can also affect the patient's hope and trust in surgeon's expertise, and have a considerable effect on the communication with the surgeon and the other physicians in the team.[12] A scientific, stepwise disclosure method has a positive effect on patients' quality of life, reducing patient's stress and maintaining hope,[13] increasing satisfaction with and confidence in the health care team,[14, 15] and improving patient cooperation in treatment process.[16] Hence, clinicians' attitude toward and practice of BBN is an essential part of patient care in breast cancer.

Clinicians have different attitudes toward disclosure of bad news. A model suggested by the World Health Organization (WHO) distinguishes three disclosure models regarding clinician-patient communication and decision-making style:[17] full disclosure, where the physician tells all the truth to the patients, and clinical decision-making is considered the patient's responsibility; non-disclosure, where the physician has a dominant role, and the patient will be dependent on the clinicians' decision-making and play a passive role; and individual disclosure, where delivering of information will be done based on the patients' preference.[18]

Prior studies showed that physicians' tendency to each disclosure model is under the influence of the following factors: institutional norms, previous specific training for BBN, preference of patients' families[19], patients' and clinicians' characteristics, time considerations,[20] organizational considerations, and clinicians' work experience.[9, 21] Cultural and social norms are important factors influencing clinicians' attitudes toward BBN, eg clinicians' inclination to family-centered decision-making style in non-Western nations,[22, 23] vs. the higher tendency toward patients' autonomy in Western countries.[24, 25] Thus, telling the truth is not a simple task; instead, it is a dynamic process that concerns not only the disclosure of the truth to patients, but also communication between clinician and the patients as well as their families according to social norms.[26]

BBN is a complex practice which requires a variety of skills such as communication, understanding, and empathy.[27] From this point of view, some studies offer various models and protocols that guide clinicians on how to disclose bad news to their patients.[6, 28, 29] One of the most important guidelines is SPIKES, which is designed in six phases. In this acronym "S" stands for *setting up* the interview, "P" assessing the patient's *perception*; "I" obtaining the patient's *invitation*, "K" giving *knowledge* and information to the patient, "E" addressing the patient's *emotions* with empathic responses, and "S" *strategy* and *summary*.[6] ABCDE is another guideline for BBN five steps of which are as follows: Advance preparation, Build a therapeutic environment/ relationship, Communi-cate well, Deal with the patient and family reactions, and Encourage and validate emotions.[30]

Previous studies usually highlighted that "giving bad news" includes several steps: (a) the pre-delivery phase including preparation of the appropriate space and time, paying attention to patient's cultural background, considering patient's needs, assessing what patients know, and the amount of information he needs to know; (b) the delivery phase, which is dedicated to providing the patients with all necessary information and clarifying any misunderstanding; and (c) the post-delivery phase consisting of patient follow-up. This stage includes responding to any patient question, giving emotional support and providing empathy, addressing the next step, and closing the session.[31-33]

The existing literature on the physicians' perception and practice of BBN shows a global trend toward full disclosure of bad news to cancer patients.[12,34-39]

However, as stated above, there are many other parameters affecting the truth-telling and physicians' perception of disclosure method for BBN. The physicians' personal characteristics are among the most important factors in this regard.[1] In this context, attitude and belief will be among the best predictors for the future behavior when they are easy to recall and stable over time.[40] Henderson *et al*. indicated that knowledge was not significantly related to nursing practice and that attitude moderated the relation between knowledge and practice; so attitudes and beliefs have direct effects on nursing practice.[41] Beach *et al*. showed that physician's attitude has an impact on healthcare quality and communication with patients.[42] One study suggested that the physicians' attitudes toward BBN might affect their behavior,[43] although it has notbeen examined despite its implications. Apparently, another element that affects disclosure manner is a transcultural factor. Locatelli *et al*. observed that Italian physicians' age and gender influenced telling bad news to the older cancer patients and managing emotional reactions.[44] Special BBN training is another element that impacts physicians' disclosure manner.[45-47] Therefore, it is essential to consider beliefs and transcultural factors in analyzing physicians' BBN approaches.

Considering the high prevalence of breast cancer in all countries,[11] including Iran,[48] there are insufficient studies on the clinicians' attitudes toward, perception, and practice of disclosing bad news to breast cancer patients. The purpose of this study was to assess Iranian clinicians' perception and

practice of telling bad news to breast cancer patients according to disclosure models. Besides, the influence of transcultural factors on the physicians' perception and practice of disclosing bad news to breast cancer patients were evaluated.

## Methods

A cross-sectional design was used to examine physicians' practice of delivering bad news to breast cancer patients based on the perception of disclosure models (full-disclosure, non-disclosure, and individual disclosure) and two protocols for BBN, like SPIKES and ABCDE.

The sample of the present study included 207 Iranian clinicians (surgeons, hematology-oncology, radiologists, radiation oncologists, nurses, and midwives) working in medical centers of Tehran, particularly at wards treating breast cancer patients. They were recruited via purposive sampling. The sample size was calculated according to previous studies that showed the percentage of physicians who informed patients about their cancer diagnosis was about 45%,[49, 50] a confidence level of 95%, and margin of error of %0.675 [51] (15% prevalence). From December 2015 until March 2016, all eligible participants were informed about the aim of the study, and those who were willing to participate were included. They had full cooperation in the survey and completed the questionnaire.

### *Ethical approval*

The study was approved by the Research Ethics Committee of Tehran University of Medical Sciences.

### *Measurement tools*

#### *Attitude Toward Breaking Bad News scale*

Physicians' perception of disclosure model for BBN was measured by using the Attitude Toward Breaking Bad News scale developed by Borjalilu and colleagues[52] according to WHO disclosure model. The scale comprises three factors with 12 items rated on 5-point Likert-type scale ranging from 1 (completely agree) to 5 (completely disagree). The "full disclosure" factor consists of 5 items (Cronbach's alpha = 0.746), the "non-disclosure" factor 5 items (alpha = 0.834), and the "individualized disclosure" 2 items (alpha = 0.795).

#### *Physicians' Practice of Breaking Bad News*

Physicians' practice was assessed using the practice of BBN scale. The instrument was developed based on SPIKES and ABCDE models of BBN.[52] It comprises 20 items divided into 6 subscales including Preparation (4 items), Setting of the interaction (3 items), Communication (4 items), Using the word "cancer" (2 items), Patient's right to know (2 items), and Closing the interview and summarizing (5 items). Items were rated on a 5-point Likert-type scale ranging from 1 (never) to 5 (always). The subscales were shown to have acceptable internal consistency (Preparation: $\alpha$ = 0.765, Setting of the interaction: $\alpha$ = 0.63, Communication: $\alpha$ = 0.65, Using the word "cancer": $\alpha$ = 0.793, Patient's right to know: $\alpha$ = 0.759, and Closing the interview and summarizing: $\alpha$ = 0.7).

Data regarding physicians' demographic and career characteristics were collected, which included the following: age, gender, specialty, medical work experience in the oncology setting, job title, frequency of giving bad news within the past three months, minimum and maximum time (minutes) spent on disclosing bad news to patients, the need for special BBN training, and the need for guidelines on how to deliver bad news.

### *Statistical analysis*

We used Statistical Package for Social Sciences (SPSS) version 22 for data analysis. Descriptive statistics (mean, standard deviation, minimum, and maximum) were used to describe variables, and independent *t* test was performed to compare the physicians' perception and practice of BBN between genders. For comparison of physicians' BBN practice based on their perceptions of BBN models and transcultural factors (age, work experience, and receiving special BBN training), the one-way analysis of variance (ANOVA) along with the Tukey post hoc test was used. Finally, linear regression model was used to examine the association of physicians' practice with their perception of BBN and transcultural factors. Cronbach's $\alpha$ was calculated to assess the reliability of physician's attitude and practice scales for BBN to breast cancer patients. Level of statistical significance was set at 0.05.

## Results

A total of 207 participants completed the questionnaires. There were 119 females (57%) and 88 males (43%) clinicians (age: 38.1 ± 9.1 years, range: 21–61) practicing in different fields (surgery: 52 (25%), radiation oncology: 38 (18.5%), nursing: 42 (20%), hematology-oncology: 31(15%), radiology: 30 (14.5%), and midwifery: 14 (7%)).

Of 207 participants, 123 (59.56%) worked in educational hospitals (faculty members = 51 (24.5%), clinical fellowship members = 19 (9.1%), specialists = 14 (6.7%), and residents = 39 (18.8%)), and 84 (40.44%) were employed in general hospitals. The average work experience of physicians in the field of oncology was 4.03 ± 6 years.

Fifty-eight percent of participants had disclosed bad news to less than 5 breast cancer patients within the past three months. The minimum and maximum amount of time participants would spend on giving bad news to patients was 5 and 15 minutes. The results showed that only 24 of the clinicians (11.5%)

**Table 1.** Characteristics of participants (N = 207)

| Variables | | N(%) |
|---|---|---|
| Gender | Male | 88 (43%) |
| | Female | 119 (57%) |
| Age | < 30 | 60 (29%) |
| | 30–50 | 127 (60%) |
| | > 50 | 20 (11%) |
| Specialty | Hematology-oncology | 31 (15%) |
| | Surgery | 52 (25%) |
| | Radiology | 30 (14.5%) |
| | Radiation oncology | 38 (18.5%) |
| | Nursing | 42 (20%) |
| | Midwifery | 14 (7%) |
| Medical work experience in the oncology setting | < 10 | 81 (39%) |
| | 10–20 | 24 (11%) |
| | > 20 | 6 (3%) |
| Job title | Faculty member | 51 (24.5%) |
| | Clinical fellow | 19 (9.56%) |
| | Specialist | 14 (6.7%) |
| | Resident | 39 (18.8%) |
| | Private health sector | 84 (40.44%) |
| Number of bad news delivered within the past 3 months | < 5 | 121 (58%) |
| | 5–10 | 37 (18%) |
| | > 10 | 43 (21%) |
| | No response | 6 (3%) |
| Minimum time spent on giving badnews | | Median = 5 min |
| Maximum time spent on givingbad news | | Median = 15 min |
| Breaking bad news training | Yes | 24 (11.5%) |
| | No | 99 (48%) |
| | Somewhat | 84 (40.5%) |
| Need for guidelines on delivering bad news tailored to Iranian sociocultural context | Yes | 169 (82%) |
| | No | 38 (18%) |
| Preferred occasion for breaking bad news | Upon confirmation of diagnosis | 120 (58%) |
| | During treatment | 24 (12%) |
| | After treatment | 23 (11%) |
| | Upon patient's asking | 40 (19%) |

had received special training on BBN, and a large proportion of participants (82%, n = 169) expressed a need for appropriate guideline for delivering bad news to breast cancer patients according to the Iranian sociocultural context. Fifty-eight percent of participants preferred to deliver the bad news of cancer to patients when a definitive diagnosis was made (Table 1).

*Physicians' practice and perception of disclosure model for BBN*

The mean scores for disclosure models were 21± 2 (full disclosure), 6± 1 (individual disclosure), and 15± 4 (non-disclosure). Descriptive analysis of the study variables is shown separately for physicians' practice and three disclosure models in Table 2.

*Difference in clinicians' practice by their perception of disclosure model for BBN*

For the comparison of groups, we checked the assumptions (normality and homogeneity) of one-way ANOVA and independent t tests. The results indicated that the assumption was met. Afterwards, one-way ANOVA was done to compare the clinicians' practice of BBN to breast cancer patients by their perception of disclosure models (full disclosure, non-disclosure and individual disclosure) (Table 3).

As revealed by ANOVA analysis, there was a significant difference in total mean scores of clinicians' practice for the three perception of BBN disclosure models [F (4, 202)= 7.0391, P= 0.005]. Post hoc analysis showed that clinicians with a full disclosure attitude had significantly higher scores compared with clinicians with other two attitudes. In subscale comparisons, there was a significant effect of disclosure attitude on clinicians' using the word "cancer" [F (4, 202)= 9.745, P= 0.001]. Post hoc comparison showed that clinicians with a full disclosure attitude towards BBN tended to use the word "cancer" more frequently than those with other two attitudes. Also, there was a significant effect of disclosure attitude on "Patients' right to know" subscale for the three attitudes [F (4, 202) = 8.026,

**Table 2.** Descriptive analysis of variables

| Variables | | Mean | SD | Minimum | Maximum |
|---|---|---|---|---|---|
| Perception of Disclosure model | Full disclosure | 21 | 2 | 13 | 25 |
| | Non-disclosure | 15 | 4 | 4 | 25 |
| | Individual disclosure | 6 | 1 | 2 | 10 |
| Subscale and total scores for Practice | Preparation | 16 | 3 | 4 | 20 |
| | Setting of the interaction | 11 | 2 | 3 | 15 |
| | Communication | 14 | 1 | 10 | 20 |
| | Using the word "cancer" | 7 | 2 | 2 | 10 |
| | Patients' right to know | 6 | 1 | 3 | 10 |
| | Closing the interview and summarizing | 20 | 3 | 5 | 25 |
| | Total score for practice | 76 | 87 | 48 | 97 |

**Table 3.** Difference in clinicians' practice by perception of disclosure model for BBN

| Practice | Disclosure model for breaking bad news | | | F | Sig. |
|---|---|---|---|---|---|
| | Full disclosure Mean (SD) | Non-disclosure Mean (SD) | Individual disclosure Mean (SD) | | |
| Preparation | 18 (2) | 15 (3) | 16 (2) | 4.35 | 0.09 |
| Setting of the interaction | 13 (1) | 10 (2) | 14 (2) | 7 | 0.087 |
| Communication | 16 (1) | 14 (1) | 15 (1) | 7.06 | 0.325 |
| Using the "cancer" word | 9 (1) | 7 (2) | 7 (1) | 9.74 | 0.001 |
| Patient's right to know | 7 (2) | 6 (1) | 7 (1) | 8.02 | 0.002 |
| Closing the interview and Summarizing | 22 (2) | 20.03 (3) | 21 (3) | 6.12 | 0.531 |
| Total score of practice | 87 (6) | 75 (9) | 83 (7) | 7.03 | 0.005 |

P= 0.002]. Post hoc analysis revealed that clinicians with the full disclosure attitude scored significantly higher than those with other two attitudes, implying that they respected the patients' right to be informed about their medical conditions more than did their colleagues with other two attitudes. Finally, there was no significant difference in the mean scores for preparation [F (4, 202)= 4.356, P= 0.09], setting the interaction (F (4, 202)= 7, P= 0.087], communication [F (4, 202) = 7.065, P= 0.325], and closing the interview and summarizing [F (4, 202)= 6.128, P= 0.531] for the three disclosure attitudes.

*Differences in clinicians' perception of disclosure model for BBN and practice by age*

The comparison of the mean scores for the different disclosure models by age demonstrated a significant effect of age on non-disclosure attitude [F (3, 203)= 3.26, P= 0.002]. Post hoc analysis showed that clinicians under 30 years of age had significantly higher scores (13.01± 4.14) on non-disclosure attitude compared with other age groups. Similarly, a significant effect of age was observed for the clinicians' practice scores [F (3, 203)= 8.71, P= 0.001]. Post hoc analysis indicated that the mean score for practice of BBN in 30–50-year age group was significantly higher (79± 7.41) than that of other age groups.

*The effect of clinicians' gender on their perception of disclosure model for BBN and practice*

The results of this study showed significant gender difference in the scores for non-disclosure attitude (t= 2.169, P= 0.03). Female clinicians had higher mean score for the non-disclosure attitude compared with the males (15± 4.1). Also, there was a significant gender difference in the total mean score for the clinicians' practice (t = 2.11, P= 0.036), with females having higher mean score compared with males (79.1± 6.1)

*Differences in clinicians' perception of disclosure model for BBN and practice by work experience*

There was a significant effect of job experience on perception of disclosure models for non-disclosure [F (3, 203)= 2.045, P= 0.001] and individual disclosure attitudes [F (3, 203)= 1.12, P= 0.027]. Post hoc analyses indicated that the mean score for non-disclosure attitude was significantly higher in the group with under 10 years of work experience (14± 3) compared with that of other two groups, and the mean score for individual disclosure for the group with 10–20 years of work experience (6.41± 01) was significantly higher than those for the other groups. Finally, there was no significant difference in the total mean score for the clinicians' practice of BBN for the three work experience groups.

*Differences in clinicians' perception of disclosure model for BBN and BBN practice by receiving special training*

There was a significant difference in full-disclosure attitude scores by "receiving special BBN training" [F (3, 203)= 2.09, P= 0.001]. Post hoc analysis indicated that the mean score for full-disclosure attitude was significantly higher for the group who had received training (22 ± 2.1) compared with the other two groups. Receiving BBN training

also had significant effect on non-disclosure attitude [F (3, 203)= 1.01, P= 0.001]. Post hoc analysis indicated that the mean score for non-disclosure was significantly higher for the group with training (15± 3.04) compared with the other two groups. The scores for individual disclosure attitude were also significantly different for different BBN training groups [F (3, 203)= 0.89, P= 0.001], with the mean score for individual-disclosure attitude for the group with BBN training being significantly higher (6.05± 1.25) than that for the other groups. Finally, there was a significant difference in the total mean scores for clinicians' BBN practice by special BBN training [F (3, 203)= 2.028, P= 0.001], and post hoc analysis indicated that the mean overall BBN practice score for the group with BBN training (81± 7.1) was significantly higher than that for the groups who had not received any training or had received little training.

*Prediction of clinicians' practice from their perception of disclosure model for BBN and transcultural factors*

The regression model for prediction of clinicians' practice from their perception of disclosure model for BBN was significant [F (3, 203)= 17.11, P= 0.001] and was able to explain 32% of the variance in clinicians' practice. Also, the regression models for prediction of clinicians' practice from their age [F (3, 203)= 15.81, P= 0.001], gender [F (3, 203) = 4.45, P= 0.001], and receiving BBN training [F (3, 203)= 7.15, P= 0.001] were significant and explained 17%, 11%, 9% of the variance in clinicians' practice, respectively. However, medical experience in the field of oncology was not a significant predictor of clinicians' practice.

**Discussion**

The aim of the study was to determine clinicians' perception of disclosure models and practice of delivering bad news to breast cancer patients in Iranand to explore differences in practice according to perception of disclosure models.

Our results showed that the majority of clinicians who participated in this study used full-disclosure and individual disclosure models for BBN. From the total mean scores for practice and their subscales, which mostly fall above the minimum scores, it seems that clinicians had acceptable practice for giving bad news to breast cancer patients. Previous studies support this finding.[16, 53] It seems that clinicians have a tendency toward full disclosure of the bad news to cancer patients in Iran, like Western countries.[54] We found that a large majority of clinicians (91%) believed that "most of the patients want to know the truth about their illness" or "disclosure of the diagnosis of breast cancer to patients is necessary" (87%). According to prior studies,[16, 55] most clinicians (90%) believed that disclosure of bad news would enable patients to cooperate in the treatment process and decrease confusion and ambiguity for the patients and their families (81%). Regarding disclosure of breast cancer, clinicians reported that they spent a minimum of 5 minutes and a maximum of 15 minutes per case. It may be due to organization barriers[1] (lack of enough time and private place), engagement in different activities[56] (clinical education and research activities in the educational hospital), and/or individual barriers[57] (insufficient skills or knowledge and lacking a sense of responsibility). Thus, it is highly recommended that these potential barriers to delivering bad news to patients be explored through further research.

In our study, a significant difference was observed for clinicians' BBN practice by their perception of disclosure models for BBN (P= 0.001), and their perception of disclosure models explained 32% of the variance in their practice. Post hoc analysis showed that clinicians with attitude toward full disclosure reported better practice for BBN to breast cancer patients than clinicians with different disclosure models (P= 0.001). As mentioned, attitude directly affects health care practice, as shown in previous research.[41] It seems that attitude is the most effective element in the practice of the clinicians who participated in the study. Clinicians who preferred full disclosure model for BBN had better disclosure manners and made appropriate arrangements for this task. But other clinicians with tendency for non-disclosure and individual disclosure models had lower scores on the professional practice of BBN scale, probably due to their beliefs and attitudes. Regarding the relationship between attitude and behavior, research indicates that attitude accessibility (easy to recall) and stability (stable information) are the main factors affecting attitude retrieval and reconstruction.[40] Therefore, it is important to work on clinicians' attitude in medical schools and educational hospitals. Also, one of the significant differences in clinicians' practice was related to using the word "cancer" (P< 0.05). Post hoc analysis showed that clinicians with tendency toward full disclosure model used "cancer" more frequently than those with tendency for other models (P< 0.05). We also found that the majority of clinicians (77%) did not agree that the use of the word "cancer" would lead to panic in patients, which is consistent with the protocols for BBN.[40] This finding is similar to the reports on the physicians' practice in countries like Australia[58] and Canada[59] where truth disclosure is an established routine. However, in Asia and the Middle East, physicians, patients and their families usually try to avoid using the word "cancer," because in these cultures "cancer" is equivalent to death or incurable illnesses; therefore it produces such negative emotions as fear, stress, and helplessness in cancer patients.[60-62] Hence,

future research is necessary to determine the preference of Iranian women with breast cancer and their families regarding the use of the term "cancer," or other words such as "tumor" or "mass," when the diagnosis is disclosed to them.

Our results showed a significant difference in clinicians' practice of respecting "patients' right to know" (P< 0.05). Post hoc analysis showed that physicians with tendency for full disclosure model believed that patients had the right to be informed about their medical conditions and breast cancer (P< 0.05). Respecting patients' right to be informed of their conditions, which is asserted in medical ethics, has also been observed in previous studies[63, 64] However, research has demonstrated that in some Asian countries, such as China and Japan,[23,65, 66] as well as some European countries, for example Spain and Italy,[61] the patients' families tend to ask clinicians to refrain from disclosing the truth about diagnosis or prognosis to patients. Accordingly, it is necessary to develop an appropriate strategy according to breast cancer patients' right to know and their families' preferences for disclosure of bad news.

In this study, we observed a significant difference between clinicians' perception of disclosure model and practice of BBN by age and medical experience in oncology setting (P< 0.05). Post hoc analyses showed that younger clinicians preferred to use non-disclosure model for delivering bad news (P< 0.005). Locatelli *et al*.[44] and Baile[21] also reported similar findings. It may be because they lack the skills to deal with the difficult situation of telling the truth and they cannot manage the process of BBN. We also found that the majority of older clinicians (30–50 year age group) with 10–20 years of work experience preferred individual disclosure model and that their practice of giving bad news was better than those of the younger ones (P< 0.005). There are several explanations for this finding. Studies have shown that some breast cancer patients do not want to hear everything from the surgeons and would prefer information that gave them hope and maintained a personal clinical relationship with the surgeon.[12] Azu showed that breast cancer patients in the United States believed that physicians were supposed to know about the appropriate amount of information that should be delivered to each patient.[67] Also, Lobb *et al*. reported that half of the women preferred hearing positive information, e.g. chance of cure.[68] For Iranian women with breast cancer, creating hope and building trust are the preferences for clinicians' manner of disclosure.[69] Against this background, other studies indicated that women undergoing screening mammography wanted truthful results of imaging from radiologists[70, 71] and agreed that the radiologist should communicate the results directly to them.[72] As the evidence is not conclusive toward one specific approach, it may be reasonable that physicians with longer work experience in cancer treatment practice the individual disclosure model for giving bad news. It is likely that they would be aware of the patients' needs and socio-demographic status due to their extensive experience and would select the appropriate information and frame it to be disclosed to their patients. In our survey, middle-aged clinicians with enough work experience and appropriate skills reported better practice of BBN. Moreover, regression analysis showed that age explained 17% of the variance in clinicians' practice, but work experience (in years) did not prove to be a significant predictor; so clinicians' age is an important factors in their practice of BBN.

The results of this study confirmed that clinicians' gender affected their perception of disclosure model for BBN and practice for informing breast cancer patients, explaining 11% of the variance in the clinicians' practice. In the disclosure model we observed a significant gender difference for non-disclosure model (P< 0.05), with the females having higher mean score for the non-disclosure than the males. Further, there was a significant gender difference in the total mean score for the clinicians' practice (P< 0.05), and the female clinicians had better practice for giving bad news to breast cancer patients than males physicians. Our results are consistent with other studies about doctor-patient relationship. Compared with male physicians, female clinicians tend to spend more time with each patient, display better communication skills, and be more effective in triggering positive emotions in their patients.[73] They usually disclose more information to patients than their male counterparts do,[74] and their communication style is more commonly a patient-centered approach.[75] Furthermore, male clinicians tend to favor a direct manner of giving information to patients,[76] compared with indirect approaches preferred by female clinicians.[77] It is plausible that female clinicians are better able to avoid disclosure dilemma (attention to patients' autonomy vs paternalism) or deal with negative emotions of breast cancer and lack of skills for managing this situation. For an in-depth description, we suggest that male and female physicians' experiences regarding delivering bad news to breast cancer patients be explored in future studies.

The result of our survey showed that there was a significant difference in perception of disclosure models and practice of delivering bad news between clinicians who had received special BBN training and those who had not received training (P< 0.005), and that receiving special training for BBN explained 9% of the variance the clinicians' practice. Post hoc analysis showed that participants with special BBN training had higher mean scores for the full-disclosure and individual disclosure, and those who had not received training had higher mean scores for the non-disclosure (P< 0.005). Physicians who had received special BBN training had better practice

than the group without any training (P< 0.005). Novack *et al* reported that medical school and hospital training impact clinicians' attitude toward truth-telling in favor of full disclosure of cancer diagnosis to patients.[78] Prior research has indicated that communication skills training can improve clinicians' interviewing skills and affect their attitude.[79] Also, BBN training courses van improve communication skills,[45, 46] increase self-efficacy for giving bad news,[80] elicit appropriate levels of physiological arousal,[81] and promote competence for patient care. Results from our study reflect an essential role of BBN training. However, we observed a lack of sufficient training among the clinicians who participated in this study. Only 11.5% of the clinicians reported that they had received specific training in BBN, similar to other studies in this regard.[35, 63, 82-84] Therefore, the lack of training is one of the reasons that giving bad news to breast cancer patients is a difficult task for physicians.

It seems that lack of a context-based protocol for delivering bad news is a barrier to clinicians' practice. A considerable majority of the clinicians in our survey (82%) expressed the need for appropriate culturally-adjusted guideline regarding giving bad news to breast cancer patients in Iran. Therefore, it is necessary to design a BBN protocol compatible with Iranian breast cancer patients and their family member preference, considering both clinicians' attitude regarding disclosing bad news and the culture of Iranian society. For example, study shows that resorting to religious and spiritual sources can help some patients to better cope with their cancer situation, particularly in an Islamic country.[85] In that study, 86% of clinicians endorsed that after informing breast cancer patients, they reminded patient as they believed that everything was in the hands of God, and he is the healer. Hence, it seems necessary to develop a guideline for delivering bad news according to Iranian cultural context.

We have attempted to describe clinicians' preferences for and practice of BBN in breast cancer setting and discuss the main factors affecting this process. But our study has some limitations. First, generalization of the results must be done with caution due to the cross-sectional nature of the surveys. Second, the results of this study were produced by self-report measurement method. We recommend that future studies use observational method for assessing clinicians' practice.

Despite these limitations, our results highlighted some evidence that would be useful regarding its practical implication. It emphasized the need for special BBN training to change the clinicians' attitude toward truth disclosure and improve their BBN skills. Our survey indicated that physicians show interest in training courses; therefore, the training programs should be designed according to the needs of patients and physicians with respect to Iranian socio-culture environment. Furthermore, developing a context-based protocol seems essential.

Moreover, the results of this study have implications for designing curriculum in medical education and ethics so that appropriate protocols according to Iranian culture based on clinicians' preferences and practice can be developed. To achieve this, however, we need to know about Iranian women's as well as their families' preferences.

**Conflict of Interest**

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**References**

1. Oikonomidou D, Anagnostopoulos F, Dimitrakaki C, Ploumpidis D, Stylianidis S, Tountas Y. Doctors' Perceptions and Practices of Breaking Bad News: A Qualitative Study From Greece. Health communication. 2017;32(6):657-66.
2. http://www.wma.net/en/30publications/10policies/c8/.
3. Buckman R. Breaking bad news: why is it still so difficult? British medical journal (Clinical research ed). 1984;288(6430):1597.
4. Heyse-Moore L. Speaking of Dying: A practical Guide to using counselling skills in Palliative Care: Jessica Kingsley Publishers; 2008.
5. Rollins LK, Hauck FR. Delivering bad news in the context of culture: a patient-centered approach. JCOM. 2015;22(1).
6. Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES—a six-step protocol for delivering bad news: application to the patient with cancer. The oncologist. 2000;5(4):302-11.
7. Buckman RA. Breaking bad news: the SPIKES strategy. Community oncology. 2005;2(2):138-42.
8. Surbone A, Zwitter M, Rajer M, Stiefel R. New challenges in communication with cancer patients: Springer Science & Business Media; 2012.
9. Shaw J, Brown R, Heinrich P, Dunn S. Doctors' experience of stress during simulated bad news consultations. Patient education and counseling. 2013;93(2):203-8.
10. Stovall MC. Oncology Communication Skills Training: Bringing Science to the Art of Delivering Bad News. J Adv Pract Oncol. 2015;6(2):162-6.
11. Gomez SL, Von Behren J, McKinley M, Clarke CA, Shariff-Marco S, Cheng I, *et al*. Breast cancer in Asian Americans in California, 1988–2013: increasing incidence trends and recent data on breast cancer subtypes. Breast

.Cancer Research and Treatment. 2017:1-9.
12. Mendick N, Young B, Holcombe C, Salmon P. Telling "everything" but not "too much": the surgeon's dilemma in consultations about breast cancer. World journal of surgery. 2011;35(10):2187.
13. Tang WR, Fang JT, Fang CK, Fujimori M. Truth telling in medical practice: students' opinions versus their observations of attending physicians' clinical practice. Psycho-Oncology. 2013;22(7):1605-10.
14. Mohammadnejad E. Nurses' experiences regarding truth telling: a phenomenological study. Iranian Journal of Medical Ethics and History of Medicine. 2013;6(1):53-63.
15. Burgers C, Beukeboom CJ, Sparks L. How the doc should (not) talk: When breaking bad news with negations influences patients' immediate responses and medical adherence intentions. Patient education and counseling. 2012;89(2):267-73.
16. Managheb SE, Hosseinpour M, Mehrabi F. Patient's viewpoints about how to break bad news. Iranian Journal of Medical Ethics and History of Medicine. 2013;6(4):68-79.
17. De Valck C, Bensing J, Bruynooghe R. Medical students' attitudes towards breaking bad news: An empirical test of the World Health Organization model. Psycho-Oncology. 2001;10(5):398-409.
18. Ellis P. Attitudes towards and participation in randomised clinical trials in oncology: a review of the literature. Annals of Oncology. 2000;11(8):939-45.
19. Cherny NI. Factors influencing the attitudes and behaviors of oncologists regarding the truthful disclosure of information to patients with advanced and incurable cancer. Psycho-Oncology. 2011;20(12):1269-84.
20. Dickson D, Hargie O, Brunger K, Stapleton K. Health professionals' perceptions of breaking bad news. International Journal of Health CareQuality Assurance. 2002;15(7):324-36.
21. Baile WF, Lenzi R, Parker PA, Buckman R,Cohen L. Oncologists' attitudes toward and practices in giving bad news: an exploratory study. Journal of Clinical Oncology. 2002;20(8):2189-96.
22. Gonçalves JF, Castro S. Diagnosis disclosure in a Portuguese oncological centre. Palliative medicine. 2001;15(1):35-41.
23. Kakai H. A double standard in bioethical reasoning for disclosure of advanced cancer diagnoses in Japan. Health Communication. 2002;14(3):361-76.
24. Rogg L, Aasland OG, Graugaard PK, Loge JH. Direct communication, the unquestionable ideal? Oncologists' accounts of communication of bleak prognoses. Psycho-Oncology. 2010;19(11):1221-8.
25. Walsh RA, Girgis A, Sanson-Fisher RW. Breaking bad news 2: What evidence is available to guide clinicians? Behavioral Medicine. 1998;24(2):61-72.
26. Surbone A. Telling the truth to patients with cancer: what is the truth? The lancet oncology. 2006;7(11):944-50.
27. Eggly S, Penner L, Albrecht TL, Cline RJ, Foster T, Naughton M, *et al*. Discussing bad news in the outpatient oncology clinic: rethinking current communication guidelines. Journal of Clinical Oncology. 2006;24(4):716-9.
28. Uprety D, Kasireddy V. Breaking Bad News in Cancer Patients. SM J Community Med. 2015;1(1):1005.
29. Rabow MW, Mcphee SJ. Beyond breaking bad news: how to help patients who suffer. Western Journal of Medicine. 1999;171(4):260.
30. Fields SA, Johnson WM. Physician-patient communication: breaking bad news. West Virginia Medical Journal. 2012;108(2):32-6.
31. Liénard A, Merckaert I, Libert Y, Bragard I, Delvaux N, Etienne A-M, *et al*. Is it possible to improve residents breaking bad news skills? A randomised study assessing the efficacy of a communication skills training program. British journal of cancer. 2010;103(2):171.
32. Ptacek J, Eberhardt TL. Breaking bad news: a review of the literature. Jama. 1996;276(6):496-502.
33. Tuffrey-Wijne I. A new model for breaking bad news to people with intellectual disabilities. Palliative medicine. 2013;27(1):5-12.
34. Adler DD, Riba MB, Eggly S. Breaking bad news in the breast imaging setting. Academic radiology. 2009;16(2):130-5.
35. Perry ZH, Rosenblatt A, Biderman A. Breaking bad news: Attitudes of physicians and patients in primary care. Annals of Behavioral Science and Medical Education. 2011;17(2):17-25.
36. Friedrichsen M, Milberg A. Concerns about losing control when breaking bad news to terminally ill patients with cancer: physicians' perspective. Journal of palliative medicine.2006;9(3):673-82.
38. Kazemi A, Pursoleimani A, Fakhari A, Madaen K. Truth telling in medicine: views of Tabriz University of Medical Sciences. Iranian Journal of Medical Ethics and History of Medicine. 2010;3(2):54-63.
38. Gurevich M, Devins GM, Wilson C, McCready D, Marmar CR, Rodin GM. Stress response syndromes in women undergoing mammography: a comparison of women with and without a history of breast cancer. Psychosomatic medicine. 2004;66(1):104-12.
39. Jiang Y, Li J-y, Liu C, Huang M-j, Zhou L, Li M, *et al*. Different attitudes of oncology clinicians toward truth telling of different stages of cancer.

Supportive care in cancer. 2006;14(11):1119-25.
40. Glasman LR, Albarracin D. Forming attitudes that predict future behavior: a meta-analysis of the attitude-behavior relation. Psychological bulletin. 2006;132(5):778-822.
41. Henderson JS, Kashka, M.S. and Larson, A.M. Effect of knowledge, attitude, and belief on nurses' practice regarding urinary incontinence in adults. Urol Nurs. 2000.;20(5), p.291.
42. Beach MC, Roter DL, Wang N-Y, Duggan PS, Cooper LA. Are physicians' attitudes of respect accurately perceived by patients and associated with more positive communication behaviors? Patient education and counseling. 2006;62(3): 347-54.
43. Tang WR, Hong JH, Rau KM, Wang CH, Juang YY, Lai CH, *et al*. Truth telling in Taiwanese cancer care: patients' and families' preferences and their experiences of doctors' practices. Psycho-Oncology. 2017;26(7):999-1005.
44. Locatelli C, Piselli P, Cicerchia M, Repetto L. Physicians' age and sex influence breaking bad news to elderly cancer patients. Beliefs and practices of 50 Italian oncologists: the G.I.O.Ger study. Psycho-oncology. 2013;22(5):1112-9.
45. Gorniewicz J, Floyd M, Krishnan K, Bishop TW, Tudiver F, Lang F. Breaking bad news to patients with cancer: A randomized control trial of a brief communication skills training module incorporating the stories and preferences of actual patients. Patient education and counseling. 2017;100(4):655-66.
46. Pastor DK, Cunningham RP, White PH, Kolomer S. We Have to Talk: Results of an Interprofessional Clinical Simulation for Delivering Bad Health News in Palliative Care. Clinical Simulation in Nursing. 2016;12(8):320-7.
47. Berney A, Carrard V, Schmid Mast M, Bonvin R, Stiefel F, Bourquin C. Individual training at the undergraduate level to promote competence in breaking bad news in oncology. Psycho-Oncology. 2017.
48. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report.Cancer epidemiology. 2015;39(4):519-27.
49. Li JY, Liu C, Zou LQ, Huang MJ, Yu CH, You GY, *et al*. To tell or not to tell: attitudes of Chinese oncology nurses towards truth telling of cancer diagnosis. Journal of clinical nursing. 2008;17(18):2463-70.
50. Ozdogan M, Samur M, Artac M, Yildiz M, Savas B, Bozcuk HS. Factors related to truth-telling practice of physicians treating patients with cancer in Turkey. Journal of palliative medicine. 2006;9(5):1114-9.
51. Charan J, Biswas T. How to calculate sample size for different study designs in medical research? Indian journal of psychological medicine. 2013;35(2):121.
52. Borjalilu S, Karbakhsh M, Mirsharifi R, Davoodzadeh K, Aghili M, Kaviani A. Measuring Attitude and Practice of Physician toward Breaking Bad News to the Breast Cancer Patients: Development and Validation of a Questionnaire. Archives of Breast Cancer. 2016;3(2):41-9.
53. Zamani A, Shahsanai A, Kivan S, Hematti S, Mokarian F. Iranian Physicians and Patients Attitude toward Truth Telling of Cancer. Journal of Isfahan Medical School. 2011;29(143).
54. Wuensch A, Tang L, Goelz T, Zhang Y, Stubenrauch S, Song L, *et al*. Breaking bad news in China–the dilemma of patients' autonomy and traditional norms. A first communication skills training for Chinese oncologists and caretakers. Psycho-Oncology. 2013;22(5):1192-5.
55. Tabak N, Itzhaki M, Sharon D, Barnoy S. Intentions of nurses and nursing students to tell the whole truth to patients and family members. Journal of clinical nursing. 2013;22(9-10):1434-41.
56. Li J, Gao XH, Yang XM, Jing P, Yu SY. Whether, when, and who to disclose bad news to patients with cancer: a survey in 150 pairs of hospitalized patients with cancer and family members in China. Psycho-Oncology. 2012;21(7):778-84.
57. Warnock C, Buchanan J, TOD AM. The difficulties experienced by nurses and healthcare staff involved in the process of breaking bad news. Journal of advanced nursing. 2017.
58. Clayton JM, Hancock KM, Butow PN, Tattersall MH, Currow DC. Clinical practice guidelines for communicating prognosis and end-of-life issues with adults in the advanced stages of a life-limiting illness, and their caregivers. The Medical Journal of Australia. 2007;186(12):77.
59. Canadian Patient Safety Institute Canadian Disclosure Guidelines: Being open with patients and families. 2011. Nov cJwpcetdpd.
60. Aein F, Delaram M. Giving bad news: a qualitative research exploration. Iranian Red Crescent Medical Journal. 2014;16(6).
61. Tsoussis S, Papadogiorgaki M, Markodimitraki E, Delibaltadakis G, Strevinas A, Psyllakis M, *et al*. Disclosure of cancer diagnosis: the Greek experience. J BUON. 2013;18(2):516-26.
62. Beyraghi N, Mottaghipour Y, Mehraban A, Eslamian E, Esfahani F. Disclosure of cancer information in Iran: a perspective of patients, family members, and health professionals. Iranian journal of cancer prevention. 2011;4(3):130.
63. Arbabi M, Roozdar A, Taher M, Shirzad S, Arjmand M, Mohammadi MR, *et al*. How to break bad news: Physicians' and nurses' attitudes. Iranian journal of psychiatry. 2010;5(4):128.
64. Abazari P, Taleghani F, Hematti S, Ehsani M.

Exploring perceptions and preferences of patients, families, physicians, and nurses regarding cancer disclosure: a descriptive qualitative study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2016;24(11): 4651-9.
65. Tieying Z, Haishan H, Zhao M, Li Y, Fang P. Health professionals' attitude towards information disclosure to cancer patients in China. Nursing Ethics. 2011;18(3):356-63.
66. Pang A, Ho S, Lee S-C. Cancer physicians' attitude towards treatment of the elderly cancer patient in a developed Asian country. BMC Geriatrics. 2013;13(1):35.
67. Azu MC, Jean S, Piotrowski JM, O'Hea B. Effective methods for disclosing breast cancer diagnosis. American journal of surgery. 2007;194(4):488-90.
68. Lobb EA, Butow PN, Kenny DT, Tattersall MH. Communicating prognosis in early breast cancer: do women understand the language used? Med J Aust. 1999;171(6):290-4.
69. Fallah R AM. Effective physician-patient relationship at the time of receiving breast cancer diagnosis: a qualitative content analysis of patients' preferences. J Kermanshah Univ Med Sci. 2013 Apr 13;17(1):23-9.
70. Levin KS, Braeuning MP, O'Malley MS, Pisano ED, Barrett ED, Earp JA. Communicating results of diagnostic mammography: what do patients think? Acad Radiol. 2000;7(12):1069 76.
71. Elwyn TS, Fetters MD, Sasaki H, Tsuda T. Responsibility and cancer disclosure in Japan. Social science & medicine (1982). 2002; 54(2):281-93.
72. Liu S, Bassett LW, Sayre J. Women's attitudes about receiving mammographic results directly from radiologists. Radiology. 1994;193(3):783-6.
73. Roter DL, Hall JA, Aoki Y. Physician gender effects in medical communication: a meta-analytic review. Jama. 2002;288(6):756-64.
74. Hall JA, Roter DL. Do patients talk differently to male and female physicians? A meta-analytic review. Patient Educ Couns. 2002;48(3):217-24.
75. Roter DL, Hall JA. Physician gender and patient-centered communication: a critical review of empirical research. Annual review of public health. 2004;25:497-519.
76. Roter DL, Geller G, Bernhardt BA, Larson SM, Doksum T. Effects of obstetrician gender on communication and patient satisfaction. Obstetrics and gynecology. 1999;93(5 Pt 1):635-41.
77. Meeuwesen L, Schaap C, van der Staak C. Verbal analysis of doctor-patient communication. Social science & medicine (1982). 1991;32(10):1143-50.
78. Novack DH, Plumer R, Smith RL, Ochitill H, Morrow GR, Bennett JM. Changes in physicians' attitudes toward telling the cancer patient. Jama. 1979;241(9):897-900.
79. Jenkins V, Fallowfield L. Can communication skills training alter physicians' beliefs and behavior in clinics? Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2002;20(3):765-9.
80. Bragard I, Etienne AM, Merckaert I, Libert Y, Razavi D. Efficacy of a communication and stress management training on medical residents' self-efficacy, stress to communicate and burnout: a randomized controlled study. Journal of health psychology. 2010;15(7):1075-81.
81. Meunier J, Merckaert I, Libert Y, Delvaux N, Etienne AM, Lienard A, *et al*. The effect of communication skills training on residents' physiological arousal in a breaking bad news simulated task. Patient Educ Couns. 2013;93(1):40-7.
82. Imanipour M, Karim Z, Bahrani N. Role, perspective and knowledge of Iranian critical care nurses about breaking bad news. Australian critical care : official journal of the Confederation of Australian Critical Care Nurses. 2016;29(2):77-82.
83. Al-Mohaimeed AA, & Sharaf, F. K. Breaking Bad News Issues: A Survey Among Physicians. Oman Med J. 2013;28(1), 20–25. .
84. Narayan A, Dromi S, Meeks A, Gomez E, Lee B. Breaking Bad News: A Survey of Radiology Residents' Experiences Communicating Results to Patients. Current problems in diagnostic radiology. 2017.
85. Salem A, Salem AF. Breaking bad news: current prospective and practical guideline for Muslim countries. Journal of cancer education : the official journal of the American Association for Cancer Education. 2013;28(4):790-4.

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# The Relationship Between Breast Cancer and VDR Gene Polymorphisms

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ABSTRACT

**Background:** Vitamin D serves several cancer protective roles within the human body. Vitamin D functions through binding with the VDR encoded by VDR gene. It has been demonstrated that polymorphism in VDR gene would influence expression and/or function of the VDR protein. The researchers found that the most important VDR gene polymorphisms that are associated with tumorigenesis include Fok1 (rs2228570), Bsm1 (rs1544410), Taq1 (rs771236), and Apa1 (rs7975232) .The purpose of this study was to assess the association between Fok1, Bsm1, and Taq1 polymorphisms and breast cancer development.

**Methods:** In this study, 50 patients suffering from breast cancer with less than 6 months after the diagnosis of breast cancer and 50 healthy control individuals were included. Restriction fragment length polymorphism PCR (RFLP-PCR) was used to determine the genotype of polymorphisms.

**Results:** Statistical results showed that among the studied polymorphisms, Tt genotypes of Taq1 polymorphism have correlations with breast cancer development ($P < 0.001$, $OR = 5.51$, 0.95 $CI = 2.30\text{-}13.21$).

**Conclusion:** The results of the present clearly demonstrated that there is a relationship between Taq1 polymorphism in VDR gene and development of breast cancer.

## Introduction

Breast cancer is the most common cancer among women worldwide and, after lung cancer, it is the second main cause of death among them.[1] There are various risk factors in breast cancer including age, gender, benign tumors of the breast, early menopause, late menarche, hormone therapy, chest exposure to radiation, alcohol consumption, combined use of estrogen and progesterone, diethylstilbestrol consumption, genetic factors, postmenopausal obesity, first pregnancy after the age of 30, lack of breastfeeding, and environmental factors.[2] Genetic factors in breast cancer include changing the level of gene expression, epigenetic modifications, and polymorphisms (DNA Sequence alterations).[3]

The role of vitamin D among the various environmental factors that play a key role in cancer progression is noticeable. Vitamin D is available in 2 forms: vitamin D2 in plants and Vitamin D3 in the human skin. Vitamin D in body comes from sun exposure (up to 90%) and food supplements.[4] Several enzymatic steps and genes are involved in vitamin D metabolism.[5] The first occurs in the liver and the second in the kidneys, which construct the most common biologically active form.[6] The most

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important role of vitamin D is the regulation of bone metabolism. Also, it has a protective function on cancer through the regulation of gene expression, the reduction of invasiveness and angiogenesis, proliferation, differentiation, and the apoptosis of several cancer cell lines.[7-9] This process occurs through binding vitamin D to its receptor. Vitamin D receptor (VDR) is expressed in more than 30 human tissues.[10]

The VDR gene is on the long arm of chromosome 12 with at least 5 promoters and 11 exons.[11] Previous studies have demonstrated the impact of polymorphisms in VDR gene on the expression and/or function of the VD protein.[12] Among 200 polymorphisms described in VDR, Fok1, Bsm1, Taq1, Apa1, EcoRV, and Cdx2 are more frequently associated with tumorigenesis, although data are yet controversial in this filed.[11] Epidemiological studies and laboratory investigations have proposed the increased cancer risk would be related with the level of vitamin D and its expressed receptor (VDR).[13]

*Polymorphism Fok1*

This polymorphism is located in exon 2, next to the 5'-UTR region of VDR gene and causes the transition of C to T at this position. The Fok1 polymorphism has 2 alleles; the shorter VDR (C allele) has higher transcription activity compared to the longer type (T allele).[12] Despite no significant difference in DNA binding, ligand affinity, and transactivation affinity between 2 VDR forms, the shortened VDR variant showed higher potency than the longer one.

*Polymorphism Bsm1*

Polymorphism Bsm1 is in intron 8, where guanosine converts to adenosine and it may be associated with poly-A sequence in 3'-UTR region; hence, it may affect VDR gene expression via the regulation of mRNA stability.[14]

*Polymorphism Taq1*

This polymorphism is located in exon 9 and, instead of T nucleotide, has a C nucleotide. The polymorphisms in the 3'-UTR region of the gene are associated with linkage disequilibrium (LD) and allele frequencies of these polymorphisms seem to differ within populations.[13]

In this study, we have concentrated on the distribution of VDR *Fok1*, *Bsm1*, and *Taq1* polymorphisms in patients with breast cancer in Isfahan, compared with a healthy population.

## Methods

*Study population*

The present study includes case and control groups. In this study, 50 patients suffering from breast cancer with less that 6 months after the diagnosis of breast cancer were referred to two breast cancer centers in Isfahan, Iran. Also, 50 healthy control individuals were included. Healthy women without breast cancer were randomly selected among the women who, visited Alzahra hospital for routine mother and child healthcare. The study was approved by the Ethics Committee of Iran National Science Foundation and the questionnaire and informed consent forms were completed by the study subjects. Demographic data such as age, familial, or sporadic status and types of breast tumors were obtained (Table 1).

*DNA extraction, SNP selection, and genotyping*

In this survey, 3-5cc peripheral blood was taken from participants. Genomic DNA was extracted from samples by the salting-out method. The quality and concentration of extracted DNA were measured, using NanoDrop® ND-1000 spectrophotometer at 260nm and 280nm wavelengths. Specific PCR primers were designed through BLAST website (http:// blast.ncbi.nlm.nih.gov/Blast.cgi) and single nucleotide polymorphisms (SNPs) database (dbSNP 129; http://www.ncbi.nlm.nih.gov/projects/SNP/) and Genomic DNA was amplified by PCR protocol as follow (Table 2).

We focused on 3 well-characterized polymorphisms. PCR (RFLP) was used to determine the genotype of polymorphisms. PCR-RFLP analysis was performed in 10µL of reaction volume, containing 1x PCR buffer (75 mM Tris-HCl, pH8.8, 20 mM $(NH_4)_2SO_4$, 0.01% (v/v) Tween 20), 2 mM $MgCl_2$, 0.2 mM dNTP , 0.2 mM of each primer (Table 2), 40 ng of DNA, and 0.3 U of Taq DNA polymerase. The touchdown PCR program was performed for Fok1(cycle:30 s, initial denaturation:95$^{°C}$ for 4 min, Denaturation: 95$^{°C}$ for 1 min, Anneling: 70$^{°C}$ for 1 min), Bsm1(cycle: 30s, initial denaturation: 94$^{°C}$ for 4 min, Denaturation: 94$^{°C}$ for 1 min, Anneling: 66$^{°C}$ for 1:30 min), and Taq1(cycle: 30 s, initial denaturation: 95$^{°C}$ for 4 min, Denaturation: 95$^{°C}$ for 1 min, Anneling: 65$^{°C}$ for 1 min, and 72$^{°C}$ for 5 min for each primer [final extension]).

The PCR products (5 µL) of VDR gene were digested in a 20 µL reaction volume for 7h with 1.5 U of Fok1, Bsm1, and Taq1 restriction endonucleases (Fermentas, St. Leon-Rot, Germany) at 37$^{°C}$. The digested PCR product was separated, using electrophoresis on 3% agarose gel by ethidium bromide and it was analyzed, using UV light after staining.

The product alleles of the VDR gene at the restriction enzyme site Fok1, Bsm1, and Taq1 involved a T→C (Fok1), a C→T (Bsm1), and a C→T (Taq1) transition. The PCR products were digested with appropriate restriction endonuclease per manufacturer's instruction (Macrogene, South Korea). Digested products of the product alleles of cutting by Fok1, Bsm1, and Taq1 enzymes were indicated by f, b, and t, while undigested alleles were

**Table 1.** The demographic parameters for patients and control group

| Variations | Case | Control | P-Value(p<0.05) |
|---|---|---|---|
| N | 50 | 50 | |
| Age | 49.61±12.21 | 42.70±14.05 | 0.012 |
| Family history | | | |
| Yes | 9(19.6%) | | 0.306 |
| No | 37(80.4%) | | 0.306 |
| Types of breast tumors | | | |
| Lobular Carcinoma Insitu | 8(15%) | | 0.215 |
| Ductal Carcinoma Insitu | 8(15%) | | 0.112 |
| Invasive Lobular Carcinoma | 5(10%) | | 0.304 |
| Invasive Ductal Carcinoma | 12(25%) | | 0.257 |

assigned as F, B, and T, respectively. In order to confirm the RFLP results, randomly selected PCR products were sequenced.

*Statistical analysis*

The data were analyzed by SPSS (Version.18), using Chi-square ,independent sample t test, and logistic regressionwith 95% confidence intervals (CIs). Chi-square test and independent t test were performed. P value less than 0.05 was considered statistically significant.

**Results**

To investigate the VDR gene polymorphisms, we randomly selected 50 patients with breast cancer, with the mean age of 47.18 ± 14.36 years and 50 healthy subjects, with the mean age of 43.70 ± 14.70 years. Independent t test showed that the average age of the two groups did not have any difference (P = 0.23). Moreover, Chi-square test did not show any differences between the two groups regarding menopausal status (P=0.17).

The histopathology reports of the patients' tumors showed 62% Positive and 38% Negative estrogen receptor expression. Progesterone receptor (PR) expression was positive in 62% of patients. The Her-2 over expression was detected in 30 % of the breast tumors.

The frequencies of each allele for both groups are shown in Table 3.

The data suggest that the T allele may contribute in susceptibility to breast cancer, either in heterozygote or homozygote state. There were no association between Taq1 SNP and tumor characteristics including ER, PR, and Her-2 status.

**Table 2.** Sequence of the primers and PCR–RFLP product characteristics

| Primer name | Sequence | PCR product length (bp) | Digested length (bp) |
|---|---|---|---|
| Fok1-F | GCACTGACTCTGGCTCTGAC | 341 | 60 and 281 |
| Fok1-R | ACCCTCCTGCTCCTGTGGCT | | |
| Bsm1-F | GCAACCAAGACTACAAGTACCGCGTCA | 845 | 194 and 651 |
| Bsm1-R | TTTTCTCCCTCTTCTCACCTCTAACCA | | |
| Taq1-F | CTGGCACTGACTCTGGCTCT | 634 | 207 and 427 |
| Taq1-R | GGGCTCACCTGAAGAAGCCT | | |

**Table 3.** Fok1, Bsm1, and Taq1 polymorphisms and breast cancer

| Genotype | | Breast cancer (N=50) | | Control (N= 50) | P value | OR (95%CI) |
|---|---|---|---|---|---|---|
| | | Breast Cancer | Relative Frequency (%) | Relative Frequency (%) | | |
| Fok1 | | | | | 0.14 | 0.67(0.11-4.17) |
| | FF | 34(68) | F 0.94 | F 0.96 | | |
| | Ff | 13(26) | f 0.06 | f 0.04 | | |
| | ff | 3(6) | | | | |
| Bsm1 | | | | | 0.50 | 0.91(0.40-2.10) |
| | BB | 12(24) | B 0.66 | B 0.68 | | |
| | Bb | 21(42) | b 0.34 | b 0.32 | | |
| | bb | 17(34) | | | | |
| Taq1 | | | | | **<0.001** | 5.51(2.30-13.21) |
| | TT | 2(4) | T 0.74 | T 0.34 | | |
| | Tt | 35(70) | t 0.26 | t 0.66 | | |
| | tt | 31(26) | | | | |

## Discussion

Breast cancer is a common cancer with major public health implications. In 1919, vitamin D was originally discovered by Edward Mellanby [15] and in 1969, the vitamin D receptor (VDR) was discovered by Norman.[16] Recent studies demonstrate that not only vitamin D has the main function in bones, but also it significantly affects differentiation and cell proliferation. The metabolite of vitamin D, 1,25-dihydroxycholecalciferol (1,25[OH]2D3) can suppress cell proliferation in cancer cells.[17] One study suggested that vitamin D effects, for the most part, are correlated with nuclear VDR.[18]

Many human tissues express VDR like breast, prostate, bone, etc.[19] In recent years, many molecular epidemiological studies (case-control studies and nested case-control studies) were conducted on women to investigate the associations of different VDR polymorphisms with breast cancer. The association of all mentioned polymorphisms (Fok1, Bsm1, and Taq1) and breast cancer were investigated in different studies.[9, 20-23] Taq1 was associated with breast cancer.[21]

In a study, Abbas *et al.* showed a significant association between the Taq1 polymorphism and increased breast cancer risk in estrogen receptor positive patients. They emphasized concerning the strong linkage disequilibrium of 3 polymorphisms; the combinations of 3 variants may be more discriminating as risk factors than a single one.[24]
Perna *et al*. demonstrated a significant prognostic value of Taq1 in patients with breast cancer without any risk for women both heterozygous and homozygous for t allele.[25]

In a Swedish study in the field of breast cancer, a trend was found towards a higher survival rate, especially among those tamoxifen-treated estrogen receptor positive patients and homozygous for the rare Taq1 allele.[26] However, Perna *et al.* reported increased death rate in rare homozygous carriers Taq1 homozygous genotype compared with homozygous carriers with the common allele.[25] This study confirms our findings. In the present study, the statistical results showed that among the studied polymorphisms, Tt genotypes of Taq1 polymorphism correlate with breast cancer (P< 0.001, OR=5.51, 0.95 CI= 2.30-13.21). In the mentioned polymorphism, Fok1 is the one that has most frequently been studied regarding its association with different types of cancer.

Several lines of studies have reported a significant association between the Fok1 polymorphism and different types of cancer including multiple myeloma, breast, prostate, and ovarian cancer,[11] while others did not observe any significant associations.[11] For example, Sinotte *et al.*, Gapska *et al.*, and McKay *et al.* reported increased risk among ff carriers on Fok1,[27-29] whereas, Anderson *et al.* reported decreased risk among ff carriers.[30] Curran *et al.*, Guy et al., Abbas *et al.*, Engel *et al.*, Rollison *et al.,* Fuhrman *et al.*, Mishra *et al.*, and Shahbazi *et al.* reported no association between ff carriers and breast cancer risk.[21-24, 31-34] As the last polymorphism, Guy *et al.* reported an increased risk of breast cancer for bb genotype.[22]
Another study reported Bsm1 polymorphism in LD with the poly-A tail sequence in the 3' UTR with a higher risk of breast cancer and bb genotype.[35] Ruggiero *et al.* showed no statistically different distribution of Bsm1 polymorphism in case and control groups,[33] while two-fold higher prevalence of the bb genotype was found in metastatic cancer group and percentage of BB women with metastases was half in control group.[22, 36] On the other hand, no significant association between the Bsm1 polymorphism and breast cancer risk made a different study, but we should note that this study included only a limited number of Turkish cases. Three other studies referring to Taiwanese women[37] and Caucasian women were associated with BB genotype with increased breast cancer risk.[5] Hou *et al.* showed an association between Bsm1 B allele and increased breast cancer risk. [37]

As the results of studies in various cancers are inconsistent, the role of vitamin D in the development and progression of cancer is still unknown and further studies are required. In conclusion, as the result of the present study showed, VDR Taq1 RFLP seems to be associated with breast cancer. T allele could be considered as risk allele and t allele as the protective allele. On the other hand, we found a higher prevalence of Tt genotype among patients with breast cancer in comparison with health controls. The VDR may represent an important target for breast cancer prevention.

### Conflict of Interest

The authors declare that they have no conflict of interests.

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### References

1. Smigal C, Jemal A, Ward E, Cokkinides V, Smith R, Howe HL, *et al.* Trends in breast cancer by race and ethnicity: update 2006. CA: A Cancer Journal for Clinicians. 2006;56(3):168-83.
2. Najm MZ, Zaidi S, Siddiqui WA, Husain SA. Immunohistochemical expression and mutation study of prohibitin gene in indian female breast cancer cases. Medical Oncology. 2013;30(3):1-7.
3. Wacholder S, Hartge P, Prentice R, Garcia-Closas M, Feigelson HS, Diver WR, *et al.* Performance of common genetic variants in breast-cancer risk models. New England Journal of Medicine.

2010;362(11):986-93.
4. Norman AW. Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system. American Journal of Clinical Nutrition. 1998;67:1108-10.
5. McCullough ML, Stevens VL, Diver WR, Feigelson HS, Rodriguez C, Bostick RM, *et al.*Vitamin D pathway gene polymorphisms, diet, and risk of postmenopausal breast cancer: a nested case-control study. Breast Cancer Research. 2007;9(1):R9.
6. Tuohimaa P. Vitamin D, aging, and cancer. Nutrition Reviews. 2008;66(suppl 2):147-52.
7. Fedirko V, Riboli E, Tjønneland A, Ferrari P, Olsen A, Bueno-de-Mesquita HB, *et al.*Prediagnostic 25-hydroxyvitamin D, VDR and CASR polymorphisms, and survival in patients with colorectal cancer in western European populations. Cancer Epidemiology Biomarkers & Prevention. 2012;21(4):582-93.
8. Bauer SR, Hankinson SE, Bertone-Johnson ER, Ding EL. Plasma vitamin D levels, menopause, and risk of breast cancer: dose-response meta-analysis of prospective studies. Medicine. 2013;92(3):123-31.
9. Chen P, Hu P, Xie D, Qin Y, Wang F, Wang H. Meta-analysis of vitamin D, calcium and the prevention of breast cancer. Breast Cancer Research and Treatment. 2010;121(2):469-77.
10. Deeb KK, Trump DL, Johnson CS. Vitamin D signalling pathways in cancer: potential for anticancer therapeutics. Nature Reviews Cancer. 2007;7(9):684-700.
11. Köstner K, Denzer N, Mueller CS, Klein R, Tilgen W, Reichrath J. The relevance of vitamin D receptor (VDR) gene polymorphisms for cancer: a review of the literature. Anticancer Research. 2009;29(9):3511-36.
12. Grant WB, Garland CF, Holick MF. Comparisons of estimated economic burdens due to insufficient solar ultraviolet irradiance and vitamin D and excess solar UV irradiance for the United States. Photochemistry and Photobiology. 2005;81(6):1276-86.
13. Sweeney C, Curtin K, Murtaugh MA, Caan BJ, Potter JD, Slattery ML. Haplotype analysis of common vitamin D receptor variants and colon and rectal cancers. Cancer Epidemiology Biomarkers & Prevention. 2006;15(4):744-9.
14. Ingles SA, Haile RW, Henderson BE, Kolonel LN, Nakaichi G, Shi C-Y, *et al.* Strength of linkage disequilibrium between two vitamin D receptor markers in five ethnic groups: implications for association studies. Cancer Epidemiology Biomarkers & Prevention. 1997;6(2):93-8.
15. Mellanby E. An experimental investigation on rickets. Nutrition Reviews. 1976;34(11):338-40.
16. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. The American Journal of Clinical Nutrition. 2008;88(2):491-9.
17. Thorne J, Campbell MJ. The vitamin D receptor in cancer. Proceedings of the Nutrition Society. 2008;67(02):115-27.
18. Welsh J. Vitamin D metabolism in mammary gland and breast cancer. Molecular and Cellular Endocrinology. 2011;347(1):55-60.
19.Raimondi S, Johansson H, Maisonneuve P, Gandini S. Review and meta-analysis on vitamin D receptor polymorphisms and cancer risk. Carcinogenesis. 2009;30(7):1170-80.
20. Bretherton-Watt D, Given-Wilson R, Mansi JL, Thomas V, Carter N, Colston KW. Vitamin D receptor gene polymorphisms are associated with breast cancer risk in a UK Caucasian population. British Journal of Cancer. 2001;85(2):171.
21. Curran JE, Vaughan T, Lea RA, Weinstein SR, Morrison NA, Griffiths LR. Association of A vitamin D receptor polymorphism with sporadic breast cancer development. International Journal of Cancer. 1999;83(6):723-6.
22. Guy M, Lowe LC, Bretherton-Watt D, Mansi JL, Peckitt C, Bliss J, Wilson RG, Thomas V, Colston KW. Vitamin D receptor gene polymorphisms and breast cancer risk. Clinical Cancer Research. 2004 Aug 15;10(16):5472-81
23. Lowe LC, Guy M, Mansi JL, Peckitt C, Bliss J, Wilson RG, *et al.* Plasma 25-hydroxy vitamin D concentrations, vitamin D receptor genotype and breast cancer risk in a UK Caucasian population. European Journal of Cancer. 2005;41(8):1164-9.
24. Abbas S, Nieters A, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, *et al.* Vitamin D receptor gene polymorphisms and haplotypes and postmenopausal breast cancer risk. Breast Cancer Research. 2008;10(2):31.
25. Perna L, Butterbach K, Haug U, Schöttker B, Müller H, Arndt V, *et al.* Vitamin D receptor genotype rs731236 (Taq1) and breast cancer prognosis. Cancer Epidemiology Biomarkers & Prevention. 2013;22(3):437-42.
26. Lundin A-C, Söderkvist P, Eriksson B, Bergman-Jungeström M, Wingren S. Association of breast cancer progression with a vitamin D receptor gene polymorphism. Cancer Research. 1999; 59(10):2332-4.
27. Sinotte M, Rousseau F, Ayotte P, Dewailly E, Diorio C, Giguere Y, Berube S, Brisson J. Vitamin D receptor polymorphisms (FokI, BsmI) and breast cancer risk: association replication in two case–control studies within French Canadian population. Endocrine-Related Cancer. 2008;15(4):975-83.
28.Gapska P, Scott RJ, Serrano-Fernandez P, Huzarski T, Byrski T, Kładny J, Gronwald J,

Górski B, Cybulski C, Lubinski J, Dębniak T. Vitamin D receptor variants and breast cancer risk in the Polish population. Breast Cancer Research and Treatment. 2009 Jun 1;115(3):629-33.

29. McKay JD, McCullough ML, Ziegler RG, Kraft P, Saltzman BS, Riboli E, *et al.* Vitamin D receptor polymorphisms and breast cancer risk: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium. Cancer Epidemiology Biomarkers & Prevention. 2009;18(1):297-305.
30. Anderson LN, Cotterchio M, Cole DE, Knight JA. Vitamin D-related genetic variants, interactions with vitamin D exposure and breast cancer risk among Caucasian women in Ontario. Cancer Epidemiology and Prevention Biomarkers. 2011:cebp-0300.
31. Fuhrman BJ, Freedman DM, Bhatti P, Doody MM, Fu Y-P, Chang S-C, *et al.* Sunlight, polymorphisms of vitamin D-related genes and risk of breast cancer. Anticancer Research 2013;33(2):543-51.
32. Mishra DK, Wu Y, Sarkissyan M, Sarkissyan S, Chen Z, Shang X, Ong M, Heber D, Koeffler HP, Vadgama JV. Vitamin D receptor gene polymorphisms and prognosis of breast cancer among African-American and Hispanic women. PLoS One. 2013;8(3):e57967.
33. Ruggiero M, Pacini S, Aterini S, Fallai C, Ruggiero C, Pacini P. Vitamin D receptor gene polymorphism is associated with metastatic breast cancer. Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics. 1998;10(1):43-6
34. Shahbazi S, Alavi S, Majidzadeh-a K, GhaffarPour M, Soleimani A, Mahdian R. BsmI but not FokI polymorphism of VDR gene is contributed in breast cancer. Medical Oncology. 2013;30(1):393-7.
35. Khan MI, Bielecka ZF, Najm MZ, Bartnik E, Czarnecki JS, Czarnecka AM, *et al.* Vitamin D receptor gene polymorphisms in breast and renal cancer: current state and future approaches (review). Int J Oncol. 2014;44(2):349-63.
36. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H, Mohr SB, *et al.* The role of vitamin D in cancer prevention. American Journal of Public Health. 2006;96(2):252-61.
37. Hou M-F, Tien Y-C, Lin G-T, Chen C-J, Liu C-S, Lin S-Y, *et al.* Association of vitamin D receptor gene polymorphism with sporadic breast cancer in Taiwanese patients. Breast Cancer Research and Treatment. 2002;74(1):1-7.

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# Neoadjuvant Metformin Added to Systemic Therapy Increases Pathological Complete Response in Breast Cancer: A Cross-sectional Study, Mexico Hospital, Costa Rica

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ABSTRACT

**Background:** Metformin shows anti-proliferative effect on tumor cells. We studied the effect of metformin on achieving complete pathological response (pCR) in breast cancer patients receiving neoadjuvant therapy in a Latin American population.

**Methods:** We conducted a cross-sectional study in Mexico Hospital, Costa Rica, from January 2007 to December 2015. Women with early-stage or locally advanced breast cancer receiving neoadjuvant systemic treatment were recruited for the study. Univariate and multivariate models were used to compare the pCR rate with metformin plus standard therapy versus standard treatment alone.

**Results:** Of 53 included women with early-stage or locally advanced breast cancer were included, 14 received metformin with systemic therapy, and 39 had systemic therapy alone. Only 15% of the patients had diabetes mellitus. The pCR rate was in the metformin group was 64.3% compared with 23.1% in the systemic therapy-alone group (OR: 6.0, 95% CI: 1.60–22.53, P= 0.008). This finding was confirmed after adjustment for potential confounders, suggesting that the use of metformin increased the pCR likelihood regardless of breast cancer subtype (adjusted OR: 5.56, 95% CI: 1.27–24.3, P = 0.02). There was a trend of achieving pCR in patients with Ki-67 > 55%. However, it did not reach statistical significance when metformin was added, suggesting that probably a high Ki-67 level in the presence of metformin is not a predictor factor of pCR.

**Conclusion:** This is the first study conducted in a Latin American population showing that metformin with systemic therapy increases pCR regardless of the intrinsic molecular subtype or Ki-67 levels. These findings encourage prospective studies to evaluate the role of neoadjuvant metformin in this population.

## Introduction

According to the World Health Organization, breast cancer (BC) is one of the leading causes of morbidity and mortality worldwide with approximately 14 million new cases in 2012.[1] In 2015, Costa Rica reported a BC incidence rate of 42.25 per 100 000 women.[2]

BC is considered not a single disease, but a group of different entities with diverse pathological features, clinical implications, and outcomes.3 Estrogen and progesterone receptors as well as HER2 expression (using immunohistochemistry), in conjunction with clinicopathological characteristics such as tumor grade, tumor size, and nodal involvement, are useful for establishing the management and prognosis of these patients.[4] Gene expression microarrays in BC have led to identifying of at least five molecular subtypes, labeled as luminal A, luminal B, HER2+, basal-like, and

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normal breast-like.[5] These BC subtypes have been associated with significant differences in overall survival as well as response to systemic therapy.[6,7]

A recent meta-analysis showed that patients with BC who attain a pathological complete response (pCR) in the breast and axilla after neoadjuvant systemic treatment might have a better survival rate, mainly in aggressive tumors such as HER2 or triple-negative (TN) subtypes.[8] Following this finding, the use of presurgical chemotherapy became very common, and biomarkers such as HER2, and hormone receptor (HR) status have been frequently used to indicate the implementation of this therapeutic approach. Furthermore, other markers have been explored to predict pCR, including Ki-67, which is a non-histone nuclear cortex protein expressed in the cell nucleus during the G1, S, G2, and M phases of the cell cycle. High Ki-67 levels have been associated with an increased chance of achieving pCR and therefore improved survival.[9-11]

It has been proposed that hyperinsulinemia, insulin resistance as well as obesity influence breast cancer prognosis. Various mechanisms have been hypothesized, including increased circulating plasma levels of estrogen, insulin, insulin-like growth factor, and other hormonal factors that act to promote tumor growth and increase the risk of metastatic disease.[12-15]

Metformin is an oral biguanide used for treatment of type 2 diabetes that inhibits hepatic gluconeogenesis and increases insulin sensitivity at peripheral level, thereby improving the glycemic control.[16] Taking into account these pharmacological properties and the increasing evidence for the antitumor effect of metformin,[17] we decided to conduct a cross-sectional study to evaluate the impact of metformin on achieving pCR in breast cancer patients who received neoadjuvant chemotherapy in a Central American population. To our knowledge, this is the first study conducted in this region.

## Methods

*Study population*

After receiving approval from the institutional ethics committee, we conducted a cross-sectional study from January 2007 to December 2015 in Mexico Hospital, San Jose, Costa Rica, to evaluate the pCR rate in patients with invasive breast cancer receiving neoadjuvant systemic therapy with or without metformin. We included all women with early-stage or locally advanced, biopsy-proven invasive breast cancer who received systemic treatment neoadjuvantly. The following exclusion criteria were used: metformin use in a different proposed dosage (< 1 g/day), pregnancy, unknown HR or HER2 status, ECOG > 2, intolerance or hypersensitivity to metformin, not giving informed consent, having secondary or concurrent malignancies except for controlled non-melanoma skin cancer or cervical carcinoma in situ.

*Treatment and pathology assessments*

Patients included were previously evaluated in the multidisciplinary tumor board. Overall, all patients received preoperative systemic therapy based on anthracylines (epirubicin) and cyclophosphamide with or without 5-fluorouracil, followed by taxanes (paclitaxel). In case of HER2 overexpression—determined using IHC or fluorescence in situ hybridization (FISH) trastuzumab was added to taxanes. Neoadjuvant hormonal treatment was allowed without concomitant chemotherapy. After systemic therapy, patients underwent surgery (radical mastectomy, simple mastectomy, or conserving surgery) according to initial stage of the disease and response to systemic treatment. Also, the axilla was managed with sentinel node biopsy or axillary lymph node dissection. Adjuvant radiotherapy was given according to standard practice. In HR-positive tumors, adjuvant endocrine therapy was used, and HER2-positive tumors had to complete one year of adjuvant trastuzumab. When oral metformin was incorporated, the permitted dosage was 500 mg twice a day in conjunction with systemic therapy.

Two experienced BC pathologists reviewed all the biopsies. The initial diagnosis was made using a breast or axillary node core needle biopsy. The report had to include a complete IHC (ER, PR, HER2, and Ki-67 percentage), tumor grade, and histologic subtype. In case of equivocal HER2 status by IHC, FISH would be performed. A pCR was defined as the absence of invasive carcinoma in breast or the axillary nodes in the surgical specimen (ypT0, ypN0).

*Statistics*

Demographic data are summarized and showed using descriptive statistics, and categorical variables are presented as percentages. Continuous variables are given as medians and ranges. The Fisher exact test was used to determine the association between metformin, immunophenotype, and pCR. A Multivariate logistic regression analysis was implemented to find potential predictors of pCR. We used the receiver operating characteristic (ROC) curve to establish the best cut-off point of Ki-67 for prediction of pCR. A P value less than 0.05 was considered statistically significant. Data were analyzed using SPSS (V. 20.0, Chicago, IL).

## Results

We identified 81 women with invasive breast cancer who received neoadjuvant treatment. Fifty-three women with early-stage or locally advanced breast cancer fulfilled the inclusion criteria and were enrolled. Of them, 14 patients received metformin (500 mg bid PO) during chemotherapy, and 39 were

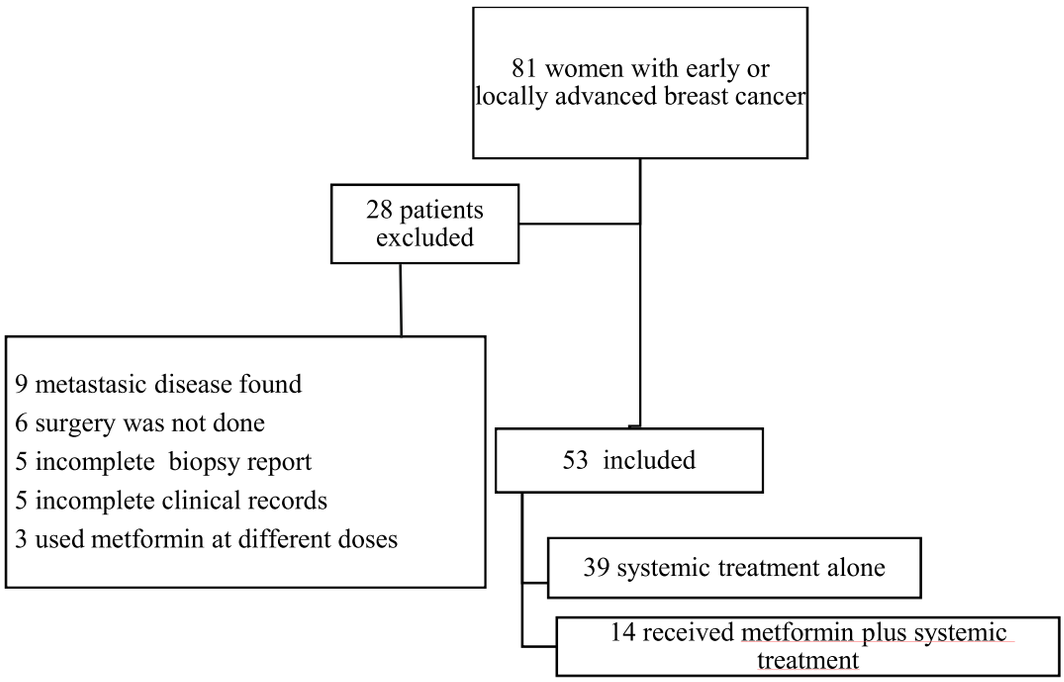


**Figure 1.** Consort diagram

**Table 1.** Patient demographics and clinical characteristics by treatment group

| Characteristics | Systemic therapy + metformin (N=14) | Systemic therapy alone (N=39) |
|---|---|---|
| Age | 50.3 (38–66) | 53.1 (22–83) |
| <50 years | 6 (42.8%) | 14 (35.9%) |
| ≥50 years | 8 (57.2%) | 25 (64.1%) |
| Clinical stagea | | |
| I | 0 (0.0%) | 0 (0.0%) |
| II | 7 (50.0%) | 17 (43.6%) |
| III | 7 (50.0%) | 22 (56.4%) |
| Tumor IHC | | |
| HER2+ | 5 (35.7%) | 12 (30.8%) |
| HER2- | 9 (64.3%) | 27 (69.2%) |
| RE+ | 3 (21.4%) | 19 (48.7%) |
| RE- | 11 (78.6%) | 20 (51.3%) |

[a] *TNM Stage according to AJCC Cancer Staging Manual 7th Ed.*

treated with chemotherapy alone. (Figure 1)

Patient demographics and clinical characteristics of the groups are presented in Table 1. The mean age of the patients was 52.48 (range: 22–83) years. Overall, 56.6% of the patients did not have any comorbidities, 28.3% had hypertension, and 15.1% had type 2 diabetes mellitus. Two patients reported dyslipidemia, 1 patient had colon carcinoma more than five years before accrual, 1 patient had hypothyroidism, and 1 patient suffered from anxiety syndrome.

Infiltrating ductal carcinoma was the most common histology (n = 49, 92.45%), followed by infiltrating lobular carcinoma (n = 2, 3.77%), medullar carcinoma (n = 1, 1.89%), and poorly differentiated carcinoma (n = 1, 1.89%). We found that 21 patients (40%) had luminal subtype, 20 (38%) had TN tumors, 7 (13%) coexpressed estrogen receptor and HER2, and 10 cases (19%) were HER2+/HR-. Twenty-eight patients (53%) had grade3 tumors, 22 (43%) exhibited grade 2 invasive breast cancer, and only 3 patients (4%) had grade 1 differentiation. In total, 35 women (67%) had lymphovascular invasion.

After neoadjuvant therapy (Table 2), 30 women (57%) had breast-conserving surgery and 23 (43%) had radical mastectomy. Eighteen patients (34%) achieved a pCR. We analyzed the pCR rate according to tumor subtype determined by IHC (Table 3). HER2-overexpressing tumors tended to predict pCR (OR: 3.88, P = 0.071), in contrast to luminal tumors, which did not achieve a pCR (OR 0.09; P = 0.01). When metformin was added to systemic therapy, a pCR rate of 64.3% was achieved, while the pCR rate in the systemic therapy-alone arm was 23.1% (OR: 6.0, 95% CI: 1.60–22.53, P = 0.008). After adjustment for potential confounders (e.g., intrinsic breast cancer subtype assessed using immunohisto-

**Table 2.** Neoadjuvant systemic treatment used

| | N | percentage |
|---|---|---|
| FEC* 75 followed by weekly paclitaxel. | 6 | 11.32% |
| FEC/EC 100 followed by weekly paclitaxel | 21 | 39.62% |
| Epirubicin followed by weekly paclitaxel + trastuzumab | 14 | 26.42% |
| Weekly paclitaxel + trastuzumab | 1 | 1.89% |
| Weekly paclitaxel alone | 1 | 1.89% |
| Dose-dense (epirubicin followed by paclitaxel) | 6 | 11.32% |
| Platinum/epirubicin/paclitaxel | 2 | 3.77% |
| Anastrozole | 2 | 3.77% |
| TOTAL | 53 | 1% |

**F= 5-Fluorouracil, E= Epirubicin, C= Cyclophosphamide*

**Table 3**. Association between IHC-determined tumor subtype and pathological complete response rate

| Subtype | With pCR, n (%) | Without pCR, n (%) | OR (95% CI) |
|---|---|---|---|
| HR+/HER2- | 1 (6.7) | 14 (93.3) | 0.09 (0.01–0.74) P = 0.01 |
| HR+/HER2+ | 2 (28.6) | 5 (71.4) | 0.75 (0.13–4.31) P = 0.555 |
| HR-/HER2+ | 6 (60) | 4 (40) | 3.88 (0.93–16.19) P = 0.071 |
| Triple-negative | 9 (42.9) | 12 (57.1) | 1.92 (0.60–6.10) P = 0.37 |
| Total | 18 | 35 | - |

**Table 4.** Multivariate analysis of potential predictors of pathological complete response

| Variable | OR (95% CI) | P |
|---|---|---|
| Metformin | 5.56 (1.27–24.3) | 0.02 |
| RE+ | 0.16 (0.01–2.39) | 0.18 |
| RE-/HER2+ | 3.23 (0.837–29.16) | 0.28 |
| Triple-negative | 1.27 (0.17–9.31) | 0.17 |

**Table 5.** Comparison of pCR by Ki-67 percentage

| Ki-67 (number) | With pCR, n (%) | Without pCR, n (%) | OR (95 CI %), P |
|---|---|---|---|
| <55% (14) | 2 (14.3%) | 12 (85.7%) | 8.0 (1.42–45.06), 0.013 |
| >55% (21) | 12 (57.1%) | 9 (42.9%) | |

chemistry), metformin use was independently associated with a higher likelihood of pCR (OR: 5.56, 95% CI: 1.27–24.3, P = 0.02) (Table 4). We also noted a trend for achieving a higher pCR rate in TN tumors when metformin was incorporated (OR: 10, 95% CI: 1.03–67.1, P = 0.053).

We decided to incorporate Ki-67 as a predictor marker for achieving pCR, with an 86% sensibility and 57% specificity when the cut-off was set at 55% (corresponding to the highest area under the ROC curve = 0.755). We found a higher chance of obtaining a pCR when Ki-67 percentage was greater than 55% (Table 5); however, when metformin was added to this model, we did not find a statistically significant increase in the rate of pCR in patients with Ki-67 > 55% (OR: 4.0, 95% CI: 0.36–44.1, P = 0.26).

We did not register any serious adverse events with metformin. Mild diarrhea was observed in 3 patients, which was controlled with short-term antidiarrheal medications. No other side effects were found.

## Discussion

Preoperative systemic therapy (neoadjuvant) is becoming popular nowadays for early-stage or locally advanced breast cancer. When this modality of treatment is given, the main purpose is to downstage the tumor for a less aggressive surgery with less postoperative complications and better cosmetic outcomes.[18] Neoadjuvant treatment also allows prompt tumor response evaluation, and the residual disease can be a prognostic factor of tumor recurrence and overall survival, mainly in high-risk histologies such as TN tumors or HER2+ invasive breast carcinomas.[6, 8] For this reason, there is a particular interest in exploring new therapies to increase the pCR rate. We decided to look at the effect of metformin plus standard therapy on the rate pCR. All the included patients were discussed in our institutional tumor board. As a result, there was a clear trend toward including more HER2+, TN, or HR-positive invasive breast cancer with high-risk features such as advanced disease or high histologic grade. This modality of treatment was also preferred in young patients, which explains the median age of 52.48 (±13.41) years. Most of the patients in our study were healthy (56.6%). This fact is very

relevant because other retrospective studies using metformin in this setting had evaluated diabetic patients.[19]

Overall, the pCR rate (ypT0/is ypN0) obtained in our research was 34%, which is higher than that reported in other studies (ranging from 14 to 19.8%).[20] Nevertheless, we have to emphasize that our study population was selected deliberately, including very responsive tumor subtypes. We found that the pCR rate was significantly higher when metformin was added to standard systemic therapy, even after adjustment for the tumor subtype, meaning that adding metformin to systemic therapy increased the likelihood of achieving pCR 5.56 times.

Metformin has shown anticancer properties, including activation of the AMP activated protein kinase (AMPK) pathway,[21] antioxidant activity, induction of apoptosis, and many others.[22] Patients with type 2 diabetes are hyperinsulinemic, and there is evidence that this condition contributes to tumorigenesis. In this scenario, metformin reverses, at least partially, hyperinsulinemia and exhibits antiproliferative properties, which might increase the effect of chemotherapy in a synergy. Preclinical research has demonstrated that metformin can sensitize tumor cells to chemotherapy through inhibition of the expression of PI3K/AKT proteins[23] and, consequently, controlling the activity of the mammalian target of rapamycin (mTOR). The combination of metformin with chemotherapy appears to inhibit mTOR activity, inducing cell cycle arrest.[24] Our study, although limited by its cross-sectional design and sample size, provides clinical evidence that metformin in conjunction with chemotherapy increases the pCR rate in the context of non-diabetic Latin American patients, which is relevant to planning prospective studies.

Ki-67 is a non-histone nuclear cortex protein expressed in all cell cycle phases except in the quiescent phase G0, reaching the peak level during mitosis. Ki-67 can serve as an indicator of tumor proliferative activity.[10, 25, 26] Higher level of Ki-67 has been hypothesized to be a predictor marker of pCR.[27, 28] A recent meta analysis involving 53 studies (10 848 patients) showed that tumors with high Ki-67 score had a better chance to respond to neoadjuvant treatment, although there was no clear cut-off.[29] In our study, there was a higher chance of obtaining a pCR when Ki-67 index was greater than 55% using ROC curve; however, when metformin was added, we were unable to find a specific Ki-67 cut-off. This might mean that, regardless of Ki-67 levels, the most important factor to obtain the pCR was metformin. This finding must be confirmed by future studies since this has not been evaluated in this specific approach, as far as we know, either in retrospective or prospective studies.

In conclusion, this is the first cross-sectional study conducted in a Latin American population showing that the use of metformin in combination with systemic therapy can increase the pCR rate in locally advanced or early breast cancer, irrespective of the histologic subtype, grade, or Ki-67 levels. These findings can encourage prospective studies using metformin in the neoadjuvant setting in our population.

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**Conflict of Interest**

We have read and understood the journal's policy on disclosing conflicts of interest and declare that we have none.

**References**

1. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin D, Forman D, Bray F. Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2013. Lyon, France: International Agency for Research on Cancer. 2014.
2. Costa Rican Ministry of Health. National Cancer Registry data base (June 2015) Available from: [https://www.ministeriodesalud.go.cr/index.php/vigilancia-de-la-salud/estadisticas-y-bases-de-datos/estadisticas/estadistica-de-cancer-registro-nacional-tumores/2722-situacion-epidemiologica-del-cancer/file.]
3. Spitale A, Mazzola P, Soldini D, Mazzucchelli L, Bordoni A. Breast cancer classification according to immunohistochemical markers: clinicopathologic features and short-term survival analysis in a population-based study from the South of Switzerland. Ann Oncol. 2009;20(4):628-35.
4. Blows FM, Driver KE, Schmidt MK, Broeks A, van Leeuwen FE, Wesseling J, *et al*. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. PLoS Med. 2010;7(5):e1000279.
5. Perou CM, Sorlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, *et al*. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747-52.
6. Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, *et al*. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res. 2005;11(16):5678-85.
7. Norum JH, Andersen K, Sorlie T. Lessons learned from the intrinsic subtypes of breast cancer in the quest for precision therapy. Br J Surg. 2014;101(8):925-38.

8. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, *et al*. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72.
9. Denkert C, Budczies J, von Minckwitz G, Wienert S, Loibl S, Klauschen F. Strategies for developing Ki67 as a useful biomarker in breast cancer. Breast. 2015;24 Suppl 2:S67-72.
10. Penault-Llorca F, Radosevic-Robin N. Ki67 assessment in breast cancer: an update. Pathology. 2017;49(2):166-71.
11. Sueta A, Yamamoto Y, Hayashi M, Yamamoto S, Inao T, Ibusuki M, *et al*. Clinical significance of pretherapeutic Ki67 as a predictive parameter for response to neoadjuvant chemotherapy in breast cancer; is it equally useful across tumor subtypes? Surgery. 2014;155(5):927-35.
12. Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev. 2009;30(6):586-623.
13. Gunter MJ, Hoover DR, Yu H, Wassertheil-Smoller S, Rohan TE, Manson JE, *et al*. Insulin, insulin-like growth factor-I, and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 2009;101(1):48-60.
14. DeCensi A, Gennari A. Insulin breast cancer connection: confirmatory data set the stage for better care. J Clin Oncol. 2011;29(1):7-10.
15. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371(9612):569-78.
16. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012;35(6):1364-79.
17. Chlebowski RT, McTiernan A, Wactawski-Wende J, Manson JE, Aragaki AK, Rohan T, *et al*. Diabetes, metformin, and breast cancer in postmenopausal women. J Clin Oncol. 2012;30(23):2844-52.
18. Gralow JR, Burstein HJ, Wood W, Hortobagyi GN, Gianni L, von Minckwitz G, *et al*. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. J Clin Oncol. 2008;26(5):814-9.
19. Jiralerspong S, Palla SL, Giordano SH, Meric-Bernstam F, Liedtke C, Barnett CM, *et al*. Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol. 2009;27(20):3297-302.
20. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, *et al*. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012;30(15):1796-804.
21. Shen M, Zhang Z, Ratnam M, Dou QP. The interplay of AMP-activated protein kinase and androgen receptor in prostate cancer cells. J Cell Physiol. 2014;229(6):688-95.
22. Pierotti MA, Berrino F, Gariboldi M, Melani C, Mogavero A, Negri T, *et al*. Targeting metabolism for cancer treatment and prevention: metformin, an old drug with multi-faceted effects. Oncogene. 2013;32(12):1475-87.
23. Liu Y, Zhang Y, Jia K, Dong Y, Ma W. Metformin inhibits the proliferation of A431 cells by modulating the PI3K/Akt signaling pathway. Exp Ther Med. 2015;9(4):1401-6.
24. Peng M, Darko KO, Tao T, Huang Y, Su Q, He C, *et al*. Combination of metformin with chemotherapeutic drugs via different molecular mechanisms. Cancer Treat Rev. 2017;54:24-33.
25. Gerdes J, Schwab U, Lemke H, Stein H. Production of a mouse monoclonal antibody reactive with a human nuclear antigen associated with cell proliferation. Int J Cancer. 1983;31(1):13-20.
26. Duchrow M, Schluter C, Wohlenberg C, Flad HD, Gerdes J. Molecular characterization of the gene locus of the human cell proliferation-associated nuclear protein defined by monoclonal antibody Ki-67. Cell Prolif. 1996;29(1):1-12.
27. von Minckwitz G, Sinn HP, Raab G, Loibl S, Blohmer JU, Eidtmann H, *et al*. Clinical response after two cycles compared to HER2, Ki-67, p53, and bcl-2 in independently predicting a pathological complete response after preoperative chemotherapy in patients with operable carcinoma of the breast. Breast Cancer Res. 2008;10(2):R30.
28. Yerushalmi R, Woods R, Ravdin PM, Hayes MM, Gelmon KA. Ki67 in breast cancer: prognostic and predictive potential. Lancet Oncol. 2010;11(2):174-83.
29. Chen X, He C, Han D, Zhou M, Wang Q, Tian J, *et al*. The predictive value of Ki-67 before neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis. Future Oncol. 2017;13(9):843-57.

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# Seroma Formation After Mastectomy and Axillary Dissection; A Comparison Among Blunt Dissection With Hemostat, Sharp Dissection With Metzenbaum Scissors, and Dissection With Harmonic Scissors

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ABSTRACT

**Background:** Seroma formation is a common complication after surgery for breast cancer. It may originate from dissected lymphatic ducts in axillary area. Two important predictive factors are the surgical technique, and instruments used during surgery. This study was conducted to determine the impact of three axillary dissection techniques, namely, blunt dissection with hemostat, sharp dissection with Metzenbaum scissors, and dissection with harmonic scissors, on seroma formation.

**Methods:** Patients with a tissue diagnosis of breast cancer who did not have metastasis, and were candidates for either breast conservation surgery (BCS) and sentinel lymph node biopsy (SLNB) with or without axillary lymph node dissection (ALND), or modified radical mastectomy (MRM) were included in a prospective study. Patients were randomly allocated to one of the above mentioned three groups. The incidence of seroma formation was compared among the groups.

**Results:** Sixty patients (age: 50.25 ± 10.33 years) were enrolled for the study. At the end of the study, after four weeks of postoperative follow up, 19 patients developed seroma (31.6%), of whom 5 (26.3%) had dissection with harmonic scissors, 6 (31.5%) with Metzenbaum scissors, and 8 (42.1%) were dissected bluntly. There was no significant difference among groups regarding seroma formation ($P = 0.583$).

**Conclusion:** Application of harmonic scissors for axillary dissection has no significant impact on seroma formation. However, MRM leads to significantly more seroma formation compared with BCS.

## Introduction

Breast cancer has remained the second cancer-related cause of death in women worldwide and accounts for a significant volume of cancer surgeries. Surgical procedures for breast cancer include breast conservation surgery (BCS), with or without sentinel lymph node biopsy (SLNB) or axillary lymph node dissection (ALND), and modified radical mastectomy (MRM), with the choice depending on the stage of the disease. Each technique has its own advantages and complications.[1]

Seroma formation is among the most common complications of surgery for breast cancer, with an incidence of 3% to 85%. It may significantly delay adjuvant therapy and increase the risk of infection.[2] On the other hand, surgery may be indicated for prolonged unresponsive cases.[3] The mechanism of seroma formation is not well understood; however,

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some risk factors or predictive factors are as follows: age, size of the breast, comorbidity, the number of involved axillary lymph nodes (LNs), history of previous breast or axillary surgery, and treatment with tamoxifen or heparin.[4,5] Lower fibrinogen levels in seroma compared with those in postoperative plasma[6] supports the theory that seroma most probably originates from lymph nodes.[7] MRM carries a greater risk of seroma formation than BCS does,[8] and an RCT found that seroma formation is much less after SLNB than after ALND.[9]

In conventional techniques, such as blunt dissection with hemostat and sharp dissection with Metzenbaum scissors, hemostasis is generally attained with electrocautery or ligation. Argon diathermy, laser scalpel, and ultrasonic scalpel decrease intraoperative blood loss. However, they are time-consuming and increase postoperative seroma formation and the risk of tissue thermal damage.[10,11]

This prospective study was carried out to compare the prevalence of seroma formation following surgery for breast cancer, when axillary surgery was performed using harmonic scissors, hemostat scissors, or Metzenbaum scissors.

## Methods

This was a prospective study conducted in a tertiary referral university hospital during 2013 and 2014. The primary goal of the study was to measure seroma formation in breast cancer patients who underwent BCS and SLNB (with or without ALND), or MRM when axillary dissection was performed with harmonic scissors, hemostat, or Metzenbaum scissors.

Inclusion criteria were (1) having histopathologically diagnosed breast cancer, (2) having no distant metastasis, and (3) being candidate for BCS and SLNB (with or without ALND), or BCS and ALND, or MRM. Exclusion criteria were having (1) previous breast or axillary surgery, (2) history of radiation to breast, axilla, or upper limb, (3) history of systemic chemotherapy for any reason, (4) any pathologic process involving the skin of the breast, axilla, or upper limb, (5) a motor disorder of upper limb, and (6) no consent.

Sampling was done by excel quadratic block method. Patients were randomly allocated to one of the following groups:

1. Axillary dissection using blunt dissection with hemostat. Bleedings were either cauterized or ligated.

2. Axillary dissection using sharp dissection with Metzenbaum scissors. Bleedings were either cauterized or ligated.

3. Axillary dissection using harmonic scissors. Axillary dissection was performed entirely by harmonic scissors.

Allocation was done by simple randomization technique. Patients entering the operating room were allocated to group 1, then 2, and then 3, and this round was repeated.

The surgeon, preoperative preparation, and postoperative care (including wound care, ambulation, limb activity, and physical therapy) were the same for each patient. Diagnosis of seroma formation and its evaluation was performed by the same research team member, who was a 4th-year resident of surgery. Only the operating surgeon knew which patient belonged to which group, and the patients and the researcher (the 4th-year resident) were blinded.

The study variables were age, the type of breast surgery, the type of axillary dissection, the technique of axillary dissection, the number of involved lymph nodes (pN), tumor size (pT), tumor grade, microscopic diagnosis, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, Ki-67 status, and seroma formation.

Seroma formation was defined as any clinically detectable collection of serum requiring aspiration. Drainage in the first three postoperative days was recorded. Patients were then visited 1, 2, and 4 weeks after the operation and before the start of adjuvant therapy, and were examined for seroma formation. Data were recorded, finalized, and analyzed using IMB SPSS software, version 20.

Informed consent form was signed by every patient before entering the study. Data confidentiality was observed and the patients were free to leave the study at any time. No extra charge was imposed on the patients. The researchers were committed to the World Medical Association's Declaration of Helsinki throughout the study.

## Results

Sixty patients (age: 50.25 ± 10.33) were assigned to three groups of 20 each: blunt dissection with hemostat, sharp dissection with Metzenbaum scissors, and dissection with harmonic scissors (Table 1).

Of 20 patients who had blunt axillary dissection with hemostat, 16 (80%) underwent MRM and 4 (20%) BCS; of 20 patients who received axillary dissection with Metzenbaum scissors, 10 (50%) underwent MRM and 10 (50%) BCS; and of 20 patients in the group who had axillary dissection with harmonic scissors, 12 (60%) underwent MRM and 8 (40%) BCS.

In total, 38 (63.3%) patients underwent MRM. Axillary dissection was performed using harmonic scissors in 12 (31.5%), using Metzenbaum scissors in 10 (26.5%), and using hemostat in 16 (42%) patients. Twenty-two (27.7%) patients underwent BCS. Axillary dissection was performed with harmonic scissors in 8 (36.5%), with Metzenbaum scissors in 10 (45.5%), and with hemostat in 4 (18%) patients.

The most common tissue diagnosis was invasive

After preoperative chemotherapy, a breast-conservation surgery waductal carcinoma, (n = 47, 78.3%), followed by invasive lobular carcinoma (n = 10, 16.7%) and infiltrating ductal carcinoma (n = 3, 5%). The mean tumor size was 3.4 ± 1.53 cm, and the mean number of involved axillary lymph nodes was 2.86 ± 3.27 (Table 1).

Ten (16.7%) patients were at stage Ia, 17 (28.3%) at stage Ib, 21(35%) at stage II, and 12 (20%) at stage III of breast cancer, according to TNM classification (Table 1).

Also, 34 (56.7%) patients were ER+ and PR+, 12 (20%) were HER2-positive, and 4 (6.7%) were Ki-67–positive (Table 1).

No significant difference was found among the three groups regarding age ($P = 0.4$), tumor size ($P = 0.944$), the number of involved lymph nodes ($P = 0.789$),(pathologic type of tumor ($P = 0.668$), and the stage of disease ($P = 0.978$). Neither was there any significant difference in receptor status (ER: $P = 0.934$, PR: $P = 0.934$, HER2: $P = 0.892$, and Ki-67: $P = 0.329$) (Table 1).

s possible in 22 patients (55%), and the rest of them underwent mastectomy. Pathological complete response (ypT0/is ypN0) was achieved in 13 patients (33%). Only 3 patients (15.8%) with AR-positive tumors achieved a pCR. The rate of pCR according to the expression or absence of AR, ER, PR, and HER2 is reported in Table 2. AR-positive tumors had 82% less chance of achieving a pCR compared with patients with AR-negative tumors (OR = 0.18; 95% CI, 0.04–0.75).

After four weeks of follow up, and at the end of the study, 19 (31.6%) patients developed seroma. The frequencies of seroma formation in patients in different groups were 5 (20%) (dissection using harmonic scissors), 6 (30%) (Metzenbaum scissors), and 8 (40%) (hemostat). Analysis using chi-square test showed no significant difference in seroma formation among the groups ($P = 0.583$) (Figure 1).

**Table 2.** Pathological complete response according to the Immunohistochemical expression of breast cancer receptors

| Variable | Blunt dissection with hemostat | Dissection with Metz | Harmonic scalpel | *P* |
|---|---|---|---|---|
| Age | 50.25 ± 9.27 | 48.65 ± 10.74 | 51.85 ± 11.16 | 0.400 |
| Tumor size | 34.15 ± 13.96 | 35 ± 15.55 | 33.85 ± 17.17 | 0.944 |
| Number of involved lymph nodes | 2.55 ± 2.45 | 2.95 ± 3.05 | 3.10 ± 4.20 | 0.789 |
| Stage of the disease | | | 4 (20%) | 0.978 |
| Ia | 4 (20%) | 2 (10%) | 5 (25%) | |
| Ib | 5 (25%) | 7 (35%) | 7 (35%) | |
| II | 5 (25%) | 9 (45%) | 4 (20%) | |
| III | 6 (30%) | 2 (10%) | | |
| Histologic type of tumor | | | | 0.668 |
| Invasive lobular | 4 (20%) | 2 (10%) | 4 (20%) | |
| Infiltrating ductal | 0 | 2 (10%) | 1 (5%) | |
| Invasive ductal | 16 (80%) | 16 (80%) | 15 (75%) | |
| ER expression | 12 (60%) | 9 (45%) | 11 (55%) | 0.934 |
| PR expression | 12 (60%) | 9 (45%) | 11 (55%) | 0.934 |
| HER2 expression | 4 (20%) | 7 (35%) | 3 (15%) | 0.892 |
| Ki-67 expression | 2 (10%) | 5 (25%) | 2 (10%) | 0.329 |
| Technique of surgery | | | | 0.134 |
| MRM | 16 (80%) | 10 (50%) | 12 (60%) | |
| BCS | 4 (20%) | 10 (50%) | 8 (40%) | |

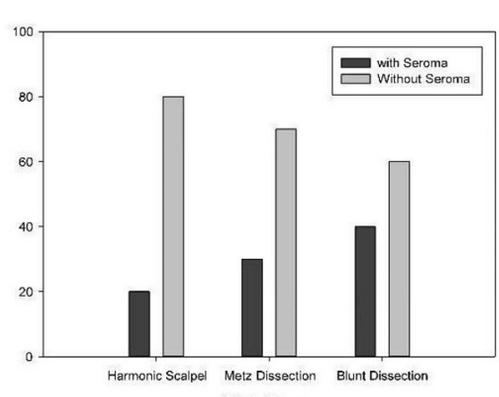


**Figure 1**. Frequency of seroma in study groups

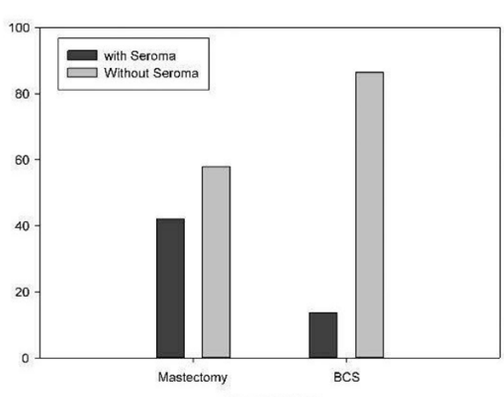


**Figure 2**. Frequency of seroma after MRM and BCS

Correlation of demographic and pathologic characteristics with seroma formation was also evaluated. No correlation was found between seroma formation and age ($P = 0.858$), tumor size ($P = 0.920$), disease stage ($P = 0.415$), the type of cancer ($P = 0.271$), ER and PR status ($P = 0.781$), HER2 expression ($P = 0.775$), or Ki-67 expression ($P = 0.778$).

Of 38 patients who underwent MRM, 16 (42.1%) developed seroma: 5 were dissected using harmonic scissors, 5 using Metzenbaum scissors, and 6 using hemostat.

Only 3 (9%) out of 22 patients who had BCS developed seroma: 1 was dissected using Metzenbaum scissors and 2 using hemostat. None of the patients who underwent BCS and were dissected with harmonic scissors developed seroma.

The difference in the incidence of seroma formation between MRM and BCS patients was significant ($P = 0.022$) (Figure 2).

**Discussion**

Although the mechanism of seroma formation is not fully understood, some of the risk factors or predictive factors are as follows: age, size of the breast, comorbidity, the number of involved axillary lymph nodes (Lns), history of previous breast or axillary surgery, and treatment with tamoxifen or heparin.[4, 5] One theory holds that seroma forms because of chronic inflammatory reaction inflicted by surgery.[5] This reaction leads to increased serosal fluid accumulation in response to elevated fibrinolytic activity in seroma and lymphatic fluid.[12] On the other hand, low fibrinogen level in seroma compared with that in postoperative plasma[6] supports the hypothesis that seroma is most probably originated from lymph nodes.[7] A combination of different techniques and instruments affects seroma formation[10] and may be the reason for various amounts of seroma reported in different studies. Radical mastectomy leads to higher rates of seroma formation than simple mastectomy do.[13,14]This difference is not significant between radical mastectomy and MRM.[14] Immediate breast reconstruction after MRM decreases the risk of seroma formation compared with delayed reconstruction.[15]

To obviate the dead space, Halstead recommended a short upper skin flap sutured to pectoral fascia at the level of lower margin of the 1st rib; the remaining wound would be covered with skin graft.[16] Orr, in 1951, used tension sutures to tighten the skin flaps to the chest wall.[17] Keyes and colleagues used multiple sutures to attach the skin flaps to the chest wall.[18] Other techniques such as suturing the flaps to subcutaneous tissue and avoiding drainage in BCS were also implicated to reduce seroma formation.[19,20]

No study, as yet, has shown the efficacy using laser scalpel or ultrasonic scissors in prevention of seroma formation.[21] Other techniques such as avoiding drainage in BCS[20] were also implicated to reduce seroma formation. Whitfield and Rainbury did not found any significant difference in seroma formation between suction drainage and closed siphon drainage.[22] Pathologic specifications of tumors and patient-related factors do not seem to affect seroma formation, except for weight, which shows a direct relation with seroma formation.[2,23] No particular relationship has been reported between seroma formation and hormone receptors, axillary lymph node involvement, the grade of the tumor, or the stage of disease.[15, 23-25] This lack of relationship also been observed for anemia, smoking, diabetes, and breast size as well as tumor size, tumor location, the size of the resected specimen, and the pathologic type of cancer.[14,24,26]

Instruments based on piezoelectric mechanism induce coagulation by denaturing collagen and elastin in soft tissue, blood, and lymphatic vessels through high-frequency vibration (50–60 MHz).[27] This produces less heat and results in less thermal energy transfer to adjacent tissues compared with electrocautery.[28] Harmonic Focus®, introduced more than a decade ago, cuts and coagulates lymphatic ducts safely and is utilized for hepatic, thyroid, and breast surgery among others.[29]

The primary outcome of this study was postoperative seroma formation, which occurred in 19 patients. There was no significant difference in age, tumor size, number of involved lymph nodes, type of the tumor, the stage of disease, and the expression of ER, PR, HER2, and Ki-67 among the groups, so the groups were matched by these variables. The studied variables including demographic specifications, the pathologic variety of the tumor, or the methods of surgery were not associated with postoperative seroma formation.

The frequency of seroma formation was lower in the harmonic scissors group than the other groups, although the difference was not significant. No patients who underwent BCS with harmonic scissors developed seroma. Although it cannot be substantiated statistically, it can be taken as a suggesting clue for future study.

There was no correlation between seroma formation and age, tumor size, the stage of disease, the type of cancer, or the expression of ER/PR/HER2/Ki-67. Therefore, it can be concluded that these factors do not relate to seroma formation.

The only variable that showed a significant correlation with seroma formation was the principal technique of mastectomy, i.e., MRM vs. BCS. Regardless of the method used for axillary dissection, seroma formation rate was higher after MRM than after BCS.

Orr *et al* published the data of 72 patients who underwent MRM, partial mastectomy with axillary dissection, or simple mastectomy. The total incidence rate of seroma formation was 11%, the highest incidence (45.67%) being observed in patients who had simple mastectomy and were

discharged at postoperative day 1.[30] Deo and Shukla[31] reported the application of harmonic scissors in MRM for the first time. They showed a decrease in intraoperative bleeding and duration of drainage compared with conventional clamp and tie. Galatius and colleagues[21] studied 59 patients who underwent surgery using harmonic scissors (n = 30) or conventional scissors (n = 29). On follow-up, 20 patients in each arm had developed seroma: a total of 40 (67%). There was no significant difference in the frequency of seroma formation between harmonic scissors and conventional ones. Lumachi *et al* conducted an RCT and showed that using harmonic scissors, compared with surgical scalpel and tying, led to significantly less seroma formation.[32]

Although no study with a similar design has been published yet, studies have produced inconsistent results. Khan and colleagues studied 150 patients who were operated using either harmonic scissors or electrocautery.[33] In the harmonic scissors group, the incidence of seroma formation was 21.3% vs. 33.3% in the electrocautery group, which was significantly less. While we had just about the same percentages in harmonic vs. Metzenbaum, the difference was not significant.

The relationship between MRM and seroma formation has been studied formerly. Gonzalez and colleagues reported seroma formation rate of 19.5% for MRM and 9.2% for BCS ($P = 0.001$).[12] In a meta-analysis by Kuroi *et al*, 51 clinical trials, 7 cohort studies, and 7 retrospective studies were included. They concluded that MRM had a significant association with seroma formation. The present study reached the same finding: MRM led to significantly higher seroma formation compared with BCS ($P = 0.022$).[23]

The limitations of this study were the small number of patients in each group, the heterogeneity of groups considering techniques of axillary dissection, heterogeneity of groups considering the extent of mastectomy, and the use of simple randomization. Also, we should have ideally divided the BCS patients into those who had BCS + SLNB, BCS + SLNB + ALND, and BCS + ALND. Again, the small number of patients in each of these subgroups would impede meaningful statistical analysis.

These limitations may have hypothetically affected our results. Therefore, we believe that a large-scale study with a better randomization method comparing the use of harmonic vs conventional scissors in patients with the same extent of mastectomy may better clarify the issue.

The use of harmonic scissors for axillary dissection in MRM, BCS with SLNB (with or without ALND), and BCS with ALND does not decrease the incidence of postoperative seroma formation significantly. Also, there is no association between age, tumor specifications, or molecular markers status and seroma formation. The only effective factor is the extent of mastectomy, with MRM leading to significantly higher rates of seroma formation than BCS.

**Conflict of Interest**

The authors have none to declare.

**References**


1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Murray T, *et al*. Cancer statistics, 2008. CA: a cancer journal for clinicians. 2008;58(2):71-96.
2. Kumar S, Lal B, Misra MC. Post-mastectomy seroma: a new look into the aetiology of an old problem. Journal of the Royal College of Surgeons of Edinburgh. 1995;40(5):292-4.
3. Stanczyk M, Grala B, Zwierowicz T, Maruszynski M. Surgical resection for persistent seroma, following modified radical mastectomy. World journal of surgical oncology. 2007;5:104.
4. Bryant M, Baum M. Postoperative seroma following mastectomy and axillary dissection. The British journal of surgery. 1987;74(12):1187.
5. Watt-Boolsen S, Nielsen VB, Jensen J, Bak S. Postmastectomy seroma. A study of the nature and origin of seroma after mastectomy. Danish medical bulletin. 1989;36(5):487-9.
6. Bonnema J, Ligtenstein DA, Wiggers T, van Geel AN. The composition of serous fluid after axillary dissection. The European journal of surgery : Acta chirurgica. 1999;165(1):9-13.
7. Bonnema J, van Geel AN, Wiggers T, Ligtenstein DA. Perioperative and postoperative tranexamic acid reduces the local wound complication rate after surgery for breast cancer. The British journal of surgery. 1994;81(11):1693.
8. Gonzalez EA, Saltzstein EC, Riedner CS, Nelson BK. Seroma formation following breast cancer surgery. The breast journal. 2003;9(5):385-8.
9. Purushotham AD, Upponi S, Klevesath MB, Bobrow L, Millar K, Myles JP, *et al*. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(19):4312-21.
10. Porter KA, O'Connor S, Rimm E, Lopez M. Electrocautery as a factor in seroma formation following mastectomy. American journal of surgery. 1998;176(1):8-11.
11. Sutton PA, Awad S, Perkins AC, Lobo DN. Comparison of lateral thermal spread using monopolar and bipolar diathermy, the Harmonic Scalpel and the Ligasure. The British journal of surgery. 2010;97(3):428-33.
12. Oertli D, Laffer U, Haberthuer F, Kreuter U, Harder F. Perioperative and postoperative tranexamic acid reduces the local wound complication rate after surgery for breast cancer.

Br J Surg. 1994;81(6):856-9.
13. Aitken DR, Hunsaker R, James AG. Prevention of seromas following mastectomy and axillary dissection. Surgery, gynecology & obstetrics. 1984;158(4):327-30.
14. Say CC, Donegan W. A biostatistical evaluation of complications from mastectomy. Surgery, gynecology & obstetrics. 1974;138(3):370-6.
15. Woodworth PA, McBoyle MF, Helmer SD, Beamer RL. Seroma formation after breast cancer surgery: incidence and predicting factors. The American surgeon. 2000;66(5):444-50; discussion 50-1.
16. Almond LM, Khodaverdi L, Kumar B, Coveney EC. Flap Anchoring Following Primary Breast Cancer Surgery Facilitates Early Hospital Discharge and Reduces Costs. Breast care. 2010;5(2):97-101.
17. Orr TG J. An incision and method of wound closure for radical mastectomy. . Annals of surgery. 1951;133:565-6.
18. Keyes EL, Hawk BO, Sherwin CS. Basting the axillary flap for wounds of radical mastectomy. AMA archives of surgery. 1953;66(4):446-51.
19. Larsen BB, Hugan C, Jr. Fixation of skin flaps in radical mastectomy by subcutaneous sutures; observations. AMA archives of surgery. 1955;71(3):419-23.
20. Schultz I, Barholm M, Grondal S. Delayed shoulder exercises in reducing seroma frequency after modified radical mastectomy: a prospective randomized study. Annals of surgical oncology. 1997;4(4):293-7.
21. Galatius H, Okholm M, Hoffmann J. Mastectomy using ultrasonic dissection: effect on seroma formation. Breast. 2003;12(5):338-41.
22. Whitfield PC, Rainsbury RM. Suction versus siphon drainage after axillary surgery for breast cancer: a prospective randomized trial. The British journal of surgery. 1994;81(4):547.
23. Kuroi K, Shimozuma K, Taguchi T, Imai H, Yamashiro H, Ohsumi S, *et al*. Evidence-based risk factors for seroma formation in breast surgery. Japanese journal of clinical oncology. 2006;36(4):197-206.
24. Antonio M, Pietra T, Domenico L, Massimo D, Ignazio R, Antonio N, *et al*. Does LigaSure reduce fluid drainage in axillary dissection? A randomized prospective clinical trial. Ecancermedicalscience. 2007;1:61.
25. Browse DJ, Goble D, Jones PA. Axillary node clearance: who wants to immobilize the shoulder? European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 1996;22(6):569-70.
26. Chilson TR, Chan FD, Lonser RR, Wu TM, Aitken DR. Seroma prevention after modified radical mastectomy. The American surgeon. 1992;58(12):750-4.
27. Brill AI. Bipolar electrosurgery: convention and innovation. Clinical obstetrics and gynecology. 2008;51(1):153-8.
28. Koch C, Friedrich T, Metternich F, Tannapfel A, Reimann HP, Eichfeld U. Determination of temperature elevation in tissue during the application of the harmonic scalpel. Ultrasound in medicine & biology. 2003;29(2):301-9.
29. Cheang T, Hanna SS, Wright FC, Law CH. Use of a collagen-sealing device in hepatic resection: a comparative analysis to standard resection technique. HPB : the official journal of the International Hepato Pancreato Biliary Association. 2006;8(3):194-9.
30. Orr RK, Ketcham AS, Robinson DS, Moffat FL, Tennant ND. Early discharge after mastectomy. A safe way of diminishing hospital costs. The American surgeon. 1987;53(3):161-3.
31. Deo SV, Shukla NK, Asthana S, Niranjan B, Srinivas G. A comparative study of modified radical mastectomy using harmonic scalpel and electrocautery. Singapore medical journal. 2002;43(5):226-8.
32. Lumachi F, Brandes AA, Burelli P, Basso SM, Iacobone M, Ermani M. Seroma prevention following axillary dissection in patients with breast cancer by using ultrasound scissors: a prospective clinical study. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2004;30(5):526-30.
33. Khan S, Khan S, Chawla T, Murtaza G. Harmonic scalpel versus electrocautery dissection in modified radical mastectomy: a randomized controlled trial. Annals of surgical oncology. 2014;21(3):808-14.

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# Adenoid Cystic Carcinoma of Breast: A Rare Case Report

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ABSTRACT

**Background:** Adenoid cystic carcinoma (AdCC) of the breast is a rare type of invasive breast cancer, accounting for less than 1% of all breast cancer cases. It is usually a low-grade tumor that rarely metastasizes to the axillary lymph nodes and distant organs. AdCC of the breast is mostly negative for estrogen receptor, progesterone receptor, and HER2-neu. However, despite being triple-negative, it has favorable outcome, and patients with AdCC of the breast generally have a good to excellent long-term survival.

**Case presentation:** Here we report a case of a 51-year-old female presenting with left breast mastalgia who was finally diagnosed with AdCC of the left breast. The patient underwent breast-conserving surgery and axillary staging followed by adjuvant chemoradiation.

**Conclusion:** Because of the rarity of AdCC of the breast, it has been difficult to conduct prospective trials to determine the best treatment option. Different types of therapy, including BCS and mastectomy with or without axillary staging with or without adjuvant chemoradiation have been reported, all with overall good to excellent long-term results. Prospective controlled trials will help in determining the best treatment.

## Introduction

Adenoid cystic carcinoma (AdCC) of the breast is a rare type of invasive breast cancer, accounting for less than 1% of all breast cancer cases. It is mostly seen in the 5th and 6th decades of life and affects both genders, although females are affected more frequently.[1-5]

Breast AdCC is a low-grade tumor that rarely metastasizes to the axillary lymph nodes and distant organs.[1-4, 6-10] Distant metastasis generally occurs in the absence of axillary lymph node involvement[2, 8, 10,] and lungs are the most commonly involved organs.[10]

Breast AdCC is usually negative for estrogen receptor, progesterone receptor, and HER2/neu (triple- negative).[1-4, 6, 11] However, unlike other triple-negative invasive breast cancers, breast AdCC has a favorable prognosis, and 5-, 10-, and 15-year survival rates have been reported to be 94–98.1%, 85–100%, and 91.4%, respectively.[1-10,12]

Because of the rarity of breast AdCC, it has been difficult to conduct prospective trials to compare different types of local and systemic treatments; therefore, there is currently no standard treatment recommendations.[1, 3, 7, 8] Different types of surgery including breast-conserving surgery (BCS) and mastectomy, with or without axillary staging, with or without adjuvant chemoradiation or hormone therapy, have been used in different studies, with overall similar good results.

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Here, we report a case of a 51-year-old female presenting with left breast mastalgia who was finally diagnosed with AdCC of the left breast.

**Case Presentation**

A 51-year-old woman referred to our breast clinic with bilateral breast pain, especially in her left breast. She had no history of previous medical or surgical diseases and was taking no medications. Her age at menarche was 13; she was 21 at her first live birth and had two children. She had an abortion and had reached menopause 3 years before. There was no family history of breast or ovarian cancers. On her physical examination, an area of tissue thickening, measuring 30 mm, was palpated in the upper central portion of her left breast. Examination of the right breast and bilateral axillary regions was unremarkable.

Bilateral digital mammography and breast ultrasound were requested. Mammography revealed an asymmetry with irregular borders in the left breast in medial and deep retroareolar area. This finding was reported to be highly suspicious for malignancy. Also, an asymmetry was detected in axillary tail of the right breast which was stable in comparison with the last year's mammography. Ultrasonography showed an irregular mass (18 × 12 mm) at 10 o'clock position in the left breast, and a hypoechoic lesion (7 × 4 mm) without blood flow in the axillary tail of the right breast. Ultrasound-guided core-needle biopsies (CNB) of both lesions were performed. Pathologic examination reported the left breast lesion as invasive carcinoma. Immunohistochemistry (IHC) staining of the lesion was negative for estrogen receptor, progesterone receptor, HER2/neu, CK20, GCDFP-15, mammaglobin, synaptophysin, and chromogranin, and positive for Ki-67 (10–20% of tumor cells) and CK7. Pathologic examination of the right breast lesion showed no evidence of malignancy.

According to pathology report of the left breast mass, and considering the patient's clinical stage, breast conserving surgery and sentinel node biopsy with the use of technetium 99 ($^{99}$Tc) injection was planned. After excision of the breast specimen, surgical margins were evaluated using frozen-section analysis and were declared clear. However, despite the injection of $^{99}$Tc at the standard dosage in the periphery of the lesion before the surgery, sentinel lymph nodes were not identified. Therefore, limited axillary dissection was done for the axillary staging.

Gross examination showed an infiltrative tumor measuring 18mm. Microscopic examination showed solid and cribriform nests of basaloid cells consistent with adenoid cystic carcinoma. (Figure 1) Immunostaining confirmed the dual epithelial and modified myoepithelial differentiation of tumor cells. (patchy staining for CK5/6, CK7, EMA and P63) The solid component constituted more than 30% of tumor, consistent with grade 3. No tumor calcification, perineural and vascular invasion were reported; clear surgical margins was confirmed. There were six lymph nodes in the axillary specimen which all showed reactive changes. (Figure 2)

According to the pathology report, which confirmed high-grade breast AdCC, and after multidisciplinary review, metastatic workup was pursued; whole-body bone scan and thoracic CT scan were normal. Abdominal ultrasound showed an echogenic mass in the posterior segment of the right lobe of the liver, followed by abdominal CT scan showing a 27 mm low attenuation mass in the right hepatic lobe in favor of metastatic lesion. For further clarification of the lesion, abdominal MRI was done which showed a 38 mm round mass with low signal intensity on T1 and high signal intensity on T2 images at the 6th segment of the right hepatic lobe, which was suggestive of a metastatic lesion. Ultrasound-guided percutaneous needle biopsy of the lesion was decided, but the patient refused to undergo biopsy. Therefore, for deciding on the best management, we had an expert radiologist repeat the ultrasound and review the MRI images. He strongly suggested the possibility of a liver hemangioma, so 99mTc-RBC scanning of the liver was performed.

The scan demonstrated a hemangioma in the right

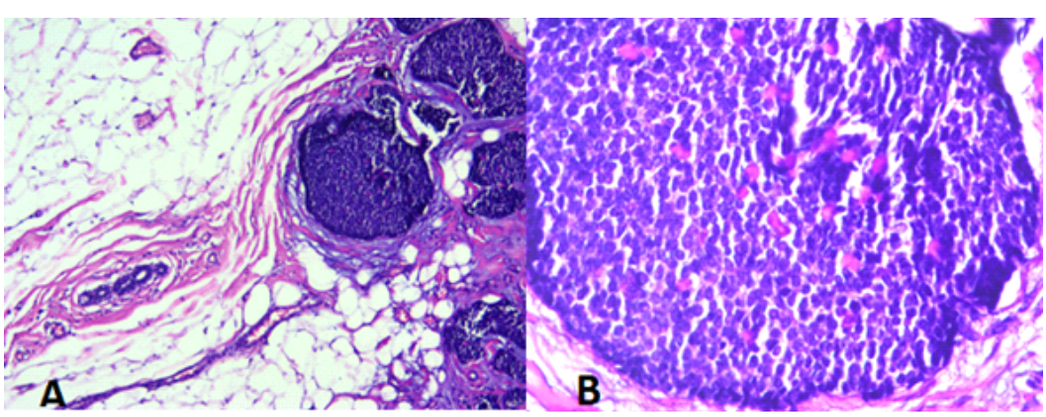


**Figure 1.** A: Photomicrograph shows breast tissue (arrow) inflitrated with cribriform and solid nests of basaloid cells morphologically consistent with adenoid cystic carcinoma, x100, H&E. B: Higher magnification of tumor, x400, H&E

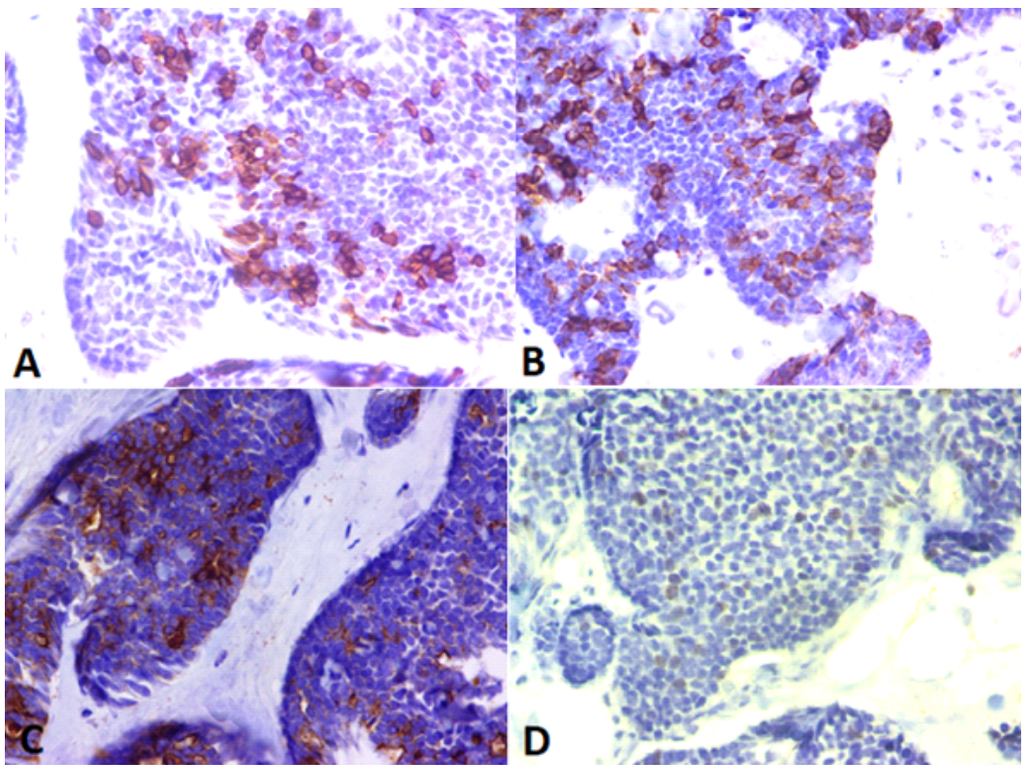


**Figure 2.** Immunostainings for CK5/6 (A), CK7 (B), EMA (C) and P63(D) confirm the presence of dual population of epithelial and modified myoepithelial cells in tumor.

hepatic lobe, and we did not pursue further workup after that.

Following the completion of metastatic workup, 4 sessions of adjuvant chemotherapy with 3-week intervals, and 30 sessions of adjuvant radiotherapy were performed. The patient has been visited twice since completion of the therapy. On the last visit, 8 months after surgery, she was symptom-free, and her physical examination was normal.

**Discussion**

Breast AdCC is a rare type of invasive breast cancer accounting for less than 1% of all breast cancers.[1,4,7,9] It is mostly seen in the 5th–6th decades of life, although there are reports of patients with younger and older ages at the time of diagnosis.[3, 4, 9] Although breast AdCC predominantly occurs in women, there have been reports of men with breast AdCC .[4-6, 11] Signs and symptoms of breast AdCC are usually similar to those of other types of breast cancer, including breast mass and breast pain. It mostly involves subareolar region, as in our patient;[2-4, 9, 11] although, in a retrospective study on 338 women, the most involved quadrant was the upper, outer quadrant.[6] Despite the preference of the malignancy for areolar region, nipple discharge is not a common symptom.[2]

Unlike AdCCs of other organs like head and neck, breast AdCCs are low-grade tumors with a good to excellent prognosis and long-term survival that rarely metastasizes to regional lymph nodes and distant sites.[1, 3, 6, 8, 11] In our patient, axillary lymph nodes were not involved, although the tumor was of high grade. Distant metastasis usually occurs in the absence of lymph node involvement.[2, 8, 10] The most common sites of distant involvement are lungs, although metastasis to brain, bone (vertebrae), liver, or kidneys has also been reported.[5,10,11]

In a review by Miyai *et al*. of seven studies on patients with breast AdCC, lymph node involvement was reported to be 0–6.1%, distant metastasis (including bone, liver, lung, and kidney) 1–20%. Also, 5- and 10 year survival rates were reported to be 88–94% and 90–94.9%, respectively.[11] In another study by Chen *et al*. on 86 breast AdCC patients, 88.4% of patients had grade 1 or 2 tumors; 100% had stage 1–2 cancer; and the rate of lymph node involvement was 2.3%.[1] A retrospective study of 244 women with invasive breast AdCC found that 92.2% of the patients had localized disease, 4.9% had regional disease, and only 7 patients had distant metastasis. The 5-year and 10-year relative cumulative survival rates were 95.5% and 93.5%, respectively, and lymph node involvement ratio was 5.5%.[2] In a retrospective study by Ghabach *et al*. on 338 women with breast AdCC, regional and distant disease was reported in less than 5% of case. The ratio of lymph node involvement was 2.5%, and the overall 5-, 10-, and 15-year relative survival rates were 98.1%, 94.9%, and 91.4%, respectively. Women aged <50 years and ≥50 years had an excellent 5-year relative survival of 94.4% and 99.0%, respectively. Ten-year relative survival was similar for both age groups (94.4%), although 15-year survival rate was slightly lower for older patients compared with the younger ones (88.9% vs

94.3%).[6]

Breast AdCCs are usually triple-negative,[1, 3, 4, 7-9, 11] as was the case for our patient, although hormone receptor- positive breast AdCCs have also been reported.[1] Unlike other triple-negative invasive breast cancers, which have worse outcomes than their positive counterparts, all breast AdCC tumors, including triple- negative ones, have good prognosis overall.[1, 2] In Chen *et al*.,[1] the rate of triple-negative tumors was 77.9%, and Kim *et al*. reported that all of their 6 patients were triple-negative.[7]

Different types of treatment including BCS and mastectomy with or without axillary staging, with or without adjuvant chemotherapy, radiation therapy or hormone therapy have been used for breast AdCC, mostly with no significant difference in outcomes.[2, 3] In our case, with the initial diagnosis of invasive carcinoma, the patient underwent BCS with sentinel lymph node biopsy followed by adjuvant radiation and chemotherapy, because of the high grade of the tumor. Because of the rarity of these tumors, it has been difficult to conduct prospective randomized trials to compare different treatment options and elucidate the best option. Existing data are mostly the results case series and retrospective studies; therefore, there is no universal guideline for treatment of breast AdCC.

The surgical approach for local breast disease control ranges from BCS to mastectomy. Regarding BCS, however, there is no consensus about the adequate surgical margin. Ro *et al*.suggested a grading system for breast AdCC based on the proportion of solid growth of the tumor: no solid element (grade 1), < 30% solid element (grade 2), and >30% solid element (grade 3). Consequently, they proposed local excision, simple mastectomy, and mastectomy with axillary node dissection for grade 1, 2, and 3 tumors, respectively.[13] Another issue is the role of adjuvant treatments, as there is no strong evidence for determining the type of adjuvant therapy (i.e., radiation vs chemotherapy) and identifying the patients who will benefit most from these therapeutic modalities.

According to some studies, mastectomy is the preferred local surgical treatment. In one study, recurrence rate following local excision was reported to be 6–37%.[3] This lower rate of recurrence may explain why mastectomy is the preferred choice of clinicians, despite the fact that there is no randomized controlled trial comparing BCS to mastectomy. A meta-analysis found that recurrence-free 10-year survival rates following mastectomy and BCS were 85.1% and 45.7%, respectively ($p < 0.05$). Six of 10 local recurrences and 7 of 8 distant metastases had occurred 5 years or later after initial treatment. It concluded that patients with breast AdCC should be treated using mastectomy followed by extended follow-up.[14]

Most reports favor BCS as the preferred local treatment, especially along with adjuvant radiation. In a case report by Ichikawa *et al*., a patient with breast AdCC underwent BCS with axillary lymph node dissection. After a 5-year follow-up, without adjuvant therapy, they reported that the patient had no clinical recurrence of the disease.15 In another study, women with breast AdCC were treated with lumpectomy (41 patients) or mastectomy (20 patients), and 40 of them received adjuvant radiotherapy (35 after lumpectomy, 5 after mastectomy). The median follow-up was 79 months, and 5-year overall survival (OS), disease-free survival (DFS), and 5-year locoregional control (LRC) rates were 94%, 82%, and 95%, respectively. Univariate analysis revealed that neither the type of surgery nor the use of postoperative radiotherapy affected survival. The 5-year LRC rate was not different between the mastectomy and BCS groups (100% vs 93%, P = 0.16). A significant correlation was observed between the use of radiotherapy and LRC for the BCS group (P = 0.03). The 5-year LRC rate was 95% for the radiotherapy arm compared with 83% (95% CI: 54%–100%) for the no-radiotherapy arm. In patients with positive margins, all of whom received postoperative radiotherapy, no local failure occurred. The authors concluded that BCS should be considered the preferred treatment for patients with breast AdCC and that postoperative radiotherapy should be proposed in the case of BCS.[12]

In another study, patients with breast AdCC underwent simple or modified radical mastectomy (n = 22) or lumpectomy (n = 6). Of the 6 patients who had lumpectomy, 5 also received postoperative radiation therapy. No local recurrence occurred in either group. The 5-year DFS and OS rates were 100% and 85%, respectively. The authors concluded that breast AdCC has very favorable biologic characteristics and that both lumpectomy with radiation and simple mastectomy result in good local control.[16]

In a retrospective study, Sun *et al*. followed up 478 patients with breast AdCC for a median of 59 months and reported 10-year cause-specific survival (CSS) and OS rates of 87.5% and 75.3%, respectively. The 5-year CSS rates for different treatment modalities were as follows: lumpectomy + adjuvant RT = 96.1%, lumpectomy alone = 91.8%, mastectomy alone = 90.2%, and mastectomy + adjuvant RT = 94.1% (P = 0.026). Multivariate Cox analyses revealed that lumpectomy + adjuvant RT could be an independent prognostic factor for CSS and OS. Patients who underwent lumpectomy + adjuvant RT had better survival rates than patients who had lumpectomy only (CSS: P = 0.018; OS: P = 0.031) or mastectomy only (CSS: P = 0.010; OS: P = 0.004). They concluded that breast AdCC had an excellent prognosis and suggested that BCS be used as the treatment of choice for patients with breast AdCC , along with adjuvant RT to improve survival rates.[17]

In another study on 376 patients who underwent surgery with or without postoperative adjuvant RT, 10-year absolute OS and CSS benefits were 21% and 7%, respectively (P= 0.005 and 0.12, respectively). Multivariate analysis revealed RT to be a significant predictor of overall and cause-specific survival with hazard ratios of 0.44 (95% CI: 0.22–0.88) and 0.1 (95% CI: 0.01–0.88), respectively. They concluded that RT after local surgical therapy for breast AdCC resulted in better cause-specific and overall survival rates and that "use of RT in this rare tumor should be considered in patients otherwise eligible for RT."[18]

Boujelbene *et al*. contend that BCS with postoperative radiotherapy is comparable to mastectomy alone in terms of survival, although they also acknowledged that the value of adjuvant systemic therapies is not established. They suggested that patients with breast AdCC should be under long-term follow-ups as late relapses are possible.[19]

Considering very low involvement of regional lymph nodes in breast AdCC and the inherent complications associated with axillary staging, another dilemma is whether to pursue axillary lymph node staging or dissection in patients with clinically negative axillary lymph nodes or not.

In a study on 20 patients with breast AdCC, preoperative axillary ultrasound was normal in 10 and suspicious in 3 of 13 women who had a subsequent negative lymph node fine-needle aspiration (FNA). Fifteen patients (75%) had sentinel lymph node surgery and were pathologically node-negative, while the remaining 5 had no axillary surgery. After a median follow-up of 3.6 years (range: 0.2–38.6 years), three patients experienced an in-breast recurrence. They observed no cases of nodal metastasis in 20 patients and concluded that preoperative axillary ultrasound with FNA of suspicious nodes could accurately predicted pathologic nodal stage, and that surgery might be omitted safely in patients with pure breast AdCC and a clinically negative axilla.[20] In the study of Khanfir *et al*., which was previously mentioned, 84% of the 61 node-negative women with breast AdCC had axillary lymph node dissection or sentinel node biopsy, concluding that axillary lymph node dissection or sentinel node biopsy might not be recommended.[12] In Arpino *et al*., axillary lymph node dissection was performed in 23 patients with breast AdCC, only one of whom (4%) had histologic positive lymph nodes (2 of 10), and no recurrence was detected for the patient. They concluded that axillary lymph node dissection is not helpful in clinical management of patients with breast AdCC.[16]

Considering all these reports and reviews, mastectomy as well as BCS with adjuvant radiation appear to be reasonable surgical approaches for local treatment of breast AdCC, with equivalent oncologic outcomes. The need for axillary staging in clinically negative axillary lymph nodes, as well as the need for adjuvant chemotherapy, is still unclear. The importance of prospective randomized trials to elucidate the best treatment option cannot be overemphasized.

Breast AdCC is a rare type of invasive breast cancer with good prognosis and low rate of regional lymph node and distant organ involvement. Although there is currently no universal agreement on the best treatment, different types of therapy, including BCS and mastectomy—with or without axillary staging, with or without adjuvant chemoradiation have been used, all with overall good to excellent long-term results. Prospective controlled trials will help in determining the best treatment options.

The decision to report this case was completely explained to the patient and her informed consent was obtained.

**Conflict of Interest**

None to declare.

**References**


1. Chen QX, Li JJ, Wang XX, Lin PY, Zhang J, Song CG, *et al*. Similar outcomes between adenoid cystic carcinoma of the breast and invasive ductal carcinoma: a population-based study from the SEER 18 database. Oncotarget. 2017;8(4):6206-15.
2. Thompson K, Grabowski J, Saltzstein SL, Sadler GR, Blair SL. Adenoid cystic breast carcinoma: is axillary staging necessary in all cases? Results from the California Cancer Registry. Breast J. 2011;17(5):485-9.
3. Canyilmaz E, Uslu GH, Memis Y, Bahat Z, Yildiz K, Yoney A. Adenoid cystic carcinoma of the breast: A case report and literature review. Oncol Lett. 2014;7(5):1599-601.
4. Kocaay AF,Celik SU, Hesimov I, Eker T, Percinel S, Demirer S. Adenoid Cystic Carcinoma of the Breast: A Clinical Case Report. Med Arch. 2016;70(5):392-4.
5. Yoo SJ, Lee DS, Oh HS, Kim HJ, Kim MH, Ahn YC, *et al*. Male breast adenoid cystic carcinoma. Case Rep Oncol. 2013;6(3):514-9.
6. Ghabach B, Anderson WF, Curtis RE, Huycke MM, Lavigne JA, Dores GM. Adenoid cystic carcinoma of the breast in the United States (1977 to 2006): a population-based cohort study. Breast Cancer Res. 2010;12(4):R54.
7. Kim M, Lee DW, Im J, Suh KJ, Keam B, Moon HG, *et al*. Adenoid cystic carcinoma of the breast: a case series of six patients and literature review. Cancer Res Treat. 2014;46(1):93-7.
8. Muslimani AA, Ahluwalia MS, Clark CT, Daw HA. Primary adenoid cystic carcinoma of the breast: case report and review of the literature. Int Semin Surg Oncol. 2006;3:17.
9. Alis H, Yigitbas H, Kapan S, Kalayci M, Kilic G,

Aygun E. Multifocal adenoid cystic carcinoma of the breast: an unusual presentation. Can J Surg. 2008;51(2):E36-7.
10. Silva I, Tome V, Oliveira J. Adenoid cystic carcinoma of the breast with cerebral metastisation: a clinical novelty. BMJ Case Rep. 2011;2011.
11. Miyai K, Schwartz MR, Divatia MK, Anton RC, Park YW, Ayala AG, *et al*. Adenoid cystic carcinoma of breast: Recent advances. World J Clin Cases. 2014;2(12):732-41.
12. Khanfir K, Kallel A, Villette S, Belkacemi Y, Vautravers C, Nguyen T, *et al*. Management of adenoid cystic carcinoma of the breast: a Rare Cancer Network study. Int J Radiat Oncol Biol Phys. 2012;82(5):2118-24.
13. Ro JY, Silva EG, Gallager HS. Adenoid cystic carcinoma of the breast. Hum Pathol. 1987;18(12):1276-81.
14. Sinn HP, Lehnert T, Otto HF. [Adenoid cystic cancer of the breast. Case report and meta-analysis of the literature]. Chirurg. 1993;64(3):198-202.
15. Ichikawa K, Mizukami Y, Takayama T, Takemura A, Miyati T, Taniya T. A case of adenoid cystic carcinoma of the breast. J Med Ultrason (2001). 2007;34(4):193-6.
16. Arpino G, Clark GM, Mohsin S, Bardou VJ, Elledge RM. Adenoid cystic carcinoma of the breast: molecular markers, treatment, and clinical outcome. Cancer. 2002;94(8):2119-27.
17. Sun JY, Wu SG, Chen SY, Li FY, Lin HX, Chen YX, *et al*. Adjuvant radiation therapy and survival for adenoid cystic carcinoma of the breast. Breast. 2017;31:214-8.
18. Coates JM, Martinez SR, Bold RJ, Chen SL. Adjuvant radiation therapy is associated with improved survival for adenoid cystic carcinoma of the breast. J Surg Oncol. 2010;102(4):342-7.
19. Boujelbene N, Khabir A, Boujelbene N, Jeanneret Sozzi W, Mirimanoff RO, Khanfir K. Clinical review--breast adenoid cystic carcinoma. Breast. 2012;21(2):124-7.
20. Welsh JL, Keeney MG, Hoskin TL, Glazebrook KN, Boughey JC, Shah SS, *et al*. Is axillary surgery beneficial for patients with adenoid cystic carcinoma of the breast? J Surg Oncol. 2017;116(6):690-5.

Editorial Open Access

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# Legal Aspects of Bilateral Mastectomies for Patients With or Without Mutated Genes

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Since Angelina Jolie broke the news of her bilateral mastectomy and oophorectomy, most breast surgeons have regularly been facing the question of this type of surgery whatever the age of the patient.[1] Familial breast cancers have received a lot of media coverage. They are often aggressive with bad prognosis, and the discovery of predisposing genes, such as mutated *BRCA1* and *BRCA2,* has opened a window of hope. For the first time it was possible to prevent cancer by the identification of the gene and removal of the targeted organ.[2]

Surgery and the identification of constitutional genomic alterations have been merged for the benefits of our patients. However, several difficulties appeared quickly in the management of the patients according to their presentation with cancer or before the cancer diagnosis. Bilateral mastectomy could be discussed when the patient is tested positive for *BRCA* mutation. However, when the patient had cancer in a high-risk family, until recently, the results of the tests took very long to obtain, and this prevented the medical team from offering the best choice to the patient. This is not the case anymore, and the results can now be obtained in a few weeks for a reasonable price. On the other hand, aside from the *BRCA* mutations, new predisposition genes have been discovered, including high-penetrance *p53*, and *PALB2*, and other genes called VUS (variants of unknown significance) in which the risk is unknown or very low.[3] Therefore, delivering comprehensive information is increasingly becoming critical for clinicians.

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To go back to the title of the paper, I will describe three situations in which legal aspects were involved, and allow to open a discussion. The first one is the story of a patient who tested positive for *BRCA1* and was offered a bilateral prophylactic mastectomy with immediate reconstruction and bilateral oophorectomy. Several members of her family had died of breast cancer and she was initially very happy to undergo surgery. A couple of years later, she told me at the clinic, "Thank you, Doctor, for saving me from dying, but I am not a woman anymore." Early menopause, loss of libido, difficult sexual relationship, depression, and a future divorce had made her life very difficult. The patient had had several sessions of counseling with the geneticist, cancer surgeon, plastic surgeon, her gynecologist, and a psychologist before surgery. Despite all the medical advice and the fact that all the medical management was uneventful, she remains actually severely depressed and she will probably lose her job soon.

The second one describes a patient who was initially treated for breast cancer with breast-conserving therapy followed by chemotherapy, radiation therapy, but not hormonal therapy, because she had triple-negative breast cancer. She was a heavy smoker. Her younger sister developed breast cancer some years later. They both were tested for the mutation and were positive for *BRCA1*. She was advised to undergo prophylactic surgery, but she delayed the decision for 8 years for personal reasons. Finally, she decided to be operated on and asked for a bilateral deep inferior epigastric perforators (DIEP). After the surgery, she had a bilateral DIEP necrosis, with several months of healing with vacuum assisted closure (VAC) therapy and secondary healing. Finally, her breasts were reconstructed with several lipofillings over a 3-year period. Like the first patient, she was severely depressed and lost her job.

The third story is the story of a 35-year-old woman who was diagnosed with triple-negative

breast cancer. She received neoadjuvant chemotherapy, followed by a lumpectomy with an oncoplasty and a contralateral symmetrization during the same operative time. There was a complete pathologic response. During the neoadjuvant treatment, the medical oncologist had asked for the presence of the mutation. The result, however, was delivered to the surgeon a month after the surgery and was positive for *BRCA1*.

Any surgeon involved in breast cancer management and reconstruction has similar stories to tell. How can we protect ourselves from legal issues arising from the cases similar to the first two cases?

The legal aspects of this new field of prophylactic surgery, i.e., removing an organ to prevent the occurrence of cancer, varies according to the countries. In France, for instance, surgery constitutes "voluntary assault and battery," but, since it is performed to prevent life-threatening conditions, it is not subject to legal action. Moreover, in the United States, when a patient decides to be operated on, if he or she signs the informed consent form, normally no lawsuit is filed against the surgeon. The legal aspects vary from one country to another.

As doctors, we must remain aware that our patients are in a permanent state of stress, first of all, because they have cancer. In addition, they have a predisposing mutation, and everything is again increased when a postoperative complication occurs. Complications after the surgery are always disastrous in breast cancer patients, but it is even worse when they occur after the hope given by the idea of prevention.

This is our responsibility as surgeons to avoid and limit the side effects of our treatments by providing the most comprehensive information possible. However, when a patient in the USA requires, due to the presence of an identified mutation, a bilateral prophylactic mastectomy for a T1N0 breast cancer, we can be surprised. Actually, about 50% of American women ask for this type of surgery. The data referring to a 30%–40% complication rate seems unable to prevent the patients from this obviously unnecessary surgery. However, American scholarly journals, as well as media, sponsored by famous surgeons, keep presenting data in favor of this type of surgery, supported by the female advocacy organizations.

If we want to avoid needless surgery in treatment of our patients and limit the consequent lawsuits, bilateral surgery must be exclusively reserved to the carriers of the mutated genes (except patients with severely dystrophic breasts).

The multidisciplinary approach (involving a geneticist, cancer surgeon, plastic surgeon, gynecologist, and a psychologist or psychiatrist) is mandatory to give the patient a more objective and comprehensive preoperative information.

The constant postoperative depression is increased by bilateral surgery, and the patients must be correctly informed about it before and after surgery. Although a good cosmetic result would limit these side effects, it is not sufficient to prevent the personal problems induced by the surgery, which will be most certainly complicated over the postoperative course. In addition, it is important to protect ourselves from patients' or their families' aggressiveness when deciding this complex surgery. Documentation of all the given information, orally and written, is necessary and can help demonstrate the objectivity and honesty of the medical team facing a patient who had put a great hope in the preventive surgery to remove the fear of cancer death but actually has to deal with the usual postoperative problems. There are few chances are that artificial intelligence will be able to solve that kind of questions in the near future.

**References**

1. Evans DG, Wisely J, Clancy T, Lalloo F, Wilson M, Johnson R, *et al.* Longer term effects of the Angelina Jolie effect: increased risk-reducing mastectomy rates in BRCA carriers and other high-risk women. Breast Cancer Res. 2015;17:143.
2. Fatouros M, Baltoyiannis G, Roukos DH. The predominant role of surgery in the prevention and new trends in the surgical treatment of women with BRCA1/2 mutations. Ann Surg Oncol. 2008;15(1):21-33.
3. Walsh T, Lee MK, Casadei S, Thornton AM, Stray SM, Pennil C, *et al.* Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. Proceedings of the National Academy of Sciences. 2010;107(28):12629-33.

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# The Risk of Breast Cancer and the Role of Chemoprevention in Women With Atypical Ductal or Lobular Hyperplasia

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ABSTRACT

**Background:** Women with atypical hyperplasia are about 4 times more likely to develop breast cancer compared with the general population. Atypical hyperplasia has been recommended to be used as a criterion for the inclusion of women in chemoprevention programs. Chemoprevention offers promise as a strategy for reducing the incidence of breast cancer in high-risk population.

**Methods:** A literature search was conducted in PubMed and Scopus databases using the search terms "breast atypia," "chemoprevention," and "risk-reducing therapy" for papers published from 1966 to Aug 2017. The search was limited to English-language papers and human studies. It yielded 114 search items. Article selection for possible inclusion was performed using the title and abstract. Finally, 12 studies were identified as eligible for inclusion in the review.

**Results:** The rates of atypical ductal hyperplasia (ADH) ranged from a low of 2 per 10000 mammograms in 1995 to a high of 6 per 10000 mammograms in 2011. Lobular neoplasia was an incidental finding in 0.5%–3.5% of core biopsies. True incidence of lobular neoplasia is unknown. Women with atypical breast lesions have a 5%–11% risk of developing breast cancer within 5 years and a 17%–26% risk of developing breast cancer within 10 years. The reported risk of breast cancer with atypical hyperplasia (ADH and ALH are often grouped together) is approximately 19% within 15 years. It is believed that the initiation of chemoprevention would be appropriate; if the 10-year breast cancer risk is 4% to 8%. Breast cancer risk reduction by chemoprevention is reported to be 32% to 55% in breast atypia.

**Conclusion:** According to our findings, patients with a diagnosis of ADH, ALH, or severe ADH should be considered for chemoprevention if they are at least 35 years of age and have no contraindications to treatment. Only 4%–20% of high-risk women decide to take chemoprevention, on average.

## Introduction

One in eight women in developed countries is expected to develop breast cancer (BC) sometime in her lifetime.[1]

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It is controversial whether breast cancer arises from premalignant lesions. In 1985, Dupont and Page reviewed more than 10 000 benign breast biopsies and, based on strict pathologic criteria, divided them into three distinct categories: non-proliferative lesions, proliferative lesions without atypia, and atypical hyperplasias. They found that breast cancer risk in women with atypical hyperplasia was 4.4 times that of the general population,[2] and subsequent research lent support to that finding.[3,4] The reported risk of breast cancer for

women with atypical hyperplasia [atypical ductal hyperplasia (ADH) and lobular hyperplasia (ALH) are often grouped together] is approximately 19% within 15 years.[5] The propensity score demonstrated that 54.7% of cancers in women could have been prevented with the use of chemoprevention at a mean follow-up of 68 months.

The standard of care for ADH found on core biopsy remains excision. Following excision, patients with ADH should be referred for breast cancer risk assessment and risk reduction counseling. Routine excision following a core biopsy diagnosis of lobular neoplasia is not indicated in cases with radiographic-pathologic concordance.[6-9] Patients with a core biopsy diagnosis of lobular neoplasia (which includes ALH and classic LCIS), deemed concordant with imaging, should be counseled regarding the increased future breast cancer risk conferred by these lesions and the need for continued surveillance.

Age and estrogen exposure (early menarche, late menopause, nulliparity, use of exogenous hormones) are risk factors for breast cancer. High risk populations for breast cancer are considered to be women with ductal or lobular carcinoma *in situ*, women with a history of thoracic radiotherapy before the age of 30 years, women who have a 5-year breast cancer risk of ≥ 1.7%,[10] and women with atypical hyperplasia. According to the modified Wellings-Jensen model of breast cancer evolution, benign breast lesions such as ADH, a result of hyperplastic enlarged lobular unit formation, may evolve into ductal carcinoma *in situ* and, eventually, develop into invasive breast malignancy.[11, 12] Currently, women with atypical hyperplasia are not included in the guidelines for high-risk women, and it has been recommended that the updated versions include them.[1] Multiple models have been developed to help with prediction of breast cancer risk, including the Gail model,[13] the Tyrer-Cuzick model,[14,15] the Claus model[16], and several others.[17]

Chemoprevention uses pharmacologic or natural agents to prevent cancer development. Women aged 35 years and older who are at high risk of breast cancer (with a 5-year predicted risk for breast cancer of at least 1.66%) are recommended to take breast cancer risk-reducing agents such as tamoxifen.[18] A key driver of breast carcinogenesis is estrogen receptor α (ESR1) signaling. Consequently, agents that modulate ESR1 activity or deplete its ligand decrease breast cancer incidence.[19] Tamoxifen has previously been shown to reduce circulating IGF-1, a surrogate endpoint biomarker for phase II chemoprevention trials.[19] Tamoxifen significantly downregulates known estrogen response genes, such as *ESR1* and *SERPINA3,* but, notably, the *Ets* oncogene family transcription factor ETV4 was also significantly downregulated. Tamoxifen exerts a significant antiproliferative effect in some, but not all women, regardless of menopausal status.[5, 20] Tamoxifen has been shown to reduce the incidence of estrogen receptor-positive, but not estrogen receptor-negative, breast cancer.[1] NSABP P-1 trial recommended the use of atypical hyperplasia as a measure for the inclusion of women in chemoprevention programs.[21]

The purpose of this study was to review the literature on the risk of breast cancer based on ductal or lobular atypia to determine the effectiveness of chemoprevention in decreasing this risk. Information provided in this review will benefit health care providers who care for women at high risk for breast cancer by providing necessary information on development and delivery of breast cancer prevention. It will help readers of the chemoprevention literature to understand its strengths and weaknesses.

## Methods

PubMed and Scopus databases were searched in August 2017 using the search terms "breast atypia," "chemoprevention," and "risk-reducing therapy." The search returned 114 results. After initial screening of titles and abstracts, 62 papers were identified for potential inclusion in the review. Reference lists of these papers were also reviewed for relevant articles. We identified 28 studies that addressed breast cancer chemoprevention in breast lesions with atypia. We searched for papers whose main goal was evaluation of breast cancer risk reduction in atypical breast lesions (ADH and ALH) by chemoprevention. Our search was limited to English-language papers and human studies. A total of 12 studies met all inclusion criteria.

## Results

### *Incidence of Atypical breast lesions*

The rates of ADH diagnosis ranged from a low of 2 per 10000 mammograms in 1995 to a high of 6 per 10000 mammograms in 2011.[22] Lobular neoplasia was an incidental finding in 0.5%–3.5% of core biopsies. True incidence of lobular neoplasia was unknown.[6-9]

### *Atypia as a cancer precursor*

Women with atypical breast lesions have 5%–11% risk of developing breast cancer within 5 years and a 17%–26% risk of developing breast cancer within 10 years.[5] McEvoy and colleagues retrospectively evaluated the outcomes of the lesions in women under age 35 diagnosed with ADH, ALH, lobular carcinoma *in situ* (LCIS), and severe ADH from 1987 to 2010. They concluded that young women with atypical breast lesions were significantly more likely to develop breast cancer and recommended that they be followed closely.[23] A meta-analysis by Dyrstad et al found the summery risk estimate for developing breast cancer following

a biopsy showing atypical hyperplasia not otherwise specified was 3.93 (95% CI: 3.24–4.76).[24] A large cohort study at the Mayo Clinic also found a similar increased risk of breast cancer in women with atypical hyperplasia. They found that 30% of the women had developed breast cancer (*in situ* or invasive) 25 years after the atypical hyperplasia was confirmed by biopsy and that the number of foci of the hyperplasia was correlated with the risk of breast cancer.[4]

*Cancer prevention in atypical lesions of the breast*

Khan et al suggested that the use of antiestrogen agents such as tamoxifen might be an effective strategy for preventing breast cancer in women with benign breast disease (BBD) as patients with BBD who had estrogen receptor-positive epithelium were more likely to develop breast cancer later in life.[25]

**Table1.** Risk estimate of breast cancer after diagnosis of atypical lesion

| Authors | Atypical lesion | OR | Cancer development | Mean (months) |
|---|---|---|---|---|
| Dyrstad *et al.*[24] | Atypical hyperplasia | 3.24–4.76 (0.95 CI) | | |
| | ADH | 2.54–4.23 (0.95 CI) | | |
| | ALH | 2.81–5.47 (0.95 CI) | | |
| Zhou *et al.*[27] | ADH | 2.93 (0.95 CI) | | |
| | ALH | 5.14 (0.95 CI) | | |
| Coopey *et al.*[5] | ADH | | 17.3% | 120 |
| | ALH | | 20.7% | 120 |
| | LCIS | | 26.7% | 120 |
| | Severe ADH | | 26% | 120 |
| | Atypical lesion (1658 patients without treatment) | | 184 (11.1%) | 86 |
| McEvoy *et al.*[23] | Atypical lesion (58) | | 7 (12%) | 68 |

Tamoxifen treatment has also been shown to reduce the risk of BBD by 28% (RR = 0.72, 95% CI: 0.65–0.79) and the risk of biopsy by 29% (RR = 0.71, 95% CI: 0.66–0.77).[26]

Coopey and colleagues evaluated women's risk of breast cancer based on atypia type to determine the effectiveness of chemoprevention in decreasing the breast cancer risk.[5] They analyzed 2938 women diagnosed with atypical breast lesions and 2459 patients with atypia in 1999 and beyond. They reported that chemoprevention had significantly reduced breast cancer risk for all atypia types (P = 0.001). In terms of age at atypia diagnosis, women aged 50 years and older (age range: 50–93) had a statistically significant reduction in breast cancer risk with chemoprevention (P = 0.001, HR = 0.34). The hazard ratio for invasive cancer with chemoprevention compared with no chemoprevention was 0.48, suggesting a 52% reduction in risk with chemoprevention (P = 0.029). Similarly, the hazard ratio for ductal carcinoma *in situ* with chemoprevention compared with no chemoprevention was 0.45, suggesting a 55% risk reduction with chemoprevention (P = 0.024). They calculated that if all women diagnosed with atypia in 1999 and beyond took chemoprevention, they could have prevented 69 out of the observed 126 (54.7%) cancers that occurred during that time period. They concluded that the breast cancer risk in atypical breast lesions could be reduced by an estimated 50% at 5 years (from 8.3% to 4.1%) and 65% at 10 years (21.3% to 7.5%) using chemoprevention.[5]

Four large trials with long-term follow-up have been conducted to evaluate the efficacy of tamoxifen treatment in preventing breast cancer in high-risk women: the Royal Marsden tamoxifen prevention trial, National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP-P1), an Italian study, and the International Breast Cancer Intervention Study I (IBIS-I).

The NSABP-P1 (1992–1997) included a total of 13954 patients, of whom 13388 (95.9%) were randomly assigned to receive, in a double-masked manner, 20 mg/day of either tamoxifen or placebo for 5 years. The incidence of breast cancer, both invasive and noninvasive, was reduced significantly as a result of tamoxifen administration. The number of cancer events in the placebo group was almost twice as many as that in the tamoxifen group. The number of invasive breast cancer cases was 175 in the placebo group vs 89 in the tamoxifen group (P < 0.00001), corresponding to a 49% reduction in the overall risk. Women who were ≥ 60 years old at randomization experienced a greater tamoxifen-associated reduction in breast cancer incidence compared with those who were < 50 at randomization (55% vs 44%). Subgroup analyses revealed that chemoprevention had reduced the risk of breast cancer by 56% among women with a history of LCIS and by 86% in women with a history of atypical hyperplasia.[18]

The Royal Marsden trial randomized 2471 eligible high-risk women to take either placebo or tamoxifen (20 mg daily) for eight years. Upon

**Table 2.** Chemoprevention effect on breast cancer risk reduction in breast atypia

| Study | | No. | Person-Years | Observed events | Expected events | RR | 95% CI |
|---|---|---|---|---|---|---|---|
| Mayo-cohort[4] | Overall atypia group | 331 | 4543 | 66 | 17 | 0.388 | 3.00–4.94 |
| NSABP-P1[18] | Women assigned to tamoxifen | 6681 | 26154 | 89 | | 0.51 | 0.39–0.66 |
| | Women assigned to placebo | 6707 | 26247 | 175 | | | |
| Boston[5] | Atypia group Without chemoprevention | 1658 | | 184 (11.1%) | 21.3% | | |
| | Atypia group assigned to chemoprevention | 615 | | 36 (5.8%) | 7.5% | HR:0.48 | 55% reduction |
| RMPT[20] | Atypia group assigned to chemoprevention | 2471 | | | | 32% reduction in risk | |

follow-up evaluation after a median of 18.4 years from randomization (years after the 8 years of tamoxifen was complete), the researchers noticed a 32% reduction in ER/PR-positive primary breast cancer incidence, a demonstration of the consistent "carryover protective effect" of long-term estrogen deprivation therapies used to treat or prevent breast cancer.[20]

In a meta-analysis by Ropka and associates, patients' decision about breast cancer chemoprevention was evaluated. They reviewed 9 studies that had reported the hypothetical uptake, i.e., the rate of participants' showing interest in getting chemoprevention medication, and 5 reporting real uptake, namely, acceptance of chemoprevention medication (mean uptake rates: 24.7% and 14.8%, respectively). Using logistic regression, they found significant correlation with type of decision (hypothetical versus real, OR: 1.65; 95% CI: 1.26–2.16), educational or decision support intervention (provided vs not, OR: 0.21; 95% CI: 0.17–0.27), and cohort risk for breast cancer (high-risk vs general population, OR: 0.65; 95% CI: 0.56–0.75). Increased uptake was consistently correlated with perceived vulnerability, and reduced uptake was correlated with concern for adverse effects.[28]

## Discussion

In this study, we reviewed published studies evaluating the association of biopsy-proven atypical lesions of the breast with the risk of developing breast cancer. Proliferative BBD with atypia confers a relative risk for future breast cancer of 4.[1, 24] The mean duration from initial diagnosis of BBD to diagnosis of breast cancer was 9.4 years.[25] As the screening methods improve, the diagnosis of atypical lesions at an early stage increases, and this relative risk is shown to be even higher in more recent studies. There are reports indicating that women with atypical breast lesions have a 5%–11% risk of developing breast cancer within 5 years and a17%–26% risk of developing breast cancer within 10 years. For LCIS, prior studies have found a 4% risk of breast cancer at 5 years, a 7%–13% risk at 10 years, and a17%–28% risk at 15 years.[5]

The Mayo Clinic study also found a similar increased risk of breast cancer in women with atypical hyperplasia. They found that 30% of the women had developed breast cancer (*in situ* or invasive) 25 years after the atypical hyperplasia was confirmed by biopsy and that the number of foci of the hyperplasia was correlated with the risk of breast cancer.[4]

A recently published consensus statement on the use of preventive therapy for breast cancer recommends that the initiation of chemoprevention would be appropriate if the 10-year breast cancer risk is 4%–8%.[29] It is estimated that up to 50% of breast cancers could be prevented among women at least 35 years old at elevated risk using currently available chemoprevention strategies.[23] The American Society of Clinical Oncology recommends discussion of chemoprevention with women who have an increased 5-year risk for breast cancer and endorses consistent use of benign breast biopsy morphology for risk classification.[30] According to our findings, patients with a diagnosis of ADH, ALH, LCIS, or severe ADH meets this criterion and should be considered for chemoprevention if they are at least 35 years old and have no contraindications to treatment. Contraindications to treatment with tamoxifen include the following: history of deep venous thrombosis, thrombotic stroke, pulmonary embolus, known inherited clotting trait, transient ischemic attack, and pregnancy.[5] Furthermore, the risk to benefit ratio of chemoprevention needs to be individualized for each patient based on menopausal status, presence of a uterus, and other comorbidities.

Most women elect not to take chemoprevention agents despite the overall risk reduction established. Only 4%–20% of high-risk women decide to take chemoprevention, on average.[5] Contributing factors to this decision include fear of potential side effects, physicians' not recommending it, and patients' perception that their breast cancer risk is not that high.[28]

Atypical hyperplasia is associated with a significant increase in the risk of developing breast cancer. This necessitates the development of management strategies such as risk-reducing therapies for women with benign breast lesions with atypia. There is still much room for improvement. Physicians should counsel patients with ADH and ALH, especially those with a life expectancy of ≥10 years, about the effectiveness of chemoprevention in decreasing their breast cancer risk. These women are considered to be at increased risk for breast cancer and must receive tailored counseling on how they might decrease their risk of breast cancer. Furthermore, the risk to benefit ratio of chemoprevention needs to be individualized for each patient.

**References**


1. Sismondi P, D'Alonzo M, Pecchio S, Bounous VE, Robba E, Biglia N. Chemoprevention or mastectomy for women at high risk of developing breast cancer. Maturitas. 2015;82(3):271-3.
2. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med. 1985;312(3):146-51.
3. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, *et al.* Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353(3):229-37.
4. Degnim AC, Visscher DW, Berman HK, Frost MH, Sellers TA, Vierkant RA, *et al.* Stratification of breast cancer risk in women with atypia: a Mayo cohort study. J Clin Oncol. 2007;25(19): 2671-7.
5. Coopey SB, Mazzola E, Buckley JM, Sharko J, Belli AK, Kim EM, *et al.* The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Breast Cancer Res Treat. 2012;136(3):627-33.
6. Wheeler JE, Enterline H, Roseman JM, Tomasulo JP, McIlvaine CH, Fitts WT, *et al.* Lobular carcinoma *in situ* of the breast (Long-term followup. Cancer. 1974;34(3):554-63.
7. Rosen PP, Kosloff C, Lieberman PH, Adair F, Braun DW, Jr. Lobular carcinoma *in situ* of the breast. Detailed analysis of 99 patients with average follow-up of 24 years. Am J Surg Pathol. 1978;2(3):225-51.
8. Schnitt SJ, Morrow M. Lobular carcinoma in situ: current concepts and controversies. In Seminars in diagnostic pathology. 1999; 16 (3): 209-223.
9. Anderson BO, Calhoun KE, Rosen EL. Evolving concepts in the management of lobular neoplasia. J Natl Compr Canc Netw. 2006;4(5):511-22.
10. Bevers TB, Ward JH, Arun BK, Colditz GA, Cowan KH, Daly MB, *et al.* Breast Cancer Risk Reduction, Version 2.2015. J Natl Compr Canc Netw. 2015;13(7):880-915.
11. Lee S, Mohsin SK, Mao S, Hilsenbeck SG, Medina D, Allred DC. Hormones, receptors, and growth in hyperplastic enlarged lobular units: early potential precursors of breast cancer. Breast Cancer Res. 2006;8(1):R6.
12. Hartmann LC, Radisky DC, Frost MH, Santen RJ, Vierkant RA, Benetti LL, *et al.* Understanding the premalignant potential of atypical hyperplasia through its natural history: a longitudinal cohort study. Cancer Prevention Research. 2014;7(2):211-7.
13. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, *et al.* Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. JNCI: Journal of the National Cancer Institute. 1989;81(24):1879-86.
14. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111-30.
15. Boughey JC, Hartmann LC, Anderson SS, Degnim AC, Vierkant RA, Reynolds CA, *et al.* Evaluation of the Tyrer-Cuzick (International Breast Cancer Intervention Study) model for breast cancer risk prediction in women with atypical hyperplasia. J Clin Oncol. 2010;28(22):3591-6.
16. Claus EB, Risch N, Thompson WD. Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. Cancer. 1994;73(3):643-51.
17. Tice JA, Cummings SR, Smith-Bindman R, Ichikawa L, Barlow WE, Kerlikowske K. Using clinical factors and mammographic breast density to estimate breast cancer risk: development and validation of a new predictive model. Annals of internal medicine. 2008;148(5):337-47.
18. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, *et al.* Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371-88.
19. Euhus D, Bu D, Xie XJ, Sarode V, Ashfaq R, Hunt K, *et al.* Tamoxifen downregulates ets oncogene family members ETV4 and ETV5 in benign breast tissue: implications for durable risk reduction. Cancer Prev Res (Phila). 2011;4(11): 1852-62.
20. Jordan VC. The 4Ps of breast cancer chemoprevention: putting proven principles into practice. AACR; 2017.
21. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast--risk assessment and management options. N Engl J Med. 2015;372(1):78-89.
22. Menes TS, Kerlikowske K, Lange J, Jaffer S, Rosenberg R, Miglioretti DL. Subsequent Breast Cancer Risk Following Diagnosis of Atypical

Ductal Hyperplasia on Needle Biopsy. JAMA Oncol. 2017;3(1):36-41.
23. McEvoy MP, Coopey SB, Mazzola E, Buckley J, Belli A, Polubriaginof F, *et al.* Breast cancer risk and follow-up recommendations for young women diagnosed with atypical hyperplasia and lobular carcinoma *in situ* (LCIS). Annals of surgical oncology. 2015;22(10):3346-9.
24. Dyrstad SW, Yan Y, Fowler AM, Colditz GA. Breast cancer risk associated with benign breast disease: systematic review and meta-analysis. Breast Cancer Res Treat. 2015;149(3):569-75.
25. Khan SA, Rogers MA, Khurana KK, Meguid MM, Numann PJ. Estrogen receptor expression in benign breast epithelium and breast cancer risk. J Natl Cancer Inst. 1998;90(1):37-42.
26. Tan-Chiu E, Wang J, Costantino JP, Paik S, Butch C, Wickerham DL, *et al.* Effects of tamoxifen on benign breast disease in women at high risk for breast cancer. Journal of the National Cancer Institute. 2003;95(4):302-7.
27. Zhou WB, Xue DQ, Liu XA, Ding Q, Wang S. The influence of family history and histological stratification on breast cancer risk in women with benign breast disease: a meta-analysis. J Cancer Res Clin Oncol. 2011;137(7):1053-60.
28. Ropka ME, Keim J, Philbrick JT. Patient decisions about breast cancer chemoprevention: a systematic review and meta-analysis. Journal of Clinical Oncology. 2010;28(18):3090.
29. Cuzick J, DeCensi A, Arun B, Brown PH, Castiglione M, Dunn B, *et al.* Preventive therapy for breast cancer: a consensus statement. Lancet Oncol. 2011;12(5):496-503.
30. Visvanathan K, Hurley P, Bantug E, Brown P, Col NF, Cuzick J, *et al.* Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology. 2013;31(23):2942-62.

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# Ductal Carcinoma *In Situ* Close to the Inked Margin: A Case Presented in Multidisciplinary Session With Clinical Discussion and Decision Making

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ABSTRACT

**Background:** For many years, the acceptable margins of the resections for ductal carcinoma *in situ* (DCIS) has been 2 mm, although, in some reports and the recent updates of some guidelines, the closer margins are also declared as acceptable in some circumstances. Despite these new recommendations, the safe margin in DCIS remains a matter of controversy in many institutional and national guidelines.

**Case Presentation:** A woman with invasive breast cancer with associated DCIS presented to our clinic. She underwent breast-conserving surgery, and pathology report showed one focus of DCIS at a distance of < 1 mm from inked margin. This case was presented in the weekly breast multidisciplinary team session of the Department of Breast Surgery, Tehran University of Medical Sciences.

**Question:** The question was whether the patient should be operated again to obtain more extensive margins for DCIS or the radiation therapy would be enough as the next step in her treatment.

**Conclusion:** According to the latest published guidelines, the members of panel decided to accept the margin and informed the patient about the risk of recurrence and the need for adjuvant radiotherapy and follow-up modalities.

## Introduction

Ductal carcinoma *in situ* (DCIS) is the growth of noninvasive malignant cells in the lumen of the mammary ducts. Screening mammography helps to detect breast lesions in an early stage. Therefore, the diagnosis rate of DCIS has increased in the past two decades because of early detection.[1]

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Breast-conserving surgery (BCS) with adequate margins and radiotherapy reduces the risk of invasive recurrence in low-risk DCIS group, although radiotherapy is more likely to be planned for patients with DCIS who have large (> 15 mm), intermediate- or high-grade tumors, or present with comedo-type central necrosis.[2]

The adequate margin in BCS for DCIS is a challenging subject. In one study, the recommended minimum adequate clear margins in low- or intermediate-grade DCIS, measuring less than 2.5 cm, was ≥ 3 mm.[3] A consensus statement by the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology

(ASTRO) considered 2 mm as standard margin that should be complemented by whole-breast irradiation. These therapeutic options are associated with lower rates of ipsilateral breast tumor recurrence (IBTR) and reexcision.[4, 5] Moreover, the consensus marked "no ink on tumor" as the adequate margin for invasive tumors.[5] The acceptable free margin is 1 mm for both *in situ* and invasive cancers according to the Association of Breast Surgery (ABS).[6] However, a new meta-analysis found no significant difference between 2-mm and more than 2-mm surgical margins in resection of DCIS. The study recommended 2 mm as the minimum acceptable safe margin in patients undergoing BCS and radiotherapy.[7]

The present article aims to explore this challenge and make the best decision for a patient whose DCIS was removed with the resection margins of <1 mm.

**Case Presentation**

A 60-year-old woman with no family history of breast cancer referred to our breast clinic with the chief complaint of the right breast mass. The mass (30 × 20 mm) was palpated in the upper outer quadrant of her right breast (near zone) without palpable axillary lymph node.

In mammography, there was an ill-defined mass containing suspicious microcalcifications in the upper outer quadrant of the right breast with a BI-RADS score of 5 (Figure 1). Ultrasonography reported a 16 × 14 mm irregular, hypoechoic mass in upper outer part of the right breast, and the axillary lymph nodes were reported as reactive. The results of core needle biopsy of the breast mass was indicative of invasive ductal carcinoma with concomitant *in situ* component with comedo necrosis.

After preparation of patient for surgery, she underwent breast conserving surgery along with oncoplastic repair (Round Block technique). Specimen mammography during surgery was performed to be certain of complete excision of the microcalcifications. Frozen study for sentinel lymph node was performed reported negative for malignancy and was confirmed in permanent evaluation. Lumpectomy specimen revealed a 35 mm firm ill-defined mass with histologic diagnosis of invasive and *in situ* ductal carcinoma. Ductal carcinoma *in situ* constituted about 20% of the tumor and lymph vascular invasion was also noted. All surgical margins were defined free except for the inferior margin which involved by DCIS with distance of 2mm. Immunohistochemistry assessment was positive for estrogen receptor, but negative for progesterone receptor and HER2neu with proliferative activity (KI67) of about 20%.

The patient was scheduled for further imaging studies to assess systemic distribution of the tumor as well as reoperation to excise the involved margin (figure 2, 3, 4). In the second operation, the inferior margin re-excision was performed with acceptable distance from the tumor grossly. Compelet excision of residual microcalcifications (tow groups that were localized with wires before second surgery) certained by specimen mammography (figure 5).

In pathologic assessment of re-excised inferior margin, multiple foci of low grade DCIS with minimum distance of 1mm to inked surgical margin was reported. The cosmetic outcome after the second operation was good again, and there were no complications associated with either surgery. All the systemic radiologic assessments were negative for metastasis.

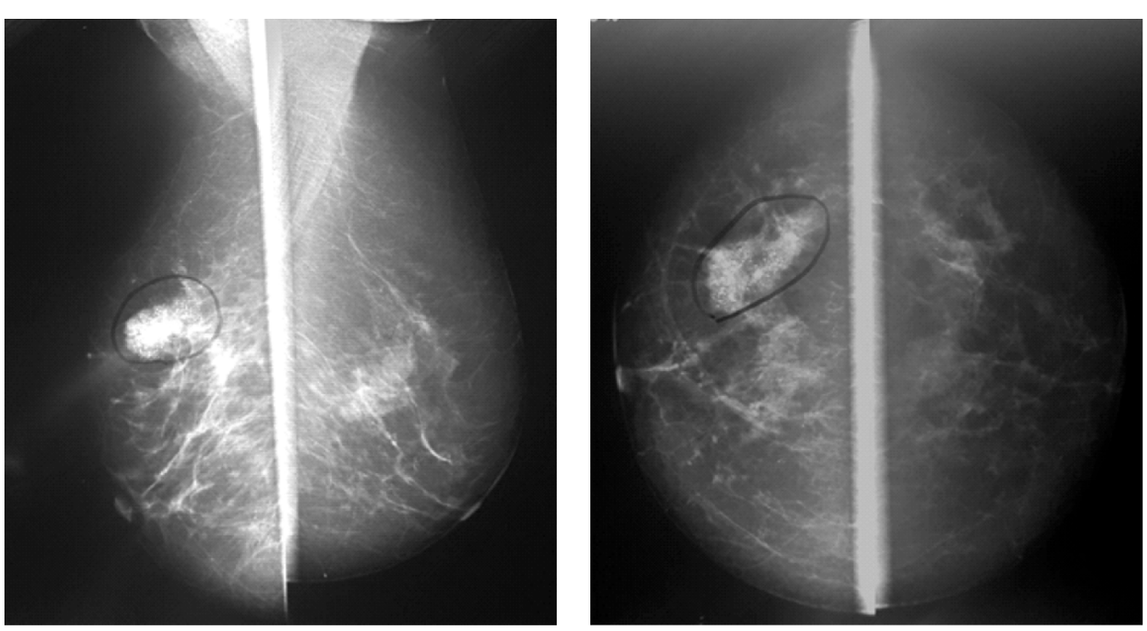

**Figure 1.** Bilateral mammography showed microcalcifications in upper outer quadrant of right breast.

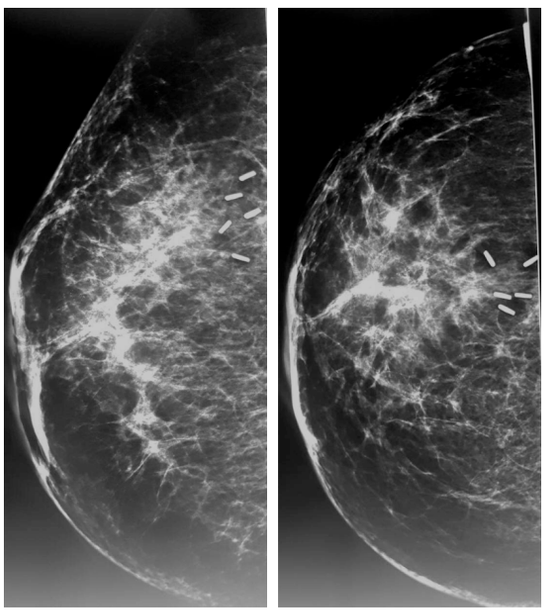

**Figure 2.**Mammography of right breast.In CC and MLO views microcalcifications and surgical clips can be seen.

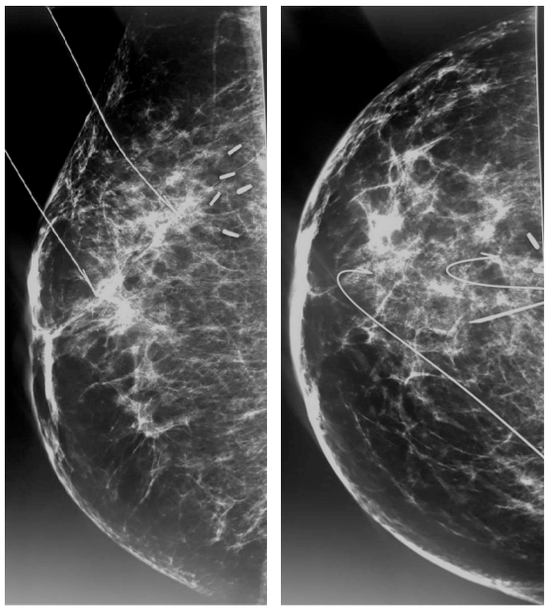

**Figure 3.** Mammography of right breast. Wire localization of microcalcifications are shown in CC and MLO views.

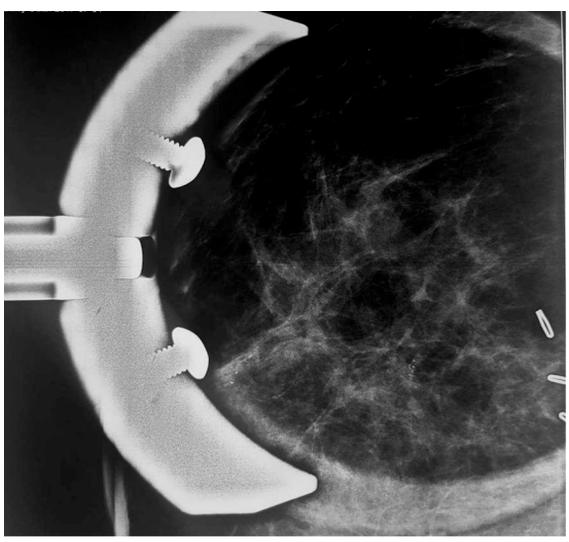

**Figure 4.** Focal compression magnification view (CC)

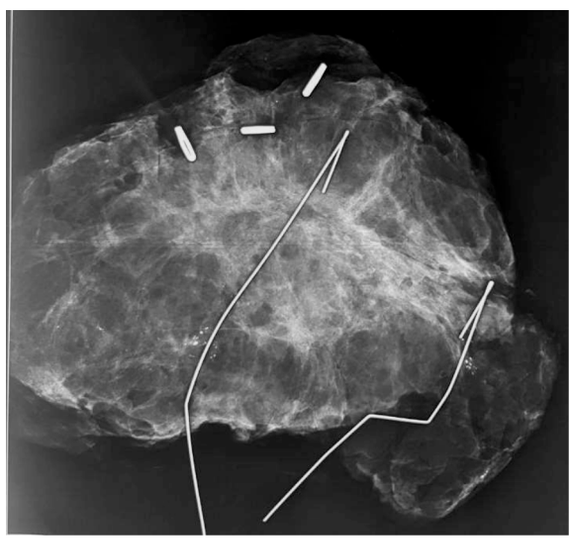

**Figure 5.** Specimen mammography which shows microcalcifications have been excised.

**Question**

The case was presented in the weekly breast multidisciplinary team session of the Department of Breast Surgery, Tehran University of Medical Sciences. The question was whether the patient should be operated again to obtain more extensive margins for DCIS or radiation therapy would be enough as the next step in the treatment of the patient.

**Discussion**

Breast-conserving therapy is the mainstay of treatment in most breast cancer patients for both invasive and *in situ* carcinomas. The therapy includes BCS, i.e., excision of the tumor with a margin of normal breast tissue, followed by whole-breast radiation therapy (WBRT). For many years, the acceptable resection margin for DCIS has been 2 mm, although, in some reports and the new updates of some guidelines, the closer margins are also marked as acceptable in some circumstances. Despite these new recommendations, the safe margin in DCIS remains a matter of controversy in many institutional and national guidelines.

*Changes in guidelines in the past years*

According to the Society of Surgical Oncology (SSO) and the American Society for Radiation Oncology (ASTRO) guidelines in 2014, the rule of "no ink on tumor" is now accepted and efficient for invasive breast tumors. Nevertheless, in the case of DCIS, the recommendations in different guidelines have changed during the past few years. While the rule of "2-mm margins" was recommended by SSO-

ASTRO-ASCO (American Society of Clinical Oncology)[8,9] and the National Institute for Health and Clinical Excellence (NICE),[9] the Association of Breast Surgery (ABS) of the United Kingdom emphasized in 2015 that just 1-mm margin would be sufficient in resection of DCIS.[10] Recently, the National Comprehensive Cancer Network (NCCN) reiterated that "no ink on tumor" rule would be enough in management of DCIS as well as invasive ductal carcinoma. This recommendation was based on the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials in 2017[9,11] and the American Society of Breast Surgeons (ASBS) recommendations.[9] This discrepancy has led to variations in management practice in breast surgery centers. For example, a study of the variation in margin policy for BCT in 79 sites in the UK and Ireland in 2016, found that 53.2% of units accepted 1-mm and 38% accepted 2-mm margins for DCIS.[6]

*Which margin width is supported by evidence?*

A meta-analysis of 20 studies including a total number of 7883 DCIS patients with known margin status treated with BCT assessed the impact of margin width on ipsilateral breast tumor recurrence (IBTR). The status of ink on tumor (i.e. positive margin) was associated with higher rates of IBTR, whereas negative margins—especially those of at least 2 mm wide—had lower rates of IBTR. The effectiveness of margins when they were more than 2 mm is not supported by evidence.[4,7,12,13] It should be taken into consideration that "negative margins" does not mean that there are not any residual DCIS in the breast.[4,14] Even in unicentric DCIS, tumor can be multifocal with the skip involvement of a segment of the breast.[4] This may happen in about two-third of well-differentiated DCIS cases. It is worth mentioning that the skipped lesions are mostly in 0 to 5 mm distance from the main lesion.[14]

Evidence shows significant decrease in IBTR for 2-mm margin in comparison with no ink on tumor (> 0 or 1 mm).[4] The other important factors in IBTR risk are biology of the tumor, younger age, symptomatic presentation, presence of necrosis,[14] side of anterior (skin) or posterior (pectoral fascia) margins, remnant microcalcification on mammography after excision, volume of DCIS tumor near the margin, cosmetic status after reexcision, life expectancy of the patient,[4] and the adjuvant chemotherapy for invasive component or endocrine therapy.[14]

A study by Edinburgh Breast Unit on 466 patients with pure DCIS treated with BCS between 2000 and 2010, showed no increase in the rate of IBTR with margins of 1–2 mm in comparison with margins > 2 mm. The researchers concluded that margin width of 1 mm is sufficient in BCS of DCIS.[12]

In a study by Memorial Sloan Kettering Cancer Center on 2996 cases of DCIS who underwent BCS from 1978–2010, in cases not receiving WBRT, wider margins were significantly associated with a lower rate of IBTR and may not be necessary in cases treated with WBRT.[15]

In a study by MD Anderson Cancer team on 1216 patients with DCIS undergoing BCS, at 10 years of follow-up, the researchers concluded that there was no significant difference in IBTR for patients with < 2-mm margins (no DCIS at the inked margin) who received adjuvant WBRT compared with patients with ≥ 2-mm margins, although local recurrence was significant in cases with < 2-mm margins not receiving WBRT.[9]

*What is appropriate in the guidelines?*

Pure DCIS: Most guidelines emphasized on 2-mm margin for pure DCIS but a margin of < 2 mm by itself is not an indication for mastectomy.[14]

DCIS with microinvasion: (size of invasive focus: ≤ 1 mm) rates of IBTR in microinvasive carcinomas are more similar to DCIS[14] and they should be managed as DCIS for optimal margin.[11]

Invasive cancer with associated DCIS: When the *in situ* component is more than 25% of the tumor bulk [called extensive intraductal component (EIC)], or the patient has lesser scattered foci of *in situ* carcinoma, management is more similar to invasive cancer than pure DCIS, even when the closer margins contain DCIS.[4] It is worth emphasizing that IBTR rates in patients with EIC-positive tumors with negative margins at BCS are equal to cases without EIC.[14] Based on NSABP trials, which defined negative margin as "no ink on tumor," clinical experience of the physician is required for the decision of reexcision in patients with margin width of < 2 mm.[13]

**Multidisciplinary team (MDT) recommendation**

For this patient with foci of DCIS at a distance of < 1 mm from inked margin, members of breast MDT in Breast Division, Imam Khomeini Hospital, Tehran University of Medical Sciences recommended that neither reexcision of the margins for the inferior side of resection nor mastectomy was needed. Factors that promoted MDT to accept width margin were the presence of an invasive component in 80% of the specimen, the age of the patient, patient's request for breast conservation, negative EIC, plan of adjuvant breast radiotherapy, plan of adjuvant chemotherapy and endocrine therapy. Thus, MDT members decided to accept the margin and informed the patient about the risk of recurrence and the need for adjuvant radiotherapy and follow-up imaging. The patient was referred to adjuvant chemotherapy and then adjuvant radiotherapy followed by endocrine therapy and follow-up imaging was planned for her.

**References**

1. Burstein HJ, Polyak K, Wong JS, Lester SC,

Kaelin CM. Ductal carcinoma *in situ* of the breast. N Engl J Med. 2004;350(14):1430-41.
2. Dodwell D, Clements K, Lawrence G, Kearins O, Thomson CS, Dewar J, *et al.* Radiotherapy following breast-conserving surgery for screen-detected ductal carcinoma in situ: indications and utilisation in the UK. Interim findings from the Sloane Project. Br J Cancer. 2007;97(6):725-9.
3. McCormick B, Winter K, Hudis C, Kuerer HM, Rakovitch E, Smith BL, *et al.* RTOG 9804: a prospective randomized trial for good-risk ductal carcinoma *in situ* comparing radiotherapy with observation. J Clin Oncol. 2015;33(7):709-15.
4. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, *et al.* Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology Consensus Guideline on Margins for Breast-Conserving Surgery With Whole-Breast Irradiation in Ductal Carcinoma in Situ. Pract Radiat Oncol. 2016;6(5):287-95.
5. Schulman AM, Mirrielees JA, Leverson G, Landercasper J, Greenberg C, Wilke LG. Reexcision Surgery for Breast Cancer: An Analysis of the American Society of Breast Surgeons (ASBrS) Mastery(SM) Database Following the SSO-ASTRO "No Ink on Tumor" Guidelines. Ann Surg Oncol. 2017;24(1):52-8.
6. Tang SS, Kaptanis S, Haddow JB, Mondani G, Elsberger B, Tasoulis MK, *et al.* Current margin practice and effect on re-excision rates following the publication of the SSO-ASTRO consensus and ABS consensus guidelines: a national prospective study of 2858 women undergoing breast-conserving therapy in the UK and Ireland. Eur J Cancer. 2017;84:315-24.
7. Marinovich ML, Azizi L, Macaskill P, Irwig L, Morrow M, Solin LJ, *et al.* The Association of Surgical Margins and Local Recurrence in Women with Ductal Carcinoma *In Situ* Treated with Breast-Conserving Therapy: A Meta-Analysis. Ann Surg Oncol. 2016;23(12):3811-21.
8. Heelan Gladden AA, Sams S, Gleisner A, Finlayson C, Kounalakis N, Hosokawa P, *et al.* Re-excision rates after breast conserving surgery following the 2014 SSO-ASTRO guidelines. Am J Surg. 2017;214(6):1104-9.
9. Kuerer HM, Smith BD, Chavez-MacGregor M, Albarracin C, Barcenas CH, Santiago L, *et al.* DCIS Margins and Breast Conservation: MD Anderson Cancer Center Multidisciplinary Practice Guidelines and Outcomes. J Cancer. 2017;8(14):2653-62.
10. Association of Breast Surgery (ABS) Consensus Margin Width in Breast Conservation Surgery 2015. 2017 [Available from: www.associationofbreastsurgery.org.uk
11. NCCN clinical practice guidelines in oncology (NCCN guidelines): breast cancer. 2017 [Available from: http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.]
12. Ekatah GE, Turnbull AK, Arthur LM, Thomas J, Dodds C, Dixon JM. Margin width and local recurrence after breast conserving surgery for ductal carcinoma in situ. Eur J Surg Oncol. 2017;43(11):2029-35.
13. Morrow M. De-escalating and escalating surgery in the management of early breast cancer. Breast. 2017;34 Suppl 1:S1-S4.
14. Pilewskie M, Morrow M. Margins in breast cancer: How much is enough? Cancer. 2018.
15. Van Zee KJ, Subhedar P, Olcese C, Patil S, Morrow M. Relationship between margin width and recurrence of ductal carcinoma in situ: analysis of 2996 women treated with breast-conserving surgery for 30 years. Annals of surgery. 2015;262(4):623.

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# A Study on Factors Predisposing to Breast Ptosis

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ABSTRACT

**Background:** Despite being a frequent plastic surgery complaint, the causes and predisposing factors for breast ptosis have not been studied profoundly. Studying ptosis causative factors will improve prevention, patient select and education, surgical outcome, and patient education. The present study aims to demonstrate the potential predisposing factors for breast ptosis.

**Methods:** In a 6-month study was conducted at the research department of Kaviani Breast Diseases Institute, Tehran, Iran, all female patients referring to the breast clinic were assessed. Patients with a background of severe comorbidities, history of breast surgery, and breast cancer were excluded. Data on demographic characteristics, current and past medical history, physical examination, and ptosis presence grade were collected.

**Results:** A total number of 141 patients, with the mean age of 35.8 years, were included. About 72% of the patients had varying grades of breast ptosis. Patients with ptosis tended to be of older age, weight, BMI, and brassiere size, were more likely to be menopausal, and had begun wearing brassiere at younger ages. The ordinal model revealed an association between ptosis and age, age at wearing brassiere, current breast size, and smaller cup size in patients.

**Conclusion:** We suggest age and breast size as the predisposing factors for breast ptosis. In our study, there was no relation between breast ptosis and history of lactation or the number of pregnancies. The effects of hormonal and menstrual status, as well as drinking and smoking habits, need to be investigated further.

## Introduction

Breast ptosis is a common complaint among plastic surgery patients. Mastopexy is a common cosmetic surgery for improving the shape of the ptotic breast, which is preformed either alone as breast lift surgery, or in combination with reduction mammoplasty or breast augmentation.[1] Despite the high prevalence of breast ptosis, only a small number of studies have demonstrated its causes and risk factors in a research-based method, and most of the suggested risk factors are based on experience.[2] Ptosis is not only a cosmetic issue of the breast, but also an important factor in therapeutic breast surgeries for breast cancer. Ptosis can affect technique selection in both oncoplastic and reconstructive breast surgeries for breast cancer patients.[3,4]

Breast ptosis can be a consequence of parenchymal maldistribution as well as connective tissue and skin dysfunction. Aging, weight change, pregnancy, menopause, and lactation are among the events in a woman's life that can affect the breasts through alterations in hormonal and structural components of

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the female body and physiology.[5,6] To the best of our knowledge, very few studies have assessed the etiologic factors of breast ptosis or have addressed the present controversies regarding the probable causes, and most were focused on lactation from a maternity rather than plastic surgery aspect. The importance and need for such studies will be prominent when one considers that knowing the risk factors not only can improve the efficacy of prevention, patient selection for surgical corrections, and the clinical outcome of such interventions, but also helps to educate patients and clarify some cultural notions. For instance, the low rates of breast-feeding in both developed and developing countries have not changed after several years of education for fear of adverse effects on breast shape and cosmetics as one of the main mentioned causes.[7,8] Surprisingly, this wrong notion does not seem to be restricted to specific cultural or geographical distribution.[9-12] One can assume that understanding the actual predisposing factors will address the aforementioned advantages in plastic surgery. Considering these facts, we designed the present study to demonstrate and determine the probable risk factors for breast ptosis.

## Methods

*Study Design and Participants*

Female patients referring to Kaviani Breast Diseases Institute in Tehran, Iran, between January and June 2013 were assessed for the presence of ptosis and its grade. We used the classification introduced by Regnault in 1976 for grading of ptosis. This classification is based on the position of the nipple: Grade I ptosis is described as the nipple being located at or up to 1 cm below the inframammary fold (IMF); in grade II, the nipple is located at a level 1 to 3 cm below IMF; and grade III ptosis is defined as the nipple being located more than 3 cm below IMF or at the inferior pole of the breast.[13]

Patients with a history of breast surgery, breast cancer, or severe underlying medical conditions causing weight change in a short period (at least a month), including Cushing's syndrome, Addison's disease, severe thyroid diseases, and metabolic syndrome, and all patients requesting cosmetic breast surgeries were excluded from the study. All the questionnaires were anonymous, and patients' data were kept confidential during the study. The study protocol was approved by the Tehran University of Medical Sciences Ethics Committee, and the informed consent was taken from patients after explaining the study and emphasizing on the confidentiality of the collected data.

*Definition of Variables*

The data regarding patients' demographics and history, such as age, age at menarche, menopause age, age at beginning to wear brassiere, weight, BMI, education level, number of pregnancies, total number of lactating months, brassieres size before pregnancy and its changes, weight gain after each pregnancy were gathered through a structured interview (all the data were self-reported except for weight and height, which were measured by the same devices). In regard to smoking, patients were categorized into two groups of smokers/ex-smokers and nonsmokers. The same stratification was applied to alcohol consumption. Current brassiere and cup sizes were determined by a surgeon, using the underbust girth for the brassiere size according to the EN 13402 dress-size standard, and the alphabetic method for cup size, both of which are the current measuring systems in Iran as well.[14-17]

*Statistical Analysis*

SPSS v. 19 (IBM Inc.) was used for data analysis. Data are presented as number (percent) or mean ± standard deviation. The means were compared using the student t test. Analysis of variance (ANOVA) was employed to compare the different grades of ptosis with interested risk factors. Factors showing significant association with ptosis in univariate analyses were put in a multivariate analysis to identify the independent associations between the potential risk factors of breast ptosis. A P value of 0.05 was considered the cut point for significant statistical difference.

## Results

A total of 141 patients were included in the study. The patients' mean age was 35.92 ± 9.42 years (ranging from 17 to 62 years). The mean age of menarche was 13.45 ± 1.58 years. The mean duration of lactation was 32.10 ± 18.70 months. Table 1 presents the detailed demographic specifications of the study population. A total number of 102 cases (72.3%) were diagnosed with varying grades of breast ptosis, while 37 (26.2%) did not have ptosis and 2 (1.5%) had pseudo-ptosis. The patients with pseudo-ptosis in the examination were assigned to the no-ptosis group. Moreover, we classified breast ptosis into two groups: minor ptosis (grade 1) and moderate to major ptosis (grades 2 and 3).

Patients with higher grades of breast ptosis tended to be of older age, higher weight, and BMI and were more likely to be menopausal. No significant differences were observed between the groups in the other variables (Table 2).

Variables showing significant difference among the three groups in univariate analyses were put in an ordinal model to investigate the independent role of each one. As shown in Table 3, older patients were more commonly diagnosed with breast ptosis (95% CI: 0.020 to 0.109, P = 0.005). The younger age at wearing brassiere was associated with higher grades of breast ptosis (95% CI: -0.533 to -0.084, P = 0.007).

Current brassiere and cup sizes were also

**Table1.** Demographic characteristics of the study population

| Variables | Categories | Mean ± SD or N (%) |
|---|---|---|
| Age | | 35.83 ± 9.42 |
| Weight (kg) | | 65.85 ± 11.07 |
| Height (cm) | | 162.12 ± 5.85 |
| BMI (kg/m2) | | 24.48 ± 4.54 |
| Age at menarche | | 13.46 ± 1.57 |
| Menopause age (N = 12) | | 45.91 ± 5.59 |
| Number of pregnancies (N = 95) | | 2.27 ± 1.36 |
| Total months of lactation (N = 86) | | 31.86 ± 18.54 |
| Weight gain after each pregnancy (N = 91) | | 7.86 ± 4.53 |
| Age at beginning to wear brassiere | | 14.28 ± 1.88 |
| Current or past smoker | No | 136 (96.5 %) |
| | Yes | 5 (3.5 %) |
| Current or past alcohol consumption | No | 133 (94.3%) |
| | Yes | 8 (5.7%) |

**Table 2.** Comparison of the variables between ptotic and non-ptotic patients

| Variables | | No ptosis | Minor Ptosis | Moderate-Major Ptosis | P value |
|---|---|---|---|---|---|
| Age | | 30.05 ± 7.64 | 38.11 ± 9.77 | 38.24 ± 8.29 | **< 0.001** |
| Age at menarche | | 13.74 ± 1.73 | 13.48 ± 1.52 | 13.18 ± 1.52 | 0.227 |
| Age at beginning to wear brassiere | | 14.97 ± 2.46 | 14.18 ± 1.82 | 13.89 ± 1.17 | **0.025** |
| Age at first pregnancy | | 24.80 ± 4.56 | 23.65 ± 4.73 | 22.89 ± 5.28 | 0.529 |
| Weight | | 58.71 ± 7.76 | 65.01 ± 9.63 | 72.26 ± 11.11 | **< 0.001** |
| BMI | | 22.13 ± 3.04 | 24.54 ± 4.25 | 28.88 ± 4.32 | **< 0.001** |
| Number of pregnancies | | 2.00 ± 1.26 | 2.20 ± 1.39 | 2.42 ± 1.36 | 0.610 |
| Lactation duration (month) | | 36.11 ± 13.10 | 28.58 ± 15.65 | 35.09 ± 22.45 | 0.258 |
| Number of breast-feedings | 0 | 1 (10%) | 1 (2.4%) | 1 (2.8%) | 0.437 |
| | 1 | 2 (20%) | 17 (40.5%) | 14 (38.9%) | |
| | 2 | 6 (60%) | 20 (47.6%) | 13 (36.1%) | |
| | ≥ 3 | 1 (10%) | 4 (9.5%) | 8 (22.2%) | |
| Weight gain after each pregnancy (kg) | | 7.40 ± 3.16 | 7.24 ± 4.58 | 8.81 ± 4.78 | 0.290 |
| Current or ex-smoker | No | 37 (94.9%) | 54 (96.4%) | 45 (97.8%) | 0.764 |
| | Yes | 2 (5.1%) | 2 (3.6%) | 1 (2.2%) | |
| Current or past alcohol consumption | No | 35 (89.7%) | 54 (96.4%) | 44 (95.7%) | 0.342 |
| | Yes | 4 (10.3%) | 2 (3.6%) | 2 (3.9%) | |
| Menstrual status | Menstruation | 39 (100%) | 48 (85.7%) | 42 (91.3%) | 0.049 |
| | Menopause | 0 | 8 (14.3%) | 4 (8.7%) | |
| Current brassiere size (cm) | | 72.31 ± 5.71 | 78.21 ± 4.99 | 81.52 ± 13.77 | **< 0.001** |
| Current cup size | A | 18 (46.2%) | 15 (26.8%) | 3 (6.7%) | **< 0.001** |
| | B | 12 (30.8%) | 29 (51.8%) | 13 (28.9%) | |
| | C | 9 (23.1%) | 10 (17.9%) | 23 (51.1%) | |
| | D | 0 | 2 (3.6%) | 6 (13.3%) | |

**Table 3.** Multivariate analysis of factors with association with breast ptosis

| | P value | 95% CI | |
|---|---|---|---|
| | | Lower | Upper |
| Age | **0.005** | 0.020 | 0.109 |
| Age at beginning to wear brassiere | **0.006** | -0.533 | -0.084 |
| Current brassier size | **< 0.001** | 0.117 | 0.268 |
| Current cup size | **< 0.001** | 0.489 | 1.461 |

**Nagelkerke = 58.8%*

independently associated with ptosis (95% CI: 0.117 to 0.268, P < 0.001 and 95% CI: 0.489 to 1.461, P < 0.001).

The relationships between ptosis grade and different factors were investigated. The mean weight . of patients was observed to be different for different grades of ptosis based on the ANOVA test (P < 0.001)

## Discussion

Despite being one of the most common cosmetic problems for women,[1] only a few studies have evaluated the impact of possible risk factors on breast ptosis, and most of the studies about breast ptosis have referred to surgical techniques for solving the problem. As it can be assumed, breast

ptosis etiology has a multi-factorial nature and can be affected by dependent and independent factors such as race, culture, body composition, and age as well as hormonal changes. Regression of the glandular tissue due to hormonal changes after menopause or pregnancy, weight loss, skin pathologies, and previous surgery have been mentioned as potential causes of breast ptosis.[2, 5] All of the 12 menopausal patients in the present study had some degrees of ptosis, providing evidence for the aforementioned effect of menopause. None of the patients in this study had a history of breast surgery or dermatochalasis.

We observed an association between the cup size and ptosis grade. Patients with no ptosis were mostly size A, while patients with minor ptosis were size B, and more than half of the patients with moderate to major ptosis had a C cup size. In this study, we inquired the weight gain after the pregnancy to evaluate its effect. The mean weight gain after the pregnancy did not show statistically significant difference between the ptosis and no-ptosis groups. Unfortunately, we did not inquire the history of weight loss and were not able to evaluate its effect on breast ptosis.

The weight of the breast itself and the laxity degree of the breast-supporting ligaments are other proposed causative factors for breast ptosis. In the present study, we considered the breast cup size as a measure of the breast volume and mass. Although the cup size is not a perfect indicator of the breast weight due to variation in breast density and the several factors affecting it, the current cup size of the patients at the study time was higher in the ptosis group compared with the no-ptosis group. Meanwhile, as the mean weight of the ptotic patients was greater, the breast cup size and breast weight might have increased as a consequence of weight and body fat distribution. However, both factors lost their significant association with ptosis in multivariate analysis. Accordingly, the causative effect of the breast volume and weight need to be assessed in a more detailed study to check whether breast volume is an independent breast ptosis risk factor, or it is merely a manifestation of higher weight and BMI as main risk factors.

Laxity of the Cooper's ligaments as another potential cause for ptosis, which is suggested mostly based on the individual observations, needs to be proved through scientific, experimental methods. As suggested by previous studies[18,19], smoking is a cause for abnormal elastic characteristics of the skin, was studied in our patients along with drinking history. There were some limitations in our study to assess the effect of cigarette smoking or alcohol consumption on the development of breast ptosis. Considering a negative attitude towards female smokers in the society, we can assume that this fact might have influenced the overall prevalence of the smoking cases in our study through patients' disclosure of their smoking status to the study team. Religious considerations can be applied to alcohol consumption besides the overall lower consumption of alcohol in the Iranian population, especially in females (relative frequency in total population = 2.31%, females = 0.56%).[20]

None of the patients in the non-ptosis group were in the menopause phase of the reproductive physiology, while 11% (12 patients) of the ptotitc patients were in this phase. This may be indicative of a protective effect of the female reproductive hormones, or it can just be a manifestation of the age factor. Our study not only confirms the previous finding that lactation has no effect on the development of breast ptosis, but adds to the literature by providing evidence for the lack of association between the number of pregnancies and breast ptosis.

Considering the available data, we suggest age and breast size as risk factors for breast ptosis. In addition, the age at beginning to wear brassiere was associated with having ptosis in our study, although it was not clear whether the patients began to wear brassiere at younger ages because of earlier onset of puberty or other considerations such as cultural issues. Obviously, further studies are needed to clarify the highly probable effects of female hormones as well as menstrual status on development of breast ptosis. The effects of smoking and alcohol consumption also need to be investigated in studies with greater sample sizes. In our study, there was no relationship between breast ptosis and breast-feeding, number of pregnancies, duration of lactation, or weight gain after pregnancy, a finding that can relieve the future mothers of the stress of developing breast ptosis following childbirth or lactation.Moreover, we suggest studies to demonstrate patients before pregnancy, during pregnancy, during lactation, and after weaning and compare with a control group. Also, another limitation of our study was generalizability of results as the included subjects were those referring to a private clinic..

**Conflict of Interest**

All the authors declare that they have nothing to disclose.

**References**

1. Ibrahim AM, Sinno HH, Izadpanah A, Vorstenbosch J, Dionisopoulos T, Markarian MK, et al. Mastopexy for breast ptosis: Utility outcomes of population preferences. Plast Surg (Oakv). 2015;23(2):103-7.
2. Rinker B, Veneracion M, Walsh CP. Breast ptosis: causes and cure. Ann Plast Surg. 2010;64(5):579-84.
3. Kaviani A, Safavi A, Mohammadzadeh N, Jamei K, Ansari-Damavandi M, Salmon RJ.

Oncoplastic surgery in breast conservation: a prospective evaluation of the patients, techniques, and oncologic outcomes. Am J Surg. 2014;208(5):727-34.
4. Najafi M, Salmon R, Kaviani Oncological Outcome of Oncoplastic Breast Surgery: A Review of the Literature. Archives of Breast Cancer. 2015;2(1):5-14.
5. Higdon KK, Grotting JC. Mastopexy. Plastic Surgery: Breast. 5. 3rd ed: Elsevier Health Sciences; 2013. p. 119-51.
6. Nahai F, Boehm KA. CHAPTER 30 - Superior Pedicle Extension Mastopexy A2 - Hall-Findlay, Elizabeth J. In: Evans GRD, editor. Aesthetic and Reconstructive Surgery of the Breast. Edinburgh: W.B. Saunders; 2010. p. 475-82.
7. GartnerLM, Morton J, Lawrence RA, Naylor AJ, O'Hare D, Schanler RJ, *et al.* Breastfeeding and the use of human milk. Pediatrics. 2005;115(2):496-506.
8. RyanAS, Zhou W, Arensberg MB. The effect of employment status on breastfeeding in the United States. Womens Health Issues. 2006;16(5):243-51.
9. Weichert C. Breast-feeding: First thoughts. Pediatrics. 1975;56(6):987-90.
10. Foster SF, Slade P, Wilson K. Body image, maternal fetal attachment, and breast feeding. J Psychosom Res. 1996;41(2):181-4.
11. McLennan JD. Early termination of breast-feeding in periurban Santo Domingo, Dominican Republic: mothers' community perceptions and personal practices. Rev Panam Salud Publica. 2001;9(6):362-7.
12. Pisacane A, Continisio P, Italian Work Group on B. Breastfeeding and perceived changes in the appearance of the breasts: a retrospective study. Acta Paediatr. 2004;93(10):1346-8.
13. Regnault P. Breast ptosis. Definition and treatment. Clin Plast Surg. 1976;3(2):193-203.
14. BSI. Size Designation of Clothes – Part 1: Terms, Definitions and Body Measurement Procedure. . Milton Keynes: British Standards Institute; 2001. p. BS EN 13402-1
15. BSI. Size Designation of Clothes - Part 2: Primary and secondary dimensions. London: BSI Standards; 2002. p. BS EN 13402-2
16. BSI. Size Designation of Clothes - Part 3: Measurements and Intervals.: BSI Standards; 2004. p. BS EN 13402-3
17. Magee J, McClelland B, Winder J. Current issues with standards in the measurement and documentation of human skeletal anatomy. J Anat. 2012;221(3):240-51.
18. Daniell HW. Smoker's wrinkles. A study in the epidemiology of "crow's feet". Ann Intern Med. 1971;75(6):873-80.
19. Boyd AS, Stasko T, King LE, Jr., Cameron GS, Pearse AD, Gaskell SA. Cigarette smoking-associated elastotic changes in the skin. J Am Acad Dermatol. 1999;41(1):23-6.
20. Nikfarjam A, Hajimaghsoudi S, Rastegari A, Haghdoost AA, Nasehi AA, Memaryan N, *et al.* The Frequency of Alcohol Use in Iranian Urban Population: The Results of a National NetworkScale Up Survey. Int J Health Policy Manag. 2016;6(2):97-102.

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# Epstein-Barr Virus is Associated With Aggressive Subtypes of Invasive Ductal Carcinoma of Breast (Her2+/ER- and Triple Negative) and With Nuclear Expression of NFκB p50

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ABSTRACT

**Background:** A growing body of evidence suggests a possible role for Epstein-Barr virus (EBV) in the pathogenesis of a subset of breast cancers, with many of these studies highlighting an increased association between EBV and aggressive forms of breast carcinoma. This study aimed to further investigate this issue by assessing the possible association between EBV and the Her2+/ER- and Triple negative sub types of invasive ductal carcinoma (IDC).

**Methods:** An immunohistochemical marker for EBV (Epstein-Barr virus nuclear antigen 1 (EBNA1) clone E1-2.5) was applied to tissue micro array sections. The tissue micro array's contained 58 cases of Her2+/ER- IDC, 57 cases of triple negative IDC and 67 cases of luminal like IDC. Each case was scored as positive or negative for nuclear expression of EBNA1 in tumour cells using standard light microscopy. Clinical and pathological details where noted for each case, as was the nuclear expression of NFκB p50.

**Results:** EBV infection was apparent in 43.2% of all cases. By subtype EBV was evident in 31 (57.4%) Her2+/ER- cases, 28 (49.1%) triple negative cases, and 14 (24.1%) luminal like cases; with a significant association being noted between the Her2+/ER- and triple negative cases and EBV infection (P 0.001). This association was primarily linked with ER negativity, Her2 status showed no significant association with EBV infection. There were no significant associations with other clinical and pathological characteristics. Of the 53 cases demonstrating NFκB p50 nuclear staining, 37 (69.8%) were also infected by EBV (P <0.001).

**Conclusion:** This study provides evidence that EBV is associated with aggressive subtypes of IDC (Her2+/ER- and triple negative) as well as providing evidence for a link between EBV and NFκB p50 nuclear expression, although the nature of these associations remains unclear.

## Introduction

Epstein-Barr virus is known to be associated with a number of epithelial tumours, including nasopharyngeal carcinoma[1] and a subset of gastric carcinomas.[2] Over the past 20 years a growing body of evidence has also suggested a role for EBV in a subset of sporadic breast cancers.[3-13] The first of these studies identifying EBV with breast cancer in 1995 failed to identify it with any particular histological type.[12,13] Following on from this Fina *et al*.[9] conducted a large multi centric study in 2001, this appeared to confirm both the association of EBV with breast cancer and the lack of any correlation with clinical or pathological characteristics (age, histological grade, tumour size, nodal status). However, more recent investigations have highlighted associations between

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EBV and high histological grade, nodal involvement, and young age of onset,[3,5-7] while a meta-analysis published in 2012 appeared to demonstrate an association between EBV infection and elevated breast cancer risk.[14] There is also some evidence to suggest a link between EBV and ER status. Using immunohistochemistry (IHC) to detect Epstein-Barr virus nuclear antigen 1 (EBNA1) Murray et al[5] found a strong association between the 2B4-1 EBNA1 clone and ER negative tumours, although this was in the absence of PCR detectable EBV genetic material. Following on from this, two further studies using polymerase chain reaction (PCR) based methods[3, 4] demonstrated a clear relationship between EBV and ER negative breast tumours; although some investigators[6, 7] have failed to demonstrate significant associations between EBV and ER negative tumours this was largely due to small sample sizes, overall the data appears to be in favour of an association. However, as yet no clear molecular mechanism has been demonstrated to explain this. The relationship between EBV and Her2 status is unclear at present; there is evidence of Her2 overexpression in *in-vitro* models using EBV infected breast cancer cell lines.[15] However, of the three studies to investigate this issue in human breast tissue, the first failed to demonstrate any association between EBV and Her2,[4] while the second demonstrated a weak association between EBV and Her2 gene amplification.[3] In the third study by Glenn *et al.* in 2012[6] all the Her2 expressing tumours were also found to be infected by EBV, although, due to the small sample size this was not considered significant.

From the evidence set out above it appears that breast tumours infected by EBV have a more aggressive nature, although this is not yet conclusive, and the manner of the relationship remains uncertain. Following on from the studies outlined above, the primary aim of this investigation was to further examine the relationships between EBV infection and the aggressive triple negative and Her2+/ER- subtypes of invasive ductal carcinoma (defined by receptor status). It was hypothesised that both of these subtypes would demonstrate significantly higher levels of EBV infection compared to the luminal like group (ER+/Her2- and ER+/Her2+/PR+). However, considering the evidence outlined above it was expected that ER status would have a greater impact than Her2 status. In order to test this IHC was used to examine expression levels of EBNA1 in 182 cases of breast cancer in tissue micro arrays (TMA's), the use of IHC would allow EBV infection to be localised to tumour cells. The clinical and pathological characteristics of the tumours were also assessed to determine if there was a relationship with EBV infection; these included age, histological grade, tumour size, nodal involvement and Ki67 status. In addition to this NFκB nuclear expression was also assessed, as this transcription factor is known to be associated with EBV in gastric and nasopharyngeal carcinoma.[16-18]

## Method

*Tissue specimens*

The study used TMA's (BR1503b, BR1504, BR1505, US BIOMAX) consisting of 410 cores of invasive ductal carcinoma in total, there were 2 cores from each case (total of 205 cases of IDC). The cases were grouped according to subtype of IDC (as defined by ER/PR/Her2 receptor expression). Cases that did not match the receptor expression patterns were discounted from the study.

ER/PR and Her2 had been scored previously (information provided by US BIOMAX), ER/PR were considered positive if more than 1% of tumour cells were positive with an intensity of 1 (week) or stronger (>2 using the Allred scoring method). A Her2 score of 3+ was considered positive, a score of 0/1+ was considered negative. For the purposes of this study a score of 2+ was considered equivocal and the case was discounted (no FISH data available).

There were 58 cases of Her2+/ER- IDC (ER-, PR+/-, Her2+), 57 cases of triple negative IDC (ER-, PR-, Her2-) and 67 cases of luminal-like IDC (ER+, PR+/-, Her2- and ER+, PR+, Her2+). The proliferation level of each case had also been determined by US BIOMAX prior to the study using Ki67. The proliferation level was considered low if ≤20% of tumour cells expressed Ki67 or high if >20% of tumour cells expressed Ki67. Information about the clinical and pathological characteristics of the cases (Age, Grade, Size, and Nodal involvement) was provided by US BIOMAX, this data can be seen in Table 1. NFκB p50 nuclear staining was assessed by IHC within the testing laboratory using the method outlined below. TMA's were stained using an EBNA1 monoclonal antibody, and were visualised according to the method outlined below. If the two cores from a single case did not display the same staining characteristics the result was considered equivocal and the case was discounted from the study.

*Antibodies and control material*

Commercially available control material was used that was known to stain strongly for EBV (245S, CELLMARQUE), and NFκB (326S, CELLMARQUE). To assess NFκB nuclear staining the NFκB p105/p50 antibody was used (clone 5D10, mouse monoclonal IgG1, ABCAM), diluted 1:200. To assess EBV infection the EBNA1 antibody was used (clone E1-2.5, mouse monoclonal IgG1, ABCAM), diluted 1:2000. Both antibodies were diluted using common antibody diluent (HK156-5KE, BIOGENIX).

*Immunohistochemistry (IHC)*

The tissue micro arrays were de waxed in xylene taken through graded alcohols and re hydrated. TMA's were then immersed in 10% hydrogen peroxide for 10 minutes to block endogenous peroxidase activity and retrieved according to manufacturer's guidelines (heat mediated using the DAKO Pascal chamber and pH6.0 buffer [RE7113, NOVACASTRA]). After rinsing in wash buffer (HK583-5KE, BIOGENIX), the TMA's were stained using a BIOGENIX i6000 with appropriate antibodies. Commercial control tissue was included with each staining run, the negative control was stained using a mouse IgG1 negative control (X0931 mouse monoclonal IgG1, DAKO). The antibodies were visualised using the SuperSensitive Polymer HRP (diaminobenzidine) kit (QD430-XAKE, BIOGENIX). Sections were then counterstained using Mayer's haemalum, differentiated in 0.25% acid alcohol, blued using ammonium water and were dehydrated in alcohol, cleared in xylene and coversliped. Sections were viewed and graded (positive/negative) using standard light microscopy, only nuclear staining within breast tumour cells was considered positive.

*Statistical analysis*

Statistical analysis was carried out using a statistical package for social sciences (SPSS) version 20 (PASW, IBM Corp. USA 2011). Associations between categorical data were assessed using the Chi-square test ($\chi^2$) or Fisher's exact test where appropriate. The Mantel-Haenszel test was used when appropriate to assess the associations between categorical data where a third variable acted as a possible confounding factor to the two variables of primary interest. Using the Bonferroni correction, a P value <0.005 was considered significant. Risk analysis was used to determine odds ratios (OR) and confidence intervals (CI).

**Results**

*EBV (EBNA-1 nuclear positivity) results*

182 cases of invasive ductal carcinoma were assessed using IHC for the presence of EBV (EBNA1) in the nuclei of tumour cells. 13 cases were either unreadable or displayed equivocal staining and were discounted from the study. 169 cases remained that were eligible consisting of 58 cases of luminal like IDC (34.3%), 54 cases of Her2+/ER- IDC (32.0%), and 57 cases of triple negative IDC (33.7%). EBNA1 staining patterns broken down according to the clinical and pathological characteristics of the cases can be seen in Table 1.

EBNA1 staining was evident in the tumour cells of 73 cases (43.2%), with a statistical power greater than 0.80; there was no evidence of EBNA1 staining in surrounding tissue or infiltrating lymphocytes. A significant association can be seen between EBV infection and the three IDC subtypes investigated [$\chi^2(2) = 13.85$, P 0.001]; with EBNA1 positive breast tumour cells present in 31 (57.4%) of the Her2+/ER- cases and 28 (49.1%) of the triple negative cases, but only 14 (24.1%) of the luminal like cases. A three way analysis of the IDC subtypes association with EBV infection showed that the most significant difference was between the Her2+/ER- and luminal like subtypes [$\chi^2(1) = 12.88$, P <0.001], with the odds ratio indicating that EBV infection was 4.24 times more likely in the Her2+/ER- subtype (95% CI, 1.89-9.50). The difference between the triple negative and luminal like sub types was also shown to be (borderline) significant [$\chi^2(1) = 7.74$, P 0.005], with the odds ratio indicating that EBV infection was 3.03 times more likely in the triple negative subtype (95% CI, 1.37-6.71). There was no significant difference between the Her2+/ER- and triple negative sub types.

*Receptor, clinical and pathological staining patterns*

A significant association was shown between ER negativity and EBV infection [$\chi^2(1) = 13.07$, P <0.001], with 53.2% of ER negative tumours shown to be EBNA1 positive, compared to only 24.1% of ER positive tumours. Based on the odds ratio, EBV infection is 3.57 times more likely in ER negative tumours (95% CI 1.76-7.24). It was noted that both the Her2+ and PR- groups overlapped significantly with the ER- group (54 Her2+ cases in the ER- group, 108 PR- cases in the ER- group), therefore the Mantel-Haenszel test was used to adjust for ER status when assessing PR status and Her2 status. Adjusting for ER status no significant association was found between PR status and EBV infection [Mantel-Haenszel $\chi^2(1) = 0.03$, P 0.863], similarly no association was evident between Her2 status and EBV infection [Mantel-Haenszel $\chi^2(1) = 0.69$, P 0.405].

Adjusting for tumour subtype a significant association was shown between NFκB p50 nuclear staining and EBV infection [Mantel-Haenszel $\chi^2(1) = 15.80$, P <0.001], with 69.8% of tumour cells demonstrating NFκB p50 nuclear staining also shown to be EBNA1 positive. Based on the odds ratio EBV infection is 4.11 times more likely in those tumours demonstrating nuclear expression of NFκB p50 (95% CI 2.03-8.35). However, there were no significant relationships between EBNA1 positivity and age at diagnosis, histological grade, tumour size, nodal involvement or Ki67 status (see Table 1).

**Discussion**

Many of the investigations to date have utilised PCR or EBV encoded small RNAs (EBERs) *in situ* hybridisation as the primary detection methods. However, PCR has been criticised for detecting EBV DNA in infiltrating lymphocytes (laser capture micro dissection used in later studies should have

**Table 1.** EBV (EBNA1) staining according to the clinical and pathological characteristics (by case)

| Characteristics | | N (cases) | (EBNA1) EBV+ (%) | (EBNA1) EBV- (%) | P value |
|---|---|---|---|---|---|
| All | | 169 | 73 (43.2) | 96 (56.8) | |
| Age | <50 | 80 | 30 (37.5) | 50 (62.5) | 0.10 |
| | ≥50 | 89 | 43 (48.3) | 46 (51.7) | |
| Histological grade | Grade I | 16 | 6 (37.5) | 10 (62.5) | 0.34 |
| | Grade II | 124 | 57 (46.0) | 67 (54.0) | |
| | Grade III | 23 | 7 (30.4) | 16 (69.6) | |
| Tumour size | <2 cm | 10 | 4 (40.0) | 6 (60.0) | 0.56 |
| | ≥2 cm | 158 | 68 (43.0) | 90 (57.0) | |
| Nodal involvement | N- | 139 | 58 (41.7) | 81 (58.3) | 0.27 |
| | N+ | 30 | 15 (50.0) | 15 (50.0) | |
| Ki67 status | Low | 91 | 38 (41.8) | 53 (58.2) | 0.40 |
| | High | 78 | 35 (55.1) | 43 (44.9) | |
| NFκB p50 status | Negative | 116 | 36 (31.0) | 80 (69.0) | **<0.001** |
| | Positive | 53 | 37 (69.8) | 16 (30.2) | |
| Estrogen receptor | Positive | 58 | 14 (24.1) | 44 (75.9) | **<0.001** |
| | Negative | 111 | 59 (53.2) | 52 (46.8) | |
| Progesterone receptor | Positive | 47 | 12 (25.5) | 35 (74.5) | 0.86 |
| | Negative | 122 | 61 (50.0) | 61 (50.0) | |
| Her2 status | Positive | 60 | 33 (55.0) | 27 (45.0) | 0.40 |
| | Negative | 109 | 40 (36.7) | 69 (63.3) | |
| Subtype | Luminal like | 58 | 14 (24.1) | 44 (75.9) | **0.001** |
| | Her2+/ER- | 54 | 31 (57.4) | 23 (42.6) | |
| | Triple negative | 57 | 28 (49.1) | 29 (50.9) | |

alleviated this issue), and reports have indicated an EBER negative form of EBV infection could be present in breast tumour cell.[3, 14, 19] A number of investigations have also used immunohistochemistry as either the primary or secondary detection system, allowing identification of cell type (differentiating infected tumour cells from infiltrating lymphocytes). However, a number of different markers (EBNA1, EBNA2, latent membrane protein 1 (LMP1), and LMP2A) have been used in various studies leading to conflicting results. Recent work appears to indicate that EBNA1 and LMP2A are both positive while LMP1 and EBERs are negative in breast cancer.[19] The reliability of some of the earlier IHC studies must also be questioned due to technical concerns, an early showed strong staining of tumour cells using the 2B4-1 EBNA1 clone while failing to demonstrate the presence of EBV genetic material within the same cells,[5] this clone has subsequently been found to cross react with the MAGE4 protein, a testis tumour antigen also expressed in some breast cancers.[20] The immunohistochemistry method has been used in the present study, allowing the investigator to ensure EBV was localised to breast tumour cells. The EBNA1 monoclonal antibody (clone E1-2.5) was employed to detect EBV, as EBNA1 is thought to be expressed though all the latent phases of viral infection.[4] The E1-2.5 clone was chosen as it has been shown to be more reliablethan the 2B4 clone.[7,20]

Previous investigations have demonstrated EBV positivity ranging from 21-63% with a mean of 35.5% (SD=10.9) when considering all forms of investigation, when considering only IHC staining using EBNA1 the range is 25-55% and the mean is 35.4% (SD=10.3).[3-13, 19, 21] Although the results of the present study are slightly above the mean (43.2%), they are well within the range and fall within 1SD. The higher level of positivity in the current study may be due to the nature of the sample. Previous investigations used samples representative of the population norm in terms of receptor expression; due to the nature of this investigation the sample contained more ER- and Her2+ cases than would normally be expected. However, due to the nature of the investigation (using TMA's), it was not possible to accurately classify lymphocytic infiltration of the tumour tissue. This should be considered when viewing these results.

Gene expression studies have identified five primary subtypes of breast cancer (invasive ductal carcinoma, no special type), Luminal A, Luminal B, Normal like, Basal like and Her2 positive.[22] However, from an oncologist's point of view breast cancer patients fall in to one of three groups, ER positive, Her2 positive and triple negative,[23] as these groups represent distinct prognostic outcomes.[24] A

strong association was demonstrated between EBV infection and tumour subtype (P=0.001), with EBV infection shown to be more prevalent in the Her2+/ER- and triple negative subtypes of invasive ductal carcinoma. This points towards a possible role for EBV in the pathogenesis of these breast cancer subtypes, both of which are typically high grade and aggressive.[25] This study directly investigates the association between EBV infection and the high risk IDC subtypes (Her2+/ER- and Triple negative) in an organised manner, and backs up the work of previous authors associating EBV infection with aggressive (ER-) breast tumours.[3,4]

To gain a greater understanding of the nature of this relationship receptor (ER, PR, Her2) receptor expression profiles were examined (although data on ER, PR, and Her2 clones used for this was not available), with Mantel-Haenszel analysis being used to adjust for ER status. As can be seen from the results ER negativity appears to be the dominant factor in the association between EBV and the aggressive breast cancer sub types, with the odds ratio suggesting that EBV infection is 3.57 times more likely in ER negative tumours (P <0.001). However, the nature of the relationship remains unclear, as no molecular mechanism has been outlined as yet to explain the association. It may be that the higher proportion of ER negative cells in the basal layer makes these cells more susceptible to the transfer of EBV infection from infiltrating lymphocytes, although the recent report by Khan *et al.*[26] failed to find a correlation between EBV infected infiltrating lymphocytes and ER negative breast tumours. Further studies are needed to examine this issue, as the small size of the cores in the TMA's limited the ability of the investigator to fully screen for infiltrating lymphocytes in the present study. No association was evident between the EBV infected tumour cells and PR receptor expression, confirming the findings of previous authors.[3,4,7] As outlined in the introduction the evidence for an association between EBV infection and Her2 expression is mixed, it was reported by Lin *et al.*[15] that infection of breast cancer cell lines by EBV leads to activation of the Her2/Her3 signalling axis and elevated Her2 expression through the action of the BARF0 gene product. EBV has also been shown to induce EGFR expression in cervical carcinoma cell cultures through the action of NFκB p50,[27] and recent evidence suggests that the ERBB2 gene is amplified in a subset of EBV linked gastric carcinomas.[28] Taken together this evidence suggests that an intimate relationship may exist between EBV and the Her family of receptors in a range of carcinomas. However, in this current study no association was observed between EBV infection and Her2 overexpression. This is broadly in agreement with previous studies that have examined this relationship which found either weak associations,[3] or a lack of any significant association.[4,6]

The clinical and pathological profiles (patient age, histological grade, tumour size, and nodal involvement) of the EBV positive and EBV negative tumours were investigated as relationships between these factors and EBV have been noted in previous studies. An early study demonstrated a significant association between EBNA1 staining (using the 2B4-1 clone) and tumour size, tumour grade and nodal involvement; presence of the EBNA1 protein was found to be associated primarily with grade 3 tumours greater than 50 mm with more than 3 lymph nodes positive for metastases.[5] However, this study failed to demonstrate the presence of the EBV genome using PCR, and the reliability of the 2B4-1 clone must also be questioned as outlined earlier in the discussion. A further study in 2008 showed support for the association between EBV infection and high grade node positive tumours,[7] although no significant association was evident between EBV infection and tumour size. Another study in 2011[3] demonstrated an association between EBV positivity and high tumour grade, however, no other clinical or pathological factors were significant (excluding receptor expression status). A final study by Glenn et al. in 2012[6] indicated that EBV was associated with a younger age of diagnosis. In the present study no associations were evident between EBV infection of breast tumours and age, histological grade, tumour size or nodal involvement; this is in accordance with the majority of previous investigations,[4,8,10,11] including a large multi centric study by Fina *et al.* in 2001.[9] The scores used to grade the IDC sub-types in the TMA's used were not available, so it was not possible to assess if EBV infection was associated with different scores for nuclear pleomorphism, or tubule formation. However, the relationship between EBV positivity and Ki67 status was assessed; Ki67 measures the proliferation activity of tumours and is becoming increasingly important in breast cancer prognostic tests such as IHC4+C.[29, 30] However, no significant association was evident. None of the previous studies investigating EBV and breast cancer have observed Ki67 status.

NFκB is a rapid acting primary transcription factor found in most cell types that acts as a master regulator of cellular responses to stress; it serves as a primary means of relaying signals from the extracellular environment to the nucleus in order to initiate a genetic program. Aberrant expression of NFκB has been associated with a number of cancers.[31] In breast cancer it has been found to be correlated with ER/PR negativity, and is associated with the Her2 positive and basal like subtypes;[32, 33] NFκB p50 and p65 are both elevated in these cancer types, however, levels of NFκB p50 have been shown to be significantly higher than p65. NFκB has also been strongly linked to radiotherapy and anti estrogen therapy resistant forms of breast cancer.[31, 34]

Increased NFκB expression is normally the result of physiological changes leading to its activation. In the case of breast cancer, Her2 positive and basal like tumours have a solid growth pattern that leads to increased hypoxia towards the centre of the tumour mass, NFκB is one of the transcription factors governing cellular responses to hypoxia.[33] EBV has been linked to NFκB in both gastric and nasopharyngeal carcinoma.[16-18] In addition, a series of investigations have demonstrated EGFR receptor up regulation due to the activation of EGFR promoters by NFκB p50/p50/Bcl-3 complexes,[27, 35] this was through the action of the LMP1 C-terminal activating region 1(CTAR1). A further study in the same series indicated that this LMP1-CTAR1 mediated up regulation of EGFR by p50/p50/Bcl3 complexes is not dependent on the standard NFκB pathway,[36] indicating a distinct role for EBV in tumour genesis. The results from the present study indicate that there is an unexpectedly strong association between EBV infection and nuclear expression of NFκB p50 in cases of invasive ductal carcinoma ($P < 0.001$); the Mantel-Haenszel common odds ratio indicated that NFκB p50 nuclear expression was 4.11 times more likely in tumours infected with EBV (after adjusting for tumour sub-type). However, the nature of this association remains unclear; from the evidence outlined earlier in the discussion it is unlikely that EBV LMP1 is interacting with NFκB, it is possible that LMP2A interacts with NFκB in EBV linked breast cancer as is the case in EBV linked gastric carcinoma.[17, 37] It seems clear from the results of this investigation as well as from previously published data that EBV is not associated with Her2 in breast cancer;[4] therefore, it is possible that LMP2A interacts with the NFκB pathway to confer resistance to apoptotic stimulus in cases of EBV linked breast cancer, as is the case in EBV linked gastric carcinoma.[17] Further studies should be carried out to confirm these initial findings, and investigate the association between EBV and NFκB in breast cancer.

The primary aim of this study was to investigate a possible association between EBV infection and aggressive sub types of invasive ductal carcinoma. The data clearly indicates an association, with EBV infection significantly more prevalent in the triple negative (49.1%) and Her2+/ER- (57.4%) sub types compared to the luminal like sub type (24.1%). It was further demonstrated that a significant association is present between EBV infection and ER negativity, however, no significant associations exist between EBV infection and either PR status or Her2 status. The nature of the relationship between ER negativity and EBV infection remains unclear, with additional investigations needed to determine if ER negativity is involved in the aetiology of a possible sub set of EBV linked aggressive breast tumours, due to the limitations inherent with commercial TMA's further work may be required to confirm these results. A surprisingly strong association was also noted between EBV infection and nuclear expression of NFκB p50 (independent of tumour sub-type), although the nature of this relationship remains unclear, and further studies are necessary to confirm these results and to determine how EBV interacts with NFκB. This study failed to find evidence of associations between EBV infection and other clinical and pathological characteristics (age, histological grade, nodal involvement, tumour size and Ki67 status).

**Conflict of Interest**

The author has no conflict of interest in relation to this article.

**References**


1. Burgos JS. Involvement of the Epstein-Barr virus in the nasopharyngeal carcinoma pathogenesis. Medical oncology. 2005;22(2):113-21.
2. Fukayama M, Ushiku T. Epstein-Barr virus-associated gastric carcinoma. Pathology, research and practice. 2011;207(9):529-37.
3. Mazouni C, Fina F, Romain S, Ouafik L, Bonnier P, Brandone JM, *et al.* Epstein-Barr virus as a marker of biological aggressiveness in breast cancer. British journal of cancer. 2011;104(2): 332-7.
4. Hachana M, Amara K, Ziadi S, Romdhane E, Gacem RB, Trimeche M. Investigation of Epstein-Barr virus in breast carcinomas in Tunisia. Pathology, research and practice. 2011;207(11):695-700.
5. Murray PG, Lissauer D, Junying J, Davies G, Moore S, Bell A, *et al.* Reactivity with A monoclonal antibody to Epstein-Barr virus (EBV) nuclear antigen 1 defines a subset of aggressive breast cancers in the absence of the EBV genome. Cancer research. 2003;63(9): 2338-43.
6. Glenn WK, Heng B, Delprado W, Iacopetta B, Whitaker NJ, Lawson JS. Epstein-Barr virus, human papillomavirus and mouse mammary tumour virus as multiple viruses in breast cancer. PloS one. 2012;7(11):e48788.
7. Fawzy S, Sallam M, Awad NM. Detection of Epstein-Barr virus in breast carcinoma in Egyptian women. Clinical biochemistry. 2008;41(7-8):486-92.
8. Joshi D, Quadri M, Gangane N, Joshi R, Gangane N. Association of Epstein Barr virus infection (EBV) with breast cancer in rural Indian women. PloS one. 2009;4(12):e8180.
9. Fina F, Romain S, Ouafik L, Palmari J, Ben Ayed F, Benharkat S, *et al.* Frequency and genome load of Epstein-Barr virus in 509 breast cancers from different geographical areas. British journal of cancer. 2001;84(6):783-90.

10. Preciado MV, Chabay PA, De Matteo EN, Gonzalez P, Grinstein S, Actis A, *et al.* Epstein-Barr virus in breast carcinoma in Argentina. Archives of pathology & laboratory medicine. 2005;129(3):377-81.
11. Zekri AR, Bahnassy AA, Mohamed WS, El-Kassem FA, El-Khalidi SJ, Hafez MM, *et al.* Epstein-Barr virus and breast cancer: epidemiological and molecular study on Egyptian and Iraqi women. Journal of the Egyptian National Cancer Institute. 2012;24(3):123-31.
12. Labrecque LG, Barnes DM, Fentiman IS, Griffin BE. Epstein-Barr virus in epithelial cell tumors: a breast cancer study. Cancer research. 1995;55(1):39-45.
13. Luqmani Y, Shousha S. Presence of epstein-barr-virus in breast-carcinoma. International journal of oncology. 1995;6(4):899-903.
14. Huo Q, Zhang N, Yang Q. Epstein-Barr virus infection and sporadic breast cancer risk: a meta-analysis. PloS one. 2012;7(2):e31656.
15. Lin JH, Tsai CH, Chu JS, Chen JY, Takada K, Shew JY. Dysregulation of HER2/HER3 signaling axis in Epstein-Barr virus-infected breast carcinoma cells. Journal of virology. 2007;81(11):5705-13.
16. Tang W, Morgan DR, Meyers MO, Dominguez RL, Martinez E, Kakudo K, *et al.* Epstein-barr virus infected gastric adenocarcinoma expresses latent and lytic viral transcripts and has a distinct human gene expression profile. Infectious agents and cancer. 2012;7(1):21.
17. Fukayama M, Hino R, Uozaki H. Epstein-Barr virus and gastric carcinoma: virus-host interactions leading to carcinoma. Cancer science. 2008;99(9):1726-33.
18. Ren Q, Sato H, Murono S, Furukawa M, Yoshizaki T. Epstein-Barr virus (EBV) latent membrane protein 1 induces interleukin-8 through the nuclear factor-kappa B signaling pathway in EBV-infected nasopharyngeal carcinoma cell line. The Laryngoscope. 2004;114(5):855-9.
19. Lorenzetti MA, De Matteo E, Gass H, Martinez Vazquez P, Lara J, Gonzalez P, *et al.* Characterization of Epstein Barr virus latency pattern in Argentine breast carcinoma. PloS one. 2010;5(10):e13603.
20. Murray PG. Epstein-Barr virus in breast cancer: artefact or aetiological agent? The Journal of pathology. 2006;209(4):427-9.
21. Xue SA, Lampert IA, Haldane JS, Bridger JE, Griffin BE. Epstein-Barr virus gene expression in human breast cancer: protagonist or passenger? British journal of cancer. 2003;89(1):113-9.
22. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, *et al.* Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009;18(4):1157-66.
23. Reis-Filho JS, Tutt AN. Triple negative tumours: a critical review. Histopathology. 2008;52(1):10818.
24. Carey LA, Dees EC, Sawyer L, Gatti L, Moore DT, Collichio F, *et al.* The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. Clinical cancer research : an official journal of the American Association for Cancer Research. 2007;13(8):2329-34.
25. Peppercorn J, Perou CM, Carey LA. Molecular subtypes in breast cancer evaluation and management: divide and conquer. Cancer investigation. 2008;26(1):1-10.
26. Khan G, Philip PS, Al Ashari M, Houcinat Y, Daoud S. Localization of Epstein-Barr virus to infiltrating lymphocytes in breast carcinomas and not malignant cells. Experimental and molecular pathology. 2011;91(1):466-70.
27. Thornburg NJ, Raab-Traub N. Induction of epidermal growth factor receptor expression by Epstein-Barr virus latent membrane protein 1 C-terminal-activating region 1 is mediated by NF-kappaB p50 homodimer/Bcl-3 complexes. Journal of virology. 2007;81(23):12954-61.
28. Cancer Genome Atlas Research N. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014; 513(7517):202-9.
29. Barton S, Zabaglo L, A'Hern R, Turner N, Ferguson T, O'Neill S, *et al.* Assessment of the contribution of the IHC4+C score to decision making in clinical practice in early breast cancer. British journal of cancer. 2012;106(11):1760-5.
30. Cuzick J, Dowsett M, Pineda S, Wale C, Salter J, Quinn E, *et al.* Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the Genomic Health recurrence score in early breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011;29(32):4273-8.
31. Ahmed KM, Cao N, Li JJ. HER-2 and NF-kappaB as the targets for therapy-resistant breast cancer. Anticancer research. 2006;26(6B):4235-43.
32. Shapochka DO, Zaletok SP, Gnidyuk MI. Relationship between NF-kappaB, ER, PR, Her2/neu, Ki67, p53 expression in human breast cancer. Experimental oncology. 2012;34(4):35863.
33. Biswas DK, Iglehart JD. Linkage between EGFR family receptors and nuclear factor kappaB (NF-kappaB) signaling in breast cancer. Journal of cellular physiology. 2006;209(3):645-52.
34. Yde CW, Emdal KB, Guerra B, Lykkesfeldt AE. NFkappaB signaling is important for growth of antiestrogen resistant breast cancer cells. Breast

cancer research and treatment. 2012;135(1):67-78.
35. Kung CP, Raab-Traub N. Epstein-Barr virus latent membrane protein 1 induces expression of the epidermal growth factor receptor through effects on Bcl-3 and STAT3. Journal of virology. 2008;82(11):5486-93.
36. Kung CP, Raab-Traub N. Epstein-Barr virus latent membrane protein 1 modulates distinctive NF- kappaB pathways through C-terminus-activating region 1 to regulate epidermal growth factor receptor expression. Journal of virology. 2010;84(13):6605-14.
37. HinoR, Uozaki H, Inoue Y, Shintani Y, Ushiku T, Sakatani T, *et al.* Survival advantage of EBV-associated gastric carcinoma: survivin up-regulation by viral latent membrane protein 2A. Cancer research. 2008;68(5):1427-35.

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# Breast Cancer Risk Factors in Patients With Endometriosis

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ABSTRACT

**Background:** Endometriosis is a common chronic inflammatory, estrogen-dependent disease with characteristics similar to cancer. Epidemiological studies of the association between endometriosis and breast cancer have yielded inconsistent results. The present study aimed to investigate the association between endometriosis and breast cancer risk factors.

**Methods:** This case-control study (with 222 persons in each group) was conducted in Arash Women's Hospital from 2014 to 2017. Women with laparoscopically proven endometriosis were considered as cases. Controls were selected from women who had previous laparoscopic surgery due to any reason, and the absence of endometriosis was confirmed in them.

**Results:** Multivariate logistic regression analysis by considering the risk factors (age, body mass index, gravidity, age at first pregnancy, age at menarche, history of breast-feeding, history of oral contraceptive and hormone use, history of miscarriage and induced abortion, breast cancer in first-degree relatives, and physical activity) revealed that endometriosis was positively association with age at first pregnancy (OR = 1.16, 95% CI: 1.08-1.25; P < 0.001), history of oral contraceptive use (OR = 3.91, 95% CI: 1.92-7.95; P <0.001), and history of hormone use (OR = 5.82, 95% CI: 2.70-12.56; P <0.001), and negatively associated with gravidity (OR = 0.61, 95% CI: 0.42-0.91; P = 0.01), and history of breast-feeding (OR = 0.37, 95% CI: 0.16-0.86; P = 0.02).

**Conclusion:** Women with endometriosis have some of the breast cancer risk factors in their history, and these risk factors (gravidity, age at first pregnancy, history of breast-feeding, and OCP or hormone use) can change the risk of endometriosis as they increase or decrease the risk of breast cancer.

## Introduction

Cumulative exposure of a woman to exogenous estrogens causes hormonal abnormalities that will accompany her during reproductive life cycle and is considered an established risk factor for breast cancer.

Endometriosis is a common chronic inflammatory, estrogen-dependent disease which affects approximately 10%-15% of women of reproductive age. However, its prevalence may be as high as 25%-30% in infertile women.[1, 2] Many women are asymptomatic, while others experience varying

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degrees of chronic pelvic pain, dysmenorrhea, or dyspareunia. Endometriosis has characteristics similar to cancer, including cell invasion, unrestrained growth, development of new blood vessels, and a decrease in the number of cells undergoing apoptosis.[3] Furthermore, endometriosis, like cancer, is characterized by metastasis and recurrence, and the 5-year recurrence rate of endometriosis after laparoscopy has been reported to be 40%-50%.[4] However, endometriosis is not categorized as a malignant disorder, and malignant transformation of endometriosis occurs only in 1% of cases.[5]

Several studies have shown a possible association between ovarian cancer and endometriosis.[6-8] A 1997 study in Sweden, with a large sample size and long-term (11.4 years) follow-up, reported that ovarian cancer rate in patients with endometriosis was about two times higher than the general population. They also found these women to have a 30% increased risk of breast cancer.[8] However, subsequent epidemiological studies examining the association between endometriosis and breast cancer provided inconsistent results.[8-14]

Therefore, the aim of this study was to evaluate the association between breast cancer risk factors and endometriosis.

## Methods

*Study Population*

This case-control study was approved by the Ethics Committee of Tehran University of Medical Sciences. Oral informed consent was obtained from all participants. The study was performed in Arash Women's Hospital during the period 2014-2017. Women with endometriosis were considered as cases, providing us with a case group of 222 women. The diagnosis was confirmed using laparoscopic surgery. An equal number of controls were selected from women who had previously undergone laparoscopic surgery due to any reason (pelvic pain, dysmenorrhea, unknown infertility, etc.), and the absence of endometriosis was confirmed in them.

Women with a history of any type of cancer, history of head and neck radiotherapy, and positive genetic test for breast cancer (*BRCA1, BRCA2*) were excluded. Demographic information and breast cancer risk factors [age, body mass index (BMI), gravidity, age at first pregnancy, age at menarche, history of breast-feeding, history of oral contraceptive and hormone use, history of abortion, history of breast cancer in first-degree relatives, and weekly physical activity (hours)] were obtained by a trained midwife through face-to-face interview. BMI is defined as weight divided by height squared (kg/m$^2$). Weekly physical activity was the total hours per week that a woman exercised.

*Statistical Analysis*

Categorical and continuous variables are presented as N (%) and mean ± standard deviation, respectively. Pearson's chi-square test and independent t test were used to assess differences between baseline demographic and clinical characteristics of the study groups. Multivariate logistic regression with backward selection mode was used to examine the association between endometriosis and the possible risk factors selected based on the prior knowledge. In this model, a P value of 0.2 was used as the criteria for entering a variable in the model, whereas a P value of 0.1 was considered the threshold for a variable to stay in the model. Results are presented as odds ratio (OR) with 95% confidence intervals (CI). Statistical analysis was performed using SPSS software (version 18, Chicago, IL, USA).

## Results

Demographic and clinical characteristics of the subjects are shown in Table 1. The mean age of the subjects was 33.11 ± 5.88 (range: 19-45) years. Only three women were in postmenopausal status (one in the case and 2 in the control group). Independent t test showed no significant difference in age at menarche and physical activity between the case and the control groups ($P > 0.05$). However, other variables were significantly different between the two groups ($P < 0.05$) (Table 1). After univariate logistic regression analysis by considering the P value of < 0.2, the variables age, BMI, gravidity, age at first pregnancy, history of breast-feeding, history of miscarriage and induced abortion, and history of oral contraceptive and hormone use were selected for further analysis (data not shown in the table). Multivariate logistic regression results are presented in Table 2. The results revealed that endometriosis was positively associated with age at first pregnancy (OR = 1.16, 95% CI: 1.08-1.25; P < 0.001), history of oral contraceptive use (OR = 3.91, 95% CI: 1.92-7.95; P < 0.001), and history of hormone use (OR = 5.82, 95% CI: 2.70-12.56; P < 0.001), and negatively associated with gravidity (OR = 0.61, 95% CI: 0.42-0.91; P = 0.01) and history of breastfeeding (OR = 0.37, 95% CI: 0.16-0.86; P = 0.02).

## Discussion

Breast cancer is the most common cancer in women. Therefore, many researchers are interested in early detection of breast cancer risk factors in high risk population. The risk of cancer development in patients with endometriosis has been investigated. We evaluated the breast cancer risk factors in endometriotic cases compared with a control group. The results of the present study showed that some of the risk factors for breast cancer, such as gravidity, age at first pregnancy, history of breast-feeding, and OCP or hormone use have the same effect on endometriosis as they have on breast cancer. It means the association of these risk factors with

**Table 1.** Comparison of demographic characteristics of the case and the control

| Variables | | Cases (n = 222) | Controls (n = 222) | P value* |
|---|---|---|---|---|
| Age (y) | | 32.03 ± 5.22 | 34.17 ± 6.25 | < 0.001 |
| BMI (kg/m2) | | 24.03 ± 3.75 | 26.25 ± 4.49 | < 0.001 |
| Duration of education (y) | | 15.13 ± 3.02 | 12.56 ± 4.00 | < 0.001 |
| Gravidity (n) | | 0.53 ± 8.60 | 1.59 ± 1.35 | 0.002 |
| Age at first pregnancy (y) | | 26.94 ± 4.98 | 22.81 ± 4.70 | < 0.001 |
| Age at menarche (y) | | 13.08 ± 1.51 | 13.10 ± 1.57 | 0.85 |
| Physical activity (h/wk) | | 3.76 ± 13.56 | 3.22 ± 7.18 | 0.60 |
| History of miscarriage | | 23 (10.4) | 41 (18.5) | 0.02 |
| History of induced abortion | | 7 (3.2) | 31 (14) | < 0.001 |
| History of breast-feeding | | 51 (23) | 147 (66.2) | < 0.001 |
| History of OCP usage | | 160 (72.1) | 92 (41.4) | < 0.001 |
| History of hormone use | | 88 (39.6) | 36 (16.2) | < 0.001 |
| Breast cancer in first-degree relatives | Yes | 31 (13.9) | 29 (13.1) | 0.60 |
| | No | 191(86.1) | 193 (86.9) | |

** Statistically significant at 0.05 level.*
*BMI: body mass index; OCP: oral contraceptive pills.*

**Table 2.** Adjusted odds ratio for endometriosis according to known risk factors in multivariate analysis

| Parameters | Adjusted OR | Lower 95% CI | Higher 95% CI | P value |
|---|---|---|---|---|
| Gravidity | 0.61 | 0.42 | 0.91 | 0.01 |
| Age at first pregnancy | 1.16 | 1.08 | 1.25 | <0.001 |
| History of breast-feeding | 0.37 | 0.16 | 0.86 | 0.02 |
| History of OCP use | 3.91 | 1.92 | 7.95 | <0.001 |
| History of hormone use | 5.82 | 2.70 | 12.56 | <0.001 |

** Statistically significant at 0.05 level. Model includes age, body mass index (BMI), gravidity, age at first pregnancy, history of breast-feeding, history of OCP use, history of hormone use, history of miscarriage, and history of induced abortion. OCP: oral contraceptive pills; CI: confidence interval.*

endometriosis and breast cancer is similar. Therefore, such results indicate the possibility of an increased risk of breast cancer in these patients. The predominant risk factors were the use of oral contraceptives and other hormones and age at first pregnancy. However, gravidity and history of breast-feeding were associated with protective effects.

Consistent with our findings, two cohort studies, both based on hospital records of endometriotic patients, have reported overall increased risk of breast cancer after a diagnosis of endometriosis.[8, 9] However, the findings of Schairer *et al.* were based on a limited number of breast cancer case,[8] and Brinton *et al.* didn't find any apparent difference in risk according to the age of diagnosis.[9]

A large case-cohort study by Bertelsen *et al.* reported the increased risk of breast cancer in women whose endometriosis were diagnosed at an older age.[10] A recent publication by Kokcu *et al.* discussed about the possible mechanisms of increased risk of malignancy in patients with endometriosis and the contributions of genetic and epigenetic variations of endometriosis and universal carcinogens that may be potential risk factors of breast or other cancers in women with endometriosis.[2]

However, the results of this study are not consistent with other studies.[11-14] The study by Brinton et al,[8] with longer follow-up, was not able to confirm the previous finding of the association between endometriosis and breast cancer.[11] Furthermore, the positive association was not manifested in two case-control studies[12, 13] and one cohort study.[14] It is worth mentioning, however, that these investigations were conducted in postmenopausal breast cancer patients,[14] and the selection of endometriosis cases was based on self-reported data,[12-14] whereas, endometriosis was confirmed by laparoscopic surgery in our study. Evidence has revealed that the etiology of endometriosis differs considering menopausal status of women, and women diagnosed with endometriosis before age 40 have reduced risk of developing breast cancer in the future. This may be attributable to cumulative exogenous estrogen levels throughout women's life or the effect of antiestrogens in younger patients with endometriosis.[10] Therefore, it seems that the differences in results could be due to the following factors: sample size, study design, diagnosis of patients (by the physician or self-reported), categorization of patients by the age of diagnosis or menopausal status, and different follow-up periods.
One of the most important risk factor for breast cancer is the family history of breast cancer. One study reported the proportion of women with a positive family history of breast cancer in first- and second-degree relatives was significantly higher in woman with endometriosis compared with the controls.[15] However, in the present study, the family history of breast cancer was similar in the case and the control group.

Cancer is a multifactorial disease influenced by strong genetic and lifestyle components, and

environmental factors and place of residency are important factors in the development of disease. Therefore, scientists should accept some differences between the results of causal studies due to the effect of environmental variables.

Consequently, it is necessary to establish a connection between world-wide cancer registration systems in order to draw a valid and reliable conclusion about the risks associated with endometriosis considering all risk factors.

This study had some advantages. Firstly, the study groups were selected according to laparoscopic results, and not based on self-reported data. Therefore, the method of selection (case and control) was more valid. Secondly, this was the first study on this subject in our population. Since the prevalence of cancer risk factors in Iran is high, and the trend is growing up,[16] and breast cancer patients with advanced stages of disease are relatively younger (about 10 years) than their western counterparts,[17] this type of study was needed to prevent the disease by setting up new screening programs in high-risk populations.

The limitation of this study was the study design. It would be better to conduct a retrospective cohort study in breast cancer patients and evaluate the history of endometriosis compared with the normal population, or carry out a prospective cohort study in endometriotic patients and follow them for a long time and evaluate them for the manifestation of any cancer in this population. The other limitation was the lack of knowledge about the stage of endometriosis and the origin of the disease.

In conclusion, we found some of the risk factors for breast cancer to have the same effect on endometriosis as they have on breast cancer. However, data on the association between endometriosis and breast cancer should be interpreted with caution because of the lack of consistency. Further study is needed to confirm the association between endometriosis and breast cancer.

For women with endometriosis, especially those with a history of OCP or hormone use and higher age at first pregnancy, counseling and screening for breast cancer are highly recommended.

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**Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**References**

1. Witz CA, Burns WN. Endometriosis and infertility: is there a cause and effect relationship? Gynecol Obstet Invest. 2002;53 Suppl 1:2-11.
2. Kokcu A. Relationship between endometriosis and cancer from current perspective. Arch Gynecol Obstet. 2011;284(6):1473-9.
3. Swiersz LM. Role of endometriosis in cancer and tumor development. Ann N Y Acad Sci. 2002;955:281-92; discussion 93-5, 396-406.
4. Boruban MC, Jaishuen A, Sirisabya N, Li Y, Zheng HG, Deavers MT, *et al.* Ovarian endometriosis associated with carcinoma and sarcoma: case report. Eur J Gynaecol Oncol. 2008;29(4):393-6.
5. Efthymiou CA. Endometriosis-associated intestinal tumours: a consequence of long-term unopposed oestrogen? Ann R Coll Surg Engl. 2009;91(3):259-60.
6. Vlahos NF, Economopoulos KP, Fotiou S. Endometriosis, in vitro fertilisation and the risk of gynaecological malignancies, including ovarian and breast cancer. Best Pract Res Clin Obstet Gynaecol. 2010;24(1):39-50.
7. Sznurkowski JJ, Emerich J. Endometriomas are more frequent on the left side. Acta Obstet Gynecol Scand. 2008;87(1):104-6.
8. Brinton LA, Gridley G, Persson I, Baron J, Bergqvist A. Cancer risk after a hospital discharge diagnosis of endometriosis. Am J Obstet Gynecol. 1997;176(3):572-9.
9. Schairer C, Persson I, Falkeborn M, Naessen T, Troisi R, Brinton LA. Breast cancer risk associated with gynecologic surgery and indications for such surgery. Int J Cancer. 1997;70(2):150-4.
10. Bertelsen L, Mellemkjaer L, Frederiksen K, Kjaer SK, Brinton LA, Sakoda LC, *et al.* Risk for breast cancer among women with endometriosis. Int J Cancer. 2007;120(6):1372-5.
11. Melin A, Sparen P, Persson I, Bergqvist A. Endometriosis and the risk of cancer with special emphasis on ovarian cancer. Hum Reprod. 2006;21(5):1237-42.
12. Moseson M, Koenig KL, Shore RE, Pasternack BS. The influence of medical conditions associated with hormones on the risk of breast cancer. Int J Epidemiol. 1993;22(6):1000-9.
13. Weiss HA, Brinton LA, Potischman NA, Brogan D, Coates RJ, Gammon MD, *et al.* Breast cancer risk in young women and history of selected medical conditions. Int J Epidemiol. 1999;28(5):816-23.
14. Olson JE, Cerhan JR, Janney CA, Anderson KE, Vachon CM, Sellers TA. Postmenopausal cancer risk after self-reported endometriosis diagnosis in the Iowa Women's Health Study. Cancer. 2002;94(5):1612-8.
15. Matalliotakis IM, Cakmak H, Mahutte N, Goumenou AG, Koumantakis G, Arici A. The familial risk of breast cancer in women with endometriosis from Yale series. Surg Oncol. 2008;17(4):289-93.
16. Mousavi SM, Gouya MM, Ramazani R,

Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Ann Oncol. 2009;20(3):556-63.
17. Montazeri A, Vahdaninia M, Harirchi I, Harirchi AM, Sajadian A, Khaleghi F, *et al.* Breast cancer in Iran: need for greater women awareness of warning signs and effective screening methods. Asia Pac Fam Med. 2008;7(1):6.

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# In Vitro Inhibition of MCF-7 Human Breast Cancer Cells by Essential Oils of *Rosmarinus officinalis*, *Thymus vulgaris L.*, and *Lavender* x *intermedia*

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ABSTRACT

**Background**: The essential oils of traditional medicinal plants, including *Rosmarinus officinalis, Thymus vulgaris* L., and *Lavender* x *intermedia* contain anticancer compounds such as lavandulyl acetate, rosmarinic acid and thymol. The aim of this study was to investigate the anticancer effects of the essential oils of *R. officinalis, T. vulgaris* L., and *L.* x *intermedia* on MCF-7 cells.

**Methods**: Essential oils were prepared from *R. officinalis*, *T. vulgaris* L., and *L.* x *intermedia* plants. Then, MCF-7 and Hu02 cells were treated with different concentrations of these essential oils for a given time. The 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) assay was used to determine the cellular viability and cytotoxicity in response to treatment with different extract concentrations. The morphological changes were studied by Hoechst and propidium iodide staining. The results were analyzed using the one-way ANOVA and Tukey test.

**Results:** All three essential oils inhibited the viability of the MCF-7 cell line in a dose-dependent manner. *T. vulgaris* L. was more potent against MCF-7 cells at 400 µg/ml concentration ($IC_{50}$ = 48.01 ± 0.94), while *R. officinalis* was moderate at 800 µg/ml concentration ($IC_{50}$ = 47.39±0.91) and the concentration for *L.* x *intermedia* was 400 µg/ml ($IC_{50}$ = 47.39 ± 0.91).

**Conclusion**: *R. officinalis*, *T. vulgaris* L. and *L.* x *intermedia* show cytotoxic activity against breast cancer in vitro. *T. vulgaris* represents a potentially selective cytostatic factor and a safe target for future development of anticancer agents.

## Introduction

Breast cancer is among the most common cancers of women all over the world and represents one of the major health threat that takes the lives of thousands of people every year.[1, 2] Factors affecting fertility, environment, lifestyle, and physical inactivity contribute to this process.[3] Breast cancer ranks first among Iranian women with diagnosed cancers.[4]

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However, few studies have been conducted regarding clinical and pathologic features and age distribution of this disease in Iran.[5, 6] For over 3500 years, plants have been used to treat cancer, but their antiproliferative potential has only been evaluated since the late 1950s. Hartwell and colleagues used podophyllotoxin and its derivatives as the first anticancer agents for the first time in the late 1960s.[7-9] The recognition of medicinal plants and extensive research on their essential oils have led to their widespread use in medicine, such that the antimicrobial and antioxidant features of essential oils, especially their anticancer properties, have

attracted a lot of attention.[10, 11] More than 60% of anticancer compounds are derived from plants, microorganisms, and marine sources.[9, 12, 13] Today, medicinal plants are being considered safe due to their low side effects relative to chemical drugs.[14] The anticancer plants contain a wide range of compounds, such as colchicine, vincristine, and podophyllotoxin, which are mitotic inhibitors binding to mitotic spindle tubular proteins and possessing alkaloids such as vinca alkaloids (*Vinca rosea*) that are used in chemotherapy.[15, 16] Plants of the mint family (Lamiaceae) can be a rich source of phytochemicals such as phytosterols, flavonoids, carotenoids, and terpenoids that act as antioxidants, annihilating free radicals and stimulating the immune system. These compounds form DNA adducts inhibiting the activity of carcinogens and also blocking metabolic pathways of cancer.[15]

*Thymus vulgaris* is a medicinal plant with therapeutic properties such as antiinflammatory, antiseptic, antitussive, antispasmodic, and antimucous effects.[17,18] The essential oil of this plant contains compounds such as eucalyptol (6.23%), camphor (15.14%), camphene (10.54%), α-pinene (8%), carvacrol (18.51%), and thymol (20.35%).19 Moreover, the plant contains inhibitor compounds for cyclooxygenase and oxidative stress, and the effect of these enzymes on the growth and segregation of cells (including cancer cells) has been confirmed.[20,21]

*Lavender* x *intermedia* belongs to Lamiaceae family and is a source of uric acid, oleanolic acid, and betulinic acid.[22] The main components of the essential oils of these plants include linalool (32.8%), linalyl acetate (17.6%), lavandulyl acetate (15.9%), alpha-terpineol (6.7%), and geranyl acetate (5%).[23]

*Rosmarinus officinalis* is also a good source of uric acid, oleanolic acid, and betulinic acid. Essential oil of rosemary contains carnosic acid (1%), carnosol (4.6%), rosmarinic acid (4%), uric acid (19.2%), and rosmanol (5%), among which rosmarinic acid is water soluble and other substances are soluble in organic solvents.[24] Rosmarinic acid is a natural phenolic compound that has several biological attributes such as antidepression, liver tissue protection, antiangiogenesis, antitumor, and anti HIV-1 infection. Several studies have shown anticancer effects of these three plants belonging to Lamiaceae family.[25-29]

The aim of the present study was to investigate the cytotoxic effects of essential oils of T. *vulgaris, L.* x *intermedia,* and *R. officinalis* on breast cancer cell lines.

## Methods

*The MCF-7 Cell line and Hu02 Cells*

The MCF-7 human breast cancer cell line and Hu02 normal human fibroblast cells (control) were purchased from Iranian Biological Resource Center (IBRC), Tehran, Iran. Cell culture materials were obtained from Gibco Company (USA), but the flasks and microplates were acquired from Griner Company (Germany).

*Collection of Plant Samples*

The samples of *T. vulgaris, L.* x *intermedia,* and *R. officinalis*, which were harvested from Boroujerd city of Lorestan Province, were confirmed by (IBRC), Tehran, Iran. Cell culture materials were the Faculty of Natural Science and deposited at the Herbarium of Boroujerd Islamic Azad University. Next, the collected plant materials were dried in a dark place and were packed in paper bags in which they were stored until the experiments were performed.

*Essential Oil Extraction*

The essential oils were extracted using the Soxhlet method. First, 400 g of crushed dried samples from the leaves of each plant was placed in a tray and ethanol was added to it as solvent to make dough. Next, the dough was placed in the thimble inside the Soxhlet apparatus. Then, the ethanol was added slowly to the bottom flask, and the condenser was placed on the apparatus. An electric stove was used to boil solvent inside the flask. Consequently, the essential oil was collected and kept in sealed bottles at +4˚C. The process lasted 5-8 hours.

*Cell Culture*

The cells were grown in RPMI-1640 (Gibco, UK) supplemented with 10% FBS (Gibco, UK), 2 mM/L glutamine, 100 unit/mL penicillin, and 100 mg/mL streptomycin (Sigma, US) in 96-well culture plates (Griner, Germany) at 37°C in a 5%-$CO_2$ incubator (Heraeus, Hanau, Germany). All experiments were performed using cells from passage 12 or lower.

*MTT Assay*

The cell viability was determined using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide l (MTT) colorimetric method. Briefly, MCF-7 cells were seeded at 10000 cells per well in 96-well culture plates and treated with different concentrations of the extracted essential oils for 24, 48, and 72 hours. Then, the cells were incubated with MTT solution (5 mg/ml in PBS) for 4 h, and the resulting purple formazan was solubilized in 100 µL of DMSO (Sigma). The absorption was measured at 570 nm and 620 nm as a reference using a 96-well plate reader (Bio-Rad, Hercules, CA, USA). Data were collected for four replicates each and were used to calculate the respective means. The percentage inhibition was calculated using the following formula. The $IC_{50}$ value was determined as the concentration of

$$\% \text{ inhibition} = \frac{\text{Mean absorbance of untreated cells (control) - Maen absorbance of treated cells}}{\text{Mean absorbance of untreated cells (control)}} \times 100$$

the complex that is required to reduce the absorbance to half of that of the control.

*Hoechst and Propidium Iodide Staining*

The effects of various concentrations of essential oils of *R. officinalis*, *T. vulgaris* L. and *L.* x *intermedia* on morphological changes were assessed by Hoechst staining. For this aim, we used a fluorescence microscope to examine cell morphology. Briefly, the cells were treated with different concentrations of essential oils of *R. officinalis*, *T. vulgaris* L., and *L.* x *intermedia* for 24, 48 and 72 hours. The medium was removed and the wells were washed with PBS (Gibson Company). Then, the samples were incubated with 100 µL of PBS + 100 µL of Hoechst solution for 6-8 minutes. Next, the cells were washed by PBS, and their nuclei were examined with a phase contrast microscope (Carl Zeiss, Jena, Germany) and finally photographed. In this stage, the cells appear blue in color. In the next stage, each well was washed with PBS and propidium stain was added. In this stage, this stain is attached to DNA grooves and makes dead cells' nuclei look red.

*Statistical Analysis*

The data were analyzed using one-way analysis of variance (ANOVA), followed by Tukey multiple comparison tests, on SPSS 20. The results are presented as mean ± SD. A P value of less than 0.05 was considered statistically significant.

**Results**

The results of the MTT assay are given in Tables 1-4 and Figures 1-4. Comparing the viability of MCF-7 breast cancer cells after 24, 48, and 72 hours showed significant differences among groups treated with various concentrations of *R. officinalis*, *T. vulgaris* L., *L.* x *intermedia*, and Taxol, which indicates that as the concentration is increased, the viability of MCF-7 cells is significantly decreased. As shown in Table 4, Taxol attenuated the cytotoxic effects of concentrations of essential oils in MCF-7 cells. In Hoechst and propidium iodide staining, live and dead cells respectively appear blue and red in color (figure 5). As the dose is increased, the number of red cells is also increased, which shows apoptosis resulting from the impact of essential oils.

*Effect of Essential Oils on the Viability of Cells*

In vitro cytotoxic effects of the essential oils on MCF-7 breast cancer cell line viability were evaluated by MTT assay and compared with the result of Taxol, a commercially available anticancer drug, the cytotoxicity of which is shown in Table 1. The comparison of cell viability at different essential oil concentrations (1000, 800, 400, 200, 100 µL/mL) and Taxol (10, 1, 0.1, 0.01, 0.001µM) disclosed similar viability rates. As shown in Figure 1, the cytomorphological effects of essential oils on MCF-7 cells at different concentrations include activation of an intracellular suicide program characterized by morphological changes like cytoplasmic and cellular shrinkage, oxidative stress, coiling, and biochemical responses leading to apoptosis. It is quite obvious from the results that the apoptosis rate of MCF-7 cells is increased with increase in the concentration of essential oil. A dose-dependent increase in cell inhibition was seen after 24, 48, and 72 h incubation. The $IC_{50}$ for *T. vulgaris* was 400 µg/mL (48.01 ± 0.94). The complete inhibition (90%) of breast cancer cells was obtained at the maximum concentration of 1000 µg/ml. These results highlight the dose- and time-dependent increase in cytotoxicity. The $IC_{50}$ value suggests that the essential oil proves to be a promising drug for chemotherapeutic treatment.

Figure 2 shows that the cytotoxic effect of *L. intermedia* essential oil is dose- and time-dependent at 1000 µg/mL ($P < 0.05$), but at lower concentrations (800, 400, and 200 µg/mL) the decrease in cell viabilty is only dose-dependent.

Also, figure 3 demonstrates a dose- and time-dependent cytotoxic effect of *T. vulgaris* essential oil at 1000 and 800 µg/mL ($P < 0.05$), but only a dose-dependent effect at lower concentrations (400, 200, and 100 µg/mL).

The cytotoxic effect of *R. officinalis* essential oil is dose- and time-dependent at 1000 µg/mL ($P < 0.05$), but only dose-dependent at lower concentrations (800, 400, 200, and 100 µg/mL) (figure 4).

**Table 1.** 50% Inhibitory Concentrations (‰ v/v) for Taxol Against MCF-7 Cells ($P < 0.05$)

| Time | 0.001 µg/mL | 0.01 µg/mL | 0.1 µg/mL | 1 µg/mL | 10 µg/mL |
|---|---|---|---|---|---|
| 24 h | 75.39 ± 0.16 | 67.45 ± 0.52 | 55.99 ± 0.86 | 51.73 ± 1.21 | 48.31 ± 1.02 |
| 48 h | 63.98 ± 0.61 | 56.33 ± 0.69 | 47.55 ± 0.73 | 33.86 ± 0.97 | 26.91 ± 1.01 |
| 72 h | 68.90 ± 0.22 | 49.94 ± 0.70 | 38.19 ± 0.82 | 27.62 ± 0.95 | 21.88 ± 1.31 |

**Table 2.** 50% inhibitory concentrations (‰ v/v) for *L. intermedia, T. vulgaris*, and *R. officinalis* Against MCF-7 Cells ($P < 0.05$)

| Time | 100 µg/mL | 200 µg/mL | 400 µg/mL | 800 µg/mL | 1000 µg/mL |
|---|---|---|---|---|---|
| *L. intermedia* | | | | | |
| 24 h | 83.61 ± 0.59 | 75.11 ± 0.72 | 66.09 ± 0.91 | 51.23 ± 1.03 | 44.52 ± 1.11 |
| 48 h | 69.25 ± 0.51 | 57.89 ± 0.66 | 42.90 ± 0.89 | 29.74 ± 1.05 | 23.80 ± 1.14 |
| 72 h | 61.28 ± 0.86 | 59.37 ± 0.75 | 44.93 ± 0.87 | 29.44 ± 0.91 | 20.89 ± 0.97 |
| *T. vulgaris* | | | | | |
| 24 h | 69.31 ± 0.70 | 59.81 ± 0.85 | 48.01 ± 0.94 | 40.22 ± 1.03 | 34.29 ± 1.06 |
| 48 h | 47.25 ± 0.71 | 38.07 ± 0.79 | 30.86 ± 0.69 | 23.79 ± 0.82 | 18.95 ± 1.99 |
| 72 h | 49.27 ± 0.65 | 38.94 ± 0.78 | 31.19 ± 0.60 | 19.94 ± 0.74 | 15.72 ± 0.88 |
| *R. officinalis* | | | | | |
| 24 h | 75.41 ± 0.77 | 68.15 ± 0.89 | 55.62 ± 0.79 | 47.39 ± 0.91 | 40.21 ± 1.04 |
| 48 h | 59.91 ± 0.66 | 46.73 ± 0.66 | 38.55 ± 0.80 | 25.33 ± 0.84 | 21.07 ± 1.02 |
| 72 h | 57.34 ± 0.72 | 49.18 ± 0.83 | 38.99 ± 0.75 | 23.65 ± 0.80 | 18.48 ± 0.96 |

**Table 3.** 50% inhibitory concentrations (‰ v/v) for *L. intermedia, T. vulgaris*, and *R. officinalis* against Hu02 Cells ($P < 0.05$)

| Time | 100 µg/mL | 200 µg/mL | 400 µg/mL | 800 µg/mL | 1000 µg/mL |
|---|---|---|---|---|---|
| *L. intermedia* | | | | | |
| 24 h | 99.83 ± 0.14 | 90.63 ± 0.98 | 76.24 ± 0.69 | 61.44 ± 0.52 | 57.85 ± 0.48 |
| 48 h | 82.63 ± 0.73 | 74.46 ± 0.84 | 67.32 ± 0.71 | 53.28 ± 0.62 | 48.41 ± 0.54 |
| 72 h | 78.37 ± 0.64 | 73.92 ± 0.65 | 61.87 ± 0.76 | 46.63 ± 0.99 | 42.97 ± 0.79 |
| *T. vulgaris* | | | | | |
| 24 h | 98.54 ± 0.35 | 87.46 ± 0.68 | 68.38 ± 0.88 | 52.84 ± 0.77 | 49.76 ± 0.49 |
| 48 h | 85.33 ± 0.47 | 77.59 ± 0.81 | 62.81 ± 0.63 | 46.93 ± 0.48 | 43.41 ± 0.78 |
| 72 h | 76.79 ± 0.92 | 70.63 ± 0.75 | 56.12 ± 0.75 | 40.82 ± 0.56 | 35.88 ± 1.19 |
| *R. officinalis* | | | | | |
| 24 h | 98.35 ± 0.83 | 89.32 ± 0.72 | 75.87 ± 0.63 | 60.98 ± 0.86 | 56.97 ± 0.85 |
| 48 h | 90.26 ± 0.51 | 81.47 ± 0.94 | 63.91 ± 0.84 | 49.61 ± 0.58 | 46.35 ± 0.93 |
| 72 h | 83.61 ± 0.69 | 75.84 ± 0.91 | 58.72 ± 0.93 | 42.19 ± 0.89 | 39.94 ± 0.97 |

**Table 4.** 50% inhibitory concentrations (‰ v/v) for *L. intermedia, T. vulgaris*, and *R. officinalis* essential oils + Taxol against MCF-7 cells ($P < 0.05$).

| Time | 100 + 0.001 µg/mL | 200+ 0.01 µg/mL | 400 + 0.1 µg/mL | 800 + 1 µg/mL | 1000 + 10 µg/mL |
|---|---|---|---|---|---|
| *L. intermedia* + Taxol | | | | | |
| 24 h | 79.24 ± 0.67 | 68.57 ± 0.84 | 62.40 ± 0.88 | 46.84 ± 0.96 | 41.33 ± 1.04 |
| 48 h | 62.53 ± 0.49 | 51.33 ± 0.59 | 36.67 ± 0.73 | 25.93 ± 0.85 | 21.58 ± 0.95 |
| 72 h | 54.37 ± 0.36 | 52.48 ± 0.72 | 41.06 ± 0.69 | 24.57 ± 0.74 | 18.86 ± 0.73 |
| *T. vulgaris* + Taxol | | | | | |
| 24 h | 48.05 ± 0.67 | 52.61 ± 0.77 | 40.54 ± 0.88 | 38.17 ± 0.92 | 31.04 ± 0.93 |
| 48 h | 43.28 ± 0.54 | 35.81 ± 0.65 | 27.36 ± 0.58 | 20.66 ± 0.74 | 15.28 ± 0.82 |
| 72 h | 37.95 ± 0.48 | 33.76 ± 0.53 | 28.29 ± 0.52 | 16.28 ± 0.63 | 13.87 ± 0.71 |
| *R. officinalis* + Taxol | | | | | |
| 24 h | 70.95 ± 0.82 | 64.55 ± 0.80 | 50.99 ± 0.95 | 42.38 ± 0.88 | 34.25 ± 1.27 |
| 48 h | 52.08 ± 0.63 | 44.38 ± 0.72 | 34.58 ± 0.76 | 21.47 ± 0.79 | 20.64 ± 1.82 |
| 72 h | 55.41 ± 0.14 | 45.67 ± 0.84 | 32.08 ± 0.81 | 20.98 ± 0.83 | 15.93 ± 0.94 |

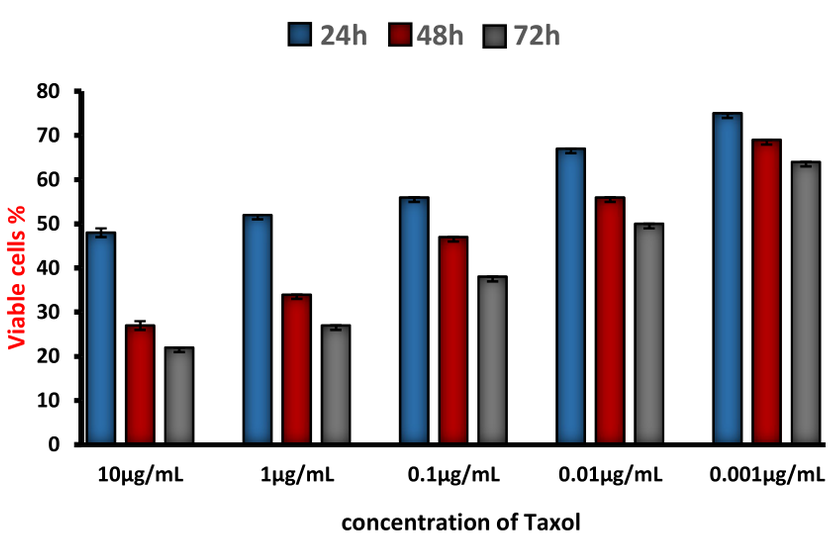


**Figure 1.** The results of one of the triplicate MTT tests

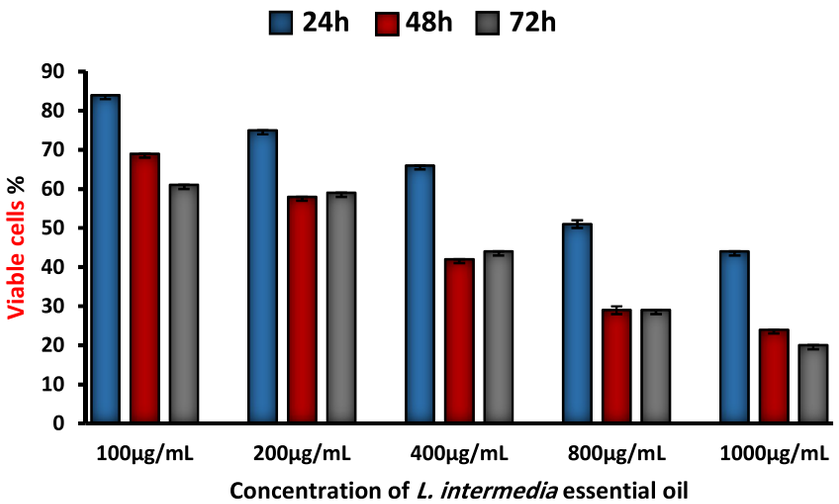


**Figure 2.** The results of one of the triplicate MTT tests

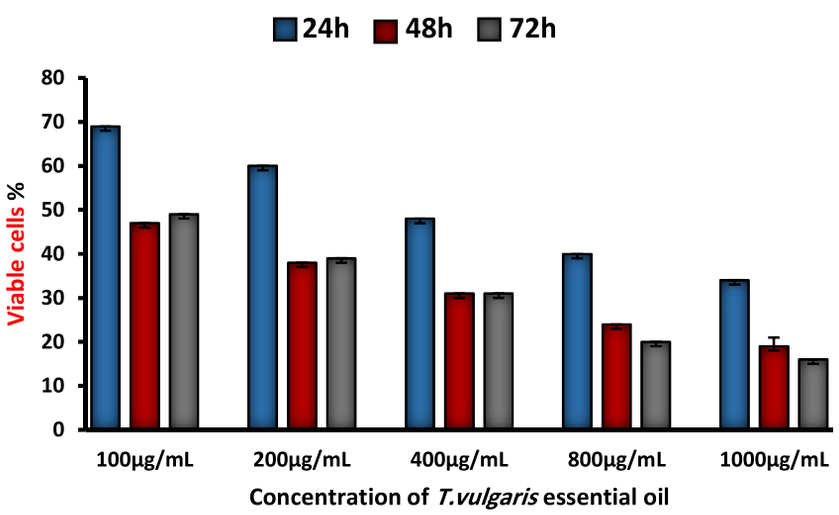


**Figure 3.** The results of one of the triplicate MTT tests

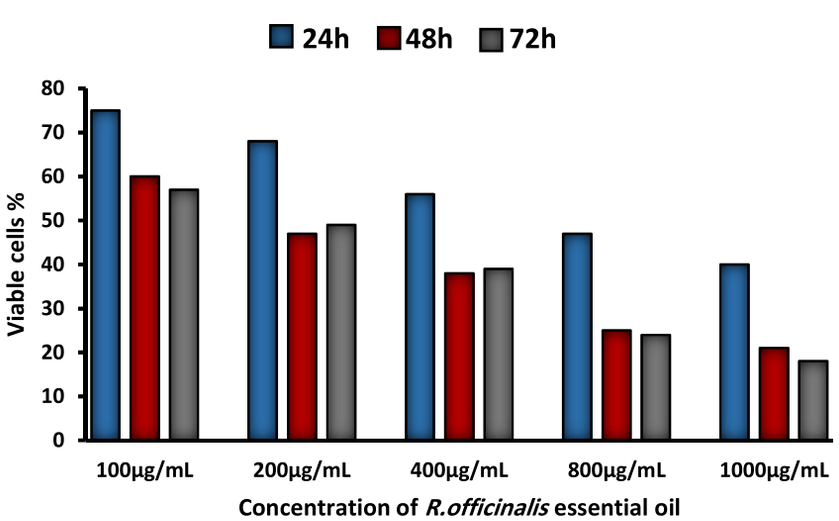


**Figure 4**. The results of one of the triplicate MTT tests.

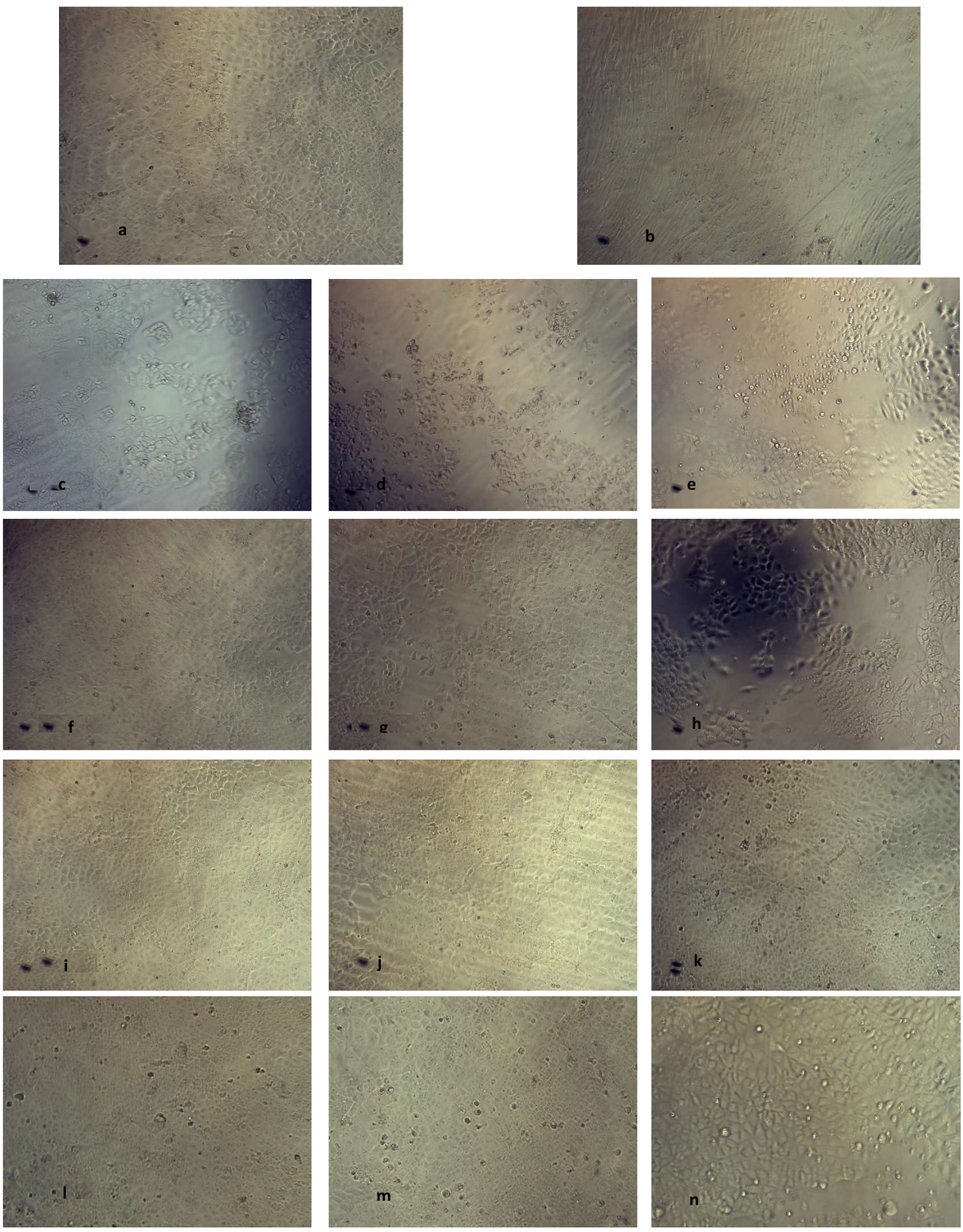


**Figure 5.** Morphlogic changes in MCF-7 and Hu02 cells treated with essential oils at 100µg/mL
a: Untreated MCF-7 cells; b: Hu02 control cells; c-e: MCF-7 cells treated with *T.vulgaris* for 24, 48, and 72 hours; f-h: MCF-7 cells treated with *R. officinalis* for 24, 48, and 72 hours; i-k: MCF-7 cells treated with *L. intermedia* for 24, 48, and 72 hours; l-n: MCF-7 cells treated with 100 + 0.001 µg/mL essential oils of *T. vulgaris* + Taxol*, R. officinalis* + Taxol, and *L. intermedia*, respectively.

**Discussion**

Recently, many studies have been conducted on the anticancer and cytotoxic effects of herbal medicines as they are associated with low side effects. In this study, we evaluated the cytotoxic and inhibitory effects of *R. officinalis, T. vulgaris L.,* and *L.* x *intermedia* essential oils against MCF-7 human breast cancer cells. Studies on the cytotoxic and inhibitory effects of rosemary essential oil on various cancer cell lines, including HL60, K562, MCF-7, MDA-MB-468, M14, A375, NCI-H82, DU-145, Hep-3B, and MDA-MB-231, has demonstrated that these effects vary depending on the cell lines.[30, 31] Research has also found that the flavonoids in rosemary inhibit the expression of Cox-2 by activating PPAR-γ. Cox-2 is an enzyme that is upregulated in malignant and premalignant cancers such as breast, colon, pancreas, lung, stomach, head and neck, skin, and pharynx.[32] Applying the essential oil of *R. officinalis* to the skin of mice prevents benzopyrene covalent binding to DNA and inhibits epidermal tumor formation. Moreover, the uric acid in *R. officinalis* prevents the binding of benzopyrene to epidermal cell DNA, and TPA to the membrane of these cells. Uric acid inhibits NF-κB pathway in cancer cells possibly by suppressing the p65 component of NF-κB and, thus, downregulating oncogenes such as Cox-2 and MMP-9, Cyclin D1, C-Jun, and C-Fas. Also, the carnosol in *R. officinalis* leaves functions in a similar manner and inhibits the activity of NF-κB.[33] In line with our findings, the anticancer properties of the compounds of the essential oils of *R. officinalis and L.* x *intermedia* have been demonstrated by other studies.[34,35,36,37]

Regarding anticancer properties of *T. vulgaris,* Sertel and colleagues demonstrated in vitro inhibition of a head and neck squamous cell carcinoma cell line treated with the plant's essential oil.[38] The present study also showed the antitumor and antitoxic effects of essential oils of *T. vulgari*s on MCF-7 cells.

our observation also indicated the cytotoxicity of Taxol and essential oils of *T. vulgaris, R. officinalis,* and *L.* x *intermedia* on MCF-7 cell line. Furthermore, the results of MTT assay in this study demonstrated that Taxol increased the cytotoxic effects of essential oils after 24, 48, and 72 hours of incubation.

Assessment of morphological changes indicates that some changes, such as nuclear disintegration, formation of apoptotic bodies, and membrane blebbing, observed in the cells treated with Taxol and essential oils are indicative of apoptosis. However, based solely on these results, we cannot demonstrate the occurrence of apoptosis and this requires specific tests such as TUNEL assay or flow cytometry-based assays.

Eventually, it can be concluded that effective compounds in essential oils of *T. vulgaris, R. officinalis,* and *L.* x *intermedia* induce cell death in MCF-7 cancer cells. Literature review and the results of various studies, as well as our results, show that these three plants of Lamiaceae family have biological and pharmacological potential, and it seems that isolating effective components of these plants as well as determining their structure and exact mechanisms of action should be the topics for future research.

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**Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial relationships that could be construed as a potential conflict of interest.

**References:**

1. Guo J, Bourre L, Soden DM, O'Sullivan GC, O'Driscoll C. Can non-viral technologies knockdown the barriers to siRNA delivery and achieve the next generation of cancer therapeutics? Biotechnology advances. 2011;29(4):402-17.
2. Vo AT, Millis RM. Epigenetics and breast cancers. Obstetrics and gynecology international. 2012;2012.
3. Pathy NB, Yip CH, Taib NA, Hartman M, Saxena N, Iau P, *et al.* Breast cancer in a multi-ethnic Asian setting: results from the Singapore–Malaysia hospital-based breast cancer registry. The Breast. 2011;20:S75-S80.
4. Alireza S, Mehdi N, Ali M, Alireza M, Reza M, Parkin D. Cancer occurrence in Iran in 2002, an international perspective. Asian Pacific journal of cancer prevention. 2005;6(3):359.
5. Rezaianzadeh A, Peacock J, Reidpath D, Talei A, Hosseini SV, Mehrabani D. Survival analysis of 1148 women diagnosed with breast cancer in Southern Iran. BMC cancer. 2009;9(1):168.
6. Harirchi I, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: results of a multi-center study. Asian pacific journal of cancer prevention. 2004;5(1):24-7.
7. Butt MS, Naz A, Sultan MT, Qayyum MMN. Anti-oncogenic perspectives of spices/herbs: A comprehensive review. EXCLI journal. 2013;12:1043.
8. Mans DR, Da Rocha AB, Schwartsmann G. Anti-cancer drug discovery and development in Brazil: targeted plant collection as a rational strategy to acquire candidate anti-cancer compounds. The oncologist. 2000;5(3):185-98.
9. Srivastava V, Negi AS, Kumar J, Gupta M, Khanuja SP. Plant-based anticancer molecules: a

chemical and biological profile of some important leads. Bioorganic & medicinal chemistry. 2005;13(21):5892-908.
10. Sylvestre M, Pichette A, Longtin A, Nagau F, Legault J. Essential oil analysis and anticancer activity of leaf essential oil of Croton flavens L. from Guadeloupe. Journal of Ethnopharmacology. 2006;103(1):99-102.
11. Mimica-Dukic N, Bozin B, Sokovic M, Simin N. Antimicrobial and antioxidant activities of Melissa officinalis L.(Lamiaceae) essential oil. Journal of agricultural and food chemistry. 2004;52(9):2485-9.
12. Møller P, Wallin H, Knudsen LE. Oxidative stress associated with exercise, psychological stress and life-style factors. Chemico-biological interactions. 1996;102(1):17-36.
13. Kidwai M, Venktaramanan R, Mohan R, Sapra P. Cancer chemotherapy and heterocyclic compounds. Current medicinal chemistry. 2002;9(12):1209-28.
14. Hoffman EJ. Cancer and the search for selective biochemical inhibitors: CRC press; 2007.
15. Craig WJ. Health-promoting properties of common herbs. The American journal of clinical nutrition. 1999;70(3):491s-9s.
16. Katzung BG, Masters SB, Trevor AJ. Basic & clinical pharmacology. 2004.
17. Lixandru Ba-E, Drăcea N, Dragomirescu CC, Drăgulescu E, Coldea IL, Anton L, *et al.* Antimicrobial activity of plant essential oils against bacterial and fungal species involved in food poisoning and/or food decay. Roum Arch Microbiol Immunol. 2010;69(4):224-30.
18. Vigo E, Cepeda A, Perez-Fernandez R, Gualillo O. In vitro antiinflammatory effect of Eucalyptus globulus and Thymus vulgaris: nitric oxide inhibition in J774A. 1 murine macrophages. Journal of Pharmacy and Pharmacology. 2004;56(2):257-63.
19. Kazemi M. Phytochemical Composition of Thymus vulgaris L. Essential Oil. Journal of Essential Oil Bearing Plants. 2015;18(3):751-3.
20. Hotta M, Nakata R, Katsukawa M, Hori K, Takahashi S, Inoue H. Carvacrol, a component of thyme oil, activates PPARα and γ and suppresses COX-2 expression. Journal of lipid research. 2010;51(1):132-9.
21. Ündeğer Ü, Başaran A, Degen G, Başaran N. Antioxidant activities of major thyme ingredients and lack of (oxidative) DNA damage in V79 Chinese hamster lung fibroblast cells at low levels of carvacrol and thymol. Food and chemical toxicology. 2009;47(8):2037-43.
22. GotfredsenE. The incomplete reference-guide to herbal medicine. Liber herbarium< http://www liberherbarum com/Pn0541 HTM>[Consulta: 23 febrero 2009]. 2013.
23. Fakhari AR, Salehi P, Heydari R, Ebrahimi SN, Haddad PR. Hydrodistillation-headspace solvent microextraction, a new method for analysis of the essential oil components of Lavandula angustifolia Mill. Journal of Chromatography A. 2005;1098(1-2):14-8.
24. Ikeda Y, Murakami A, Ohigashi H. Ursolic acid: An anti-and pro-inflammatory triterpenoid. Molecular nutrition & food research. 2008; 52(1):26-42.
25. Takeda H, Tsuji M, Inazu M, Egashira T, Matsumiya T. Rosmarinic acid and caffeic acid produce antidepressive-like effect in the forced swimming test in mice. European journal of pharmacology. 2002;449(3):261-7.
26. Huang S-s, Zheng R-l. Rosmarinic acid inhibits angiogenesis and its mechanism of action in vitro. Cancer letters. 2006;239(2):271-80.
27. Osakabe N, Yasuda A, Natsume M, Sanbongi C, Kato Y, Osawa T, *et al.* Rosmarinic acid, a major polyphenolic component of Perilla frutescens, reduces lipopolysaccharide (LPS)-induced liver injury in D-galactosamine (D-GalN)-sensitized mice. Free Radical Biology and Medicine. 2002;33(6):798-806.
28. Dubois M, Bailly F, Mbemba G, Mouscadet J-F, Debyser Z, Witvrouw M, *et al.* Reaction of rosmarinic acid with nitrite ions in acidic conditions: discovery of nitro-and dinitrorosmarinic acids as new anti-HIV-1 agents. Journal of medicinal chemistry. 2008;51(8):2575-9.
29. Osakabe N, Yasuda A, Natsume M, Yoshikawa T. Rosmarinic acid inhibits epidermal inflammatory responses: anticarcinogenic effect of Perilla frutescens extract in the murine two-stage skin model. Carcinogenesis. 2004;25(4):549-57.
30. Cheung S, Tai J. Anti-proliferative and antioxidant properties of rosemary Rosmarinus officinalis. Oncology reports. 2007;17(6):1525-31.
31 Yesil-Celiktas O, Sevimli C, Bedir E, Vardar-Sukan F. Inhibitory effects of rosemary extracts, carnosic acid and rosmarinic acid on the growth of various human cancer cell lines. Plant foods for human nutrition. 2010;65(2):158-63.
32. Liang Y-C, Tsai S-H, Tsai D-C, Lin-Shiau S-Y, Lin J-K. Suppression of inducible cyclooxygenase and nitric oxide synthase through activation of peroxisome proliferator-activated receptor-γ by flavonoids in mouse macrophages. FEBS letters. 2001;496(1):12-8.
33. Lo A-H, Liang Y-C, Lin-Shiau S-Y, Ho C-T, Lin J-K. Carnosol, an antioxidant in rosemary, suppresses inducible nitric oxide synthase through down-regulating nuclear factor-κB in mouse macrophages. Carcinogenesis. 2002;23(6):983-91.
34. Cheng A-C, Lee M-F, Tsai M-L, Lai C-S, Lee JH, Ho C-T, *et al.* Rosmanol potently induces

apoptosis through both the mitochondrial apoptotic pathway and death receptor pathway in human colon adenocarcinoma COLO 205 cells. Food and Chemical Toxicology. 2011;49(2):485-93.
35. Horiuchi K, Shiota S, Hatano T, Yoshida T, Kuroda T, Tsuchiya T. Antimicrobial activity of oleanolic acid from Salvia officinalis and related compounds on vancomycin-resistant enterococci (VRE). Biological and Pharmaceutical Bulletin. 2007;30(6):1147-9.
36. Huang M-T, Ho C-T, Wang ZY, Ferraro T, Lou Y-R, Stauber K, *et al.* Inhibition of skin tumorigenesis by rosemary and its constituents carnosol and ursolic acid. Cancer research. 1994;54(3):701-8.
37. Talib WH, Mahasneh AM. Antiproliferative activity of plant extracts used against cancer in traditional medicine. Scientia pharmaceutica. 2010;78(1):33-46.
38. Sertel S, Eichhorn T, Plinkert PK, Efferth T. Cytotoxicity of Thymus vulgaris essential oil towards human oral cavity squamous cell carcinoma. Anticancer research. 2011;31(1):81-7.

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# Targeting Breast Cancer With Bio-inspired Virus Nanoparticles

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ABSTRACT

**Background:** Viral nanoparticles are biodegradable, biocompatible, self-assembling, and highly symmetric, and can be produced in large quantities. Several plant viral nanoparticles (VNPs) have been exploited in different areas of nanobiotechnology, especially drug delivery in cancer therapy. In this study, a flexuous plant virus called potato virus X (PVX) is presented with a unique nanoarchitecture which can increase tumor homing and penetration. Thus, this study aimed to investigate the potential of PVX for delivering Herceptin (HER) in different breast cancer cells and normal cells.

**Methods:** PVX was conjugated to HER by EDC/Sulfo-NHS in two steps. After confirming the conjugation, PVX-HER efficacy and drug activity were investigated in HER2-positive (SKBR3 and SKOV3), HER2-negative (MCF-7 and MDA-MBA-21), and non-tumorigenic epithelia breast cancer (MCF-12A) cell lines after treatment with 10 and 20 µg of the drug. Then, PVX-HER was imaged in SKBR3 cells in to study the nuclear accumulation of the drug at different concentrations.

**Results:** An increased cytotoxic efficiency was observed for PVX-HER vs free-HER in SKBR3 and SKOV3 cell lines. However, the efficacy of PVX-HER failed to increase in MCF-7, MDA-MB-231, and MCF-12A cell lines compared with free-HER after 24 hours. In addition, compared with free-HER, Herceptin nuclear accumulation was increased in SKBR3 cells treated with PVX-HER. Further, the PVX-HER treatment resulted in reduced tumor growth in the HER2-positive cells lines. Finally, a direct relationship was observed between the imaging results and MTT assay in SKBR3.

**Conclusion:** PVX-HER displays a significantly greater cytotoxic activity compared with free-HER in HER2-positive cells.

## Introduction

Nanotechnology is one of the emerging sciences which has attracted a lot of attention in medicine.[1] Generally, nanoparticles are defined as molecules measuring 1 to 100 nanometers. Nanoparticles represent a remarkable structural diversity including dots, nanotubes, wires, and capsuls.[2] In recent years, the use of nanoparticles in medicine has increased, contributing greatly to reductions in effective drug dose, drug side effects, cost, and toxicity.[3]

Nowadays, different nanoparticles have been identified, and most of them are chemical. There are currently various groups of nanoparticles used in medicine, including synthetic and biological nanomaterials. Each of these particles has advantages and disadvantages[4] Viral nanoparticles (VNPs) are naturally occurring bionanomaterials based on pathogenic or nonpathogenic bacterial, plant, or animal viruses. VNPs have self-assembling systems that enable them to proliferate in large quantities within a short time. In addition, they are highly symmetrical, biocompatible, and biodegradable.

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VNPs from plants are preferable to those from animals due to their safety.[5] One of the most popular rod-shaped VNPs is potato virus X (PVX), which is considered an important economic filamentous virus of 515 × 12 nm in size belonging to the genus *Potexvirus* and the family *Alphaflexiviridae*. The virus encompasses economically important pathogens worldwide, with variable symptoms. PVX has a single-stranded positive-sense RNA genome which is approximately 6400 nucleotides long with a cap and poly(A) tail. The genome contains five open reading frames (ORFs) which encode proteins of 166, 25, 12, 8, and around 26 kDa, respectively. Esfandiari *et al.* reported a new isolate of PVX (PVX-Iran, accession no. FJ461343) (figure 1).[6] Over the last decade, virus research has been led toward the beneficial use of viruses independent of their potential pathogenesis.[7]

PVX nanoparticles are used for imaging, drug delivery, and diagnosis.[8] Further, PVX could increase tumor homing and penetration, compared to spherical cowpea mosaic virus (CPMV).[9] Conjugation of PVX to doxorubicin (PVX-DOX) caused a reduction in tumor growth.[10]

The present study aimed to evaluate the PVX for drug delivery in targeted therapy. In addition, based on the results, the PVX-Iran conjugated to Herceptin (PVX-HER) increased the death of two breast cancer cell lines (SKBR3 and SKOV3).[11]

Herceptin (trastuzumab) is an FDA-approved antitumor for breast cancer. It is a humanized monoclonal antibody which can be regarded an effective treatment for HER2-positive breast cancer.[12] Breast cancer is the most common type of cancer among women.[13,14] The present study focused on the use of PVX for delivering Herceptin in HER2-positive, HER2-negative, and normal cells. Herceptin was loaded onto the surface of an isolated PVX6 particles (PVX-HER) by EDC/Sulfo-NHS and accordingly the efficacy of the approach had been examined in SKBR3 and SKOV3 after characterization.[11] In the present study, two triple-negative breast cancer cell lines (MDA-MB-231 and MCF-7), along with MCF-12A non-tumorigenic mammary epithelial cell line, as control normal cells, were examined. Finally, tracking the free-HER and PVX-HER were evaluated in the cells using fluorescent microscopy.

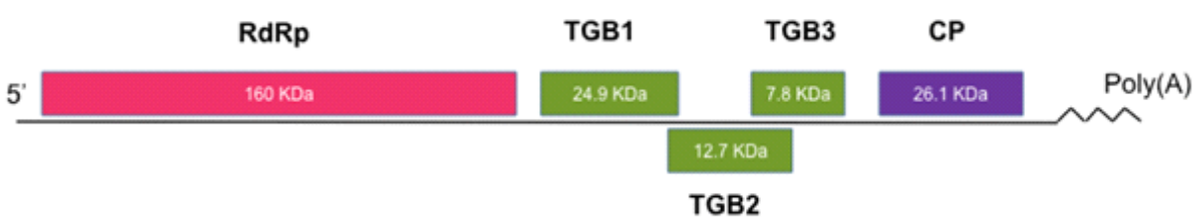


**Figure 1.** Genome organization of PVX-Iran and the proteins encoded by the genome

## Methods

Nicotiana benthamiana is a common experimental host in propagating PVX in large amounts. N. benthamiana leaves were inoculated with phosphate buffer (pH 7.2) for the purpose of purification, which caused an increase in virus accumulation after 2 to 3 weeks, and the leaves were harvested and purified as described previously.[15]

To prepare PVX-HER nanoparticles, we incubated PVX (5 µg µl$^{-1}$) with an EDC/Sulfo-NHS (N- hydroxysulfosuccinimide) cross-linker for 4 hours in reaction buffer (0.5 M NaCl, 0.1 M MES, pH 6). In order to remove the unconjugated free linker, the reaction was quenched by 2-mercaptoethanol and Biogel P-10 column (Bio-Rad). Accordingly, HER (50 µg µl$^{-1}$) was conjugated to PVX-EDC/Sulfo-NHS for 2 h in 0.1 M NaCl buffer (pH 7.5). Then, PVX-HER nanoparticles were purified by a Biogel P-10 column (Biorad).[11] In the present study, the characterization was conducted using Zetasizer (ZEN 3600, Malvern) and also with Western blotting using a PVX-specific primary antibody (DSMZ, PV-0027) and a secondary goat polyclonal antibody against rabbit IgG-HRP (Abcam, ab6721).

*Cell Culture*

SKBR3 and SKOV3, as HER2+ cells lines, and MDA-MB-231 and MCF-7 (as HER2- cells lines) were cultured in RPMI-1640 medium (RPMI, Gibco) supplemented with 10% (v/v) fetal bovine serum (FBS, Gibco) and 1% (v/v) penicillin-streptomycin (Pen-Strep, Gibco). Then, MCF-12A cells as a normal breast cancer was grown in Dulbecco's modified Eagle's medium (DMEM, Gibco) supplemented with 10% (v/v) FBS, 1% (v/v) pen-strep. Finally, all cells were seeded in 96-well plate (*SPL*, Life Sciences, Gyeonggi, Korea) and incubated at 37°C and 5% $CO_2$ in a humidified environment.

*Cytotoxicity Evaluation*

Cells were washed with PBS after reaching a minimum 75% confluence. To this end, they were trypsinized with 0.25% (w/v) trypsin-EDTA (Gibco,

Germany) and seeded at $5\times10^3$ cells per well in a 96-well flat-bottomed plate. Following 24 h incubation at 37°C and 5% $CO_2$, the cells were washed with PBS and treated with free-PVX and PVX-HER at HER concentrations of 10 and 20 µg. After incubation for 24 h, an MTT assay was done according to the manufacturer's protocol. Briefly, 50 mM of MTT solution was added to each well, and the plate was incubated at 37°C with 5% $CO_2$ for 4 h. Then, the MTT dye was reduced at the viable cells, developing purple crystals. The MTT solution was then removed and the cells were suspended in 200 µl DMSO in order to dissolve formazan crystals, and the plate was read at 570 nm. Finally, the data were normalized to the untreated control wells for each experiment. The assays were performed in triplicate and repeated in three independent experiments.

*Tracking of PVX–HER in Cells*

First, HER2/neu-positive breast cancer cells (SKBR3) were cultured. After reaching the cells confluency, they were seeded onto coverslips (SPL, 20012) in 24-well plates ($5\times10^4$ cell/well) and incubated at 37°C, 5% CO2. In the next step, cells were washed and treated with free-HER (10 µg) and PVX-HER (10 or 20 µg). After 4 hours, the cells were washed, fixed in cold solution containing methanol/ethanol (1:1), and washed with PBS. Additionally, 4% BSA in 1X PBS was used for 30 min at room temperature. PVX antibody (DSMZ, PV-0027) was added and shaken for 90 minutes. Finally, the coverslips were washed with PBST (phosphate-buffered saline with Tween-20) and mounted by donkey anti-rabbit IgG-PE (Santa Cruz, sc-3745). The slides were imaged with a LABEX fluorescent inverted microscope.

*Statistical Analysis*

Data were analyzed using analysis of variance (ANOVA), along with LSD post hoc test, on SPSS 16.0. Results are reported as mean ± standard error of mean (SEM). Before determining the level of significance for the tests, the normality of data distribution was tested using Kolmogorov-Smirnov and Shapiro-Wilk tests. The difference in values was significant if the P value was less than 0.001. All experiments were performed in triplicate and repeated at least 3 times.

**Results**

After conducting the mechanical inoculation of N. *benthamiana,* mosaic symptoms were observed within 3 weeks. About 1 mg of pure PVX was extracted from each gram of infected plant. Western blotting with human antibody demonstrated a protein band of HER with a molecular weight of 55 kDa and PVX-HER conjugate with a molecular weight of 83 kDa. Also, the value obtained by Zetasizer for HER-PVX was -6.0 that was between PVX (-21.4) and HER2 (-1.48) charges (figure 2).

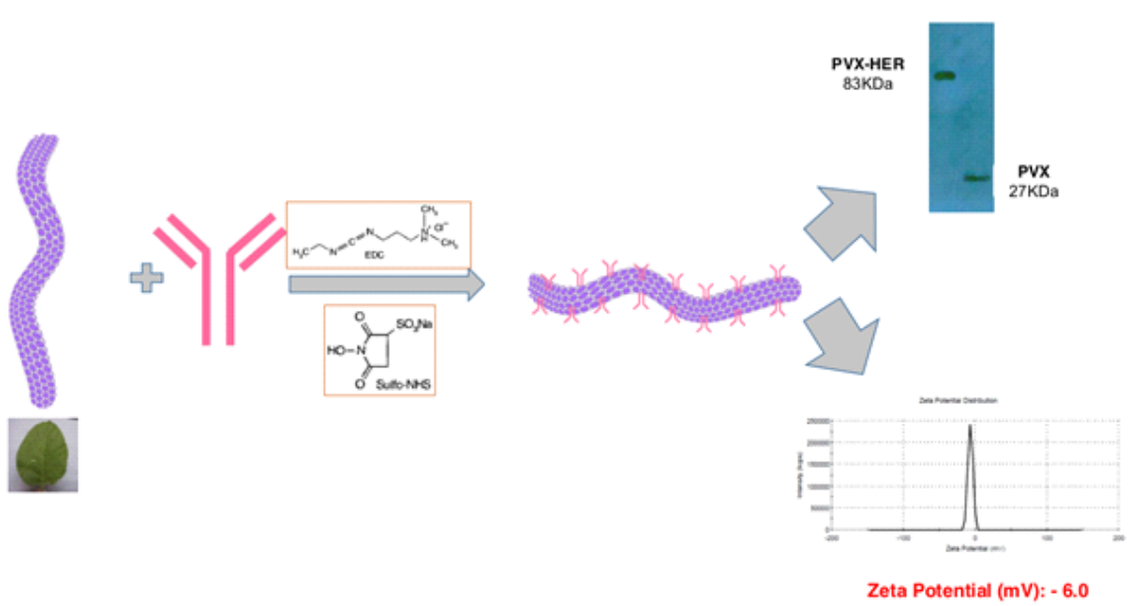


**Figure 2.** Scheme of potato virus X (PVX) conjugated to Herceptin (HER) with EDC/Sulfo-NHS in a two-step protocol western blot with PVX-specific antibody (DSMZ, PV-0027) and zeta potential was used to confirm conjugation.

In the present study, cytotoxic activity of HER-PVX against HER2-posive, HER2-negative, and normal cell lines was examined. SKBR3, SKOV3, MDA-MB-231, MCF-7, and MCF-12A cells were treated with 10 µg and 20 µg of PVX-HER and free-HER for 24 hours. The results of cell viability assay are presented in Table 1.

**Table 1.** The mean percentage ± SEM of cell viability for breast cancer cell lines by MTT

| | PVX-HER (10 µg) | Free-HER (10 µg) | PVX-HER (20 µg) | Free-HER (20 µg) |
|---|---|---|---|---|
| SKBR3 | 17.973 ± 0.005 | 47.697 ± 0.004 | 16.067 ± 0.004 | 42.510 ± 0.003 |
| SKOV3 | 28.003 ± 0.005 | 37.641 ± 0.004 | 22.916 ± 0.006 | 33.518 ± 0.002 |
| MCF-7 | 96.322± 0.010 | 98.478 ± 0.009 | 96.569 ± 0.0108 | 95.859 ± 0.0135 |
| MDA-MB-231 | 97.420 ± 0.009 | 97.856 ± 0.011 | 96.889 ± 0.005 | 96.661 ± 0.0092 |
| MCF-12A | 98.590 ± 0.010 | 98.561 ± 0.011 | 99.059 ± 0.006 | 98.559 ± 0.009 |

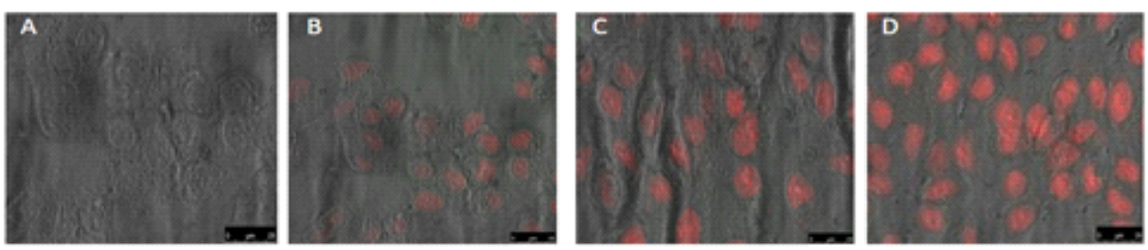


**Figure 3.** Nuclear accumulation of Herceptin in SKBR3 after 3 hours of incubation (A) control, (B) free-HER 10 µg, (C) PVX-HER 10 µg, and (D) PVX-HER 20 µg.

In addition, fluorescence microscopy was performed to monitor Herceptin accumulation in the cells in order to investigate the efficacy of PVX-HER compared with free-HER. SKBR3 cells were treated with free-HER (10 µg) and PVX-HER (10 µg and 20 µg) for 4 hours. Herceptin accumulated inside the nuclei of SKBR3 cells after 3 hours (figure 3). Localized delivery of Herceptin in the nucleus is more than that of cytoplasm.[16] Fluorescence intensity is positively correlated with nuclear Herceptin accumulation. Thus, the greater fluorescence intensity in the cells treated with PVX-HER compared with free-HER indicates the greater efficacy of the PVX delivery system.

## Discussion

The use of VNPs in medicine has expanded rapidly over the past 20 years to span a wide range of applications from imaging to targeted drug delivery. VNPs are naturally occurring bionanomaterials with unique symmetrical outer surface.[17] They are biodegradable, nontoxic for mammals,[18] and are produced at lower costs.[19] Some studies have emphasized their use as contrast agents in MRI imaging and as facilitators in drug delivery.[5,20]

PVX is the type member of the genus *Potexvirus* with flexible rod particles measuring 515 ×13 nm.[21] PVX has proved more effective in tumor homing and penetration compared with spherical or isometric virus.[20]

During recent years, the benefits of PVX have increased the use of this virus as a VNP, which have been emphasized in different cases such as the use of PVX for drug delivery system for Doxorubicin (DOX)[10] and Herceptin for cancer therapy.[11] The development of coadministered PVX-DOX in situ vaccination for treatment is a possibility.[22]

Herceptin is the trade name for trastuzumab, approved by the FDA in 1998 in order to treat human epidermal growth factor receptor (HER) 2-positive breast cancer. Herceptin is an expensive monoclonal antibody which can cause serious side effects.[23] The conjugation of drugs to nanoparticles helps to enhance therapeutic efficacy and reduce side effects.[24]

In the previous study, PVX-HER nanoparticles significantly increased the death rate of HER2-positive cancer cells (SKBR3 and SKOV3). In the present study, the effect of this nanoparticle on other cell lines was investigated to complete the previous information. Thus, the effect of PVX-HER on cell viability was tested in SKBR3 (breast cancer) and SKOV3 (ovarian cancer) as HER2-positive cells, MDA-MB-231 (breast cancer) and MCF-7 (breast cancer) as HER2-negative cell lines, and MCF-12A as a nontumorigenic epithelial breast cell line. The results of ANOVA indicated a significantly increased cell death in SKBR3 (figure 4-A) and SKOV3 (figure 4-B) cell lines when treated with PVX-HER compared with free-HER. However, in MDA-MB-231 (figure 4-C), MCF-7 (figure 4-D), and MCF-12A (figure 4-E) cell lines, there was no significant difference in the mean absorption values between PVX-HER and free-HER. Therefore, the results provide a clear answer to how PVX-HER works on breast cancer cells. Further, SKBR3 cells were expected to address the question about the uptake of PVX-HER in the cells based on the results obtained by MTT assay. Fluorescence microscopy was used to monitor nuclear accumulation of Herceptin. As reported in previous studies, Herceptin accumulated within the nuclei of the SKBR3 cells after 3h.[16] Then, a greater nuclear accumulation of Herceptin was observed in SKBR3 cells treated with 10 and 20 µg of PVX-HER compared with 10 µg of free-HER, indicating the greater efficacy of the PVX-based drug delivery systems.

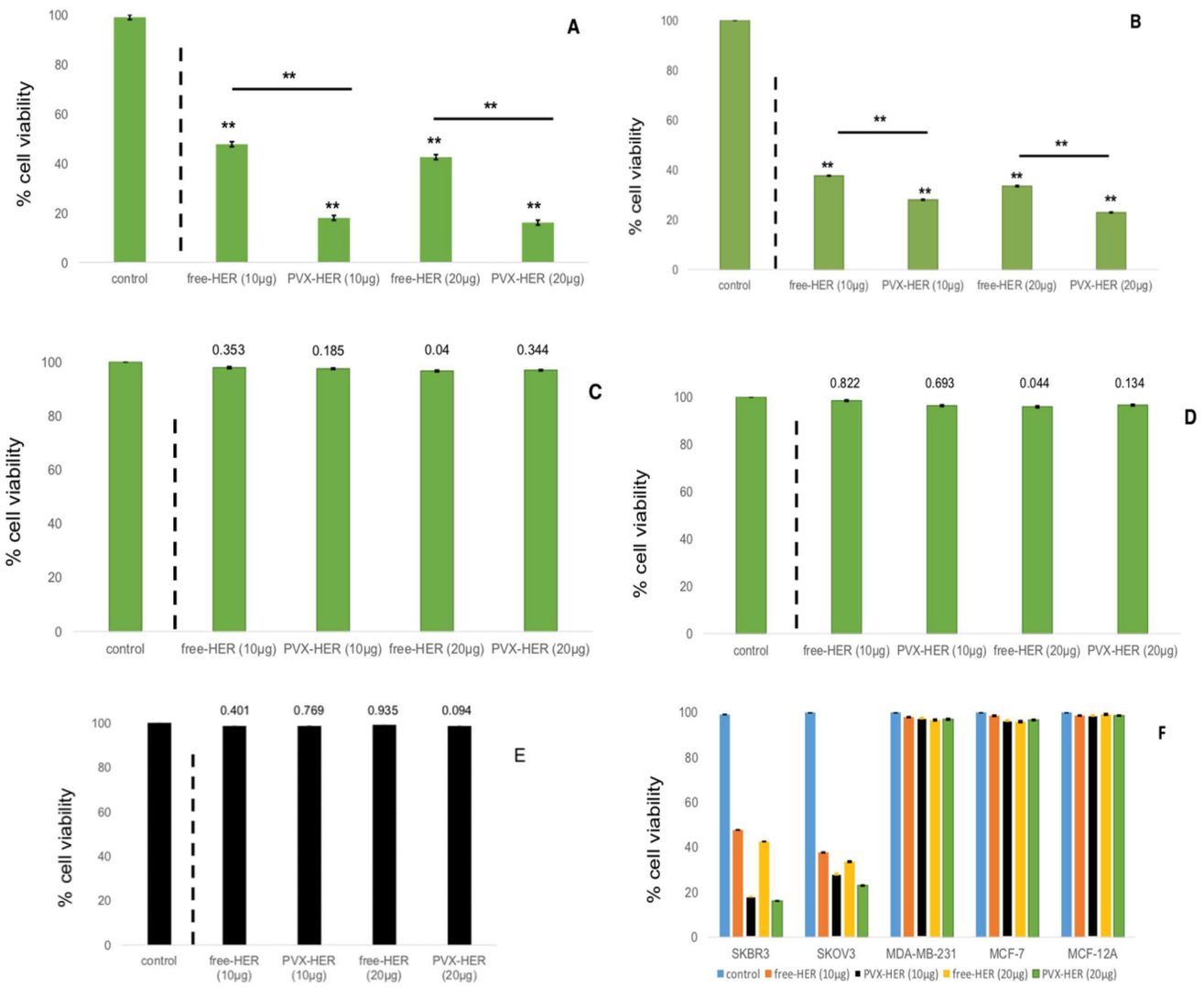


**Figure 4.** In vitro cell viability were determined using MTT assay after 24 h treatment with free-HER (10 µg), PVX-HER (10 µg), free-HER (20 µg), PVX-HER (20 µg), and control. Data represent normalized mean values in SKBR3 (A), SKOV3 (B), MDA-MB-231 (C), MCF-7 (D), and MCF-12A (E) cell lines. Asterisks indicate significant difference between free-HER and PVX-HER in SKBR3 (A) and SKOV3 (B) cell lines **P ≤ 0.001. In the case of insignificant differences, the P values are mentioned on the columns in the MDA-MB-231 (C), MCF-7 (D), and MCF-12A (E). Cell viability in control (blue), free-HER 10 µg (orange), PVX-HER 10 µg (black), free-HER 20 µg (yellow), PVX-HER 20 µg (green) on SKBR3, SKOV3, MDA-MB-231, MCF-7, MCF-12A cell lines (F).

PVX-HER displayed a significantly greater cytotoxic activity compared with free-HER in HER2-positive cells. Therefore, the relationship between the imaging results and the MTT assay following 24 hours of incubations with 10 and 20 µg of PVX-HER may be explained. However, PVX-HER failed to increase the cytotoxic efficacy in HER2-negative and normal epithelial breast cell lines compared with free-HER (figure 4-F).

In general, based on the drug delivery features of PVX, the results of the present study were consistent with the findings of the previous studies on VNPs. Doxorubicin was covalently conjugated to CMV,[25] CPMV,[26, 27] PVX,[10] and RCNMV[28] in order to enhancethe drug delivery.

The results of this study, as the first research on PVX-HER nanoparticles, together with that of the previous study, confirm the effect of PVX-HER nanoparticles on breast cancer cells.

As conclusion, the present study recommends the use of the new isolated PVX, as a plant viral nanoparticle, for delivering Herceptin. Based on the results, Herceptin loaded onto the surface of PVX increases the drug efficacy in HER2-positive cancer cells. The results can contribute to development of filamentous plant virus-based drug delivery systems in cancer treatment.

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**Conflict of Interest**

The author declares no conflict of interests.

**References:**


1. Basavaraj K. Nanotechnology in medicine and relevance to dermatology: Present concepts. Indian journal of dermatology. 2012;57(3):169.
2. Longmire M, Choyke PL, Kobayashi H. Clearance properties of nano-sized particles and molecules as imaging agents: considerations and caveats. 2008.
3. De Jong WH, Borm PJ. Drug delivery and nanoparticles: applications and hazards. International journal of nanomedicine. 2008; 3(2):133.
4. Yildiz I, Shukla S, Steinmetz NF. Applications of viral nanoparticles in medicine. Current opinion in biotechnology. 2011;22(6):901-8.
5. Steinmetz NF. Viral nanoparticles as platforms for next-generation therapeutics and imaging devices. Nanomedicine: Nanotechnology, Biology and Medicine. 2010;6(5):634-41.
6. Esfandiari N, Kohi-Habibi M, Hohn T, Pooggin MM. Complete genome sequence of an Iranian isolate of Potato virus X from the legume plant Pisum sativum. Virus genes. 2009;39(1):141-5.
7. Young M, Debbie W, Uchida M, Douglas T. Plant viruses as biotemplates for materials and their use in nanotechnology. Annu Rev Phytopathol. 2008;46:361-84.
8. Lico C, Benvenuto E, Baschieri S. The two-faced Potato Virus X: from plant pathogen to smart nanoparticle. Frontiers in plant science. 2015;6.
9. Shukla S, Ablack AL, Wen AM, Lee KL, Lewis JD, Steinmetz NF. Increased tumor homing and tissue penetration of the filamentous plant viral nanoparticle Potato virus X. Molecular pharmaceutics. 2012;10(1):33-42.
10. Le DH, Lee KL, Shukla S, Commandeur U, Steinmetz NF. Potato virus X, a filamentous plant viral nanoparticle for doxorubicin delivery in cancer therapy. Nanoscale. 2017;9(6):2348-57.
11. Esfandiari N, Arzanani MK, Soleimani M, Kohi-Habibi M, Svendsen WE. A new application of plant virus nanoparticles as drug delivery in breast cancer. Tumor Biology. 2016;37(1):1229-36.
12. Baselga J, Albanell J. Mechanism of action of anti-HER2 monoclonal antibodies. Annals of oncology. 2001;12(suppl_1):S35-S41.
13. Armuss A. Breast cancer update. Versicherungsmedizin. 2014;66(2):68-71.
14. Hudis CA. Trastuzumab—mechanism of action and use in clinical practice. New England Journal of Medicine. 2007;357(1):39-51.
15. Esfandiari N, Arzanani MK, Koohi-Habibi M. The study of toxicity and pathogenicity risk of potato virus X/Herceptin nanoparticles as agents for cancer therapy. Cancer Nanotechnology. 2018.
16. Liu Y, Cheng D, Liu X, Liu G, Dou S, Xiao N, *et al*. Comparing the intracellular fate of components within a noncovalent streptavidin nanoparticle with covalent conjugation. Nuclear medicine and biology. 2012;39(1):101-7.
17. Lockney DM, Guenther RN, Loo L, Overton W, Antonelli R, Clark J, *et al.* The Red clover necrotic mosaic virus capsid as a multifunctional cell targeting plant viral nanoparticle. Bioconjugate chemistry. 2010;22(1):67-73.
18. Singh P, Prasuhn D, Yeh RM, Destito G, Rae CS, Osborn K, *et al.* Bio-distribution, toxicity and pathology of cowpea mosaic virus nanoparticles in vivo. Journal of controlled release. 2007;120(1):41-50.
19. Lebel M-È, Chartrand K, Leclerc D, Lamarre A. Plant viruses as nanoparticle-based vaccines and adjuvants. Vaccines. 2015;3(3):620-37.
20. Steinmetz NF. Viral nanoparticles in drug delivery and imaging. ACS Publications; 2013.
21. Steinmetz NF, Manchester M. Viral nanoparticles: tools for material science and biomedicine: Pan Stanford Publishing; 2011.
22. Lee KL, Murray AA, Le DH, Sheen MR, Shukla S, Commandeur U, *et al.* Combination of plant virus nanoparticle-based in situ vaccination with chemotherapy potentiates antitumor response. Nano letters. 2017;17(7):4019-28.
23. Nahta R, Esteva FJ. Herceptin: mechanisms of action and resistance. Cancer letters. 2006; 232(2):123-38.
24. Glasgow MD, Chougule MB. Recent developments in active tumor targeted multifunctional nanoparticles for combination chemotherapy in cancer treatment and imaging. Journal of biomedical nanotechnology. 2015; 11(11):1859-98.
25. Zeng Q, Wen H, Wen Q, Chen X, Wang Y, Xuan W, *et al.* Cucumber mosaic virus as drug delivery vehicle for doxorubicin. Biomaterials. 2013;34(19):4632-42.
26. Aljabali AA, Shukla S, Lomonossoff GP, Steinmetz NF, Evans DJ. Cpmv-dox delivers. Molecular pharmaceutics. 2012;10(1):3-10.
27. Pokorski JK, Breitenkamp K, Liepold LO, Qazi S, Finn M. Functional virus-based polymer–protein nanoparticles by atom transfer radical polymerization. Journal of the American Chemical Society. 2011;133(24):9242-5.
28. Cao J, Guenther RH, Sit TL, Opperman CH, Lommel SA, Willoughby JA. Loading and release mechanism of red clover necrotic mosaic virus derived plant viral nanoparticles for drug delivery of doxorubicin. Small. 2014; 10(24):5126-36.

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# Delivering Bad News: Deal with Collusion for Love

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Bad news is "any news that adversely and seriously affects an individual's view of his or her future,"[1] and talking about one's cancer diagnosis is one of them. Delivering bad news is a complex, necessary communication skill that should be effectively learned, especially by oncologists. Giving bad news has two key parts: transferring information to patients and responding to patients' emotional reactions.[2]

Every patient has a unique cultural and family background; therefore, individualized care communication is critical.

On a typical day in my office, I was sitting behind my desk and waiting for the next patient to arrive. A man in his thirties poked his head around my office door and mentioned that the patient was his mother and desperately asked me not to reveal anything about her diagnosis to her.

"Doctor, my mother is 86 years old and hope is the only thing that has kept her alive. My father passed away last year, and I don't want her to suffer more," he said. Then he stared at me for a few seconds waiting for my approval.

He left the room and quickly returned while pushing his mother in a wheelchair. She was referred to me by her oncologist for palliative care consultation. The woman in the wheelchair had such a big smile on her face that I dared to crack a joke about how his son was pushing the wheelchair and if she was not happy about the ride, I would have his driver's license revoked.

Noticing "terminal breast cancer" on her consultation sheet erased the smile from my face. Her oncologist had left the note that she was "NOT suitable for any invasive treatment." The son was still standing behind the wheelchair signaling by constantly moving his hands to remind me to keep our big secret. It was so distracting that I decided to find an excuse to send him away. "Sir, please pick up a new patient folder from the front desk at the end of the corridor."

As soon as he left, the mother leaned toward me and whispered, "I have advanced cancer and I'm going to die soon. I don't want my son to know how bad this is. He has already had enough pain since his father passed away last year." I instantly realized that the situation is more complicated than I expected, and I should act very tactfully. The son returned with the folder and I struggled to pretend nothing happened in his absence.

"What can I do for you, Mrs. A?" I asked. It was not my usual opening question. Before she had a chance to say anything, her son jumped in and said: "She has an old peptic ulcer that makes her uncomfortable, especially after eating; and also she needs some appetite pills to gain more weight."

It was time for me to make a serious face and asking him to allow his mother to answer the questions. "Yes, yes, he's right. My stomach is painful all the time, and I feel nauseous every time I try to …," she stopped speaking. After an uncomfortable pause, she suddenly broke down in tears and asked her son to forgive her for not being able to stay with him long enough.

There was not much work for me to do. The "news" were broken. I was not certain how they would react to this new situation. Perhaps it would help to bring them closer to each other.

This is a common scenario in my clinic: "collusion for love!" Every day I see patients with terminal cancer who have no clue about their conditions, and I am warned by their relatives not to disclose the diagnosis or prognosis to them. In this particular case, it was more complicated: a tripartite collusion. Although collusion with relatives is not recommended, sometimes (especially in busy clinics) it is a more convenient option for physicians than disclosure.

While western medicine emphasizes honest

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disclosure of bad news to patients by physicians, depending on the cultural context, every patient needs an individualized response from the physician.

In today's Iranian palliative care practice, considering the family dynamics is unavoidable for the physician to provide the best solution. This dynamic is referred to as "relational autonomy." In eastern societies in which family unit is the main supporting source for the patients—economically, emotionally, socially, and spiritually—dealing with family's involvement in patients' medical decision making is deemed critical.[3] Changing the paradigm from just giving bad news to "sharing news" is a more preferred policy. This strategy has its own challenges and barriers, but, by learning and following the available guidelines, physicians can achieve the best results.[2]

**Conflict of Interest**

The authors have nothing to disclose.

**References**

1. Buckman R. Breaking bad news: why is it still so difficult? Br Med J (Clin Res Ed). 1984;288: 1597-9.
2. Parker PA, Banerjee SC. Sharing serious news with cancer patients: strategies that can help. Oncology. 2018;32(7):334-338.
3. Ho A. Relational autonomy or undue pressure? Family's role in medical decision-making. Scand J Caring Sci. 2008;22(1):128-35.

Review Article Open Access

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# Diagnostic Efficacy of Technetium-99m-Sestamibi Scintimammography in Comparison with Mammography to Detect Breast Lesions: A Systematic Review

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ABSTRACT

**Background:** To systematically review the performance of scintimammography compared with mammography in detecting breast lesions.

**Methods:** A literature search was performed in PubMed and ScienceDirect databases with "scintimammography AND breast lesions," "mammography AND breast lesions," "diagnostic value," and "accuracy" as keywords to identify all related studies published in English from January 1, 2000, to August 1, 2017. Twenty-five studies, with a total of 4094 patients with clinically suspicious breast lesions, were included in the final analysis to assess the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of scintimammography vs. mammography in detecting breast lesions.

**Results:** The sensitivity and specificity of mammography were 75.82 ± 10.53 (95% confidence interval [CI], 50-84) and 59.58 ± 22.79 (95% CI, 20-91.4), respectively. The PPV and NPV of mammography were 75.60 ± 2.21 (95% CI, 42-93) and 61.62 ± 1.67 (95% CI, 39.1-86), respectively. The sensitivity of scintimammography was 86.64 ± 8.84 (95% CI, 58.3-100), and the specificity was 83.42 ± 10.74 (95% CI, 60-100). The PPV and NPV of scintimammography were 82.10 ± 11.65 (95% CI, 58-98.30) and 81.02 ± 17.00 (95% CI, 45-100), respectively.

**Conclusions:** Although mammography has a high sensitivity in the examination of older patients with fatty breast tissue, it is less reliable in detecting breast lesions in young and premenopausal patients with dense breasts. Diagnostic accuracy of scintimammography, as a functional imaging modality, is not affected by breast density, contrary to mammography. Therefore, scintimammography can improve the specificity of mammography.

## Introduction

Breast cancer is the most frequent malignancy in women, affecting 1 in 13 women in their lifetime.[1-4] Patients with breast cancer who have it detected at an early stage will have a better survival rate.[5] The most widely used tool for detection of breast cancer, besides the physical examination, is mammography, which has a high accuracy in detecting breast lesions.[6] The sensitivity of mammography in patients with dense breasts may be low;[7] and, in patients with fibrocystic changes of the breast, mammographic detection of breast carcinoma may be difficult. Mammography has low specificity in distinguishing

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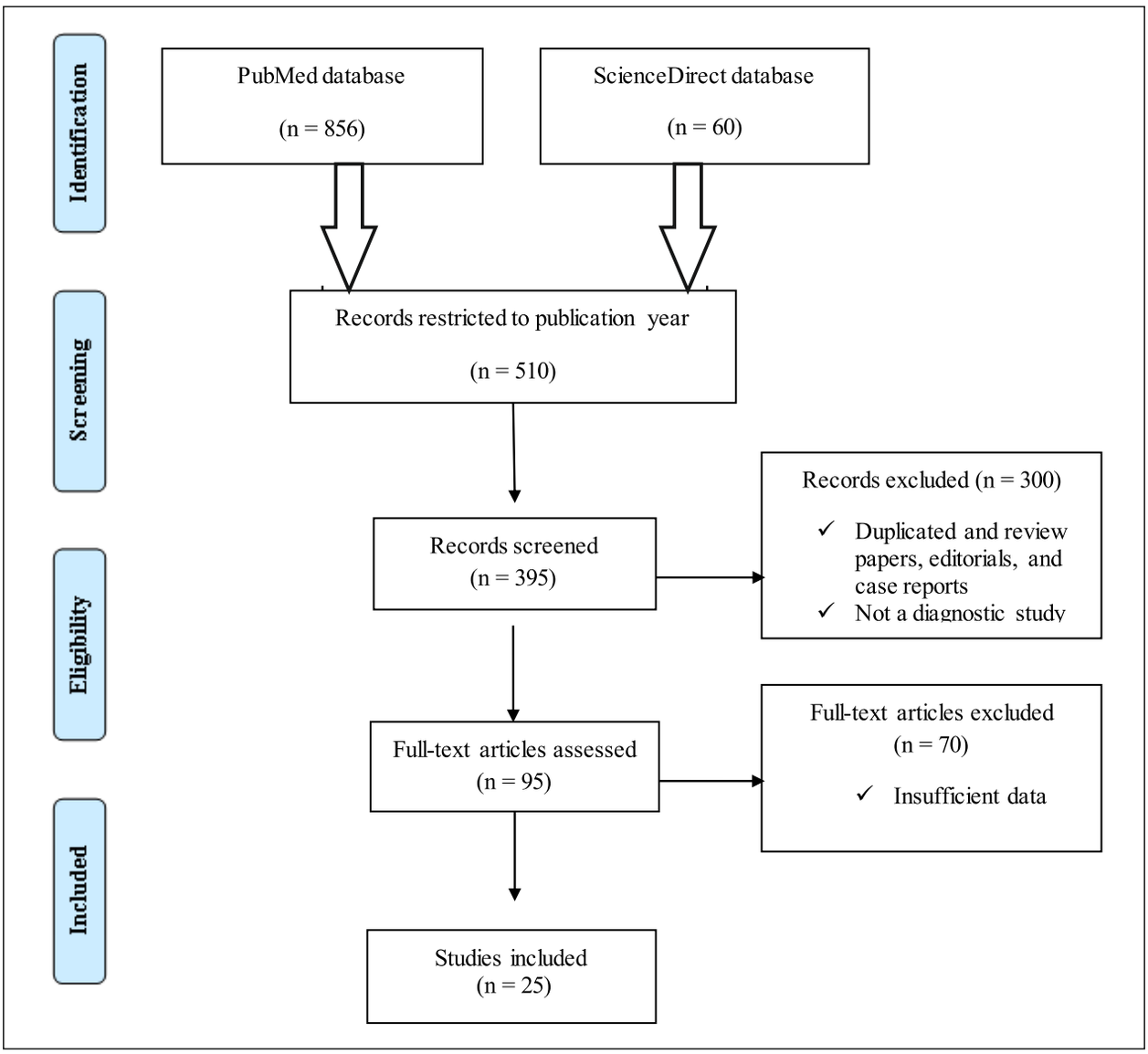


**Figure 1.** Flowchart summarizing search strategy and study selection

between malignant and benign processes. Therefore, it is impossible to detect breast lesions using mammography alone in some cases.[8,9]

The high rate of breast biopsies in patients with benign lesions has encouraged the use of non-invasive imaging modalities with greater accuracy such as magnetic resonance imaging (MRI), ultrasound (US), positron emission tomography (PET), and scintigraphy.[10] Recently, it was demonstrated that technetium-$^{99m}$-sestamibi ($^{99m}$Tc-MIBI) accumulates in different types of tumors. For suspected breast lesions, some studies demonstrated that scintigraphy with $^{99m}$Tc-MIBI differentiated benign from malignant lesions.[11] $^{99m}$Tc-MIBI scintigraphy is a noninvasive diagnostic modality in evaluating breast carcinoma in the field of nuclear medicine.

The aim of the present systematic review was to compare the performance of scintimammography with mammography in the detection of breast lesions.

## Methods

*Search strategy*

A literature search was performed in PubMed and ScienceDirect databases using the following keywords: "scintimammography (mammoscintigraphy) AND breast lesions," "mammography AND breast lesions," "diagnostic value," and "accuracy." Articles that cited related studies were also searched to find any related publication (using PubMed, Europe PubMed Central, and Google Scholar citation tracking tools). An updated search strategy was developed in order to identify all related papers published in English from January 1, 2000, to August 1, 2017. The full search strategy is presented in Figure 1.

*Selection of studies*

Titles and abstracts obtained from the literature search were examined for eligibility. Information given in the titles and abstracts had to suggest that the study (1) included patients with suspected breast

lesions, (2) conducted scintimammography or mammography in those patients, and (3) evaluated diagnostic values of the tests (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]). Full-text articles were retrieved for further assessment.

*Inclusion/exclusion criteria*

Studies were included if they assessed sensitivity, specificity, PPV, or NPV of scintimammography or mammography in the diagnosis of breast lesions. We included studies with or without comparator groups. Editorials, case reports, and review articles were excluded. All eligible papers were compared independently assessed by two authors for predefined inclusion criteria.

*Data extraction*

Two authors independently extracted the following data from each included study: the first author's name, publication year, journal, country, details of study design, number of patients and their characteristics, index test or tests, reference standard, sensitivity, specificity, PPV, and NPV. The diagnostic performance of scintimammography and mammography in the detection of breast lesions was assessed by comparing index test results with the reference standards. Any discrepancies between the two researchers were resolved through consensus.

The patients were classified as true positive (TP) when both the index test (i.e., scintimammography or mammography) and the reference standard (pathological assessment) detected breast lesion, true negative (TN) when neither test detected breast lesion, false negative (FN) when the index test failed to detect a breast lesion identified by the reference standard, and false positive (FP) when the index test incorrectly suggested a breast lesion not detected by the reference standard. Sensitivity was defined as TP/(TP+FN) and specificity as TN/(TN+FP).

*Quality assessment*

We used the revised Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) to evaluate the quality of the included studies. Assessment of the risk of bias and applicability concerns were performed in 4 domains including patient selection, index test, reference standard, and flow and timing. Applicability concern and risk of bias were judged as low, high, or unclear for the various QUADAS domains.[12]

*Statistical analysis*

SPSS 16 was used for data analysis using descriptive statistics. Sensitivity, specificity, PPV, and NPV, along with 95% confidence intervals (CIs), were calculated for each study.

**Table 1.** Main characteristics of the studies evaluating the diagnostic value of scintimammography

| First author (Year) | Number of patients | Mean age (Year) | Index test | Sensitivity (%) | Specificity (%) | PPV* (%) | NPV** (%) |
|---|---|---|---|---|---|---|---|
| Chen (2000)[13] | 35 | ___ | Scintimammography (Planar) | 77.8 | 88.2 | ___ | ___ |
| Prats (2001)[14] | 253 | 53.5 | Scintimammography (Planar) | 91 | 71 | 81 | 85 |
| | | | Palpable lesions | 97 | 57 | 82 | 86 |
| | | | Nonpalpable lesions | 77 | 83 | 78 | 82 |
| Yildizi (2001)[15] | 63 | 55 | Scintimammography (Planar) | 100 | 96 | 88 | 100 |
| Koukouraki (2001)[16] | 116 | ___ | Scintimammography (Planar) | 95 | 80 | 92 | 86 |
| Aguilar (2001)[17] | 36 | 57 | Scintimammography (Planar) | 78.9 | 72.2 | 75 | 76.5 |
| Horne (2001)[18] | 35 | 53.5 | Scintimammography (Planar) | 89.4 | 80 | 85 | 85.7 |
| Bagni (2003)[19] | 45 | 51 | Scintimammography (Planar) | 84 | 71 | 94 | 45 |
| Sampalis (2003)[20] | 1243 | 56 | Scintimammography (Planar) | 93 | 87 | 58 | 98 |
| Myslivecek (2004)[21] | 303 | ___ | Scintimammography (Planar) | 82 | 91 | ___ | ___ |
| | | | Scintimammography (SPECT) | 92 | 91 | | |
| Fondrinier (2004)[22] | 41 | ___ | Scintimammography (Planar) | 58.3 | 81 | 78 | 63 |
| Cicco (2004)[23] | 40 | 52 | Scintimammography (Planar) | 87.5 | 60.0 | 72.4 | 80 |
| Kim (2005)[24] | 520 | ≤45 | Scintimammography (Planar) | 79.6 | 78.6 | ___ | ___ |
| | | >45 | | 85.7 | 77.5 | | |
| Prats (2007)[25] | 308 | 54 | Scintimammography (Planar) | 85 | 95 | 80 | 96 |
| | | | Palpable lesions | 97 | 94 | 91 | 98 |
| | | | Nonpalpable lesions | 68 | 96 | 68 | 96 |
| Usmani (2008)[26] | 36 | 47.13 | Scintimammography (Planar) | 86 | 88 | 96 | 64 |
| Habib (2009)[27] | 28 | ___ | Scintimammography (Planar) | 93.3 | 71.4 | 87.5 | 83.3 |
| Cesare (2011)[28] | 172 | ___ | Scintimammography (SPECT) | 100 | 93.5 | 92.5 | 100 |

**PPV: Positive predictive value; **NPV: Negative predictive value*

## Results

Twenty-five studies assessing the sensitivity, specificity and/or PPV and NPV of scintimammography or mammography in the detection of breast lesions were included in the analysis. The studies included a total of 4094 patients (age: 51.68 ± 4.07 y) with clinically suspicious breast lesions. Table 1 shows the main characteristics of the 16 studies evaluating the diagnostic value of scintimammography, and Table 2 shows the main characteristics of the 3 studies assessing the diagnostic value of mammography. Six studies compared the diagnostic value of scintimammography with mammography (Table 3).

Sensitivity and specificity of mammography were 75.82 ± 10.53 (95% CI, 50-84) and 59.58 ± 22.79 (95% CI, 20-91.4), respectively. Also, mammography had a PPV of 75.60 ± 2.21 (95% CI, 42-93) and an NPV of 61.62 ± 1.67 (95% CI, 39.1-86).

The sensitivity of scintimammography was 86.64 ± 8.84 (95% CI, 58.3-100), and its specificity was 83.42 ± 10.74 (95% CI, 60-100). PPV and NPV of scintimammography were 82.10 ± 11.65 (95% CI, 58-98.30) and 81.02 ± 17.00 (95% CI, 45-100), respectively.

**Table 2.** Main characteristics of the studies evaluating the diagnostic value of mammography

| First author (Year) | Number of patients | Mean age (Year) | Index test | Sensitivity (%) | Specificity (%) | PPV* (%) | NPV** (%) |
|---|---|---|---|---|---|---|---|
| Hoi (2000)[29] | 60 | 60 | Mammography | 84 | 80 | 93 | 63 |
| Chen (2002)[30] | 60 | 60 | Mammography | 84 | 80 | 93 | 63 |
| Kotsianos-Hermle (2009)[31] | 97 | 97 | Mammography | 76.5 | 91.4 | ___ | ___ |

**PPV: Positive predictive value; **NPV: Negative predictive value*

**Table 3.** Main characteristics of the studies evaluating the diagnostic value of mammography

| First author (Year) | Number of patients | Mean age (Year) | Index test | Sensitivity (%) | Specificity (%) | PPV* (%) | NPV** (%) |
|---|---|---|---|---|---|---|---|
| Mulero (2000)[32] | 109 | ___ | MG (dense breasts) | 81 | 28 | ___ | ___ |
| | 8 | under 30 | MG (young females) | 50 | 20 | ___ | ___ |
| | 24 | ___ | MG (previous surgery) | 80 | 42 | ___ | ___ |
| | | | SM (dense breasts) | 88 | 90 | ___ | ___ |
| | | | SM (young females) | 100 | 100 | ___ | ___ |
| | | | SM (previous surgery) | 80 | 100 | ___ | ___ |
| Sun (2000)[33] | 81 | 55 | MG | 83 | 47 | ___ | ___ |
| | | | SM (Planar) | 88 | 87 | ___ | ___ |
| Lumachi (2001)[34] | 87 | 47 | MG | 80.6 | 60.0 | 90.6 | 39.1 |
| | | | SM (Planar) | 80.6 | 93.3 | 98.3 | 50.0 |
| Cwikła (2003)[35] | 154 | ___ | MG | 69 | 72 | 81 | 57 |
| | | | SM (Planar) | 87 | 65 | 81 | 75 |
| Krishnaiah (2003)[36] | 94 | 44 | MG | 65 | 72 | 42 | 86 |
| | | | SM (Planar) | 83 | 83 | 59 | 94 |
| Ozulker (2010)[37] | 46 | 46 | MG | 81 | 63 | 54 | 86 |
| | | | SM (Planar) | 93 | 86 | 78 | 96 |

MG: Mammography; SM: Scintimammography; *PPV: Positive predictive value; **NPV: Negative predictive value

## Discussion

Although mammography has high sensitivity in the examination of older patients with fatty breast tissue, it is less reliable in detecting breast lesions in patients with dense breasts, breast implants, and architectural distortion after radiation therapy or surgery.[7] In a mammography unit with both a rhodium (Rh) anode and a molybdenum (Mo) anode, filtered with rhodium and molybdenum, respectively, the mammograms obtained by using the Mo/Mo combination were preferred. However, the mammograms obtained with the Rh/Rh combination were better than the Mo/Mo mammograms for young patients with dense breasts.[38]

$^{99m}$Tc-MIBI scintigraphy plays an important role in localizing the breast tumors when ultrasound or mammography is not contributory. Diagnostic accuracy of scintimammography, as a functional imaging modality, is not affected by breast density, contrary to mammography, because of the advantages of labeling with $^{99m}$Tc sestamibi radiopharmaceutical. Its uptake in the lesion involves several causes, including mitochondrial activity, angiogenesis, and presence of malformed vessels, but does not depend on the presence of architectural distortion and localized variation in breast density.[39-45]

The intensity of $^{99m}$Tc-MIBI uptake varies from mild to high depending on factors such as the type, size, location, and hormonal factors. The size of the lesion affects sensitivity. The sensitivity for palpable lesions is significantly higher than that for nonpalpable ones.[46,47] Another clinical application of $^{99m}$Tc-MIBI scintigraphy is the detection of patients with microcalcifications. Scintimammography seems to be helpful in differentiating malignant from benign calcifications and leads to a decrease in the frequency of breast biopsies.[48] Some studies had separated the statistics for palpable and nonpalpable lesions because of the difference in management strategy.[14, 25, 49] Palmedo reported that the total specificity and sensitivity of 99mTc-MIBI scintimammography were 69% and 71%, respectively; for palpable lesions, however, the specificity and sensitivity of scintimammography increased to 91% and 83%, respectively.[49] Palmedo reported similar results in another research and showed that the total sensitivity of scintimammography was 88%, increasing to 100% for palpable lesions.[50] Another study reported that the sensitivity of scintimammography in detecting nonpalpable lesions was 78.3% compared with 89.1% for mammography; but, in palpable lesions, the sensitivity of scintimammography (91.3%) was higher than the sensitivity of mammography (78.2%).[51] Based on the clinical studies, $^{99m}$Tc-MIBI scintimammography is more accurate than mammography in differentiating palpable breast lesions. Therefore, the utility of the technique has been emphasized to decrease the frequency of breast biopsies.[1] As mentioned, the sensitivity of scintimammography can be affected by tumor size, and the specificity and sensitivity of $^{99m}$Tc-MIBI scintimammography increase for palpable breast lesions.[49, 50] Therefore, attempts have been made to enhance the sensitivity of scintimammography for the detection of cancer, especially for nonpalpable and ≤1-cm lesions.[52, 53] Myslivecek compared the specificity and sensitivity of scintimammography in detecting primary breast lesions with both single-photon emission computed tomography (SPECT) and planar images (Table 1). The results showed that SPECT scintimammography was slightly (10%) more sensitive than planar scintigraphy.[21] Taillefer and Khalkhali reported PPV values of 97.7% and 76.9%, respectively, and NPV values were 81% and 97%, respectively.[54, 55] Palmedo reported that in 60% of false-negative (FN) mammograms, scintimammography was able to detect malignant lesions true-positive (TP).[49] It is worth mentioning that scintimammography with $^{99m}$Tc-MIBI or $^{99m}$Tc-sestamibi scintimammography is a noninvasive imaging modality and highly sensitive test in detecting primary breast lesions.[49,54,55]

The present systematic review demonstrates the high diagnostic value of scintimammography with $^{99m}$Tc-MIBI as a complementary method that improves the specificity of mammography and is potentially able to reduce the frequency of breast biopsies. Scintimammography is a noninvasive, low–radiation dose diagnostic method and an easy-to-perform procedure which may offer additional information above that provided by conventional radiology, especially in young, premenopausal patients with dense breasts and in patients who are on hormone replacement therapy, where the sensitivity of mammography is limited by the characteristics of the breast tissue. Technetium-99m-sestamibi scintimammography has the potential to determine the metabolic state of microcalcification, primary breast lesion, axillary lymph node detected by other imaging modalities. Scintimammography may discriminate between benign and malignant breast lesions in patients with a palpable mass or when the lesion size is more than 10 mm.

However, mammography has a high sensitivity in the examination of older patients with fatty breast and is associated with a small amount of radiation exposure. Mammography has a better spatial resolution compared with scintimammography. Nevertheless, the development and general availability of high-resolution cameras dedicated to breast imaging will probably allow scintimammography to become of routine use.

**Conflict of Interest**

The authors have no potential conflict of interest concerning the content of the present article.

**References**


1. Pan L, Han Y, Sun X, Liu J, Gang H. FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis. J Cancer Res Clin Oncol. 2010;136(7):1007-22.
2. Pennant M, Takwoingi Y, Pennant L, Davenport C, Fry-Smith A, Eisinga A, *et al.* A systematic review of positron emission tomography (PET) and positron emission tomography/computed tomography (PET/CT) for the diagnosis of breast cancer recurrence. Health Technol Assess. 2010;14(50):1-103.
3. Warning K, Hildebrandt MG, Kristensen B, Ewertz M. Utility of 18FDG-PET/CT in breast cancer diagnostics--a systematic review. Dan Med Bull. 2011;58(7):A4289.
4. Heydarheydari S, Haghparast A. Diagnostic Value of PET/CT in Comparison with Other Conventional Imaging Modalities for the Evaluation of Breast Cancer Recurrence: A Systematic Review of the Literature. Archives of Breast Cancer. 2016;3(3):77-82.
5. Helvie MA, Chang JT, Hendrick RE, Banerjee M. Reduction in late-stage breast cancer incidence in the mammography era: Implications

for overdiagnosis of invasive cancer. Cancer. 2014;120(17):2649-56.
6. Hall FM. Screening mammography—potential problems on the horizon. Mass Medical Soc; 1986.
7. Brem RF, Tabár L, Duffy SW, Inciardi MF, Guingrich JA, Hashimoto BE, *et al.* Assessing improvement in detection of breast cancer with three-dimensional automated breast US in women with dense breast tissue: the SomoInsight Study. Radiology. 2014;274(3): 663-73.
8. PRESSMAN PI. Delayed diagnosis of breast cancer as a result of normal mammograms. Archives of Surgery. 1983;118(8):992-.
9. Sickles EA. Mammographic features of 300 consecutive nonpalpable breast cancers. AJR Am J Roentgenol. 1986;146(4):661-3.
10. Moriguchi SM, LA DEL, Griva BL, Koga KH, ET DAS, H DELV, *et al.* Accuracy of (99m)Tc-sestamibi scintimammography for breast cancer diagnosis. Exp Ther Med. 2010;1(1):205-9.
11. Campeau RJ, Kronemer KA, Sutherland CM. Concordant uptake of Tc-99m sestamibi and Tl-201 in unsuspected breast tumor. Clin Nucl Med. 1992;17(12):936-7.
12. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, *et al.* QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine. 2011;155(8):529-36.
13. Chen S, Liu W, Mao Y, Zhu W, Yao Z, Sun X, *et al.* 99mTc-MIBI and 99mTc-MDP scintimammography for detecting breast carcinoma. Chin Med J (Engl). 2000;113(5):4003.
14. Prats E, Banzo J, Merono E, Herranz R, Carril J. 99mTc-MIBI scintimammography as a complement of the mammography in patients with suspected breast cancer. A multicentre experience. The Breast. 2001;10(2):109-16.
15. Yildiz A, Colak T, Gungor F, Ozugur S, Boz A, Tuncdemir F, *et al.* Diagnostic value of 99mTc MIBI scintimammography in patients with breast lesions. Rev Esp Med Nucl. 2001;20(4):276-81.
16. Koukouraki S, Koukourakis M, Vagios E, Velidaki A, Tsiftsis D, Karkavitsas N. The role of 99mTc-sestamibi scintimammography and colour Doppler ultrasonography in the evaluation of breast lesions. Nuclear medicine communications. 2001;22(11):1243-8.
17. AguilarJ, Andrés B, Nicolás F, Muelas M, Pérez-Flores D, Aguayo JL. Value of 99mTc-MIBI scintimammography in women with impalpable breast lesions seen on mammography. The European journal of surgery. 2001;167(5):344-6.
18. Horne T, Pappo I, Cohen-Pour M, Baumer M, Orda R. 99Tcm-tetrofosmin scintimammography for detecting breast cancer: a comparative study with 99Tcm-MIBI. Nuclear medicine communications. 2001;22(7):807-11.
19. Bagni B, Franceschetto A, Casolo A, De Santis M, Bagni I, Pansini F, *et al.* Scintimammography with 99mTc-MIBI and magnetic resonance imaging in the evaluation of breast cancer. Eur J Nucl Med Mol Imaging. 2003;30(10):1383-8.
20. Sampalis FS, Denis R, Picard D, Fleiszer D, Martin G, Nassif E, *et al.* International prospective evaluation of scintimammography with 99mTechnetium sestamibi. The American journal of surgery. 2003;185(6):544-9.
21. Myslivecek M, Koranda P, Kaminek M, Husak V, Hartlova M, Duskova M, *et al.* Technetium-99m-MIBI scintimammography by planar and SPECT imaging in the diagnosis of breast carcinoma and axillary lymph node involvement. Nucl Med Rev Cent East Eur. 2004;7(2):151-5.
22. Fondrinier E, Muratet JP, Anglade E, Fauvet R, Berger V, Lorimier G, *et al.* Clinical experience with 99mTc-MIBI scintimammography in patients with breast microcalcifications. Breast. 2004;13(4):316-20.
23. De Cicco C, Trifiro G, Baio S, Sierra ML, Pizzamiglio M, Cassano E, *et al.* Clinical utility of 99mTc-Sestamibi scintimammography in the management of equivocal breast lesions. Cancer Biother Radiopharm. 2004;19(5):621-6.
24. Kim SJ, Kim IJ, Bae YT, Kim YK, Kim DS. Comparison of quantitative and visual analysis of Tc-99m MIBI scintimammography for detection of primary breast cancer. Eur J Radiol. 2005;53(2):192-8.
25. Prats E, Razola P, Sainz J, Tardín L, Andrés A, Abós M, *et al.* Scintimammography with 99mTc-MIBI in clinical practice. Repercussion on the clinical management of the patient. Revista española de medicina nuclear (English Edition). 2007;26(3):153-9.
26. Usmani S, Khan HA, Javed A, Al Mohannadi S, Al Huda FA, Al Shammary I. Functional breast imaging with Tc 99m Mibi for detection of primary breast lesion and axillary lymph node metastases. Gulf J Oncolog. 2008(4):52-7.
27. Habib S, Maseeh uz Z, Hameed A, Niaz K, Hashmi H, Kamal S. Diagnostic accuracy of Tc-99m-MIBI for breast carcinoma in correlation with mammography and sonography. J Coll Physicians Surg Pak. 2009;19(10):622-6.
28. DeCesare A, De Vincentis G, Gervasi S, Crescentini G, Fiori E, Bonomi M, *et al.* Single-photon-emission computed tomography (SPECT) with technetium-99m sestamibi in the diagnosis of small breast cancer and axillary lymph node involvement. World J Surg. 2011; 35(12):2668-72.
29. Hoi Y, Hsieh J, Tsai S, Sun S, Kao C. Usefulness of technetium-99m tetrofosmin mammoscintigraphy as compared to mammography for detecting and differentiating palpable breast masses of young Taiwanese women. Anticancer

research. 2000;20(3B):2061-4.
30. Chen D, Jeng L, Kao A, Lin C, Lee C. Usefulness of mammoscintigraphy with thallium-201 single photon emission computed tomography to differentiate palpable breast masses of young Taiwanese women when comparing with mammography. Neoplasma. 2002;49(5):334-7.
31. Kotsianos-Hermle D, Hiltawsky KM, Wirth S, Fischer T, Friese K, Reiser M. Analysis of 107 breast lesions with automated 3D ultrasound and comparison with mammography and manual ultrasound. Eur J Radiol. 2009;71(1):109-15.
32. Mulero F, Nicolas F, Castellon MI, Fuentes T, de la Cruz P, Roca V, *et al.* [99m Tc-MIBI scintigraphy compared to mammography in the diagnosis of breast cancer in dense, operated and young women breasts]. Rev Esp Med Nucl. 2000;19(5):344-9.
33. Sun S, Hsieh J, Tsai S, Ho Y, Lee J, Kao C. The role of Tc-99m methoxyisobutylisonitrile scintima-mmography as compared to mammography in evaluating palpable breast masses of Taiwanese women. Anticancer research. 2000;20(3B):21336.
34. Lumachi F,Ferretti G, Povolato M, Marzola MC, Zucchetta P, Geatti O, *et al.* Accuracy of technetium-99m sestamibi scintimammography and X-ray mammography in premenopausal women with suspected breast cancer. Eur J Nucl Med. 2001;28(12):1776-80.
35. Cwikła J, Buscombe J, Kolasińska A, Holloway B, Hilson A. Evaluation of scintimammography as an additional test to conventional mammography in detection of breast cancer. Ginekologia polska. 2003;74(5):362-70.
36. Krishnaiah G, Sher-Ahmed A, Ugwu-Dike M, Regan P, Singer J, Totoonchie A, *et al.* Technetium-99m sestamibi scintimammography complements mammography in the detection of breast cancer. Breast J. 2003;9(4):288-94.
37. Ozülker T, Ozülker F, Ozpaçaci T, Bender O, Değirmenci H. The efficacy of (99m) Tc-MIBI scintimammography in the evaluation of breast lesions and axillary involvement: a comparison with X-rays mammography, ultrasonography and magnetic resonance imaging. Hellenic journal of nuclear medicine. 2010;13(2):144-9.
38. Kimme-Smith C, Wang J, DeBruhl N, Basic M, Bassett LW. Mammograms obtained with rhodium vs molybdenum anodes: contrast and dose differences. AJR Am J Roentgenol. 1994;162(6):1313-7.
39. Omar WS, Eissa S, Moustafa H, Farag H, Ezzat I, Abdel-Dayem HM. Role of thallium-201 chloride and Tc-99m methoxy-isobutyl-isonitrite (sestaMIBI) in evaluation of breast masses: correlation with the immunohistochemical characteristic parameters (Ki-67, PCNA, Bcl, and angiogenesis) in malignant lesions. Anticancer Res. 1997;17(3B):1639-44.
40. Tierney S, Fenlon H, Phelan N, O'sullivan P, Ennis J, Gorey T. Scintimammography in the assessment of local recurrence following conservative breast surgery. The British Journal of Surgery-Supplement. 1998;85:51.
41. Cutrone JA, Khalkhali I, Yospur LS, Diggles L, Weinberg I, Pong EM, *et al.* Tc-99m Sestamibi Scintimammography for the Evaluation of Breast Masses in Patients with Radiographically Dense Breasts. Breast J. 1999;5(6):383-8.
42. Zegel H, Heller L, Edell S, Squires F, Rubin J. Tc-99m sestamibi scintimammography in the mammographically dense breast. Clin Nucl Med. 1999;24(12):968-74.
43. Kolasinska A, Cwikla J, Buscombe J, Parbhoo S, Davidson T, Holloway B, *et al.* 63. Scintimammography in recurrent breast cancer: A primary or secondary role? Nuclear Medicine Communications. 2000;21(4):389.
44. Kuhn JC, Siegel A, Poplack S, Arrick B. Chest wall recurrence of breast cancer detected by scintimammography. Clin Nucl Med. 2000; 25(2):104-6.
45. Usmani S, Khan HA, Niaz K, Uz-Zaman M, Niyaz K, Javed A, *et al.* Tc-99m-methoxy isobutyl isonitrile scintimammography: imaging postexcision biopsy for residual and multifocal breast tumor. Nuclear medicine communications. 2008;29(9):826-9.
46. Fliquete MP, Giménez JC, Vázquez CF, Más CA, Vázquez CA. Role of 99mTc-Sestamibi in the diagnosis of breast cancer. Report on 100 cases. Revista espanola de medicina nuclear. 1999;18(6):436-41.
47. Tofani A, Sciuto R, Semprebene A, Festa A, Pasqualoni R, Giunta S, *et al.* 99Tcm-MIBI scintimammography in 300 consecutive patients: factors that may affect accuracy. Nuclear medicine communications. 1999; 20(12):111321.
48. Bekis R, Derebek E, Balci P, Kocdor MA, Degirmenci B, Canda T, *et al.* 99mTc sestamibi scintimammography. Screening mammographic non-palpable suspicious breast lesions: preliminary results. Nuklearmedizin. 2004;43(1):16-20.
49. Palmedo H, Biersack H, Lastoria S, Maublant J, Prats E, Stegner H, *et al.* Scintimammography with technetium-99m methoxyisobutylisonitrile: results of a prospective European multicentre trial. European journal of nuclear medicine. 1998;25(4):375-85.
50. Palmedo H, Schomburg A, Grunwald F, Mallmann P, Krebs D, Biersack H-J. Technetium-99m-MIBI scintimammography for suspicious breast lesions. Journal of Nuclear Medicine. 1996;37(4):626-30.
51. Wilczek B, Aspelin P, Bone B, Pegerfalk A, Frisell J, Danielsson R. Complementary use of scintimammography with 99m-Tc-MIBI to

triple diagnostic procedure in palpable and non-palpable breast lesions. Acta Radiol. 2003;44(3):288-93.
52. Brem RF, Schoonjans JM, Kieper DA, Majewski S, Goodman S, Civelek C. High-resolution scintimammography: a pilot study. J Nucl Med. 2002;43(7):909-15.
53. Kim BS, Moon BI, Cha ES. A comparative study of breast-specific gamma imaging with the conventional imaging modality in breast cancer patients with dense breasts. Ann Nucl Med. 2012;26(10):823-9.
54. Khalkhali I, Cutrone J, Mena I, Diggles L, Venegas R, Vargas H, *et al.* Technetium-99m-sestamibi scintimammography of breast lesions: clinical and pathological follow-up. J Nucl Med. 1995;36(10):1784-9.
55. Taillefer R, Robidoux A, Lambert R, Turpin S, Laperrière J. Technetium-99m-sestamibi prone scintimammography to detect primary breast cancer and axillary lymph node involvement. Journal of Nuclear Medicine. 1995;36(10): 1758-65.

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# Management of Benign Phyllodes Tumor With Close Margins: A Case Presented in Multidisciplinary Session With Clinical Discussion and Decision Making

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ABSTRACT

**Background:** Phyllodes tumors (PTs) are a small group of fibroepithelial breast lesions, which are classified as benign, borderline, or malignant. Traditionally, a margin of 1 cm has been suggested as the standard of care for all groups of PTs. According to new studies and recent updates, the recurrence rate of benign PT is low and not associated with the surgical margin status. There is still a controversy for PT surgical margin.

**Case Presentation:** A woman with the primary diagnosis of fibroadenoma in core needle biopsy underwent surgery. The pathology report showed benign PT and margins about 1 mm in some areas. This case was presented in the weekly breast multidisciplinary team session of the Department of Breast Surgery, Tehran University of Medical Sciences.

**Question:** The question was whether re-excision was necessary to achieve the safe surgical margin.

**Conclusion:** In accordance with the latest published evidence, the members of the panel decided to accept the margin, informed the patient about the risk of recurrence, and recommended close follow-up.

## Introduction

Phyllodes tumors (PT) are rare fibroepithelial tumors that can affect women of all ages, with the median age at presentation being 45 years.[1] Since the description of "cystosarcoma phyllodes" by Johannes Mueller first in 1838, numerous synonyms and histologic classification systems have been introduced. The World Health Organization (WHO) prefers the use of "phyllodes tumors."[2] These tumors are classified as benign, borderline, or malignant based on histologic parameters such as mitotic activity, stromal cell atypia, stromal overgrowth, stromal heterologous component, stromal necrosis, and infiltration of normal breast tissue.[3]

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Core needle biopsy constitutes the pathological basis of the preoperative diagnosis of PT; however, it is not accurate enough to offer perfect guidance for surgical decisions.[4] The high underestimation rate in these conditions makes the surgical planning complicated. When the tumor to breast ratio is too high to allow a satisfactory cosmetic outcome with segmental excision, total mastectomy either with or without reconstruction could be considered.[5] Axillary lymph node dissection is recommended to be performed only for clinically suspicious nodes, although it is unlikely that malignant cells would be found in them.[6] There is no evidence for an effective role of adjuvant chemotherapy in the treatment of PT.[7] Controversy exists as to the size of initial resection and need for revision surgery to achieve adequate margins. Guidelines have advocated wide excision with margins ≥ 1 cm for all kinds of PT.[7, 8] However, this cannot always be achieved, as the observation of margins closer than 1 cm in pathologic evaluation is common—a situation that

often questions the necessity of a surgical revision of margins.

**Case Presentation**

A 46-year-old woman with a family history of breast cancer presented to our breast clinic with a chief complain of the left breast mass. The mass, measuring 20 × 20 mm, was palpable in the upper outer quadrant of her left breast. It was soft, nontender, and mobile with a regular border. No palpable axillary lymph node was found. In mammography, there was an ill-defined mass in the upper outer quadrant of the left breast with a BIRADS score of 3. Ultrasonography reported an oval-shaped, well-circumscribed hypoechoic lesion measuring 19 × 15 mm with lobulated borders at the 2-o'clock position parallel to the skin. Internal vascularity was seen within the mass and ultrasonography did not show any suspicious axillary lymph nodes with scoring of 4a in BIRADS assessment categories. Pathology report of core needle biopsy of the mass was fibroadenoma. The patient underwent surgery out of concern due to the family history. Analysis of permanent pathology sections showed clefts of epithelial cells surrounded by hypercellular stroma. Stromal cells displayed mild pleomorphism with scanty mitotic figures (0-1 per 10 high-power fields [HPF]) with no evidence of necrosis. These findings suggested benign PT. All surgical margins were free, and the closest margins were located at the superior, and lateral area. They were both 1 mm.

**Question**

The case was presented at the weekly breast multidisciplinary team session at the Department of Breast Surgery, Tehran University of Medical Sciences. The question was whether the patient should be reoperated on to obtain more extensive margins.

**Discussion**

Each type of PT requires different management. Malignant PTs are characterized by marked stromal cellularity and atypia, infiltrative margins, high mitotic rate (more than 10 mitoses per 10 HPF), and the presence of stromal overgrowth.[9-11] Surgery is the standard treatment for malignant PT. Surgical margins of ≥ 1 cm are accepted by most resources and guidelines.[7, 8, 12-14] The surgery includes breast-conserving surgery or mastectomy depending on the size of the tumor.[9,15-17] It has been accepted that lymph node dissection is not recommended.[6, 12-14] Adjuvant therapies (radiotherapy and chemotherapy) have no clearly defined role in the treatment of nonmetastatic malignant PT. Several studies suggest that adjuvant radiotherapy could reduce local recurrence when adequate surgical margins cannot be achieved.[11,14,18-21] Hormone therapy is not effective against malignant PT.[14, 22, 23] Borderline PTs have a greater degree of stromal cellularity and atypia, a mitotic rate of 4 to 9 mitoses per 10 HPF, microscopic infiltrative borders, and a lack of stromal overgrowth.[9-11] The approaches to breast surgery, axillary management, and the surgical margins in the borderline PT are almost the same as malignant PT.[5-9, 12-14, 17] Previous studies and guidelines suggested that margin-negative excision was not an adequate treatment for borderline PT and often recommended a margin width of at least 10 mm.[7, 8, 24-26] Patients with borderline PTs are usually cured with surgery and should not be offered chemotherapy.[14] The use of radiotherapy for borderline PT is controversial, but several studies recommend it when the sufficient margin cannot be achieved.[11, 14, 18-21] Hormone therapy for borderline PT is ineffective.[14,22,23]

Benign tumors are characterized by an increased stromal cellularity with mild to moderate cellular atypia, circumscribed tumor margins, low mitotic rates (less than 4 mitoses per 10 HPF), and a lack of stromal overgrowth.[9-11] Although surgical management of malignant and borderline PTs are similar, there is a controversy about management of benign PTs. The main discussion is about the surgical margins and the rate of recurrence. In earlier reports, benign, borderline, and malignant PTs had local recurrence rates of 8, 21, and 36 percent.[27,28] A review article studied the relationship between surgical margins and the rate of recurrence in all kinds of PT (Table 1).[29] For many years, the acceptable resection margin for PT has been 10 mm. The authors of some guidelines such as the National Comprehensive Cancer Network (NCCN) and MD Anderson believe that a margin of ≥ 1 cm should be applied to all types of PT.[7, 8] The editors of *Diseases of the Breast* agree with this approach,[12] but the American Society of Breast Surgeons (ASBS) suggests that benign PT diagnosed after excision can be managed with close follow-up.[13] According to Up-To-date, authors accept a narrower but clear margin for benign PT.[14] The reason scientists have agreed with the wide excision is that surgical margin is one of the causes of recurrence.[30-35] Wider excisions appear to reduce the risk of local recurrence, while close margins cause local recurrence in all types of PTs.[30,36] Recent studies have shown that, regardless of surgical margin status, benign PT has a very low rate of local recurrence.[1,24,37-41] Barth and Kim et al showed that no clinical, histologic, or surgical factor influences local recurrence of benign PT.[24,37] Several researchers found that there was no statistical advantage of a 10-mm margin compared with a 1-mm one in benign PT.[29, 31, 37, 42-44] Furthermore, when benign PT is unexpectedly diagnosed at ultrasound-guided, vacuum-assisted excision, clinical follow-up may be preferred over further surgery.[40, 41] There are some data that support the negative margin for benign PT.[24, 42] Cowan et al found that patients with benign PT and positive margins on initial excision might be

**Table 2.** Main characteristics of the studies evaluating the diagnostic value of mammography

| Author | Recurrence in benign PT | Recurrence in borderline PT | Recurrence in malignant PT | Margin definition |
|---|---|---|---|---|
| Karim et al[51] | 3/30 (10%) | 3/20 (15%) | 2/6 (33%) | 10 mm |
| Bhargav et al[52] | 3/7 (42.8%) | 2/5 (40%) | 4/13 (31%) | 10 mm |
| Guillots et al[53] | 7/114 (6.1%) | 8/37 (21%) | 0/14 | 10 mm |
| Lin et al[54] | 0/8 | 3/13 (23%) | 6/12 (50%) | 10 mm |
| Kim et al[55] | 5/50 (10%) | 3/22 (13%) | 1/10 (10%) | 1 mm |
| Kim et al[37] | 5/145 (3.4%) | 6/33 (18%) | 7/15 (46%) | 1 mm |
| Sawalhi and Al-Shatti[44] | 2/16 (12.5%) | 1/9 (11%) | 6/17 (35%) | 1 mm |
| Tan et al[56] | 48/399 (12%) | 16/103 (15%) | 16/50 (32%) | Focal involvement of the margin |
| Tsang et al[57] | 15/92 (16.3%) | 12/42 (28%) | 6/21 (28%) | Focal involvement of the margin |
| Jang et al[31] | 12/82 (14.6%) | 9/42 (21%) | 10/40 (23%) | Focal involvement of the margin |
| Nishimura et al[58] | 3/29 (10%) | 0/11 | 3/3 (100%) | Focal involvement of the margin |
| Wei et al[48] | 9/80 (11%) | 10/63 (16%) | 12/49 (24%) | Focal involvement of the margin |

managed conservatively.[39] Recent studies suggest that the close follow-up approach could be sufficient in cases of benign PT diagnosed postoperatively, even if margins were < 1 cm.[25, 32, 45, 46] A 1-mm margin in benign PT has been advocated recently.[33, 44, 47-49] It seems that benign PTs are seen differently than borderline and malignant PTs. Onkendi and colleagues showed that the extent of surgical resection does not affect disease-free survival in patients with borderline and malignant PT.[17] Sevinc recommended that revision surgery should not be performed for close or positive surgical margins for benign and borderline PT.[50]

**Multidisciplinary team (MDT) recommendation**

For this patient with benign PT and 2 close margins about 1 mm, members of breast MDT in Breast Surgery Department, Imam Khomeini Hospital, Tehran University of Medical Sciences, did not recommend re-excision. Factors that helped MDT to accept these margins were the very low rate of local recurrence of benign PT, good prognosis, and the patient's concern. Thus, MDT members decided to accept the margin and informed the patient about the risk of recurrence and the need for follow-up imaging.

**Conflict of Interest**

The authors have nothing to disclose.

**References**


1. Moutte A, Chopin N, Faure C, Beurrier F, Ho Quoc C, Guinaudeau F, *et al.* Surgical Management of Benign and Borderline Phyllodes Tumors of the Breast. The Breast Journal. 2016;22(5):547-52.
2. FA T, P D. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. in: World Health Organization Classification of Tumors. Lyon: IARC Press; 2003.
3. Rosen PP. Rosen's breast pathology: Lippincott Williams & Wilkins; 2001.
4. Zhou Z-R, Wang C-C, Sun X-J, Yang Z-Z, Yu X-L, Guo X-M. Diagnostic performance of core needle biopsy in identifying breast phyllodes tumors. Journal of Thoracic Disease. 2016;8(11):3139-51.
5. Contarini O, Urdaneta LF, Hagan W, Stephenson SE, Jr. Cystosarcoma phylloides of the breast: a new therapeutic proposal. The American surgeon. 1982;48(4):157-66.
6. Poynter GN, Monica R, S. JPA. National Surgical Patterns of Care for Primary Surgery and Axillary Staging of Phyllodes Tumors. The Breast Journal. 2009;15(1):41-4.
7. Network NCC. Breast Cancer 2017 [Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
8. MD CA, MD FA, MD DA, MD EA, MD BA, MD GB, *et al.* phyllodes tumor The University of Texas MD Anderson Cancer Center: MD Anderson Cancer Center [updated 2015. Available from:https://www.mdanderson.org/content/dam/mdanderson/documents/for-physicians/algorithms/ cancer-treatment/ca-treatment-phyllodes-web-algorithm.pdf.
9. Reinfuss M, Mitus J, Duda K, Stelmach A, Rys J, Smolak K. The treatment and prognosis of patients with phyllodes tumor of the breast: an analysis of 170 cases. Cancer. 1996;77(5):910-6.
10. Parker S, Harries S. Phyllodes tumours. Postgraduate Medical Journal. 2001;77(909):428-35.
11. Hawkins RE, Schofield JB, Fisher C, Wiltshaw E, McKinna JA. The clinical and histologic criteria that predict metastases from cystosarcoma phyllodes. Cancer. 1992;69(1):141-7.
12. Harris JR, Lippman ME, Morrow M, Osborne CK. Diseases of the Breast. 5th ed. china: Wolters Kluwer Health; 2014.
13. Surgeons ASoB. Consensus Guideline on Concordance Assessment of Image-Guided Breast Biopsies and Management of Borderline or High-Risk Lesions 2016 [Available from: https://www.breastsurgeons.org/about/statements/PDF_Statements/Concordance_and_High%20RiskLesions.pdf.

14. MD AMG, MD FBC, MD FC. Phyllodes tumors of the breast. In: MD LJP, MD DFH, editors.uptodate. Waltham, MA: uptodate; 2018.
15. Chaney AW, Pollack A, McNeese MD, Zagars GK, Pisters PW, Pollock RE, *et al.* Primary treatment of cystosarcoma phyllodes of the breast. Cancer. 2000;89(7):1502-11.
16. Macdonald OK, Lee CM, Tward JD, Chappel CD, Gaffney DK. Malignant phyllodes tumor of the female breast: association of primary therapy with cause-specific survival from the Surveillance, Epidemiology, and End Results (SEER) program. Cancer. 2006;107(9):2127-33.
17. Onkendi EO, Jimenez RE, Spears GM, Harmsen WS, Ballman KV, Hieken TJ. Surgical treatment of borderline and malignant phyllodes tumors: the effect of the extent of resection and tumor characteristics on patient outcome. Annals of surgical oncology. 2014;21(10):3304-9.
18. Soumarova R, Seneklova Z, Horova H, Vojkovska H, Horova I, Budikova M, *et al.* Retrospective analysis of 25 women with malignant cystosarcoma phyllodes--treatment results. Archives of gynecology and obstetrics. 2004;269(4):278-81.
19. Pezner RD, Schultheiss TE, Paz IB. Malignant phyllodes tumor of the breast: local control rates with surgery alone. International journal of radiation oncology, biology, physics. 2008;71(3):710-3.
20. Parker SJ, Harries SA. Phyllodes tumours. Postgrad Med J. 2001;77(909):428-35.
21. Belkacemi Y, Bousquet G, Marsiglia H, Ray-Coquard I, Magne N, Malard Y, *et al.* Phyllodes tumor of the breast. International journal of radiation oncology, biology, physics. 2008;70(2):492-500.
22. Burton GV, Hart LL, Leight GS, Jr., Iglehart JD, McCarty KS, Jr., Cox EB. Cystosarcoma phyllodes. Effective therapy with cisplatin and etoposide chemotherapy. Cancer. 1989;63(11):2088-92.
23. Telli ML, Horst KC, Guardino AE, Dirbas FM, Carlson RW. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. Journal of the National Comprehensive Cancer Network :JNCCN. 2007;5(3):324-30.
24. J. Barth R J. Margin negative, breast conserving resection: adequate for benign phyllodes tumors, but inadequate therapy for borderline and malignant phyllodes tumors. Breast cancer research and treatment. 2013;142(2):463-4.
25. Ben Hassouna J, Damak T, Gamoudi A, Chargui R, Khomsi F, Mahjoub S, *et al.* Phyllodes tumors of the breast: a case series of 106 patients. American journal of surgery. 2006;192(2):141-7.
26. Chen WH, Cheng SP, Tzen CY, Yang TL, Jeng KS, Liu CL, *et al.* Surgical treatment of phyllodes tumors of the breast: retrospective review of 172 cases. Journal of surgical oncology. 2005;91(3):185-94.
27. Barth RJ, Jr. Histologic features predict local recurrence after breast conserving therapy of phyllodes tumors. Breast cancer research and treatment. 1999;57(3):291-5.
28. Barth RJ, Jr., Wells WA, Mitchell SE, Cole BF. A prospective, multi-institutional study of adjuvant radiotherapy after resection of malignant phyllodes tumors. Annals of surgical oncology. 2009;16(8):2288-94.
29. Shaaban M, Barthelmes L. Benign phyllodes tumours of the breast: (Over) treatment of margins - A literature review. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2017;43(7):1186-90.
30. Asoglu O, Ugurlu MM, Blanchard K, Grant CS, Reynolds C, Cha SS, *et al.* Risk factors for recurrence and death after primary surgical treatment of malignant phyllodes tumors. Annals of surgical oncology. 2004;11(11):1011-7.
31. Jang JH, Choi MY, Lee SK, Kim S, Kim J, Lee J, *et al.* Clinicopathologic risk factors for the local recurrence of phyllodes tumors of the breast. Annals of surgical oncology. 2012;19(8):2612-7.
32. Tan EY, Tan PH, Yong WS, Wong HB, Ho GH, Yeo AW, *et al.* Recurrent phyllodes tumours of the breast: pathological features and clinical implications. ANZ journal of surgery. 2006;76(6):476-80.
33. Wei J, Tan Y-T, Cai Y-C, Yuan Z-Y, Yang D, Wang S-S, *et al.* Predictive factors for the local recurrence and distant metastasis of phyllodes tumors of the breast: a retrospective analysis of 192 cases at a single center. Chinese Journal of Cancer. 2014;33(10):492-500.
34. Abdalla HM, Sakr MA. Predictive factors of local recurrence and survival following primary surgical treatment of phyllodes tumors of the breast. Journal of the Egyptian National Cancer Institute. 2006;18(2):125-33.
35. Co M, Chen C, Tsang JY, Tse G, Kwong A. Mammary phyllodes tumour: a 15-year multicentre clinical review. Journal of clinical pathology. 2018;71(6):493-7.
36. Rodrigues MF, Truong PT, McKevitt EC, Weir LM, Knowling MA, Wai ES. Phyllodes tumors of the breast: The British Columbia Cancer Agency experience. Cancer radiotherapie : journal de la Societe francaise de radiotherapie oncologique. 2018;22(2):112-9.
37. Kim S, Kim JY, Kim DH, Jung WH, Koo JS. Analysis of phyllodes tumor recurrence according to the histologic grade. Breast cancer research and treatment. 2013;141(3):353-63.
38. Borhani-Khomani K, Talman ML, Kroman N, Tvedskov TF. Risk of Local Recurrence of

Benign and Borderline Phyllodes Tumors: A Danish Population-Based Retrospective Study. Annals of surgical oncology. 2016;23(5):1543-8.
39. Cowan ML, Argani P, Cimino-Mathews A. Benign and low-grade fibroepithelial neoplasms of the breast have low recurrence rate after positive surgical margins. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2016; 29(3):259-65.
40. Kim GR, Kim EK, Yoon JH, Kim MJ, Moon HJ. Recurrence Rates of Benign Phyllodes Tumors After Surgical Excision and Ultrasonography-Guided Vacuum-Assisted Excision. Ultrasound quarterly. 2016;32(2):151-6.
41. Ouyang Q, Li S, Tan C, Zeng Y, Zhu L, Song E, *et al.* Benign Phyllodes Tumor of the Breast Diagnosed After Ultrasound-Guided Vacuum-Assisted Biopsy: Surgical Excision or Wait-and-Watch? Annals of surgical oncology. 2016; 23(4):1129-34.
42. Dixon JM. breast surgery 5th ed. china: Elsevier; 2013.
43. Kim G-E, Kim J-H, Lee KH, Choi YD, Lee JS, Lee JH, *et al.* Stromal Matrix Metalloproteinase-14 Expression Correlates With the Grade and Biological Behavior of Mammary Phyllodes Tumors. Applied Immunohistochemistry & Molecular Morphology. 2012;20(3):298-303.
44. Sawalhi S, Al-Shatti M. Phyllodes tumor of the breast: a retrospective study of the impact of histopathological factors in local recurrence and distant metastasis. Annals of Saudi medicine. 2013;33(2):162-8.
45. Zurrida S, BartoliC, Galimberti V, Squicciarini P, Delledonne V, Veronesi P, *et al.* Which therapy for unexpected phyllode tumour of the breast? European journal of cancer (Oxford, England : 1990). 1992;28(2-3):654-7.
46. Mishra SP, Tiwary SK, Mishra M, Khanna AK. Phyllodes tumor of breast: a review article. ISRN surgery. 2013;2013:361469.
47. S T, M D. Breast surgery. Edinburgh: Saunders Elsevier; 2014. p. 272.
48. Wei J, Tan YT, Cai YC, Yuan ZY, Yang D, Wang SS, *et al.* Predictive factors for the local recurrence and distant metastasis of phyllodes tumors of the breast: a retrospective analysis of 192 cases at a single center. Chin J Cancer. 2014;33(10):492-500.
49. Tremblay-LeMay R, Hogue JC, Provencher L, Poirier B, Poirier E, Laberge S, *et al.* How Wide Should Margins Be for Phyllodes Tumors of the Breast? Breast J. 2017;23(3):315-22.
50. Sevinc AI, Aksoy SO, Guray Durak M, Balci P. Is the extent of surgical resection important in patient outcome in benign and borderline phyllodes tumors of the breast? Turkish journal of medical sciences. 2018;48(1):28-33.
51. Karim RZ, Gerega SK, Yang YH, Spillane A, Carmalt H, Scolyer RA, *et al.* Phyllodes tumours of the breast: a clinicopathological analysis of 65 cases from a single institution. Breast (Edinburgh, Scotland). 2009;18(3):165-70.
52. Bhargav PR, Mishra A, Agarwal G, Agarwal A, Verma AK, Mishra SK. Phyllodes tumour of the breast: clinicopathological analysis of recurrent vs. non-recurrent cases. Asian journal of surgery. 2009;32(4):224-8.
53. Guillot E, Couturaud B, Reyal F, Curnier A, Ravinet J, Lae M, *et al.* Management of phyllodes breast tumors. Breast J. 2011;17(2):129-37.
54. Lin CC, Chang HW, Lin CY, Chiu CF, Yeh SP. The clinical features and prognosis of phyllodes tumors: a single institution experience in Taiwan. International journal of clinical oncology. 2013;18(4):614-20.
55. Kim GE, Kim JH, Lee KH, Choi YD, Lee JS, Lee JH, *et al.* Stromal matrix metalloproteinase-14 expression correlates with the grade and biological behavior of mammary phyllodes tumors. Applied immunohistochemistry & molecular morphology: AIMM. 2012;20(3):298-303.
56. Tan PH, Thike AA, Tan WJ, Thu MM, Busmanis I, Li H, *et al.* Predicting clinical behaviour of breast phyllodes tumours: a nomogram based on histological criteria and surgical margins. Journal of clinical pathology. 2012;65(1):69-76.
57. Tsang JY, Mendoza P, Putti TC, Karim RZ, Scolyer RA, Lee CS, *et al.* E-cadherin expression in the epithelial components of mammary phyllodes tumors. Human pathology. 2012;43(12):2117-23.
58. Nishimura R, Tan PH, Thike AA, Tan MH, Taira N, Li HH, *et al.* Utility of the Singapore nomogram for predicting recurrence-free survival in Japanese women with breast phyllodes tumours. Journal of clinical pathology. 2014;67(8):748-50.

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# Effect of Acceptance and Commitment Group Therapy on Quality of Life and Resilience of Women With Breast Cancer

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ABSTRACT

**Background:** Breast cancer diagnosis always causes a great deal of stress and results in significant changes in the patient's routine life, which—apart from physical injuries—can lead to loss of social functioning and increased risk of mental disorders. Psychological resilience may be a protective factor in dealing with stressful clinical situations. The present study aimed at investigating the effect of acceptance and commitment group therapy on the quality of life and resilience of women with breast cancer.

**Methods:** This study had a quasi-experimental, pre-post intervention design with a control group. Twenty women with breast cancer (stages I or II) were randomly assigned to an intervention or a control group. The intervention consisted of eight weekly sessions of acceptance and commitment group therapy. Follow-up evaluations were carried out two months after the intervention. The Quality of Life Questionnaire-Core 30 (QLQ-C30), Quality of Life Questionnaire-Breast Cancer (QLQ-BR23), and the Connor-Davidson Resilience Scale (CD-RISC) were used in this study.

**Results:** Sixteen patients completed the study. Compared with the control group, significant improvements were observed in the total and subscale scores on QLQ-C30 (partial $\eta 2 = 0.40$), QLQ-BR23 (partial $\eta 2 = 0.73$), and CD-RISC scores (partial $\eta 2 = 0.94$) and ($P < 0.01$) in the intervention group.

**Conclusion:** Acceptance and commitment program appears to be an effective therapeutic intervention for improving quality of life and resilience of breast cancer patients. Therefore, we suggest that this intervention be provided along with medical treatments to improve quality of life and resilience of breast cancer patients.

## Introduction

Breast cancer is a heterogeneous condition where prognosis and survival are affected by multiple factors.[1] The incidence rate of breast cancer has increased in Iran recently, making it the most common cancer among women.[2] The diagnosis and treatment of breast cancer could be followed by a lot of psychological problems, which could lead to more severe symptoms, slower recovery, and poorer health outcomes.[3] For example, it has been shown that cancer diagnosis and treatments are associated with concurrent psychological symptoms such as depression,[4] anxiety,[5] and psychosocial sequel of pain including fear,[6] insomnia,[7] or agitation.[8] Besides, these patients experience difficulties in marital satisfaction and communication with family and also in their relationships with their spouse and children. Therefore, because of perceived social, cognitive, and emotional problems, breast cancer patients tend

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to have a poor quality of life.[9] Quality of life is an important consideration when providing care to cancer patients.[10] It has been demonstrated that decreased health-related quality of life caused by chemotherapy side-effects may predispose patients to early discontinuation of treatment,[11] while studies on breast cancer survivors have shown that a good quality of life may benefit breast cancer patients.[12] Quality of life is a broad, multidimensional concept reflecting patients' perceptions of both positive and negative aspects of their life with regard to physical health, psychological state, level of independence, social relationships, personal beliefs and their relationships to salient features of their environment.[13] The concept has attracted the attention of researchers, and there is a growing consensus that it should be one of the main components of medical practice and research.[14]

In addition, the contribution of resilience to the compliance of patients with breast cancer is highlighted by a number of studies.[15] Resilience is an individual's ability to adaptively respond to hardship, stress, and adversity and has been defined as the capacity to "bounce back" from negative events without succumbing to despair.[16] A study on survivors of breast, stomach, and lung cancers showed that resilience was associated with better quality of life and lower levels of depression. Another study examining fatigue in cancer patients undergoing radiation therapy showed that resilience was an important psychological predictor of quality of life and coping.[17]

Acceptance and commitment therapy (ACT), which the American Psychological Association acknowledges as a modality of treatment for some psychiatric conditions,[18] emphasizes acceptance and mindfulness and focuses on strategies to induce behavior change guided by the patient's personal values to improve functioning and coping with persistent symptoms.[19] The treatment approach in ACT is to encourage patients to acknowledge and accept mental experiences to increase their ability to work with problems that cannot be solved. ACT interventions involve addressing six core psychopathological processes including acceptance, cognitive defusion, self as a context, values, being present, and committed action.[20] A recent review has identified studies using ACT in the contexts of lung, breast, blood, and bladder cancers.[21] It is expected that ACT has the potential to become a particularly well-suited approach to treating people with breast cancer as it offers a model of healthy adaptation to difficult circumstances. This is the first study to use ACT to improve quality of life and resilience in people with breast cancer. If ACT proves effective in this trial, it could be recomme-nded to be integrated into treatment plans for breast cancer patients.

However, despite providing valuable preliminary data, these studies either had a small sample or failed to report cancer stages. Therefore, this study was conducted to examine these hypotheses:

A: Acceptance and commitment group therapy affects the quality of life of women with breast cancer.

B: Acceptance and commitment group therapy affects the resilience of women with breast cancer.

**Methods**

A quasi-experimental study with a pre-post intervention design and a 2-month follow-up was carried out from March 2016 to December 2016. Breast cancer patients from the Oncology Department of the Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, were recruited for this study. Participation in the study was offered to all breast cancer patients who came for follow-up in the oncology wards in March and April 2016. The planned sample size was N = 20. In general, it is believed that the size of groups is set by the goals and priorities of groups, and it is recommended that the participants in each group be limited to 6 to 8 people because of paying attention to the needs of individual members.[22] Then, 20 patients were randomly assigned to either the intervention or control group. All participants were Iranian women treated for breast cancer, and we used the following inclusion criteria: (1) having histologically confirmed primary breast cancer (stages I or II) (2) being aged 18 and above; (3) being literate and fluent in the Persian language; (4) having no history of mental disorder or psychiatric problem; (5) having no cognitive deficits; (6) being cooperative with treatments; and (7) having completed the initial surgical and oncological treatment at least 2 months before the inclusion. Participants were excluded from the study if (1) they had serious physical problems that would preclude them from following the intervention, (2) they missed more than two sessions of therapy, and (3) they participated in concurrent psychological treatment, studies or rehabilitation (i.e. relaxation, mindfulness, psycho-education, or ACT). Finally, 4 participants were excluded during the examination because they declined to participate or started to use psychiatric drugs.

The study received the approval of the local ethics committee. Each participant gave written informed consent for participation. The privacy of participants was protected, and also the confidentiality of records and personal accounts was maintained. It was also suggested to the control group that, after completing the research, they can attend another acceptance and commitment group therapy held by the researcher.

The Iranian versions of the Quality of Life Questionnaire-Core 30 (QLQ-C30) and Quality of Life Questionnaire-Breast Cancer (QLQ-BR23) were used to measure the quality of life in this study.

The QLQ-C30 is the core module that examines

the total quality of life in the course of cancer disease. The questionnaire contains 30 questions comprising a global health scale, 5 functional scales (physical, emotional, cognitive, social, and role-playing), 3 symptom scales (fatigue, nausea and vomiting, and pain), and a number of individual items (dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties).[23] In the functional scales, higher scores represent a better level of functioning, while, in the case of symptom scales/items, higher scores mark a higher level of symptomatology or problems.[24] The QLQ-BR23 is a 23-item breast cancer–specific questionnaire about the common side effects of therapy, body image, sexuality, and the outlook for the future, which cannot be used alone but has to be administered along with QLQ-C30.[25] The QLQ-BR23 is scored in a similar fashion to the QLQ-C30. Both of the questionnaires have been translated into Persian and validated by Montazeri *et al.* Cronbach's alpha coefficient for multi-item scales (to test the reliability of QLQ-C30) ranged from 0.48 to 0.95 at baseline and from 0.52 to 0.98 at follow-up administration of the questionnaire.[25] The alpha coefficient of the Persian version of the QLQ-BR23 was 0.65 to 0.95 in the initial interview and 0.72 to 0.92 at the time of follow-up (two months).[26]

The Connor-Davidson Resilience Scale (CD-RISC) is comprised of 25 items rated on a 5-point scale (0 to 4). The scale has a total score between 0 and 100, with higher scores corresponding to greater resilience. Reliability (0.87), validity (0.89), and factor analytic structure of the scale were evaluated, and reference scores for study samples were calculated.[27] In general, the findings indicate that the Iranian version of CD-RISC provides a reliable and valid measure of resilience and can be used in clinical trials. Cronbach's alpha coefficient is reported 0.89 and the validity of the scale is ranged from 0.41 to 0.64.[28]

The process of the study was divided into four stages: (1) Recruiting subjects, carrying out pretests, and informing the participants of what the course would give them and what was required to attend the course. Also, the participants were offered the opportunity to discuss what the expected from the program. (2) Intervention: the intervention groups received eight 2-hour sessions (one session per week) of ACT, while the control group was placed on a waiting list. The description of therapeutic intervention is mentioned below:

Session 1: Providing an opportunity for participants to become acquainted with the purposes of the intervention; using creative frustration.

Session 2: Teaching the harmful role of suppressing feelings and thoughts; practicing mindfulness skills.

Session 3: Defining the concept of acceptance and identifying values; the practice of scanning the body according to mindfulness.

Session 4: Setting values based on goals; practicing how to solve barriers and problem; setting goals based on values; defusion exercise using the metaphor of bus passengers; classification of thoughts exercise.

Session 5: Practicing to consider the thought just as a thought; practicing defusion from verbal threats; mindfulness exercise. The assignment was designed with the aim of initiating work on the commitment and allowing barriers to be identified.

Session 6: Identifying traces in the value path and acceptance awareness training; identifying the goals along the path with values; examining useful solutions to barriers and learning daringness; examining the barriers to a valuable life.

Session 7: Learning the impact of thoughts; acknowledging that the disease (primary suffering) is unavoidable, but the meaning we give to the disease (secondary suffering) is a choice and also learning that pursuing commitment is not enough; commitment to actions and values even in the face of obstacles and exploring the barriers to satisfaction.

Session 8: Teaching primary suffering and secondary suffering by drawing a circular diagram; group satisfaction survey and teaching what one can achieve in his or her path of values.[29]

(3) Carrying out the posttest. (4) Carrying out the follow-up test after two months and data collection. Since the study design is quasi-experimental with multivariate repeated measures, multivariate analysis of variance (MANOVA) with repeated measurements was used to evaluate the assumptions. After data collection, data normality was tested using the Kolmogorov-Smirnov test, and, based on their normal distribution, parametric tests were used. SPSS software version 16 was used for data analyses. The significance level was set at 0.05.

## Results

According to Mauchly's Test of Sphericity, the assumption of sphericity was violated for scores on QLQ-C30, $\chi^2(2) = 0.41$, $P < 0.05$. Therefore, the Greenhouse-Geisser correction was used in the present study. The scores on QLQ-BR23 met the sphericity assumption, $\chi^2(2) = 2.19$, $P > 0.05$; therefore, the Sphericity test was used in the present study.

**Table 1.** Mean quality of life and resilience scores

| Statistical components / Measure | | Groups: ACT | Groups: Control |
|---|---|---|---|
| QLQ-C30 | Pretest | 39.28 | 47.00 |
| | Posttest | 63.98 | 45.08 |
| | Follow-up | 54.71 | 44.12 |
| QLQ-BR23 | Pretest | 39.85 | 38.60 |
| | Posttest | 71.13 | 38.22 |
| | Follow-up | 61.15 | 39.76 |
| Resilience | Pretest | 14.25 | 16.44 |
| | Posttest | 72.50 | 29.25 |
| | Follow-up | 67.12 | 27.12 |

**Table 2.** Results of repeated Measures ANOVA to evaluate the effect of acceptance and commitment group therapy on quality of life

| Measure | Statistical indicators | Sum of squares | df | Mean Square | F | Sig. | Partial Eta Squared |
|---|---|---|---|---|---|---|---|
| QLQ-C30 | Tests | 1046.88 | 1.47 | 712.24 | 9.32 | 0.003 | 0.40 |
| | Groups | 1013.38 | 1 | 1013.38 | 8.66 | 0.01 | 0.38 |
| | Group*test | 1727.08 | 1.47 | 1157.69 | 15.39 | 0.01 | 0.38 |
| QLQ-BR23 | Tests | 1920.46 | 2 | 960.23 | 38.65 | 0.0001 | 0.86 |
| | Groups | 3407.25 | 1 | 3407.25 | 93.13 | 0.0001 | 0.86 |
| | Group*test | 2006.70 | 2 | 1003.35 | 40.39 | 0.0001 | 0.74 |

*Examination of hypotheses*

*A: Acceptance and commitment group therapy is effective in improving the quality of life of women with breast cancer*

Quality of life (QLQ-C30): F = 9.32, partial $\eta^2 = 0.40$ (P = 0.003). There was no difference in quality of life scores among the 3 time points in the control group (Table 1). The mean quality of life scores for the intervention group were: pretest = 39.28, posttest = 63.98, and 2-month follow-up = 54.71. The results indicate that quality of life score increased significantly during the trial. The difference between posttest and follow-up scores was not significant (P ≤ 0.01) so it could be concluded that intervention was effective, and the result was retained over time.

Quality of life (QLQ-BR23): F = 38.65, partial $\eta^2 = 0.73$ (P ≤0.01). The mean quality of life scores for the intervention group were: pretest = 39.85, posttest = 71.13, and 2-month follow-up = 61.15. The results indicate that quality of life score increased significantly during the trial, although the difference between posttest and follow-up scores was not significant (P ≤ 0.01). It could be concluded that intervention was effective, and the result was retained over time. No difference was observed in QLQ-BR23 scores among the 3 time points (Table 1). The assumption of sphericity was violated for the functional and global health scales of the QLQ-C30 and the symptom scales of the QLQ-BR23; consequently, Huynh-Feldt correction was used in their analysis.

The obtained F values (155.71, 25.72, 7.34, 125.39, and 152.51) were significant for all scales (partial η2: 0.34-0.91, P < 0.01). Therefore, there were significant differences in the scores on scales of quality of life among the 3 time points and also between the intervention and control groups (P < 0.01). The mean QLQ-C30 functional scale scores for the intervention group were: pretest = 29.16, posttest = 81.38, and 2-month follow-up = 71.11; the mean scores on symptom scales were pretest = 75.34, posttest = 19.56, and 2-month follow-up = 26.60; and the mean scores on global health scale were pretest = 37.57, posttest = 67.70, and 2-month follow-up = 51.90. The mean scores on QLQ-BR23 functional scales for the intervention group were: pretest = 32.34, posttest = 60.33, and 2-month follow-up = 66.14; the mean scores on symptom scales were: pretest = 65.27, posttest = 17.22, and 2-month follow-up = 29.16; and the mean scores on quality of life scale were: pretest = 39.85, posttest = 71.13, and 2-month follow-up = 56.15. There was a significant difference between pretest and posttest quality of life scores; however, the difference between posttest and 2-month follow up values was not significant.

**Table 3.** Results of repeated measures ANOVA to evaluate the effect of acceptance and commitment group therapy on quality of life scales

| Subscale | Statistical indicators | Sum of squares | df | Mean Square | F | Sig. | Partial Eta Squared |
|---|---|---|---|---|---|---|---|
| Functional scales (QLQ-C30) | Tests | 7879.74 | 2 | 3939.78 | 152.51 | 0.0001 | 0.91 |
| | Groups | 6422.07 | 1 | 6422.07 | 119.44 | 0.0001 | 0.89 |
| | Group*test | 4902.00 | 2 | 2451.00 | 94.88 | 0.0001 | 0.87 |
| Symptom scales (QLQ-C30) | Tests | 8070.22 | 1.39 | 5797.22 | 125.36 | 0.0001 | 0.90 |
| | Groups | 8516.04 | 1 | 8516.04 | 86.36 | 0.0001 | 0.86 |
| | Group*test | 6728.76 | 1.39 | 4833.58 | 104.52 | 0.0001 | 0.88 |
| Global health scales (QLQ-30) | Tests | 2637.15 | 2 | 1318.57 | 7.34 | 0.03 | 0.34 |
| | Groups | 2134.48 | 1 | 2134.48 | 13.90 | 0.002 | 0.34 |
| | Group*test | 1154.70 | 2 | 577.35 | 3.21 | 0.05 | 0.20 |
| Functional scales (QLQ-BR23) | Tests | 2645.69 | 2 | 1322.84 | 25.72 | 0.0001 | 0.64 |
| | Groups | 1628.48 | 1 | 1628.47 | 18.41 | 0.0001 | 0.56 |
| | Group*test | 2593.24 | 2 | 1296.62 | 25.21 | 0.0001 | 0.64 |
| Symptom scales (QLQ-BR23) | Tests | 1005.65 | 1.07 | 9325.65 | 155.71 | 0.0001 | 0.91 |
| | Groups | 1133.41 | 1 | 1333.41 | 3.62 | 0.001 | 0.49 |
| | Group*test | 1715.87 | 1.07 | 1592.09 | 26.58 | 0.0001 | 0.65 |

**Table 4.** Repeated measures ANOVA to evaluate the effect of acceptance and commitment group therapy on resilience of women with breast cancer

| Source of Changes \ Measure | Sum of squares | df | Mean Square | F | Sig. | Partial Eta Squared |
|---|---|---|---|---|---|---|
| Tests | 12192.40 | 1.34 | 9080.49 | 240.86 | 0.0001 | 0.94 |
| Groups | 8759.88 | 1 | 8759.88 | 141.50 | 0.0001 | 0.91 |
| Group*test | 5141.63 | 1.34 | 3829.32 | 101.57 | 0.0001 | 0.91 |

We concluded that the intervention was effective, and the result was preserved over time. The scores for the control group were not significantly different among the 3 time points (Table1).

*B: Acceptance and commitment group therapy is effective on the resilience of women with breast cancer*

According to Mauchly's Test of Sphericity [$\chi^2(2) = 16.89$, $P < 0.01$] variances of differences between all the combinations of the conditions related to the resilience of the studied groups were not equal; therefore, the Huynh-Feldt correction was used.

According to the obtained $F = 240.86$ and partial $\eta^2 = 0.94$, $P < 0.01$ (Table 4), there are significant differences among pretest, posttest, and follow-up resilience scores (Table 4). The mean resilience scores for the intervention group were: pretest = 14.25, posttest = 72.50, and 2-month follow up = 67.12. A reduction in posttest and follow-up scores can be seen in the control group (Table 1).

## Discussion

The current study investigated the effectiveness of acceptance and commitment group therapy in improving the quality of life and resilience of women with breast cancer. The results indicated that ACT intervention was able to significantly enhance the scores on all scales of QLQ-C30, QLQ-BR23, and CD-RISC, and the effect almost remained stable over the follow-up period.

According to Yalom and Vinograd,[30] most of the breast cancer patients are affected by pessimistic thoughts, hopelessness, despair, loneliness, and fear of death because of suppressing their feelings about their illness. Consequently, their participation in group psychotherapy sessions and dealing with their feelings can lead to a different perspective on the human's life meaning.[30] Also, all aspects of their lives are significantly influenced by the traumatic experience of "losing the breasts," which are the attributes of femininity.[31] Research has shown that reducing depression, anxiety, and other psychological complications caused by cancer and cognitive and emotional acceptance of the disease by the patient have higher effectiveness than standing against the disease.[32] The findings of this research were in agreement with previous researches which all support the efficiency of acceptance and commitment therapy to improve patients' quality of life.[32-38] It could be concluded that ACT improves quality of life by directly focusing on effective life in valuable areas.[21] ACT serves this purpose by exposing the patient to negative thoughts, emotions, and feelings in a controlled manner.[39]

Our results also showed that acceptance and commitment group therapy promotes resilience among breast cancer patients, which is Consistent with previous studies.[40-45] It could be that ACT helps people to play a more significant role in the challenges they face, regain hope, and step forward on the road to a meaningful and genuine life.[46] Also, it can increase self-efficacy and the sense of empowerment, both of which contribute to increased resilience. A feeling of competence and capability is necessary for resiliency, and it is only in this case that an individual can step out of his passive position and start dealing with the challenges and managing his or her life.[26]

A limitation of the present study was that it had only one intervention group, so the effect of ACT was not compared with other interventions. On the other hand, this is the first study in Iran that investigates the effect of acceptance and commitment group therapy on quality of life and resilience among women with breast cancer. There is a hope that the results of this research will encourage the practitioners to give more importance to psychological aspects of the disease, which can result in better and faster treatment of the disease and improvement of patients' quality of life and resilience. Future studies should look into the effectiveness of this therapy in other types of cancers, with both genders.

## Conflict of Interest

The authors have nothing to disclose.

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## References

1. Irvin W, Jr., Muss HB, Mayer DK. Symptom management in metastatic breast cancer. Oncologist. 2011;16(9):1203-14.
2. Farahbakhsh K, Mokri Vala M. Mindfulness Based Breast Cancer Management. Review Study. Int J Chronic Dis Ther. 2016;2(6):48-51.
3. McGregor B, Ceballos R, Dolan E, Medic S,

Albano D. 87. Cognitive behavioral stress management among women at elevated risk for breast cancer. Brain Behavior and Immunity. 2009(23):S49.
4. Medeiros MC, Veiga DF, Sabino Neto M, Abla LE, Juliano Y, Ferreira LM. Depression and conservative surgery for breast cancer. Clinics (Sao Paulo). 2010;65(12):1291-4.
5. Baqutayan SMS. The effect of anxiety on breast cancer patients. Indian journal of psychological medicine. 2012;34(2):119.
6. Reyes-Gibby CC, Anderson KO, Morrow PK, Shete S, Hassan S. Depressive symptoms and health-related quality of life in breast cancer survivors. J Womens Health (Larchmt). 2012;21(3):311-8.
7. Fiorentino L, Ancoli-Israel S. Insomnia and its treatment in women with breast cancer. Sleep Med Rev. 2006;10(6):419-29.
8. Holland AJ, Davidson PW, Prasher VP, Janicki MP. Assessment of Behavioral and Psychiatric Disorders. Oxford: Blackwell Science; 2008.
9. Rastegary F. The effectiveness of coping strategies on mental health and rumination of Females with breast cancer: Islamic Azad University of Karaj; 2014.
10. Lavdaniti M. Quality of Life in Cancer Patients- A Nursing Perspective . . J Nurs Care. 2015;1:126-34.
11. Traore BM, El Fakir S, Charaka H, Benaicha N, Najdi A, Zidouh A, *et al.* Evolution of quality of life in patients with breast cancer during the first year of follow-up in Morocco. BMC Cancer. 2018;18(1):109.
12. Richardson LC, Wang W, Hartzema AG, Wagner S. The role of health-related quality of life in early discontinuation of chemotherapy for breast cancer. Breast J. 2007;13(6):581-7.
13. Lynch BM, van Roekel EH, Vallance JK. Physical activity and quality of life after colorectal cancer: overview of evidence and future directions. Expert Review of Quality of Life in Cancer Care. 2016;1(1):9-23.
14. Price MA, Bell ML, Sommeijer DW, Friedlander M, Stockler MR, Defazio A, *et al.* Physical symptoms, coping styles and quality of life in recurrent ovarian cancer: a prospective population-based study over the last year of life. Gynecol Oncol. 2013;130(1):162-8.
15. Di Giacomo D, Cannita K, Ranieri J, Cocciolone V, Passafiume D, Ficorella C. Breast cancer and psychological resilience among young women. J Psychopathol. 2016;3:9001-5.
16. Duggal D, Sacks-Zimmerman A, Liberta T. The Impact of Hope and Resilience on Multiple Factors in Neurosurgical Patients. Cureus. 2016; 8(10):e849.
17. Strauss B, Brix C, Fischer S, Leppert K, Fuller J, Roehrig B, *et al.* The influence of resilience on fatigue in cancer patients undergoing radiation therapy (RT). J Cancer Res Clin Oncol. 2007;133(8):511-8.
18. Association. AP. Psychological Treatments: APA; 2017 [updated 2011 May 28. Available from: http://www.div12.org/psychologicaltreatments/treatments/acceptance-and-commitment-therapy-for-psychosis.]
19. Hayes SC, Strosahl K, Wilson KG. Acceptance and Commitment Therapy: An experiential approach to behavior change.: New York: Guilford Press.; 1999.
20. LowJ, Serfaty M, Davis S, Vickerstaff V, Gola A, Omar RZ, *et al.* Acceptance and commitment therapy for adults with advanced cancer (CanACT): study protocol for a feasibility randomised controlled trial. Trials. 2016;17:77.
21. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and commitment therapy: model, processes and outcomes. Behav Res Ther. 2006;44(1):1-25.
22. Gladding ST. Counseling: A Comprehensive Profession. 7th ed: Savalan; 2013.
23. Fayers P, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A. EORTC QLQ-C30 Scoring Manual (3rd edition). 3 ed. Brussels: European Organisation for Research and Treatment of Cancer,; 2001.
24. Gokgoz S,Sadikoglu G, Paksoy E, Guneytepe U, Ozcakir A, Bayram N, *et al.* Health related quality of life among breast cancer patients: a study from Turkey. Global Journal of Health Science. 2011;3(2):140.
25. Montazeri A, Harirchi I, Vahdani M, Khaleghi F, Jarvandi S, Ebrahimi M, *et al.* The EORTC breast cancer-specific quality of life questionnaire (EORTC QLQ-BR23): translation and validation study of the Iranian version. Qual Life Res. 2000;9(2):177-84.
26. Connor KM, Davidson JR. Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC). Depress Anxiety. 2003;18(2):76-82.
27. Mohammadi M. Investigating the Factors Affecting Resilience in Subjects at Risk of Substance Abuse. Tehran: University of Olume Behzisti and Tavanbakhshi; 2005.
28. Brassington L, Ferreira NB, Yates S, Fearn J, Lanza P, Kemp K, *et al.* Better living with illness: a transdiagnostic acceptance and commitment therapy group intervention for chronic physical illness. Journal of Contextual Behavioral Science. 2016;5(4):208-14.
29. Yalom ID, Vinogradov S. Bereavement Groups: Techniques and Themes. International Journal of Group Psychotherapy. 1988;38(4):419-46.
30. Forman EM, Chapman JE, Herbert JD, Goetter EM, Yuen EK, Moitra E. Using session-by-session measurement to compare mechanisms of action for acceptance and commitment therapy

and cognitive therapy. Behavior therapy. 2012;43(2):341-54.
31. Dunkel-Schetter C, Feinstein LG, Taylor SE, Falke RL. Patterns of coping with cancer. Health psychology. 1992;11(2):79.
32. Johnston M, Foster M, Shennan J, Starkey NJ, Johnson A. The effectiveness of an Acceptance and Commitment Therapy self-help intervention for chronic pain. Clin J Pain. 2010;26(5):393-402.
33. Eren İ, ErdiÖ, Şahin M. The effect of depression on quality of life of patients with type II diabetes mellitus. Depression and anxiety. 2008;25(2): 98-106.
34. HuangM-F, Courtney M, Edwards H, McDowell J. Factors that affect health outcomes in adults with type 2 diabetes: a cross-sectional study. International journal of nursing studies. 2010; 47(5):542-9.
35. Matziou V, Tsoumakas K, Vlahioti E, Chrysicopoulou L, Galanis P, Petsios K, *et al.* Factors influencing the quality of life of young patients with diabetes. Journal of diabetes. 2011; 3(1):82-90.
36. Karlin BE, Walser RD, Yesavage J, Zhang A, Trockel M, Taylor CB. Effectiveness of acceptance and commitment therapy for depression: comparison among older and younger veterans. Aging Ment Health. 2013; 17(5):555-63.
37. Kahl KG, Winter L, Schweiger U. The third wave of cognitive behavioural therapies: what is new and what is effective? Current opinion in psychiatry. 2012;25(6):522-8.
38. Dionne F, Blais M, Monestes J. Acceptance and commitment therapy in the treatment of chronic pain. Sante mentale au Quebec. 2013;38(2):131-52.
39. Wicksell RK, Olsson GL, Hayes SC. Mediators of change in acceptance and commitment therapy for pediatric chronic pain. Pain. 2011; 152(12):2792-801.
40. Ernst MM, Mellon MW. Acceptance and Commitment Therapy (ACT) to Foster Resilience in Pediatric Chronic Illness. Child and Adolescent Resilience Within Medical Contexts: Springer; 2016. p. 193-207.
41. Burton NW, Pakenham KI, Brown WJ. Feasibility and effectiveness of psychosocial resilience training: a pilot study of the READY program. Psychology, health & medicine. 2010;15(3):266-77.
42. Towsyfyan N, Hossein Sabet F. The Effectiveness of Acceptance and Commitment Therapy on the Improving of Resilience and Optimism in Adolescents with Major Depressive Disorder. International Journal of Humanities and Social Science. 2017;7(3):239-45.
43. Badiee D. Investigating the Effectiveness of Acceptance and Commitment Therapy in Resiliency and Functioning of Family with Children suffering from Mental Retardation. The Caspian Sea Journal. 2016;10(1):313-9.
44. Thompson RW, Arnkoff DB, Glass CR.Conceptualizing mindfulness and acceptance as components of psychological resilience to trauma. Trauma Violence Abuse. 2011;12(4): 220-35.
45. Butler J, Ciarrochi J. Psychological acceptance and quality of life in the elderly. Qual Life Res. 2007;16(4):607-15.
46. Forman EM, Herbert JD, Moitra E, Yeomans PD, Geller PA. A randomized controlled effectiveness trial of acceptance and commitment therapy and cognitive therapy for anxiety and depression. Behavior modification. 2007;31(6):772-99.

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# Association of FGFR2 and TOX3 Genetic Variants With the Risk of Breast Cancer in Iranian Women

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ABSTRACT

**Background:** Breast cancer is the most common cause of cancer-related death in women worldwide. Novel genetic markers for breast cancer susceptibility have been identified in population-based studies. The aim of this study was to examine the association of two single-nucleotide polymorphisms (SNPs) of *FGFR2* (rs1219648) and *TOX3* (rs8051542) with the risk of breast cancer in Iranian women.

**Methods:** Breast cancer patients (n = 126) and healthy controls (n = 160) were genotyped for SNPs in *FGFR2* (rs1219648) and *TOX3* (rs8051542) using the tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR). Also, immunohistochemical tests for human epidermal growth factor receptor-2, estrogen receptor, and progesterone receptor were carried out on breast tumor tissues.

**Results:** *TOX3* (rs8051542) CC (OR = 1.24; 95% CI, 0.72-0.214; P < 0.001) and *FGFR2* (rs1219648) GG (OR = 62.0; 95% CI, 23.63-162.66; $\chi^2$ =132.775 ; P < 0.001) polymorphism was significantly associated with breast cancer. The association was also significant between breast cancer risk and *TOX3* (rs8051542) TC and *FGFR2* (rs1219648) AG variants.

**Conclusion:** Our findings suggested that genetic variants of *FGFR2* (rs1219648 AG) and *TOX3* (rs8051542 TC) can be potential candidate biomarkers for breast cancer risk.

## Introduction

Breast cancer (BC) is the most frequently diagnosed malignancy among women worldwide.[1] Also, BC is one of the most common types of malignancy among Iranian women.[2] Recent epidemiologic studies have shown that the incidence of BC is rising in Iran.[3] As with other types of cancer, BC arises from a complex interaction between genetic and environmental risk factors. Predisposing genes such as BRCA1/2 and *FGFR2* are the main genetic factors, while environmental factors include lifestyle, tobacco smoking, occupational exposures, and hormonal changes in the body.[4,5]

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Several studies have suggested that different single nucleotide polymorphisms (SNPs) are associated with BC risk.[6,7] Recent studies revealed associations between single-nucleotide polymorphisms (SNPs) in *TOX3* and *FGFR2* and breast cancer risk, and genome-wide association studies in European, Asian, and African-American populations validated these findings.[8,9] Located on chromosome 16q12, *TOX3* contains a putative high-mobility group box motif, suggesting that it may act as a transcription factor in carcinogenesis and seems a novel breast cancer susceptibility loci.[10] *FGFR2* is a member of the fibroblast growth factor receptor family with a highly conserved sequence.[11] Although many studies have reported the association between *TOX3* and *FGFR2* SNPs and BC risk, because of the differences in regional and other environmental factors, the conclusions of related reports are still uncertain.[12,13]
The aim of this study was to evaluate two SNPs

(rs8051542 in TOX3 gene and rs1219648 in *FGFR2* gene) and their association with BC risk. Also, the assessment of three markers including human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and estrogen receptor (ER) was conducted in this study.

## Methods

*Study Design and Patients*

In this study, 126 women with grade 4 breast tumors and 160 healthy controls were examined. All patients were provided with informed consent. Peripheral blood samples (3 mL) were collected from patients using K3EDTA as an anticoagulant.

*DNA Extraction*

DNA isolation from blood samples was performed using FelxiGene DNA extraction kit (Qiagen, Germany). The concentration of the isolated DNA was quantified using a NanoDrop spectrophotometer (Thermofisher, USA).

*Genotyping*

Tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) method was used to identify the genotypes of DNA samples. The DNA sequences of the SNPs rs8051542 and rs1219648 were obtained from the NCBI SNP database and used for designing the primers. Sequences of the primers have been shown in Table 1.

*Immunohistochemistry Study*

Breast carcinoma tissues were obtained from the Pathology Department of Rare Diseases Medical Center and Hazrat-e-Rasoul Medical Complex, Tehran, Iran. Immunohistochemistry study was performed to investigate ER, PR, and HER2 status.

*Statistical Analysis*

We assessed the Hardy-Weinberg equilibrium using the chi-squared ($\chi^2$) test. The data were tested for association between the gene variations and breast cancer risk. The difference in the allele and genotype frequency between cancer patients and healthy controls was determined using standard $\chi^2$. The odds ratios (OR) along with their 95% confidence intervals (95% CI) were also calculated.

**Table 1.** Inner and outer primer sequences used in the tetra-primer ARMS-PCR method

| *TOX3* (rs8051542) | | | bp |
|---|---|---|---|
| F-inner | CATGTGTTTTAAACATTTAGGTTATTAGAGTAC | C | 215 |
| R-inner | TGCTCCAATCATAGTGCTTCA | T | 168 |
| F-outer | CCAAACAGAAGAGATTCTGCTATATTTA | | 329 |
| R-outer | GTGATATTATTGCTTCATATGATCGAAT | | |
| *FGFR2* (rs1219648) | | | |
| F-inner | TCTAAAGCACGCCTATTTTACTTGACACCCG | A | 224 |
| R-inner | AGCCATGGCCATCCTTGAAGCGT | G | 164 |
| F-outer | TCCACAATGGCGCAGAATTACTTACAGTATTCC | | 334 |
| R-outer | GGTGATCCTTCACGTCTTGAAGATGTCTCC | | |

**Table 2.** Genotype frequencies for cases and controls

| SNP | Genotype | Cases, (N= 126) | % | Controls (N= 160) | % |
|---|---|---|---|---|---|
| *TOX3* (rs8051542) | | | | | |
| | CC | 57 | 45.238 | 36 | 22.5 |
| | TC | 50 | 39.682 | 106 | 66.25 |
| | TT | 19 | 15.07 | 18 | 11.25 |
| *FGFR2* (rs1219648) | | | | | |
| | AA | 14 | 11.11 | 9 | 5.625 |
| | AG | 10 | 85.71 | 146 | 91.25 |
| | GG | 84 | 3.174 | 5 | 3.125 |

## Results

The present study evaluated the association between *TOX3* (rs8051542) and *FGFR2* (rs1219648) with breast cancer risk. We also examined the relationship between these genotypes and three hormonal markers and their association with breast cancer risk factors (Table 3, Table 4, and Figure 1).

In the current study, *TOX3* (rs8051542) CC showed a significant association ( OR =1.24, 95% CI , 0.72-2.14; $\chi^2$ =16.608 ; P < 0.001) and *FGFR2* (rs1219648) GG; (OR = 62.0; 95% CI, 23.63-162.66; $\chi^2$ =132.775 ; P < 0.001) with breast cancer.

However, there was a strong, inverse association between the low-risk allele and tumor markers (Table 3) and similar to *TOX3* (rs8051542) TC (OR = 0.34; 95% CI, 0.21-0.54; $\chi^2$ =9.897; P = 0.002) and *FGFR2* (rs1219648)AG; (OR = 0.01, 95% CI, 0-0.02; $\chi^2$ = 197.342; P < 0.001)(Table 3,

**Table 3.** Comparison between genotypes

| SNP | Genotype | OR | 95% CI | $\chi^2$ | P value |
|---|---|---|---|---|---|
| *TOX3* (rs8051542) | | | | | |
| | CC | 1.24 | 0.72-2.14 | 16.608 | **<0.001** |
| | TC | 0.34 | 0.21-0.54 | 9.897 | **0.002** |
| | TT | 1.4 | 0.7-2.8 | 0.918 | 0.338 |
| *FGFR2* (rs1219648) | | | | | |
| | AA | 2.1 | 0.88-5.02 | 2.869 | 0.090 |
| | AG | 0.01 | 0-0.2 | 197.342 | **<0.001** |
| | GG | 62.0 | 23.63-162.66 | 132.775 | **<0.001** |

**Table 4.** Immunohistochemical analysis of HER2, ER, and PR status

| | ER+ | ER− | PR+ | PR− | HER2+ | HER2− |
|---|---|---|---|---|---|---|
| *TOX3* (rs8051542) | | | | | | |
| CC | 15 | 5 | 15 | 5 | 7 | 10 |
| TC | 22 | 2 | 22 | 2 | 11 | 13 |
| TT | 11 | 2 | 11 | 2 | 2 | 11 |
| P value | | 0.64 | | 0.11 | | 0.81 |
| *FGFR2* (rs1219648) | | | | | | |
| AA | 7 | 0 | 7 | 0 | 3 | 4 |
| AG | 36 | 9 | 36 | 9 | 15 | 29 |
| GG | 2 | 0 | 2 | 0 | 2 | 0 |
| P value | | **0.003** | | **0.003** | | 0.2 |

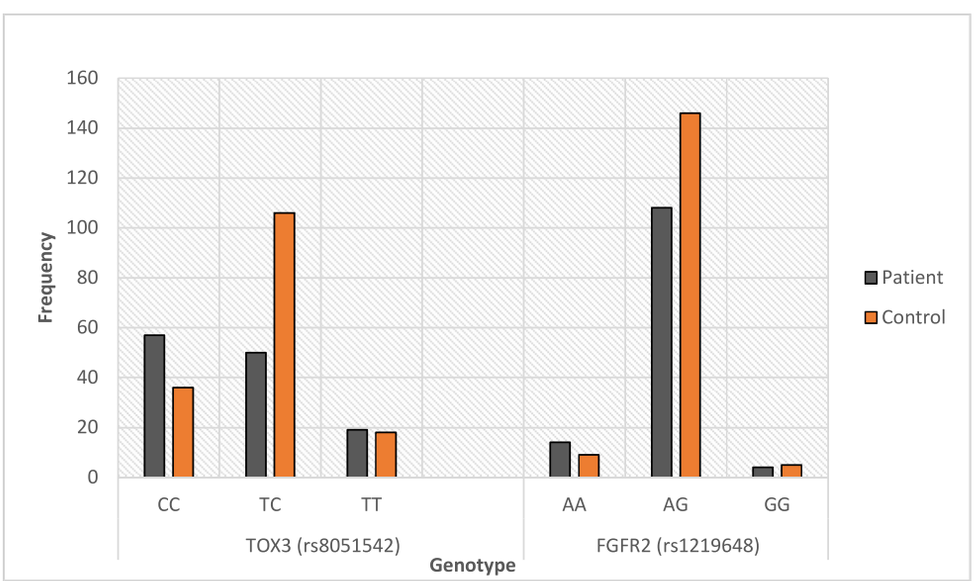


**Figure 1.** Frequencies of genotypes in cases (n = 126) and controls (n = 160)

and Figure 1). This may be attributable to significant polymorphisms of SNPs variants at low risk (Table4).

*FGFR2* (rs1219648) AG was associated with ER-positive and PR-positive tumor phenotypes. Also, the association of *TOX3* (rs8051542) TC variant with PR- and ER-positive tumors was stronger than that of CC and TT variants.

## Discussion

Recently, studies have indicated several SNPs as novel independent loci for diagnosis and prognosis of breast cancer.[14] The aim of the present study was to explore the association of SNPs in *FGFR2* and TOX3 genes with breast carcinoma subtypes. Previous reports focused on intronic SNPs in FGFR2 and proposed the gene to be a candidate locus for breast cancer.[15] Also, it was reported in similar studies that rs8051542 was significantly correlated with breast cancer risk.[16] Samson *et al* examined the *FGFR2* SNPs in southern India and showed that there was no association between *FGFR2* (C906T polymorphism) and breast cancer in this Asian population.[17] Another study genotyped rs2981582, rs1219648, rs2981578, and rs7895676 polymorphisms in *FGFR2* in breast cancer patients from northern India. The results showed that SNPs in intron 2 of *FGFR2* may contribute to genetic susceptibility to breast cancer in northern Indian population.[18] Zhang *et al* studied three SNPs in

*FGFR2* gene, including rs1219648, in a meta-analysis in China. Results of this study indicated that these polymorphisms are significantly associated with the BC risk.[19]

We observed that *FGFR2* (rs1219648) AG polymorphism is associated with ER- and PR-positive tumors. Also, the association of *TOX3* (rs8051542) TC variant with PR- and ER-positive tumors was stronger compared with CC and TT variants. These findings are consistent with several studies of *FGFR2* SNPs in BC and ER- and PR-positive tumor subtypes.

Therefore, both the high-risk and low-risk alleles (CC and TC, respectively) of *TOX3* SNP (rs8051542) are associated with BC risk. In addition, the association of TC, CC, and TT alleles in *TOX3* SNP (rs8051542) with ER+ and PR+ tumors was observed.

As conclusion, these findings suggest that genetic variants of *FGFR2* (rs1219648 AG) and *TOX3* (rs8051542 TC) can be potential candidate biomarkers for breast cancer risk.

**Conflict of Interest**

The authors have nothing to disclose.

**References**


1. DeSantis CE, Bray F, Ferlay J, Lortet-Tieulent J, Anderson BO, Jemal A. International variation in female breast cancer incidence and mortality rates. Cancer Epidemiology and Prevention Biomarkers. 2015.
2. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer epidemiology. 2015;39(4):519-27.
3. Jafari-Koshki T, Schmid VJ, Mahaki B. Trends of breast cancer incidence in Iran during 2004-2008: a Bayesian space-time model. Asian Pac J Cancer Prev. 2014;15(4):1557-61.
4. Barnard ME, Boeke CE, Tamimi RM. Established breast cancer risk factors and risk of intrinsic tumor subtypes. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2015;1856(1):73-85.
5. Houghton LC, Ganmaa D, Rosenberg PS, Davaalkham D, Stanczyk FZ, Hoover RN, *et al.* Associations of breast cancer risk factors with premenopausal sex hormones in women with very low breast cancer risk. International journal of environmental research and public health. 2016;13(11):1066.
6. Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, *et al.* Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nature genetics. 2015;47(4):373.
7. Fachal L, Dunning AM. From candidate gene studies to GWAS and post-GWAS analyses in breast cancer. Current opinion in genetics & development. 2015;30:32-41.
8. Cox DG, Curtit E, Romieu G, Fumoleau P, Rios M, Bonnefoi H, *et al.* GWAS in the SIGNAL/PHARE clinical cohort restricts the association between the *FGFR2* locus and estrogen receptor status to HER2-negative breast cancer patients. Oncotarget. 2016;7(47):77358.
9. Zanna I, Silvestri V, Palli D, Magrini A, Rizzolo P, Saieva C, *et al.* Smoking and *FGFR2* rs2981582 variant independently modulate male breast cancer survival: A population-based study in Tuscany, Italy. The Breast. 2018;40:85-91.
10. Han Y-J, Zhang J, Zheng Y, Huo D, Olopade OI. Genetic and epigenetic regulation of *TOX3* expression in breast cancer. PloS one. 2016;11(11):e0165559.
11. Machado RA, Ferreira SB, Martins L, Ribeiro MM, Martelli DR, Coletta RD, *et al.* A novel heterozygous mutation in *FGFR2* gene causing Pfeiffer syndrome. American Journal of Medical Genetics Part A. 2017;173(10):2838-43.
12. Jiang C, Yu S, Qian P, Guo R, Zhang R, Ao Z, *et al.* The breast cancer susceptibility-related polymorphisms at the *TOX3*/LOC643714 locus associated with lung cancer risk in a Han Chinese population. Oncotarget. 2016;7(37):59742.
13. He Y, Liu H, Chen Q, Sun X, Liu C, Shao Y. Relationship between five GWAS-identified single nucleotide polymorphisms and female breast cancer in the Chinese Han population. Tumor Biology. 2016;37(7):9739-44.
14. Fritsche LG, Gruber SB, Wu Z, Schmidt EM, Zawistowski M, Moser SE, *et al.* Association of Polygenic Risk Scores for Multiple Cancers in a Phenome-wide Study: Results from The Michigan Genomics Initiative. The American Journal of Human Genetics. 2018;102(6):1048-61.
15. Zhang Y, Zeng X, Liu P, Hong R, Lu H, Ji H, *et al*. Association between *FGFR2* (rs2981582, rs2420946 and rs2981578) polymorphism and breast cancer susceptibility: a meta-analysis. Oncotarget. 2017;8(2):3454.
16. Zhang L, Long X. Association of three SNPs in *TOX3* and breast cancer risk: Evidence from 97275 cases and 128686 controls. Scientific reports. 2015;5:12773.
17. Samson M, Rama R, Swaminathan R, Sridevi V, Nancy KN, Rajkumar T. CYP17 (T34C), CYP19 (Trp39Arg), and *FGFR2* (C906T) polymorphisms and the risk of breast cancer in south Indian women. Asian Pac J Cancer Prev. 2009;10(1):111-4.
18. Siddiqui S, Chattopadhyay S, Akhtar MS, Najm MZ, Deo S, Shukla N, *et al.* A study on genetic variants of Fibroblast growth factor receptor 2 (*FGFR2*) and the risk of breast cancer from North India. PLoS One. 2014;9(10):e110426.
19. Zhang Y, Lu H, Ji H, Lu L, Liu P, Hong R, *et al.* Association between rs11200014, rs2981579, and rs1219648 polymorphism and breast cancer susceptibility: A meta-analysis. Medicine. 2017;96(50).

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# Breast Cancer Trend, Incidence, and Mortality in Kerman, Iran: A 14-Year Follow-up

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ABSTRACT

**Background:** The present study aimed to investigate breast cancer trend, incidence, and mortality among Iranian women and was one of the first provincial and population-based studies to investigate breast cancer changes during 14 years in the largest province of Iran, Kerman.

**Methods:** This was a population-based longitudinal study. Information about women diagnosed with breast cancer from 2001 to 2014 was obtained from the Cancer Registry of Kerman University of Medical Sciences. Independent-samples t test, one-way analysis of variance, linear regression, time series graphs, and fitted line plots were performed using SPSS 22 and Minitab 17.

**Results:** A total of 2771 women were diagnosed with breast cancer in Kerman province from 2001 to 2014. The mean age of female patients was 49.52±12.88 years. The total incidence rate was 13.5 per 100,000 women and there was an increasing trend for incidence and age at diagnosis. Also, 254 women died from breast cancer during these 14 years and the mean mortality age was 54.16±14.33 years. There was also an increasing trend for mortality and age of death.

**Conclusion:** There is an increasing trend for incidence and mortality from breast cancer in Kerman province and this requires interventions such as appropriate screening programs. Also, enabling physicians and increasing patient awareness to identify breast cancer symptoms is necessary.

## Introduction

Cancer, with 8.8 million deaths, was the second leading cause of mortality in 2015, as 1 out of 6 deaths in the world was caused by cancer.[1] Approximately, 70% of cancer deaths occur in low- and middle-income countries,[1] and cancer incidence and mortality is increasing in developing countries.[2] Breast cancer is the second most common cancer worldwide,[3] the most common cancer in women,[4, 5] and the leading cause of death from cancer in women.[5] In 2015, 2.4 million new cases of breast cancer were diagnosed and 523 000 deaths from breast cancer were reported in the world.[6] Although more than half of the global burden of breast cancer is currently from developed countries, its incidence is rapidly increasing in developing countries.[7] Also, more than half of the deaths and about half of the new breast cancer cases occur in developing countries based on 2008 GLOBOCAN estimates.[8]

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Breast cancer is also the most common cancer in Iranian women.[4,9] It was the leading type of cancer in Iranian women, accounting for 24.6% of all cancers.[10] The mean age of breast cancer diagnosis for Iranian women is 10 to 15 years lower than that for developed and Western countries.[11,12] The mean age of diagnosis for American female breast cancer patients from 2008 to 2012 was 61 years.[13] However, in Iran, most women diagnosed with breast cancer are younger than 50 years [10,12,14,15]and most are diagnosed with invasive cancer at advanced stages.[4,10]

Studies done in Iranian women showed that low levels of knowledge[16,17] and insufficient awareness about breast cancer symptoms were among the most important factors causing delays in breast cancer diagnosis.[18] Further studies in Iran showed that empowering women through education can increase early detection of breast cancer.[19]

In developed and Western countries, such as the US, most deaths from breast cancer occur among women older than 50 years.[13] In Iran, not only are deaths from breast cancer on the rise, but a large number of deaths happen among women younger than 50 years.[20]

The present study aimed to investigate breast cancer trend, incidence, and mortality among Iranian women and was one of the first provincial and population-based studies to investigate the trends of breast cancer during 14 years in the largest province of Iran, Kerman.

## Methods

This was a longitudinal and population-based study. Information about women diagnosed with breast cancer was inquired from the Cancer Registry of Kerman Province from 2001 to 2014. This study was approved by the Deputy of Research (No: 93/460) and Ethics Committee of Kerman University of Medical Sciences (No: K/93/636).

Variables including age at diagnosis, year of diagnosis, residential location, stage and grade at diagnosis, and status (being alive or not) were extracted. Hospital medical records were used to complete the information. Death dates were obtained from the Death Registration at Kerman University of Medical Sciences. Other unknown information was collected by contacting the patient or her family.

In order to estimate the annual incidence rates, the number of new breast cancer cases for each year was divided by the total number of females in the same year. National census data for 1996, 2006, and 2011 and population growth rates were used to calculate the female population of the province in each year.

Descriptive statistics, independent-samples t-test, one-way analysis of variance, linear regression, time series graphs, and fitted line plots were performed with Excel 2016, SPSS 22, and Minitab 17.

## Results

Totally, 2771 women were diagnosed with breast cancer in Kerman province from 2001 to 2014. The mean and median ages at diagnosis were 49.52 ± 12.88 and 48 years, respectively. Also, 254 patients died of breast cancer during these 14 years, and the mean and median ages at death were 54.16 ± 14.33 years and 54 years, respectively.

Patients from rural areas ($P < 0.001$) and those with grade 3 at the time of diagnosis ($P = 0.035$), had a significantly lower age at diagnosis. Although the mean age of patients with stage III at diagnosis was also lower than the other stages, the difference was not statistically significant (Table 1).

The trend in age at diagnosis for female breast cancer patients in Kerman province during the 14 years is shown in Figure 1. As shown in the figure, the mean age at diagnosis did not show a significant trend ($P = 0.16$).

**Table 1.** Female breast cancer patient's characteristics in Kerman province, Iran

| Variable | | Frequency (%) | Age at diagnosis, Mean ± SD | P value |
|---|---|---|---|---|
| Location | City | 1677 (58.8) | 49.92 ± 12.87 | < 0.001 |
| | Rural | 439 (15.4) | 46.83 ± 12.37 | |
| | Unknown | 735 (25.8) | 50.25 ± 12.98 | |
| | Total | 2851 (100) | 49.52 ± 12.87 | |
| Stage at diagnosis | 0 | 14 (0.5) | 50.21 ± 16.52 | 0.132 |
| | I | 135 (4.7) | 48.73 ± 10.78 | |
| | II | 567 (19.9) | 48.64 ± 11.30 | |
| | III | 395 (13.9) | 47.94 ± 11.86 | |
| | VI | 89 (3.1) | 51.52 ± 13.42 | |
| | Unknown | 1651 (57.9) | 50.17 ± 13.67 | |
| | Total | 2851 (100) | 49.52 ± 12897 | |
| Grade at diagnosis | 1 | 290 (10.2) | 50.05 ± 12.89 | 0.035 |
| | 2 | 893 (31.3) | 50.01 ± 12.759 | |
| | 3 | 402 (14.1) | 48.09 ± 12.72 | |
| | Unknown | 1266 (44.4) | 49.51 ± 12.98 | |
| | Total | 2851 (100) | 49.52 ± 12.87 | |

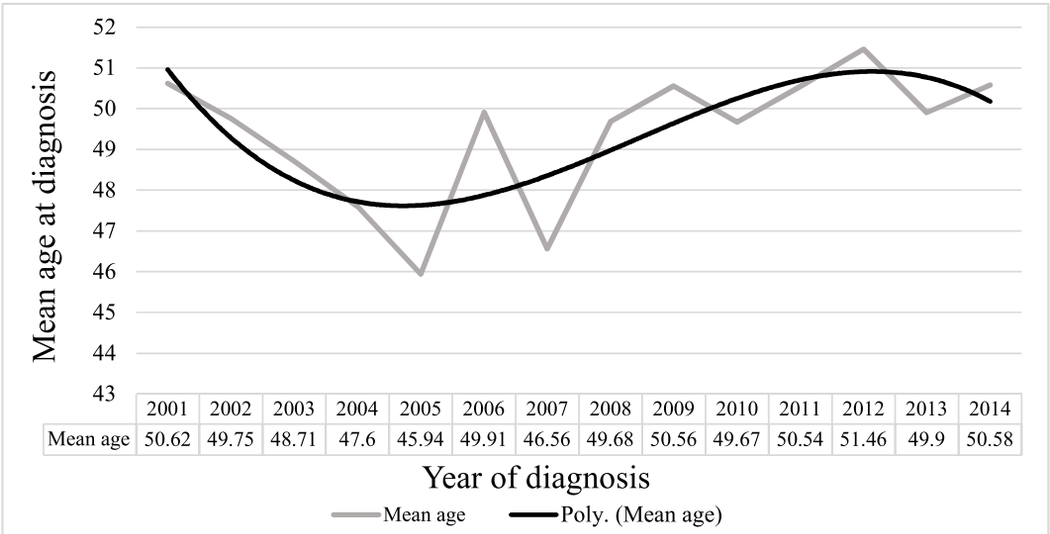



**Figure 1.** Age at diagnosis for female breast cancer in Kerman province from 2001 to 2014

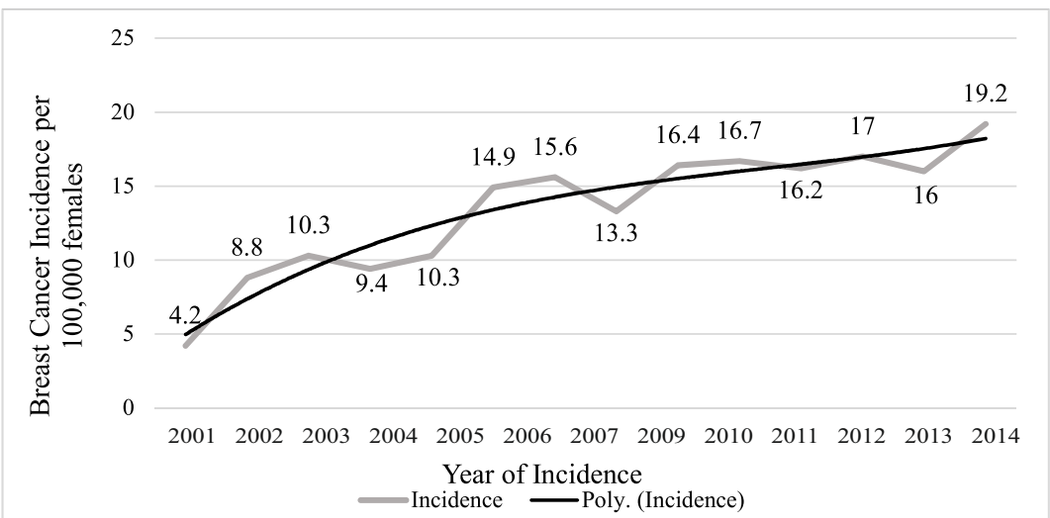
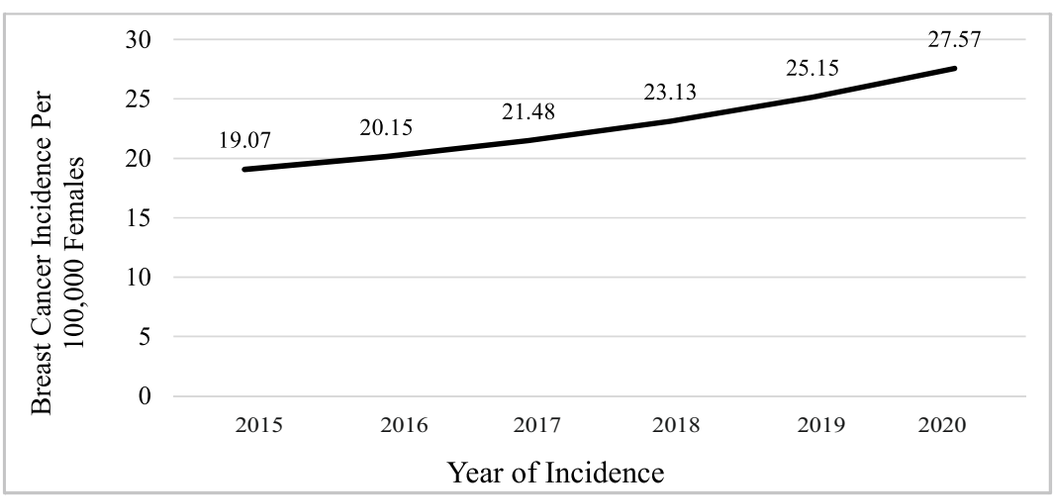



**Figure 2: a.** Breast cancer incidence in Kerman province from 2001 to 2014




**b.** Forecasting breast cancer incidence in Kerman province up to 2020

Incidence = 2.094 + (3.110 × Time) − (0.2520 × Time2) + (0.008009 × Time3)

The trend in breast cancer incidence in Kerman province from 2001 to 2014 is shown in Figure 2a. As shown in the figure, breast cancer incidence has been increasing in Kerman province ($P < 0.001$).

The forecast of breast cancer incidence in Kerman province up to 2020 is shown in Figure 2b. The best fit for the data was a third-degree model. If the incidence of breast cancer increases as predicted in Figure 2b, about 27 cases of breast cancer will happen per 100000 females in Kerman province by 2020.

Figure 3 shows the mean age of death due to female breast cancer during the 7 years in urban and rural areas of Kerman province. The mean age of death among rural women was nonsignificantly lower than that of women living in cities (P = 0.074).

A large percentage of data was missing from 2001 to 2007 (91.9%), and because of this, data for these years were not included in Figures 4 and 5.

The trend in breast cancer mortality in Kerman province from 2008 to 2014 is shown in Figure 4. Breast cancer mortality did not show a significant trend during these 7 years (P = 0.063).

The trend in mortality age for female breast cancer patients in Kerman province from 2008 to 2014 is shown in Figure 5. The mean age of death due to breast cancer had an increasing trend from 2008 to 2014 (P = 0.046).

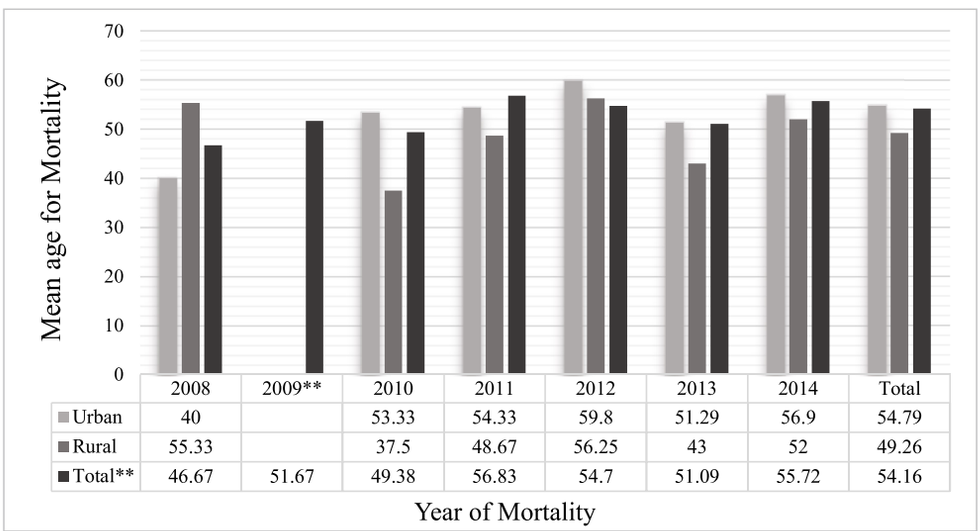



**Figure 3.** Age of death due to female breast cancer in urban and rural areas of Kerman province (2008-2014)
** *Including unknown*

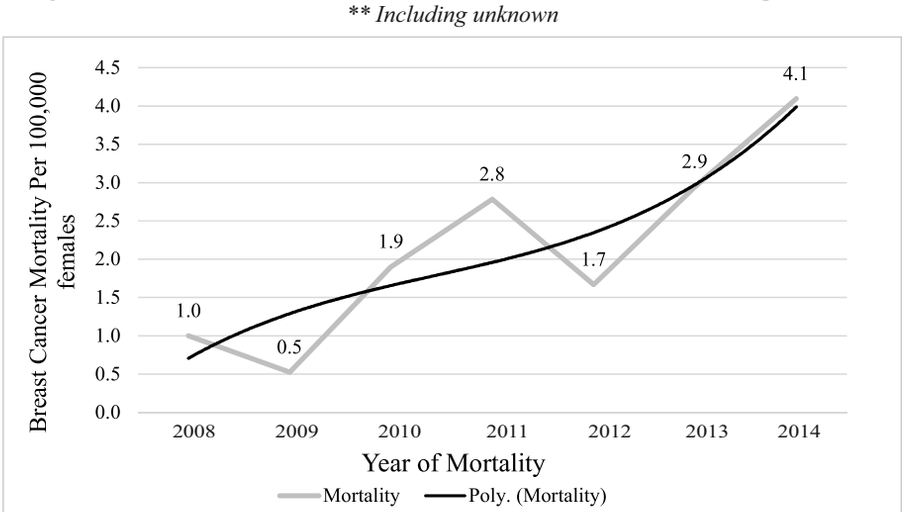



**Figure 4.** Female breast cancer mortalities in Kerman province from 2008 to 2014

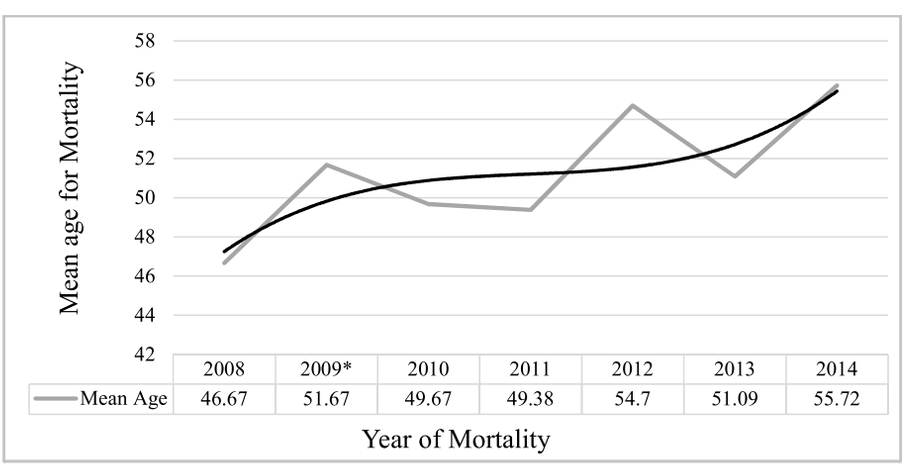



**Figure 5.** Age at death due to female breast cancer in Kerman province from 2008 to 2014
* *Including unknown*

## Discussion

The mean age at diagnosis for breast cancer was about 50 years among women in Kerman province. This age is lower in comparison with a developed country such as England, where the highest incidence of breast cancer happens after the age of 55.[21]

In the present study, the age-specific incidence rate was highest among women aged 40 to 55 years (46.22 per 100 000 females), and the median age of diagnosis was 48 years. However, according to the US National Cancer Institute, most women diagnosed with breast cancer in America were 55 to 64 years old and the median age of diagnosis of breast cancer was 62 years.[22] Also, Mousavi *et al.*, in a population-based study of the data from Tehran Cancer Registry in Iran from 1998 to 2001, showed that the mean age at diagnosis was 51 years and that although 36% of patients were aged under 40 years, the highest incidence rate was reported among women aged more than 60 years.[23]

In the present study, the incidence rate for 2012 (17 per 100 000 females) was lower than the average standardized rate for the world (43 per 100 000 females) and Asian countries including Japan, South Korea (both 52 per 100 000 females) and Singapore (65 per 100 000 females).[24]

The results of the present study showed that the age at diagnosis was significantly lower among women who lived in rural areas. In contrast, Mitchel et al, who studied breast cancer during 1999 in Australia, showed that there was no significant relationship between age at diagnosis and residential areas.[25]

The incidence rates of breast cancer in the present study was 16.7 to 19.2 per 100 000 females from 2010 to 2014, and these results were lower than a developed country such as the USA, where the average incidence was 124.9 per 100 000 females from 2010 to 2014.[22]

It seems that, compared with women in developed countries, Iranian women develop breast cancer at younger ages and visit doctors at more advanced stages of the disease. This needs more attention and appropriate screening programs.[4]

Lifestyle and behavioral and nutritional habits are risk factors for many noncommunicable diseases and cancers, including breast cancer.[26-28] In the last two decades, breast cancer has rapidly increased in the less developed regions of the world.[7, 8] Likewise, in the present study, breast cancer incidence showed an increasing trend, and this needs proper interventions including screening and periodical breast examinations.

A total of 1 426 (96.8%) BC cases undergoing mastectomy were pathologically staged. Of this number, 39.1% were stage III. The majority of cases were in stages III and IV combined (62.8%) (Figure 3). Only of 47 (3.2%) cases were residual cancers.

A total of 202 (13.7%) of the BC cases undergoing mastectomy were incompletely excised.

In the present study, although breast cancer mortality increased from 1 to 4.1 per 100 000 females from 2008 to 2014, that rate was still less than developed countries such as England and Wales.[29] The mortality rate in England showed a decreasing trend from 2002 to 2006, but the adjusted mortality rate for different age groups was 30 per 100 000 females, which is much more than Iran.[29] Also, according to the US National Cancer Institute, the mean breast cancer mortality rate in the US was 21.2 per 100 000 females from 2010 to 2014,[22] while we found a breast cancer mortality rate of 1.9 to 4.1 per 100 000 females over the same period in Kerman province—although underestimations may have occurred due to low-quality data collection in Iran.

The results of the present study showed that although the mean age of death among women who lived in the rural areas was lower, this difference was not significant. In Europe in 2014, the mortality rate decreased by 9% compared with 2009,[30] while, Taghavi *et al.* reported that breast cancer mortality had increased from 1995 to 2004 in Iran, with the increase being greater for women younger than 50 years.[20] According to Rastad *et al.*, lack of breast cancer awareness, not considering themselves at risk, fear of being diagnosed with cancer, and incorrect diagnosis and relief by physicians were among the most important factors for the delay in seeking treatment for breast cancer in Iran.[18]

Considering the growing trend in breast cancer mortality and lower age of breast cancer death in Kerman province, as well as the results of previous studies,[16] more appropriate measures should be taken to improve early diagnosis by enabling physicians and increasing patient awareness about breast cancer symptoms.

A limitation of this study was its missing data. About half of the cases had missing data on stage and grade.

In conclusion, breast cancer incidence is growing in Kerman province, and this needs appropriate interventions including screening, early detection, enabling physicians, and empowering patients to identify breast cancer symptoms. Also, providing greater access to facilities for early diagnosis and treatment of breast cancer patients in rural areas should also be considered.

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**Conflict of interest**

The authors have no conflict of interest.

**Acknowledgment**

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**References**


1. World-Health-Organization. Fact sheet: Cancer 2017. Available from: [http://www.who.int/mediacentre/factsheets/fs297/en/.]
2. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiology and Prevention Biomarkers. 2010;19(8):1893-907.
3. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, *et al.* Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. International journal of cancer. 2015;136(5): E359-E86.
4. Harirchi I, Kolahdoozan S, Karbakhsh M, Chegini N, Mohseni S, Montazeri A, *et al.* Twenty years of breast cancer in Iran: downstaging without a formal screening program. Annals of oncology. 2011;22(1):93-7.
5. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65(2):87-108.
6. Fitzmaurice C, Allen C, Barber RM, Barregard L, Bhutta ZA, Brenner H, *et al.* Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA oncology. 2016.
7. Ferlay J, Héry C, Autier P, Sankaranarayanan R. Global burden of breast cancer. Breast cancer epidemiology: Springer; 2010:1-19.
8. Ma J, Jemal A. Breast cancer statistics. Breast Cancer Metastasis and Drug Resistance: Springer; 2013:1-18.
9. Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Annals of Oncology. 2009;20(3):556-63.
10. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Ten-year national cancer registry data report. Cancer Epidemiol. 2015;39(4):519-27.
11. Vostakolaei FA, Broeders MJ, Rostami N, Van Dijck JA, Feuth T, Kiemeney LA, *et al.* Age at diagnosis and breast cancer survival in Iran. International journal of breast cancer. 2012;2012.
12. Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, *et al.* Breast cancer in Iran: an epidemiological review. The breast journal. 2007;13(4):383-91.
13. AmericanCancerSociety. Breast Cancer Facts &Figures 2015-2016. Available from: [https://www.cancer.org/ content/dam/cancer-org/research/cancer-facts-and-statistics/breast-cancer-facts-and-figures/breast-cancer-facts-and-figures-2015-2016.pdf.]
14. Babu GR, Samari G, Cohen SP, Mahapatra T, Wahbe RM, Mermash S, *et al.* Breast cancer screening among females in Iran and recommendations for improved practice: a review. Asian Pac J Cancer Prev. 2011;12(7):1647-55.
15. Vahdaninia M, Montazeri A. Breast cancer in Iran: a survival analysis. Asian pacific journal of cancer prevention. 2004;5(2):223-5.
16. Khanjani N, Noori A, Rostami F. The knowledge and practice of breast cancer screening among women in Kerman, Iran. Al-Ameen J Med Sci. 2012;5(2):221-6.
17. Asgarabad AA, Khanjani N, Saber M, Jalili S, Khedmati E. Knowledge and attitude of students at Alzahra University about breast self-examination, Iran. Journal of Health and Development. 2012;1(2):112-0.
18. Rastad H, Khanjani N, Khandani BK. Causes of delay in seeking treatment in patients with breast cancer in Iran: a qualitative content analysis study. Asian Pacific Journal of Cancer Prevention. 2012;13(9):4511-5.
19. Sabbagh MQ, Khanjani N, Fadakar M, Iranpour A. Empowerment of women visiting the health centers of Kerman by teaching Self Breast Examination in the presence of Behvarz. Iranian Journal of Breast Disease. 2014;7(1):41-51 [persian].
20. Taghavi A, Fazeli Z, Vahedi M, Baghestani AR, Pourhoseingholi A, Barzegar F, *et al.* Increased trend of breast cancer mortality in Iran. Asian Pacific Journal of Cancer Prevention. 2012; 13(1):367-70.
21. Mehdi I, Monem EA, Al Bahrani BJ, Al Kharusi S, Nada AM, Al Lawati J, *et al.* Age at diagnosis of female breast cancer in Oman: Issues and implications. South Asian journal of cancer. 2014;3(2):101.
22. National Cancer Institute. Cancer Stat Facts: Female Breast Cancer. Available from: [https://seer.cancer.gov/statfacts/html/breast.html.]
23. Mousavi SM, Mohaghegghi MA, Mousavi-Jerrahi A, Nahvijou A, Seddighi Z. Burden of breast cancer in Iran: a study of the Tehran population based cancer registry. Asian Pacific Journal of Cancer Prevention. 2006;7(4):571.
24. Youlden DR, Cramb SM, Yip CH, Baade PD. Incidence and mortality of female breast cancer in the Asia-Pacific region. Cancer biology & medicine. 2014;11(2):101-15.
25. Mitchell K, Fritschi L, Reid A, McEvoy S, Ingram D, Jamrozik K, *et al.* Rural–urban differences in the presentation, management and survival of breast cancer in Western Australia. The Breast. 2006;15(6):769-76.
26. Armstrong T, Bonita R. Capacity building for an integrated noncommunicable disease risk factor

surveillance system in developing countries. Ethnicity & disease. 2002;13(2 Suppl 2):S13-8.
27. Murray CJ, Lopez AD. Measuring the global burden of disease. New England Journal of Medicine. 2013;369(5):448-57.
28. Khazaei S, Rezaeian S, Khazaei Z, Molaeipoor L, Nematollahi S, Lak P, *et al.* National breast cancer mortality and incidence rates according to the human development index: an ecological Study. Advances in Breast Cancer Research. 2016;5(01):30.
29. Autier P, Boniol M, La Vecchia C, Vatten L, Gavin A, Héry C, *et al.* Disparities in breast cancer mortality trends between 30 European countries: retrospective trend analysis of WHO mortality database. Bmj. 2010;341:c3620.
30. Malvezzi M, Bertuccio P, Levi F, La Vecchia C, Negri E. European cancer mortality predictions for the year 2014. Annals of Oncology. 2014:138.

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# Prognostication of Breast Cancer in Ghanaian Women Receiving Modified Radical Mastectomy: A Retrospective Histopathological Study at Korle-Bu Teaching Hospital, Accra, Ghana

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ABSTRACT

**Background:** Making prognosis and identifying the patients at higher risk of mortality are important issues in breast cancer (BC) treatment. The aim of this study was to stratify BC case receiving mastectomy into prognostic risk categories using the Nottingham Prognostic Index (NPI).

**Methods:** This was a retrospective review from January 2002 to December 2014.

**Results:** Approximately 35% of all BCs diagnosed in our institution had undergone mastectomy. The mean age was 51.9 years. The mean size of the primary breast tumor was 5.8 cm and showed significant association with the histologic grade ($P = 0.001$), nodal involvement ($P < 0.001$), positive tumor margins ($P = 0.027$), and the cancer stage ($P < 0.001$). Based on the NPI sores, 1.5% of the cases would have an excellent prognosis, 10.8% a good prognosis, 55.8% a moderate prognosis, and 31.9% a poor prognosis.

**Conclusion:** The current study found that 87.7% of the women with breast had moderate to poor prognosis at the time of diagnosis. Patients are found to present late when the disease is advanced.

## Introduction

Breast cancer (BC) is the most frequently diagnosed cancer in women globally and in Ghana.[1-3] Previous institution-based publications on BC in Ghana[4] and other African countries[5] have found the disease to be common among younger women, with advanced stage at presentation.[6-11] Unfortunately, none of the previous BC publications from Ghana included data on prognostic grouping of Ghanaian women diagnosed with the disease. A number of putative prognostic factors for human BC have been reported by the American Joint Committee on Cancer (AJCC). Recognizing the prognostic factors enables greater accuracy in predicting the outcome of BC treatment. The universally acknowledged prognostic factors for BCs are the age at diagnosis, tumor size, histologic type, tumor grade, lymph node status, metastases to other organs, estrogen and progesterone receptor expression, HER2 expression, and the proliferation index. Combining these factors is of greater clinical value than considering each in isolation, and this is the basis for a number of schemes that are used to group patients into various risk categories. One of such schemes is the Nottingham Prognostic Index (NPI), which we used to group Ghanaian women with BC into prognostic categories. The aim of this study was to stratify BCs undergoing modified radical mastectomy into prognostic risk categories using the NPI.

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## Methods

*Study Design*

This was a retrospective study covering the period from 2002 to 2014. Data were collected from the Department of Pathology, School of Biomedical

Sciences, College of Health Sciences of the University of Ghana located at Korle-Bu. This institution reports between 5 ,000 and 8 ,000 histology cases yearly.

*Inclusion Criteria*

1) All female BCs.

2) Well-fixed mastectomy specimens with axillary clearance.

*Exclusion Criteria*

1) All male breast cancers.

2) Poorly fixed female mastectomy specimens.

3) Receiving neoadjuvant chemotherapy prior to mastectomy without residual malignant cells.

*Ethical consideration/informed consent*

Permission to publish the data in this manuscript was granted by the head of the Department of Pathology.

*Data Collection*

Histopathology reports and slides of confirmed BC cases included in the study were reviewed. Of the total number, BC cases who had undergone mastectomy were selected and the clinicopathological characteristics of BCs were collected.

A positive tumor margin in this study was defined as the presence of malignant cells within 2 mm of the resection margins.

The study did not include the following prognostic factors: estrogen receptor, progesterone receptor, and HER2 expression, which are not routinely performed but on request, and proliferation indices, which are not performed at all in our institution.

BCs were classified according to the World Health Organization histology classification of breast tumors (WHO 2003).[12]

Histologic grading of breast tumors was performed according to the modification of the Bloom-Richardson system by Elston and Ellis.

The cancer stage was determined using the TNM system (pathological) developed by AJCC, which uses the size of the primary tumor (T), nodal involvement (N), and presence of metastasis (M).

*Calculation of the Nottingham Prognostic Index(NPI)*

The NPI is one of the most widely used prognostic indices for patients with invasive BC. The NPI was developed in 1982 to help in the management of primary operable BC.[13, 14] Multivariate analysis identified 3 factors to be significant: tumor grade, the number of lymph nodes involved, and the size of the tumor. These are viewed as the strongest independent predictors of outcome and make up the formula to calculate the prognostic score. Cutoff points were applied to divide patients into prognostic categories of excellent, good, moderate, and poor, and these correlate strongly with the survival rate.[15] Since the development of the NPI, attempts have been made by other researchers to improve its prognostic power, with limited success. Some people have suggested modifying the variables used to determine the index or combining additional markers with it, and others have used different statistical approaches.[15,16] However, to date, the original NPI remains the gold standard for stratifying BC patients into prognostic categories.

BCs that met the following criteria were included in the calculation of the NPI:

1. Must be graded using the modified Bloom-Richardson grading system.
2. Must have stated gross primary tumor size (cm).
3. Must have lymph nodes retrieved from the axillary content.

The NPI was calculated as follows:

Lymph node involvement (L) was scored as 1-3 (No nodes: 1, 1-3 nodes: 2, and > 3 nodes: 3).

The NPI was calculated using the formula: $NPI = G + L + (S \times 0.2)$.

BC cases were put into prognostic categories and 5-year survival rates based on their NPI scores.

*Data Analyses*

Data were entered into the SPSS software version 18 (IBM, Chicago, USA). Frequency distributions and descriptive statistics were calculated. The associations between tumor variables were determined using Spearman's correlation coefficient. Finally, BCs were categorized into prognostic groupings using the NPI. P values of $< 0.05$ were considered significant.

**Results**

*Clinicopathological Characteristics of Bcs*

During the period under review 4,175 BCs were diagnosed in our institution, of which 1,473 (35.3%) received a mastectomy. There was a gradual rise in the proportion of mastectomy-receiving BC cases over the period (Figure 1).

The age of patients ranged from 14 to 94 years (M = 51.9 y, SD = 12.5), with the modal age group of 40 to 49 years (27.9%) (Figure 2).

The most common primary presentation of BC was a painless palpable lump (N = 1467, 99.6%). A total of 669 (47.6%) women with palpable lumps had skin involvements. The duration of symptoms at presentation was available for 911 (61.8%) patients, of which 79.6% had reported after 3 months of illness (Table 1).

The size of primary tumors ranged from 0.5 to 24 cm, with a mean of 5.8 cm (SD = 3.9). Half of the tumors were larger than 5.0 cm (T3) in diameter. This was followed by 595 (40.4%) tumors that were larger than 2.0 cm, but less than or equal to 5.0 cm (T2), and 141 (9.6%) tumors that were 2.0 cm or less (T1).

The major categories of BCs in this study were epithelial (97.2%), mesenchymal (1.0%), and fibroepithelial (0.95%). The great majority of the BC

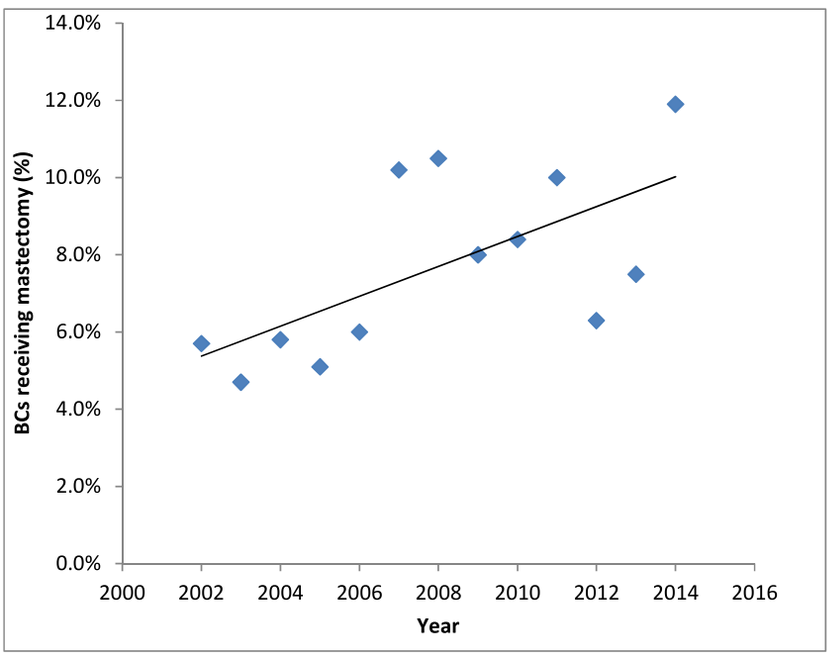


**Figure 1.** Trend in BC cases receiving mastectomy at Korle-Bu teaching hospital

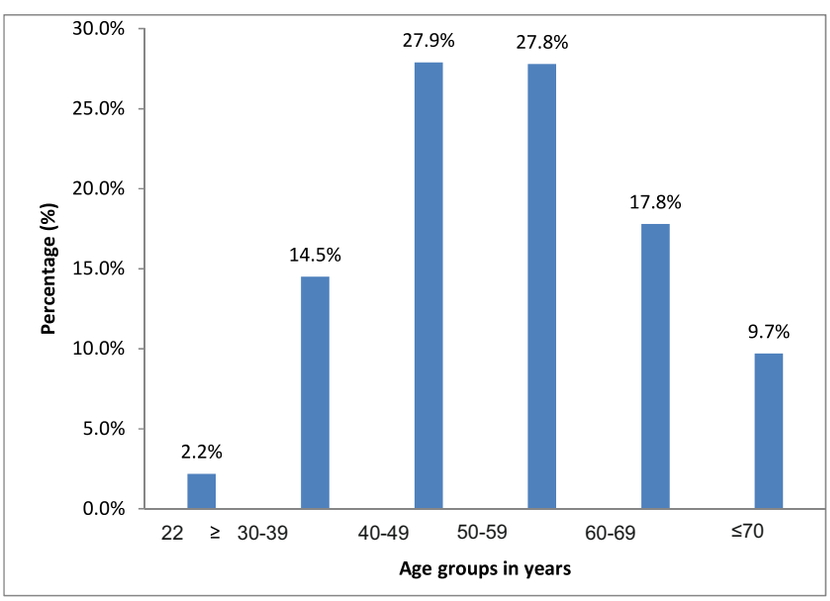


**Figure 2.** Age distribution of BCs during the period of review

**Table 1.** Symptoms and duration of BC at presentation

| Variable | | | N (%) |
|---|---|---|---|
| Primary complaint | Nipple discharge | | 6 (0.4%) |
| | Palpable breast lump | | 1467 (99.6%) |
| | Laterality | | |
| | | Right breast | 746 (50.9%) |
| | | Left breast | 713 (48.6%) |
| | | Bilateral | 8 (0.5%) |
| Additional symptoms | Skin involvement | | 699 (45.4%) |
| | Other | | 25 (1.7%) |
| Duration of symptoms at presentation (months) | 1-3 | | 186 (20.4%) |
| | 4-6 | | 172 (18.9%) |
| | 7-9 | | 108 (11.9%) |
| | 10-12 | | 224 (24.6%) |
| | 13-24 | | 134 (14.7%) |
| | >24 | | 87 (9.5%) |

**Table 2.** Histological types of BC

| Histological types of breast cancers | | N (%) |
|---|---|---|
| Epithelial | | 1432 (97.21%) |
| | Invasive ductal carcinoma, not otherwise specified (IDC-NOS) | 1296 (87.98%) |
| | Mucinous | 37 (2.51%) |
| | Lobular | 31 (2.10%) |
| | Ductal carcinoma in situ (DCIS) | 17 (1.15%) |
| | Papillary | 17 (1.15%) |
| | Neuroendocrine | 5 (0.33%) |
| | Medullary | 9 (0.7%) |
| | Apocrine | 5 (0.33%) |
| | Cribriform | 4 (0.27%) |
| | Tubular | 3 (0.20%) |
| | Squamous cell carcinoma | 4 (0.27%) |
| | secretory | 1 (0.06%) |
| | Inflammatory | 1 (0.06%) |
| | Sweat gland | 1 (0.06%) |
| Mesenchymal | | 15 (1.01%) |
| | Metaplastic | 10 (0.67%) |
| | Sarcoma | 3 (0.20%) |
| | Osteosarcoma | 1 (0.06%) |
| | malignant peripheral nerve sheath tumor (MPNST) | 1 (0.06%) |
| Fibroepithelial | | 14 (0.95%) |
| | Malignant phyllodes tumor | 14 (0.95%) |
| Tumors of the nipple | | 11 (0.74%) |
| | Paget's disease | 11 (0.74%) |
| Lymphoma | | 1 (0.06%) |
| Total | | 1473 |

subtypes were invasive ductal carcinoma, not otherwise specified (IDC-NOS) (88.0%) (Table 2).

A total of 1,458 (99%) cases undergoing mastectomy had Bloom-Richardson grading. Of this number, 42% were grade 2, 38.1% grade 3, and 19.9% grade 1. The number of cases with nodal involvement was 976 (66.3%), with the mean number of nodes involved being 3.4 (SD = 4.2, range: 1-42). Many (44%) of these cases had between 1 and 3 positive lymph nodes (Figure 3). In all, 56% had 4 or more positive lymph nodes.

A total of 1,426 (96.8%) BC cases undergoing mastectomy were pathologically staged. Of this number, 39.1% were stage III. The majority of cases were in stages III and IV combined (62.8%) (Figure 3). Only of 47 (3.2%) cases were residual cancers.

A total of 202 (13.7%) of the BC cases undergoing mastectomy were incompletely excised.

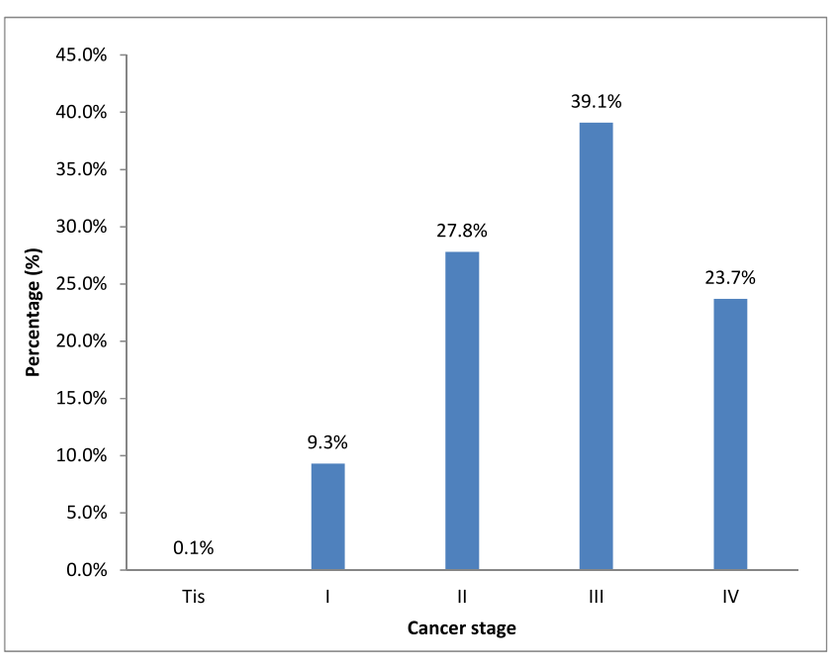


**Figure 3.** TNM staging of BC cases

**Table 3.** Association between BC prognosis indicators (By Spearman's Correlation)

| | Tumor Size | Histologic type | Tumor grade | Positive LN | Tumor Stage | Positive margins |
|---|---|---|---|---|---|---|
| Tumor Size | - | **0.003** | **0.001** | **0.000** | **0.000** | 0.027 |
| Histologic type | **0.003** | - | 0.441 | 0.300 | 0.503 | 0.350 |
| Tumor grade | **0.001** | 0.441 | - | **0.002** | **0.000** | 0.125 |
| Positive LN | **0.000** | 0.300 | **0.002** | - | **0.003** | **0.003** |
| Tumor stage | **0.000** | 0.503 | **0.000** | **0.003** | - | **0.001** |
| Positive margins | 0.027 | 0.350 | 0.125 | **0.003** | **0.001** | - |

**Table 4.** Stratification of breast cancer cases (N = 1,451) into prognostic categories using the NPI

| NPI | N (%) | Prognosis | Expected 5-year survival rate |
|---|---|---|---|
| 2.0-2.4 | 22 (1.5%) | Excellent | 93% |
| 2.4-3.4 | 157 (10.8%) | Good | 85% |
| 3.4-5.4 | 810 (55.8%) | Moderate | 70% |
| > 5.4 | 462 (31.9%) | Poor | 50% |

*Associations Between Tumor Variables*

The size of the primary tumor was significantly correlated with histologic type (P = 0.002), tumor grade (P = 0.001), positive lymph nodes (P < 0.001), positive tumor margins (P = 0.027) and the tumor stage (P < 0.001). There were also significant positive associations between other tumor variables (Table 3).

*Nottingham Prognostic Index Calculation*

A total of 1,451 (98.5%) of the cases receiving mastectomy met the criteria for the calculation of the NPI.

More than half (55.8%) had NPIs within between 3.5 and 5.4, which translates into a moderate prognosis and an expected 5-year survival rate of 70%. Only 1.5% had an excellent prognosis and an expected 5-year survival rate of 93% (Table 4). The remaining 87.7% had moderate to poor prognosis.

## Discussion

Breast cancer is the most common malignancy among women in developed and developing countries, such as Ghana.[1-3] In the current study, 35.3% of all histologically confirmed BCs had received mastectomy, with 51% of the women being younger than 50 years. This value seems to suggest that BC is still common among young Ghanaian women, as is the case with other African countries.[4-6] Patient's age at histological diagnosis is an independent prognostic factor: the younger the age the poorer the outcome after treatment.[7, 8] This have been the fate of the women in the current study.

Women commonly presented with palpable breast lumps, with 47.9% having skin involvements. This seems to suggest that women with BC in current study only present to a health facility when the disease is obvious. This may be due to the fact that there is no population-based BC screening program in the country, so lesions are not detected until they become palpable. BC women in our study are not used to self-examination of their breasts, therefore they detect their BC only when the tumor is obviously large to be felt accidentally. The current findings are in accord with some institution-based studies in Africa, which found that the disease was common in young women,[10] and that women with BC presented late,[6, 11] with large advanced tumors with skin involvement.[9,11]

The great majority (79.6%) of women with BC presented late (after 12 weeks) to health facilities, with advanced diseases. Late presentation of BC to health facilities in Ghana has been attributed to a prior visit to prayer camps, stigmatization of women with the disease, the wait-and-see attitude of patients, ignorance about the disease, financial hardship, and the hostile attitude of hospital workers and the hospital environment.[9,11] Studies in Nigerian,[17] Tunisian,[18] and South African women[19] similarly found the presentation of the disease to be late. Literature from other parts of the world for the past 30 years indicates that survival is worse for women with longer duration of symptoms.[20-23] Furthermore, the current findings are similar to the studies in the UK in the early 80s and late 90s (when routine BC screening was not commonplace), which found that most women with BC presented late with symptoms of the advanced disease and that there was a need for early detection and treatment.[24, 25] It is expected that early diagnosis and treatment would lead to a reduction in disease severity or mortality. For instance, Burgees *et al.,*[24] who defined patient delay as 12 weeks of symptoms before the first visit to the general practitioner (GP), found that 90% of their patients delayed ≥ 12 weeks in seeing the GP, and that patient delay was associated with clinical tumor sizes greater than 4 cm (P = 0.0002) and a higher incidence of locally advanced and metastatic disease (P = 0.001). There is evidence, however, that the duration of symptoms may not be associated with survival. Dennis et al and Fisher et al found that about 20% of the patients visited the GP at about 4 to 8 weeks after symptoms onset and concluded that survival after the symptoms have appeared is not related to the duration of the symptomatic period but

to established pathological criteria such as rate of growth, the tumor size, lymph node involvement, the number and location of lymph nodes involved, blood vessel invasion, and the presence of systemic metastases.[26, 27] These apparently conflicting results may be explained by differences in the cutoffs used to define delay.

The mean primary tumors size in our study was large (5.8 cm) and showed significant positive associations with the histological grade (P = 0.001), nodal involvement (P < 0.001), and the tumor stage (P < 0.001). The size of primary breast tumor is an independent prognostic factor and, together with nodal involvement, is used for staging BC.[28] Studies have shown that women with large primary are more likely to have positive lymph nodes and hence poor prognosis.[28,29] In the present study, 50% of the women had tumor sizes of greater than 5 cm, indicating that the majority of the women had a poor outcome and low survival rate. This, however, differs from Wo et al[30] who showed that very small tumors can equally have extensive lymph node involvement and hence poor survival rate.

Invasive ductal carcinoma, not otherwise specified (IDC-NOS) was the most common histological subtype of BC in this study similar to other studies.[31, 32] The grade of a breast tumor is directly related to prognosis,[33, 34] and the 5-year survival.[35, 36] The higher the tumor grade, the lower the 5-year survival rate. [35, 36] The great majority (80.1%) of the cases in this study were of high histological grade, and this may translate into a poor prognosis and a low 5-year survival rate. This finding is similar to the 76% prevalence of grade 3 tumors in Ghanaian women in the study of Stark et al,[37] who compared Ghanaian women with African American and white women diagnosed with BC.

The number of involved lymph nodes is a very important prognostic factor for invasive cancers.[38, 39] It is associated with a lower survival rate, high recurrence rate, decreased time to recurrence, and treatment failure.[38] Disease-free survival (DFS) and overall survival diminish with each additional positive axillary node.[40] It has been shown that about 70% of patients with nodal involvement will develop recurrence after mastectomy, and patients with 4 or more lymph nodes involved have a worse prognosis compared with those having fewer nodes involved.[41-43] Survival rate decreases with increased nodal involvement. With no nodal involvement, the 10-year DFS rate is between 70% and 80%. This rate declines to 35% to 40% when there are 1 to 3 positive nodes, and to 10% to 15% when ≥ 10 nodes are involved.[44] The current study found that 44% of the cases had 1 to 3 positive lymph nodes, while about 56% had 4 or more positive lymph nodes. This is consistent with Jatoi et al,[45] who found the hazard ratios for patients with 1 to 3 and ≥ 4 positive nodes to be 1.2 (95% CI, 0.8 to 1.9) and 2.5 (95% CI, 1.8 to 3.4), respectively. They concluded that patients with ≥ 4 involved nodes at diagnosis had a significantly poorer outcome after relapse compared with node-negative cases, regardless of the duration of the disease-free period. Our results suggest that nodal metastasis is a marker of an aggressive phenotype as well as being a diagnostic marker at a later point in the natural history of BC. Thus, the majority of women in this study are expected to be at increased risk for recurrence of the disease after mastectomy, treatment failure, and survival rates less than 40%.

The cancer stage at histological diagnosis showed strong positive associations with the histological grade (P < 0.001), and positive tumor margins (P = 0.001). The stage of BC determines the treatment option and the prognosis of tumors after the treatment.[46, 47] The higher the stage at diagnosis, the shorter the 5-year survival rate.[46] The majority of the BC patients in this study had stage III or IV cancers at the time of histological diagnosis and potentially a poor outcome of the disease, even with treatment, and a low 5-year survival rate.[48, 49] Furthermore, the large percentage of advanced-stage BCs in this study differs from the results of the study of Walters et al[45] in Canada, where they found that 82.9% of the BC patients were in stage I or II, while only 17.1% had stage III or IV cancer.

In this study, positive tumor margin frequency of 13.7% was found in mastectomy specimens. This value is close to the 12% for total mastectomies in Sheikh et al,50 but lower than the 20% in the study of Walters *et al*.[51] These women are therefore potentially at risk of developing local recurrence[52, 53] and systemic disease.[54,55]

The NPI is one of the most widely used prognostic indices for the management of patients with primary operable invasive BC.[13,14,56] It is the gold standard for stratifying BC patients into prognostic categories as excellent, good, moderate, and poor, which correlate strongly with the survival rate.[15] Data on the survival of BC patients after definitive diagnosis and treatment is nonexistent in Ghana. Available data from some African countries with limited resources for BC screening, diagnosis, and treatment showed varied results[16, 19, 57-59] compared with the United States of America and Canada,[60, 61] where effective screening and treatment and cancer registries are present. In the current study, based on the NPI scores, 31.9% of the women would have a poor prognosis, with an expected 5-year survival rate of 50%; 55.8% would have a moderate prognosis, with an expected 5-year survival of 70%; and only 1.5% would have an excellent prognosis, with an expected 5-year survival of 93%. The proportion of women with poor prognosis (31.9%) in this study is higher than the values observed in the Gambia (12.5%)[59] and Nigeria (24.5% and 25.6%),[58] but performs less than some African countries such as Uganda (56.4%) and South Africa (64%,

black women).[57] Furthermore, the finding from the current study also compared far less favorably with values such as 80% for South African white women,[60] 81% for the Republic of Korea,[62] 86% for Canada,[59] and 88% for the United States of America.[60,61]

In conclusion, the current study found that 87.7% of the BC cases had moderate to poor prognosis at the time of diagnosis. Patients were found to present late when the disease is advanced.

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**Conflict of Interest**

No conflict of interest.

**References**

1. Ghafoor A, Jemal A, Ward E, Cokkinides V, Smith R, Thun M. Trends in breast cancer by race and ethnicity. CA Cancer J Clin. 2003;53(6):342-55.
2. Bray F, Ren JS, Masuyer E, Ferlay J. Global estimates of cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013; 132(5):1133-45.
3. Calys-Tagoe BN, Yarney J, Kenu E, Amanhyia NAKO, Enchill E, Obeng I. Profile of cancer patients' seen at Korle Bu teaching hospital in Ghana (A cancer registry review). BMC research notes. 2014;7(1):577.
4. Quartey-Papafio J, Anim J. Cancer of the breast in Accra. 1980.
5. Ekanem VJ, Aligbe JU. Histopathological types of breast cancer in Nigerian women: a 12-year review (1993-2004). Afr J Reprod Health. 2006;10(1):71-5.
6. Clegg-Lamptey J, Hodasi W. A study of breast cancer in korle bu teaching hospital: assessing the impact of health education. Ghana Med J. 2007;41(2):72-7.
7. Albain KS, Allred DC, Clark GM. Breast cancer outcome and predictors of outcome: are there age differentials? Journal of the National Cancer Institute Monographs. 1994(16):35-42.
8. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, *et al.* Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. J Clin Oncol. 1994;12(5):888-94.
9. Clegg-Lamptey J, Aduful H, Yarney J, Adu-Aryee N, Vanderpuye V, Kyereh M, *et al.* Profile of breast diseases at a self-referral clinic in Ghana. West Afr J Med. 2009;28(2):114-7.
10. Anyanwu SN. Breast cancer in eastern Nigeria: a ten year review. West Afr J Med. 2000;19(2):120-5.
11. Ohene-Yeboah MO. An audit of excised breast lumps in Ghanaian women. West African journal of medicine. 2005;24(3):252-5.
12. Eble JN, Tavassoli FA, Devilee P. Pathology and Genetics of Tumours of the Breast and Female Genital Organs: Iarc; 2003.
13. Haybittle JL, Blamey RW, Elston CW, Johnson J, Doyle PJ, Campbell FC, *et al.* A prognostic index in primary breast cancer. Br J Cancer. 1982; 45(3):361-6.
14. Todd JH, Dowle C, Williams MR, Elston CW, Ellis IO, Hinton CP, *et al.* Confirmation of a prognostic index in primary breast cancer. Br J Cancer. 1987;56(4):489-92.
15. Rampaul RS, Pinder SE, Elston CW, Ellis IO, Nottingham Breast T. Prognostic and predictive factors in primary breast cancer and their role in patient management: The Nottingham Breast Team. Eur J Surg Oncol. 2001;27(3):229-38.
16. D'Eredita G, Giardina C, Martellotta M, Natale T, Ferrarese F. Prognostic factors in breast cancer: the predictive value of the Nottingham Prognostic Index in patients with a long-term follow-up that were treated in a single institution. Eur J Cancer. 2001;37(5):591-6.
17. Nggada HA, Yawe KDT, Abdulazeez J, Khalil MA. Breast cancer burden in Maiduguri, North eastern Nigeria. The breast journal. 2008;14(3):284-6.
18. Corbex M, Bouzbid S, Boffetta P. Features of breast cancer in developing countries, examples from North-Africa. European Journal of Cancer. 2014;50(10):1808-18.
19. Vorobiof DA, Sitas F, Vorobiof G. Breast cancer incidence in South Africa. J Clin Oncol. 2001;19(18 Suppl):125S-7S.
20. Machiavelli M, Leone B, Romero A, Perez J, Vallejo C, Bianco A, *et al.* Relation between delay and survival in 596 patients with breast cancer. Oncology. 1989;46(2):78-82.
21. Neave LM, Mason BH, Kay RG. Does delay in diagnosis of breast cancer affect survival? Breast cancer research and treatment. 1990;15(2):103-8.
22. DeVita VT, Hellman S, SA. R. Cancer: Principles & Practice of Oncology Review: Lippincott Williams & Wilkins; 2008.
23. NHSBSP. Annual review, expanding our reach-The extended age pilot scheme. 2009.
24. Macarthur C, Smith A. Delay in breast cancer and the nature of presenting symptoms. The Lancet. 1981;317(8220):601-3.
25. Burgess C, Ramirez A, Richards M, Love S. Who and what influences delayed presentation in breast cancer? British journal of cancer. 1998;77(8):1343.
26. Dennis CR, Gardner B, Lim B. Analysis of survival and recurrence vs. patient and doctor delay in treatment of breast cancer. Cancer. 1975;35(3):714-20.
27. Fisher ER, Redmond C, Fisher B. A perspective concerning the relation of duration of symptoms to treatment failure in patients with breast cancer. Cancer. 1977;40(6):3160-7.
28. Carter CL, Allen C, Henson DE. Relation of

tumor size, lymph node status, and survival in 24,740 breast cancer cases. Cancer. 1989; 63(1): 181-7.
29. Fisher B, Slack N, Katrych D, Wolmark N. Ten year follow-up results of patients with carcinoma of the breast in a co-operative clinical trial evaluating surgical adjuvant chemotherapy. Surgery, gynecology & obstetrics. 1975;140(4):528-34.
30. Wo JY, Chen K, Neville BA, Lin NU, Punglia RS. Effect of very small tumor size on cancer-specific mortality in node-positive breast cancer. Journal of Clinical Oncology. 2011;29(19):2619.
31. Adjei E. Breast cancer in Kumasi, Ghana. Ghana medical journal. 2012;46(1).
32. Edmund DM, Naaeder SB, Tettey Y, Gyasi RK. Breast cancer in Ghanaian women: what has changed? Am J Clin Pathol. 2013;140(1):97-102.
33. Bloom H. Histologic grading and prognosis in breast cancer. Br J Cancer. 1957;11:655-69.
34. Henson DE, Ries L, Freedman LS, Carriaga M. Relationship among outcome, stage of disease, and histologic grade for 22,616 cases of breast cancer. The basis for a prognostic index. Cancer. 1991;68(10):2142-9.
35. Bloom H. Further studies on prognosis of breast carcinoma. British journal of cancer. 1950;4(4):347.
36. Bloom H. Prognosis in carcinoma of the breast. British journal of cancer. 1950;4(3):259.
37. Stark A, Kleer CG, Martin I, Awuah B, Nsiah-Asare A, Takyi V, *et al.* African ancestry and higher prevalence of triple-negative breast cancer: findings from an international study. Cancer. 2010;116(21):4926-32.
38. Wilson R, Donegan W, Mettlin C, Natarajan N, Smart CR, Murphy G. The 1982 national survey of carcinoma of the breast in the United States by the American College of Surgeons. Surgery, gynecology & obstetrics. 1984;159(4):309-18.
39. Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, *et al.* Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. Jama. 2011;305(6):569-75.
40. Vinh-Hung V, Burzykowski T, Cserni G, Voordeckers M, Van De Steene J, Storme G. Functional form of the effect of the numbers of axillary nodes on survival in early breast cancer. Int J Oncol. 2003;22(3):697-704.
41. Smith JA, 3rd, Gamez-Araujo JJ, Gallager HS, White EC, McBride CM. Carcinoma of the breast: analysis of total lymph node involvement versus level of metastasis. Cancer. 1977;39(2):527-32.
42. Russo J, Frederick J, Ownby HE, Fine G, Hussain M, Krickstein HI, *et al.* Predictors of recurrence and survival of patients with breast cancer. Am J Clin Pathol. 1987;88(2):123-31.
43. FishePathologic findings from the National Surgical r ER, Anderson S, Redmond C, Fisher B. Adjuvant Breast Project protocol B-06. 10-year pathologic and clinical prognostic discriminants. Cancer. 1993;71(8):2507-14.
44. Fisher B, Bauer M, Wickerham DL, Redmond CK, Fisher ER, Cruz AB, *et al.* Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. An NSABP update. Cancer. 1983;52(9):1551-7.
45. Jatoi I, Hilsenbeck SG, Clark GM, Osborne CK. Significance of axillary lymph node metastasis in primary breast cancer. J Clin Oncol. 1999;17(8):2334-40.
46. Donegan WL. Cancer of the breast. Staging methods, primary treatment options and end results. Major Probl Clin Surg. 1979;5:221-301.
47. Merkel DE, Osborne CK. Prognostic factors in breast cancer. Hematology/Oncology Clinics. 1989;3(4):641-52.
48. Ferguson DJ, Meier P, Karrison T, Dawson PJ, Straus FH, Lowenstein FE. Staging of breast cancer and survival rates: an assessment based on 50 years of experience with radical mastectomy. Jama. 1982;248(11):1337-41.
49. Rosen PR, Groshen S, Saigo PE, Kinne DW, Hellman S. A long-term follow-up study of survival in stage I (T1N0M0) and stage II (T1N1M0) breast carcinoma. J Clin Oncol. 1989;7(3):355-66.
50. Sheikh F, Rebecca A, Pockaj B, Wasif N, McCullough AE, Casey W, *et al.* Inadequate margins of excision when undergoing mastectomy for breast cancer: which patients are at risk? Annals of surgical oncology. 2011;18(4):952-6.
51. Walters S,Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, *et al.* Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. British journal of cancer. 2013;108(5):1195.
52. Clarke DH, Le MG, Sarrazin D, Lacombe MJ, Fontaine F, Travagli JP, *et al.* Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: experience of the Institut Gustave-Roussy. Int J Radiat Oncol Biol Phys. 1985;11(1):137-45.
53. Goldstein NS, Kestin L, Vicini F. Factors associated with ipsilateral breast failure and distant metastases in patients with invasive breast carcinoma treated with breast-conserving therapy. A clinicopathologic study of 607 neoplasms from 583 patients. Am J Clin Pathol. 2003;120(4):500-27.
54. Fisher ER, Anderson S, Redmond C, Fisher B. Ipsilateral breast tumor recurrence and survival following lumpectomy and irradiation: pathological findings from NSABP protocol B-06. Semin Surg Oncol. 1992;8(3):161-6.
55. Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DL, Wolmark N, *et al.* Significance

of ipsilateral breast tumour recurrence after lumpectomy. Lancet. 1991;338(8763):327-31.
56. Burke HB, Henson DE. Criteria for prognostic factors and for an enhanced prognostic system. Cancer. 1993;72(10):3131-5.
57. Gakwaya A, Kigula-Mugambe JB, Kavuma A, Luwaga A, Fualal J, Jombwe J, *et al.* Cancer of the breast: 5-year survival in a tertiary hospital in Uganda. Br J Cancer. 2008;99(1):63-7.
58. Kene TS, Odigie VI, Yusufu LM, Yusuf BO, Shehu SM, Kase JT. Pattern of presentation and survival of breast cancer in a teaching hospital in north Western Nigeria. Oman Med J. 2010;25(2):104-7.
59. Swaminathan R, Lucas E, Sankaranarayanan R. Cancer survival in Africa, Asia, the Caribbean and Central America: database and attributes. IARC Sci Publ. 2011(162):23-31.
60. National Cancer Institute of Canada (NCIC) Canadian cancer statistics 2006. NCIC. 2006.
61. American Cancer Society (ACS) Cancer facts and figures. 2006.

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# Oncologic Outcomes with Neoadjuvant Chemotherapy and Breast Conservation for MRI Occult Breast Cancer

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ABSTRACT

**Background:** Occult primary breast cancer is a presentation of breast cancer involving lymph nodes without an identified primary tumor within the breast. Mastectomy with axillary node dissection has been the traditional management. However, reported oncologic outcomes with mastectomy have been similar to those with breast conserving therapy (axillary surgery and radiotherapy). With the increased sensitivity of MRI and its routine use in the workup of occult breast cancer, the role of mastectomy for occult breast cancer is now even less clear. We report our institutional experienc of neoadjuvant chemotherapy followed by axillary surgery and radiotherapy for women with occult breast cancer.

**Methods:** We conducted a retrospective review of women diagnosed with isolated metastatic adenocarcinoma to the axilla histologically consistent with breast adenocarcinoma without evidence of a primary breast tumor. Medical records were analyzed to gather pertinent information regarding diagnostic workup, treatment, recurrence, and survival.

**Results:** We identified seven patients treated in our institution between 2012 and 2017 who met the criteria for primary occult breast cancer. The median age at diagnosis was 63 years old (range 42-71). Subtypes by immunohistochemistry (IHC) were HER-2 positive (3 pts), triple negative (2 pts), and hormone receptor positive/HER-2 negative (2 pts). All patients received neoadjuvant chemotherapy and axillary surgery without mastectomy followed by adjuvant radiotherapy to the breast and regional nodes. Hormone receptor positive patients received adjuvant endocrine therapy. At a median follow-up of 3.5 years, all patients were alive with no local or regional recurrence of disease while one patient developed distant metastases.

**Conclusion:** A multimodality approach with neoadjuvant chemotherapy can lead to high rates of breast conservation in women with primary occult breast cancer. This approach appears to be oncologically safe.

## Introduction

Occult primary breast cancer (OPBC) is a rare clinical presentation of breast cancer with histologically proven carcinoma in lymph nodes in the absence of a primary cancer in the breast.[1-3] OPBC is estimated to represent 0.1-0.8% of all breast cancer diagnoses.[3-6] Diagnosis of OPBC requires histology and IHC consistent with breast adenocarcinoma in the absence of other suspicious lesions on breast or systemic imaging. Antibodies against tumors of breast origin can facilitate the diagnosis and include ER/PR, mammoglobin, GCDFP-15, and GATA3.[6,7] MRI has

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become the standard of care in the workup of OPBC and can identify a primary breast lesion in up to 70% of women with mammographically occult tumors.[6,7] As such, the incidence of true OPBC has decreased significantly with improved imaging. Given the rarity of true OPBC, there is limited data to guide optimal management in this setting. Several retrospective case series[4,8-12] and a population study[13] have evaluated the impact of surgical extent and radiotherapy for OPBC. These have consistently demonstrated equivalent oncologic outcomes between mastectomy compared to breast conservation with radiotherapy. Despite this, the majority of patients diagnosed with OPBC are treated with modified radical mastectomy.[13] Currently, optimal management in several aspects of OPBC remain to be defined. These include surgical management of the breast, extent of axillary surgery, and timing of systemic therapy.

We report our clinical approach and treatment outcomes in management of patients with OPBC treated at a single institution. Based on extrapolation from studies in node positive patients with intact primary tumors, we have adopted a standardized treatment algorithm for OPBC involving increased emphasis on optimal systemic therapy and radiotherapy with omission of mastectomy. Our aim is to demonstrate how a multidisciplinary treatment plan can decrease treatment morbidity without compromising oncologic outcomes in women with OPBC.

## Methods

We performed an institutional review board approved, retrospective review of patients diagnosed with OPBC between October 2012 and July 2017 at Banner University Medical Center in Tucson, Arizona. Patients were identified by querying electronic medical records. Inclusion criteria were as follow: diagnosis of adenocarcinoma involving axillary lymph nodes, biopsy pathologically consistent with breast origin, absence of disease within the breast on mammogram and MRI and absence of distant disease on systemic imaging. Patients with a prior history of invasive malignancy or ipsilateral DCIS or invasive ductal carcinoma were excluded. Medical records were analyzed to gather data including: method of diagnosis, imaging workup, tumor characteristics, systemic therapy, radiation, surgery, surveillance imaging and disease status at last date of contact.

## Results

*Patient Characteristics*

Seven patients were identified with primary occult breast cancer treated between 2012 and 2017. Patient characteristics are summarized in Table 1. The median age at diagnosis was 63 years old. (range 42-71). Method of detection was either screening mammogram (57.1%) or self-palpation (42.9%). Six out of seven patients (85.7%) had clinical stage IIA occult breast cancer while one patient had stage IIIA (14.3%). Molecular subtype as approximated by IHC was human epidermal growth factor (HER-2) positive (three patients), triple negative (two patients), and hormone receptor positive / HER-2 negative (two patients). All patients underwent mammography and dedicated breast MRI to evaluate for a breast primary. To evaluate for distant organ involvement, all patients had a metastatic workup with either PET CT (85.7%) or a CT chest/abdomen/pelvis and bone scan (14.3%). Median follow-up time from diagnosis to last contact was 41.1 months.

**Table 1.** Patient characteristics

| Variables | | N(%) |
|---|---|---|
| Age Mean (Range) | | 58 (42-71) |
| Median | | 63 |
| Method of Detection | Self palpation | 3(42.9%) |
| | Screening mammogram | 4(57.1%) |
| Stage | IIA | 6(85.7%) |
| | IIIA | 1(14.3%) |
| Clinical Stage | cT0N1M0 | 6(85.7%) |
| | cT0N2M0 | 1(14.3%) |
| Pathologic Stage | ypTxN0M0 | 4(57.1%) |
| | ypTxN1M0 | 2(28.6%) |
| | ypTxN2M0 | 1(14.3%) |
| Tumor Subtype | Luminal B | 2(28.6%) |
| | Triple Negative | 2(28.6%) |
| | HER2+ | 3 (42.9%) |
| Investigations | Mammogram, MRI, PET-CT | 6(85.7%) |
| | Mammogram, MRI, CT C/A/P | 1(14.3%) |

*Treatment*

Patients were discussed at a multidisciplinary treatment planning conference where workup and treatment strategy was agreed upon before initiation of any therapy. All patients received neoadjuvant chemotherapy, axillary surgery, and radiotherapy to the breast and regional nodes. Four patients received dose-dense doxorubicin and cyclophosphamide (ddAC) followed by weekly paclitaxel. Three of these patients completed 4 cycles of ddAC. One patient stopped ddAC after 2 cycles due to adverse events. All four received 12 cycles of weekly paclitaxel following AC. Two patients with HER-2 positive disease received Taxol and Trastuzumab while the third received Paclitaxel and Trastuzumab followed by ddAC. Both patients with ER positive tumors received adjuvant endocrine therapy with anastrozole. Following neoadjuvant chemotherapy, six out of seven patients received an axillary lymph node dissection (ALND) while one patient (triple negative with clinical complete response to

**Table 2.** Treatment received for occult breast cancer presenting as axillary lymph node metastases

| Variables | | N(%) |
|---|---|---|
| Neoadjuvant Chemotherapy | PaclitaxelTrastuzumabTrastuzumab | 2(28.6%) |
| | Paclitaxel/ddAC | 4(57.1%) |
| | PaclitaxelTrastuzumabTrastuzumab/ddAC | 1(14.3%) |
| Endocrine Therapy | | 2(28.6%) |
| Axillary Surgery | Axillary Lymph Node Dissection | 6(85.7%) |
| | Sentinel Lymph Node Dissection | 1(14.3%) |
| Radiotherapy | Breast, supraclaviular fossa | 4(57.1%) |
| | Breast, supraclavicular fossa, full axilla | 2(28.6%) |
| | Breast, supraclavicular fossa, full axilla, IM chain | 1(14.3%) |
| Disease Status at Last Follow-Up | Local/regional recurrence | 0 (0.0%) |
| | Distant recurrence | 1(14.3%) |

chemotherapy) underwent negative sentinel node biopsy alone.

All patients received adjuvant radiotherapy to the whole breast (50Gy) and supraclavicular fossa (45Gy) in 25 fractions using a mono-isocentric, three-field technique. Supraclavicular fields included the full level 1-3 axilla in five patients. In two patients (who had axillary dissection with limited residual disease), the dissected axilla was not included in the supraclavicular field.

*Outcomes*

Four patients (57.1%) had a pathologic compete response within the axilla following neoadjuvant chemotherapy (Hormone receptor positive=1, TNBC=1, HER-2 positive=2). Six of seven patients have continued with annual surveillance breast MRI in addition to annual breast tomosynthesis. At a median follow up of 41.3 months from diagnosis, all patients remain free of local or regional recurrence. One patient with HER-2 positive pleomorphic infiltrating lobular carcinoma developed osseous metastases at 57.4 months from diagnosis.

**Table 3.** Follow-up time since diagnosis

| Follow-Up Time Since Diagnosis | Time (months) |
|---|---|
| Mean | 41.1 |
| Median | 41.7 |

## Discussion

Occult breast cancer is a rare but well-defined presentation of breast cancer characterized by lymph node involvement with carcinoma of breast origin but no identifiable primary tumor within the breast. Pathogenesis is unclear, but it is generally felt to represent lymphatic dissemination from either an unidentified, occult cancer within the breast or due to dissemination from a primary tumor within the breast which has subsequently regressed. Mastectomy with axillary node dissection has been the traditional management for OPBC; primarily out of concern for sub-clinical or otherwise undetected disease within the breast. Over the last decade, the sensitivity of breast imaging (with MRI and tomosynthesis) has significantly improved the detection of small-volume breast lesions. Prior studies in OPBC have demonstrated that MRI can detect clinically and mammographically occult lesions with detection rates ranging from 43-86%.[9, 14,15]

The largest reported single institution series evaluating the utility of MRI in OPBC comes from Memorial Sloan Kettering Cancer Center. Olson *et al.* published their initial institutional results in 40 women with clinically and mammographically occult axillary adenocarcinoma. MRI identified a primary breast lesion in 70% of patients. In their series, 47% of patients underwent breast conservation. Five patients with negative MRI underwent axillary dissection and radiotherapy. Among five women with negative MRI who went on to mastectomy, one patient had an invasive tumor identified on final pathology. The authors note that the MRI performed at that time was inadequate by current standards and the region containing the tumor was outside the scan field-of-view.[16] Buchanan *et al.* reported on an updated series from the same institution on 69 patients. MRI was able to identify a breast primary in 49% of patients. Among women with negative MRI who went on to mastectomy, 25% were found to have invasive tumor in the surgical specimen with one patient having a 3cm, non-enhancing IDC. Ten patients with negative breast MRI were treated with breast conservation with ALND and breast radiotherapy and all were free of local disease at a median follow up of 4.5 years.[14]

De Bresser *et al.* conducted a systematic review and identified 8 retrospective studies which evaluated the ability of breast MRI to detect breast tumors in patients with clinically and mammographically OPBC.[17] Breast MRI was found to have 90% sensitivity with the ability to detect a previously unidentified breast cancer in more than two-thirds of patients. Breast MRI had much lower specificity ranging from 22-50%. The

authors concluded that MRI has clear utility in the workup of mammographically occult breast cancer. This study did not specifically report on outcomes of women with negative MRI treated with breast conservation.

The recognition that radiotherapy can eradicate microscopic residual disease within the breast following resection of gross disease provides rationale for applying the same approach in the occult primary setting. Following the publication of multiple large randomized trials demonstrating equivalence between mastectomy and lumpectomy plus radiotherapy, breast conservation became well-established as the standard of care for operable breast cancer. These studies demonstrated that breast conserving therapy provides equivalent disease-free and overall survival compared to mastectomy. In studies that mandated negative surgical margins, adequate axillary staging and tumors smaller than 5cm, lumpectomy plus radiation have also demonstrated equivalent local control to mastectomy.

While there are no prospective studies to guide management of OPBC, numerous retrospective series have demonstrated equivalent oncologic outcomes between mastectomy and breast conserving therapy (axillary dissection and radiation).[3, 9, 18] The results of these studies have consistently shown that patients with occult breast cancer receiving ALND followed by breast radiotherapy have similar outcomes to patients who underwent mastectomy. In contrast, patients treated with axillary surgery alone without radiotherapy have consistently had worse outcomes.

Yang *et al.* published the largest reported single institution study of breast conservation for patients with mammographically occult breast cancer. The authors compared outcomes of 214 mammographically occult breast cancer patients treated with BCT at Yale University between 1973 and 2003 and 2168 mammographically positive breast cancer and found that in breast recurrence rates after breast-conserving therapy and adjuvant radiation therapy were not significantly different between the groups.[19] Likewise, at 10 years, there was no difference in overall survival, cause-specific survival, and distant relapse between patients with occult breast cancer and mammographically positive breast cancer. Receipt of BCT was an independent predictor of nodal relapse–free survival. The authors note that regional nodal irradiation was reserved for patients who had additional risk factors for recurrence such as high nodal burden. This may have been associated with the increased rate of nodal recurrences in the BCT arm. Among patients with in-breast recurrences, patients with initially mammographically occult breast cancers were more likely to have mammographically occult disease at the time of recurrence (32%) compared to patients with initially mammographically positive disease (13%). These findings support the use of MRI for surveillance in women with OPBC treated with BCT.

Walker et. al utilized the Surveillance, Epidemiology, and EndResults (SEER database) to identify 750 patients diagnosed with T0N+ disease between 1983 and 2006 .[13] 202 patients received ALND plus radiotherapy while 268 received mastectomy. Cause specific survival at 10 years was 74.6% and was equivalent for patients treated with axillary dissection plus radiotherapy or mastectomy. Likewise, 10-year overall survival was equivalent between mastectomy and ALND plus radiotherapy at 64.9%. In contrast, 10-year OS following ALND alone without radiotherapy was significantly worse at 58.5% (n=126; log-rank P =.02). While this study lacks locoregional recurrence information (a limitation of the SEER dataset), it does support the long-term oncologic efficacy of breast conservation and radiotherapy for OPBC. Taken together with single institution series, these findings suggest that the same treatment paradigm for known-primary breast cancer yields equivalent oncologic outcomes when applied to OPBC. This is the current approach recommended in NCCN guidelines.[20]

Neoadjuvant systemic therapy has become standard management for patients with node positive breast cancer. As such, there is a strong rationale for neoadjuvant therapy in women presenting with OPBC. Rueth *et al.* reported on outcomes in 36 patients with OPBC treated at MD Anderson Cancer Center. In this series, 27 patients were treated with BCT. 70% of patients received neoadjuvant systemic therapy. At a median follow up of 64 months, the authors reported no local or regional recurrences and one distant recurrence. This series is also notable in that 92% of patients were staged with MRI.[16] Our findings are consistent with those of these authors and demonstrate equivalent outcomes with a similar treatment algorithm.

Optimal axillary management for patients with intact primary breast cancer continues to evolve. Specifically, the necessity for completion axillary dissection in patients with small volume axillary involvement is being questioned. In clinically node negative but sentinel node positive patients, axillary dissection conveys a significantly higher rate of lymphedema compared to axillary radiotherapy without improving oncologic outcomes.[21] Ongoing randomized studies are evaluating the role of completion axillary dissection in patients with clinically positive axillary nodes who convert to clinically negative following neoadjuvant chemotherapy. In our practice, sentinel node biopsy is routinely performed in women who initially presented with clinically positive axillary nodes who have converted to clinically negative following neoadjuvant chemotherapy. Patients who are found to be pathologically node negative at time of sentinel node procedure are then offered axillary radiotherapy in lieu of full axillary dissection.

One patient in our series had a negative sentinel node biopsy after chemotherapy and did not receive

completion axillary dissection. As axillary techniques become further refined, incorporation into the management of OPBC should further reduce the rates of treatment-associated toxicity.

Like any retrospective study, this case series has several limitations. Due to the rarity of occult breast cancer, our study has a small sample size. Likewise, the extended period of time over which patients were treated leads to changes in practice patterns as evidenced by the omission of axillary dissection in patients with pathologic complete response in our current practice. A series such as this can also include medical record errors. Lastly, our follow-up is still relatively short given the long latency period for breast cancer recurrence. Nonetheless, our case series is a valuable addition to the literature in that all patients had occult disease on MRI and all patients were treated with neoadjuvant chemotherapy, regarding the treatment and management of patients with primary occult breast cancer.

Given the increased sensitivity of MRI over mammography, patients diagnosed with OPBC in the current era are less likely to have gross breast involvement than patients diagnosed without MRI. As such, the therapeutic role of mastectomy for OPBC in the modern era is questionable. In our series, all patients underwent diagnostic workup with negative dedicated breast MRI in addition to digital or 3D mammography. Our series highlights the importance of a prospective, multidisciplinary approach for the management of OPBC. All patients were discussed at a multidisciplinary treatment planning conference where workup and treatment strategy were discussed before initiation of any therapy. All patients underwent neoadjuvant chemotherapy followed by axillary surgery and radiotherapy. Patients have continued routine surveillance with MRI and mammogram. At a median follow-up of 41.1 months from diagnosis, all patients remain alive and no patients have had recurrence within the breast or regional nodes. Our results are consistent with other series and support the oncologic validity of this combined-modality approach for OPBC.

**Conflict of Interest**

The authors have nothing to disclose.

**References**


1. Ettinger DS, Agulnik M, Cates JM, Cristea M, Denlinger CS, Eaton KD, *et al.* NCCN Clinical Practice Guidelines Occult primary. J Natl Compr Canc Netw. 2011;9(12):1358-95.
2. van Ooijen B, Bontenbal M, Henzen-Logmans SC, Koper PC. Axillary nodal metastases from an occult primary consistent with breast carcinoma. Br J Surg. 1993;80(10):1299-300.
3. Fayanju OM, Jeffe DB, Margenthaler JA. Occult primary breast cancer at a comprehensive cancer center. J Surg Res. 2013;185(2):684-9.
4. Rosen PP, Kimmel M. Occult breast carcinoma presenting with axillary lymph node metastases: a follow-up study of 48 patients. Hum Pathol. 1990;21(5):518-23.
5. Patel J, Nemoto T, Rosner D, Dao TL, Pickren JW. Axillary lymph node metastasis from an occult breast cancer. Cancer. 1981;47(12):2923-7.
6. Montagna E, Bagnardi V, Rotmensz N, Viale G, Cancello G, Mazza M, *et al.* Immunohistochemically defined subtypes and outcome in occult breast carcinoma with axillary presentation. Breast Cancer Res Treat. 2011;129(3):867-75.
7. Bahrami A, Truong LD, Ro JY. Undifferentiated tumor: true identity by immunohistochemistry. Archives of pathology & laboratory medicine. 2008;132(3):326-48.
8. Masinghe SP, Faluyi OO, Kerr GR, Kunkler IH. Breast radiotherapy for occult breast cancer with axillary nodal metastases--does it reduce the local recurrence rate and increase overall survival? Clin Oncol (R Coll Radiol). 2011; 23(2):95-100.
9. He M, Tang LC, Yu KD, Cao AY, Shen ZZ, Shao ZM, *et al.* Treatment outcomes and unfavorable prognostic factors in patients with occult breast cancer. Eur J Surg Oncol. 2012;38(11):1022-8.
10. Vlastos G, Jean ME, Mirza AN, Mirza NQ, Kuerer HM, Ames FC, *et al.* Feasibility of breast preservation in the treatment of occult primary carcinoma presenting with axillary metastases. Ann Surg Oncol. 2001;8(5):425-31.
11. Matsuoka K, Ohsumi S, Takashima S, Saeki T, Aogi K, Mandai K. Occult breast carcinoma presenting with axillary lymph node metastases: follow-up of eleven patients. Breast Cancer. 2003;10(4):330-4.
12. Lloyd MS, Nash AG. 'Occult' breast cancer. Ann R Coll Surg Engl. 2001;83(6):420-4.
13. Walker GV, Smith GL, Perkins GH, Oh JL, Woodward W, Yu TK, *et al.* Population-based analysis of occult primary breast cancer with axillary lymph node metastasis. Cancer. 2010;116(17):4000-6.
14. Buchanan CL, Morris EA, Dorn PL, Borgen PI, Van Zee KJ. Utility of breast magnetic resonance imaging in patients with occult primary breast cancer. Ann Surg Oncol. 2005;12(12):1045-53.
15. Olson JA, Jr., Morris EA, Van Zee KJ, Linehan DC, Borgen PI. Magnetic resonance imaging facilitates breast conservation for occult breast cancer. Ann Surg Oncol. 2000;7(6):411-5.
16. Rueth NM, Black DM, Limmer AR, Gabriel E, Huo L, Fornage BD, *et al.* Breast conservation in the setting of contemporary multimodality treatment provides excellent outcomes for patients with occult primary breast cancer. Ann Surg Oncol. 2015;22(1):90-5.
17. de Bresser J, de Vos B, van der Ent F, Hulsewe K.

Breast MRI in clinically and mammographically occult breast cancer presenting with an axillary metastasis: a systematic review. Eur J Surg Oncol. 2010;36(2):114-9.
18. McCartan DP, Zabor EC, Morrow M, Van Zee KJ, El-Tamer MB. Oncologic Outcomes After Treatment for MRI Occult Breast Cancer (pT0N+). Ann Surg Oncol. 2017.
19. Yang TJ, Yang Q, Haffty BG, Moran MS. Prognosis for mammographically occult, early-stage breast cancer patients treated with breast-conservation therapy. Int J Radiat Oncol Biol Phys. 2010;76(1):79-84.
20. Ettinger DS. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Occult Primary (Cancer of Unknown Primary Origin: National Comprehensive Cancer Network); 2017.
21. Donker M, van Tienhoven G, Straver ME, Meijnen P, van de Velde CJH, Mansel RE, *et al.* Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS):a randomised, multicentre, open-label, phase 3 non-inferiority trial. The Lancet Oncology. 2014;15(12):1303-10.

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# A Breast Cancer Patient Presenting for the First Time With a Meningioma-like Intracranial Mass

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ABSTRACT

**Background:** Breast cancer metastases to the central nervous system are more commonly multiple intracranial lesions. Rarely, in the case of single extradural metastasis, it is clinically and radiologically challenging and important to differentiate other solitary extradural masses such as meningioma. Moreover, according to the literature, it seems that there is a relationship between breast cancer and meningioma.

**Case Presentation:** We report a 54-year-old female presenting with a sudden onset of headache and seizure whose MRI showed an extra-axial intracranial mass in her brain. The patient underwent operative removal of the tumor with the clinical and radiologic diagnosis of meningioma. The pathological finding was suspected to be breast cancer metastasis. Future evaluation of her breast showed tissue distortion in the left breast and the pathologic diagnosis of the breast lesion was invasive ductal carcinoma. In a follow-up CT scan, there were multiple liver and lung metastases.

**Conclusion:** It is crucial for physicians with various specialties to be aware of different possibilities in the setting of a single extra-axial brain mass.

## Introduction

Meningioma, as the most common meningeal tumor, is an extra-axial, nonglial neoplasm that originates from meningocytes. It constitutes up to 20% of primary brain tumors. There is a female predominance, and it usually occurs in the fifth and sixth decades of life—similar to the peak incidence age for breast cancer.[1] The incidence of meningioma is 1.57 to 1.90 times greater in breast cancer patients compared with the healthy population. A hormonal relationship between breast cancer and meningioma is suggested.[2,3]

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Breast cancer metastases to central nervous system usually present as multiple intra-axial masses, but sometimes isolated dural tumors may be misdiagnosed as meningioma.[4] In cases without the diagnosis of primary breast tumor, isolated enhancing mass in skull base is in favor of meningioma rather than isolated brain metastasis, but, in the presence of primary breast cancer, metastasis from primary tumor should also be considered as differential diagnosis.

Generally, intracranial metastasis is seen in approximately 17% of patients with malignant primary tumor; however, with improved cancer treatments and the resultant prolonged survival rates, this number will increase. While 25% of intracranial metastases have some degree of meningeal involvement, isolated meningeal metastasis is seen in 1%. In addition, in cases without known clinical evidence of primary cancer, it is even rarer.[5] Here we report a case of a patient with a single extra-axial dural-based mass of unknown origin in the brain.

**Case Presentation**

A 54-year-old woman referred to Imam Khomeini Hospital of Tehran University of Medical Science with a chief complaint of a sudden onset of headache and seizure. Her brain MRI showed an extra-axial intracranial mass (Figure 1). She underwent surgery and was clinically diagnosed with menangioma. On pathologic examination, sheets of atypical epithelial cells with pleomorphic vesicular nuclei and eosinophilic cytoplasm occasionally arranged in tubular structures were identified. Comedo-type necrosis and frequent mitotic figures, all in favor of metastatic carcinoma, were also seen. Immunohisto-chemistry revealed positive reactions with CK7, GATA3, GCDFP-15, and HER2 (3+). Tests for ER, PR, CK20, CDX2, TTF1, and Napsin-A were negative. Ki67 showed30% proliferative activity. Overall findings were compatible with metastatic carcinoma of breast origin (Figure 2). We were consulted for breast evaluation. She did not have a family history of breast cancer and had a breast ultrasound with the benign result from 3 months ago. In our evaluation, we found a tissue distortion in the central upper part of the left breast and lymph nodes with a pathologic appearance in left axilla (Figure 3). We performed core needle biopsy of breast distortion, and the result of pathology was indicative of invasive ductal carcinoma with the hormonal profile the same as a metastatic brain tumor.

The patient underwent brain radiotherapy. After a while, her thoracic and abdominal computed tomography (CT) scan showed multiple lung and liver metastases.

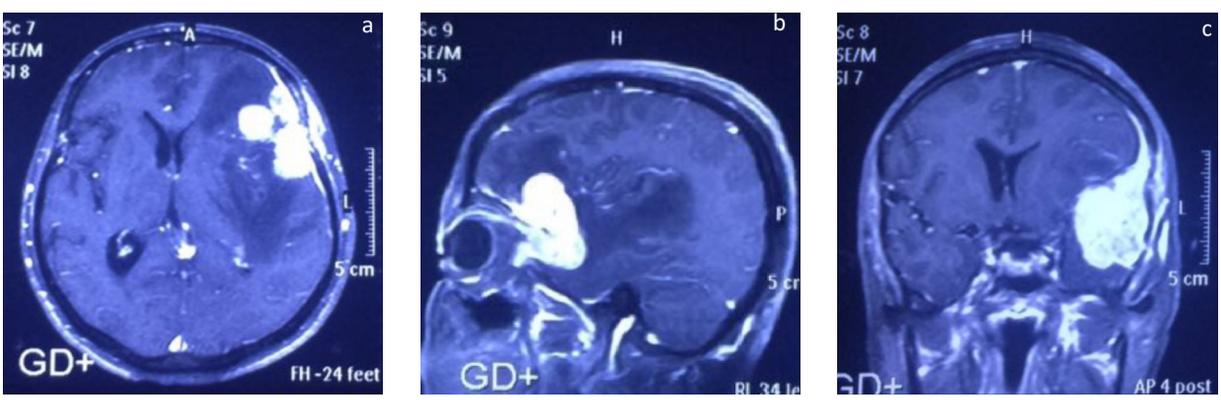


**Figure 1.** Brain MRI with contrast injection in the patient with a sudden onset of headache and seizure 1a (axial), 1b (sagittal), and 1c (coronal) images show an extra-axial dural-based avid, homogenous, enhancing mass in left side anterior skull base accompanied by a dural tail, compression on nearby parenchyma, and edema.

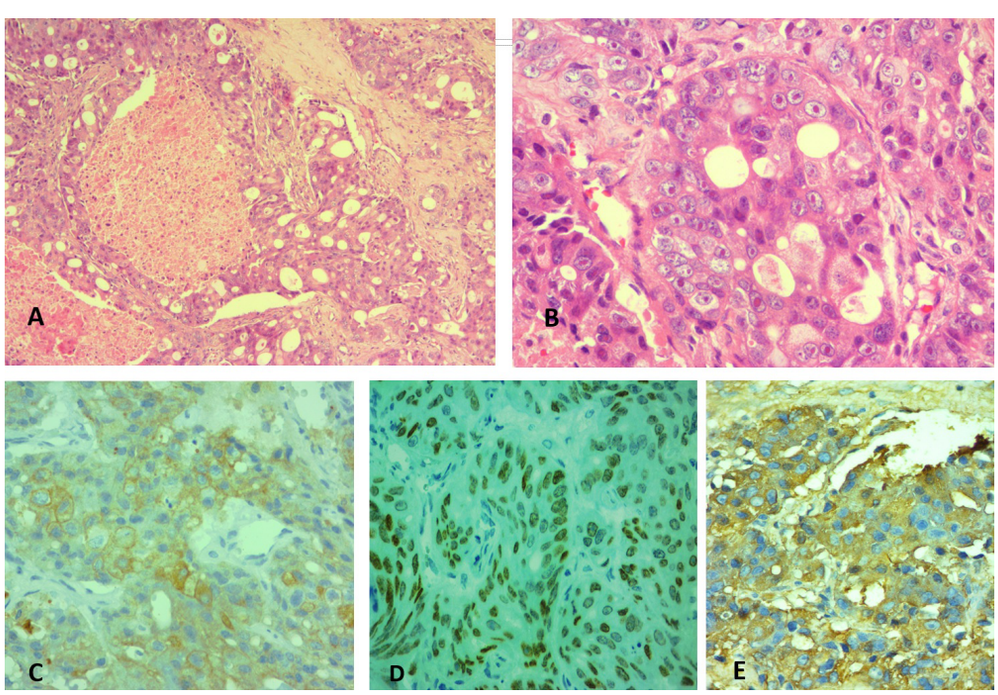


**Figure 2.** (A) and (B), microscopic examination of hematoxylin- and eosin-stained sections reveals sheets of neoplastic epithelial cells with eosinophilic cytoplasm and pleomorphic vesicular nuclei occasionally arranged in glandular structures. Central comedo-type necrosis is also seen. Immunohistochemistry reveals positive immune reaction with CK7(C), GATA3 (D), and GCDFP15 (E).

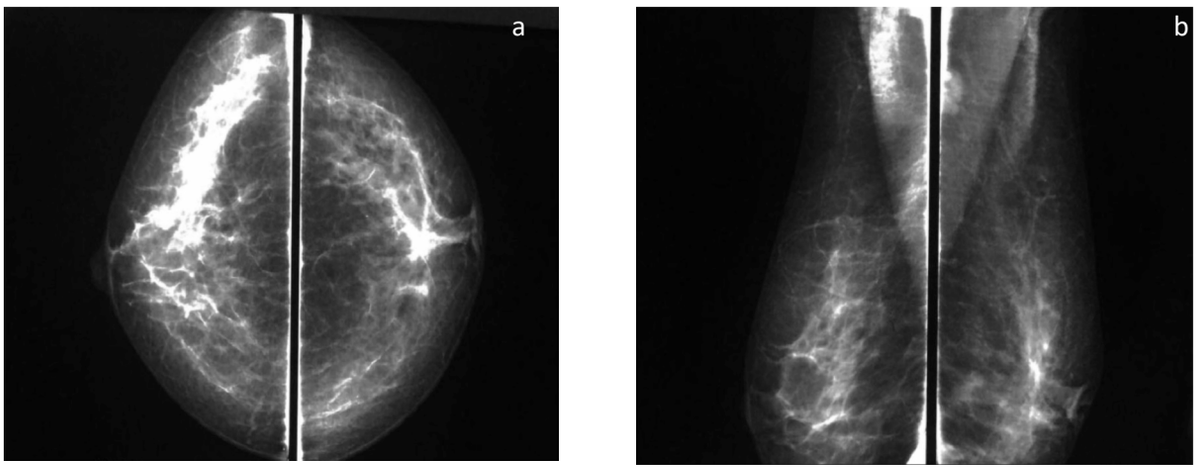


Figure 3. Mammography with craniocaudal (3a) and mediolateral oblique (3b) views taken in another imaging center, with suboptimum quality. It shows a subtle distortion in the upper central part of the left breast and a prominent left axillary lymph node. Core needle biopsy of the left breast reveals invasive ductal carcinoma.

Then, chemotherapy was started for her by the oncology team, which is continued till now.

**Discussion**

When dealing with an extra-axial intracranial mass lesion, it is crucial to consider differential diagnoses like metastases to the skull or dura other than more common primary masses such as meningioma, or subdural hematoma or collection. In imaging, dural-based metastatic masses may present as nodular or even elongated and plaque-like lesions. The surrounding cerebral cortex may be compressed, and edema incited in the underlying parenchyma. Dural tail sign (the enhancement of the meninges adjacent to tumor) on CT scan and MRI was once considered as a specific sign for meningioma; however, it is known that this sign also can be present in meningeal metastases.[3,6]

Meningioma is benign and curable and accounts for up to 20% of all intracranial tumors, while brain metastases from breast cancer have an ominous prognosis despite surgery, radiation, and chemotherapy.[4]

As the physical appearance of these tumors can be quite similar, surgeons may not distinguish a metastasis from meningioma during surgery, as was the case for our patient, and pathology will lead to diagnosis.[5]

It has been reported that breast cancer is the second most common cause of intracranial metastasis after lung cancer.[2] Metastatic pulmonary carcinoma was excluded in our case immunohistochemically. Most patients with breast cancer metastasis to the central nervous system either have synchronous multiple organ metastatic disease or soon develop it.[6]

The role of hormones in meningioma has been already proposed since meningiomas enlarge during pregnancy and express estrogen and progesterone receptors.[2]

Schmidt *et al.* reported two women with breast carcinoma who presented with clinical presentations of sphenocavernous syndrome with MRI that was misdiagnosed as basal skull meningioma, but who were found to have metastatic breast carcinoma following biopsy of the lesions. Like our patient, those cases had no history of breast malignancy.[6]

Interestingly, some patients are reported in the literature with metastasis of breast carcinoma to meningioma. It is reported that HER2-positive breast cancer cells preferentially like to deposit in the patient's meningioma. This may be due to the high vascularity, low metabolic rate, and hormonal status of meningioma.[7-9] However, in such cases, there is usually a known history of breast cancer.

Seckin *et al.* reported a 72-year-old woman presenting with nausea and vomiting, headache, reduced mentation, and amnesia initially misdiagnosed as meningioma. In this case, however, the patient also had a history of breast mass leading to metastasis.[10]

Computed tomography, MRI, and angiography may be somewhat beneficial for the differentiation of metastasis from other lesions. A hematoma or collection does not enhance and has a related history most of the times. A meningioma is dural based and shows homogenous avid enhancement, whereas a metastatic tumor is not homogenously enhanced. Gadolinium-enhanced MRI is known as the most sensitive imaging technique for the diagnosis of neural axis metastases and enhanced MRI is even superior to the enhanced CT for both brain parenchymal and leptomeningeal diseases due to its higher soft tissue contrast, higher sensitivity to the contrast enhancement, the direct multiplanar capability, and the lack of the artifacts related to the bone. It particularly helps to reveal the lesions in the posterior fossa and brainstem, where the presence of beam-hardening artifacts may be problematic in CT scan. The MRI is also superior to the CT scan for identifying multiple lesions, which is useful in differential diagnosis. Sometimes other advanced

techniques like magnetic resonance perfusion imaging are needed to differentiate between lesions. Dural metastases and meningiomas have different vasculature and perfusion characteristics which are assessed using dynamic perfusion MRI.[6]

As Conslusion, It is important for physicians to be aware of different diagnosis in the setting of a single extra-axial brain mass

**Conflict of Interest**

The authors have nothing to declare

**References**


1. Dolecek TA, Dressler EV, Thakkar JP, Liu M, Al-Qaisi A, Villano JL. Epidemiology of meningiomas post-Public Law 107-206: The Benign Brain Tumor Cancer Registries Amendment Act. Cancer. 2015;121(14):2400-10.
2. Cihan YB, Öztürk FF. Association of Carcinoma of the Breast and Meningioma: Report of a Case and Review of the Literature. Acta Oncologica Turcica. 2010;43(2):2-3.
3. Schoenberg BS, Christine BW, Whisnant JP. Nervous system neoplasms and primary malignancies of other sites. The unique association between meningiomas and breast cancer. Neurology. 1975;25(8):705-12.
4. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol. 2004;22(17):3608-17.
5. Tagle P, Villanueva P, Torrealba G, Huete I. Intracranial metastasis or meningioma? An uncommon clinical diagnostic dilemma. Surg Neurol. 2002;58(3-4):241-5.
6. Schmidt GW, Miller NR. Metastatic breast carcinoma mimicking basal skull meningioma. Clin Ophthalmol. 2007;1(3):343-6.
7. McCormack M, Rosa CS, Murphy M, Fox SB. HER2-positive breast cancer metastatic to intracranial meningioma: a case report. J Clin Pathol. 2013;66(7):633-4.
8. Sayegh ET, Burch EA, Henderson GA, Oh T, Bloch O, Parsa AT. Tumor-to-tumor metastasis: breast carcinoma to meningioma. J Clin Neurosci. 2015;22(2):268-74.
9. Baratelli GM, Ciccaglioni B, Dainese E, Arnaboldi L. Metastasis of breast carcinoma to intracranial meningioma. J Neurosurg Sci. 2004;48(2):71-3.
10. Seckin H, Yigitkanli K, Ilhan O, Han U, Bavbek M. Breast carcinoma metastasis and meningioma. A case report. Surg Neurol. 2006;66(3):324-7; discussion 7.

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# What Is the Best Risk-Reducing Decision for Breast Cancer Patients With BRCA1/2 Mutation?

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One of the most significant findings of the 1990s was the discovery of the *BRCA* gene mutation, which was a major advancement in the prevention of breast cancer. Since the *BRCA* breakthrough, screening for breast cancer susceptibility genes has become of great interest to high-risk patients and their family members.[1,2] *BRCA1* and *BRCA2* are two major genes responsible for about 5% to 10% of all breast cancer cases and 10% to 18% of ovarian cancer cases. Carriers of *BRCA1/2* mutation could have an elevated risk of 69% to 72% for breast cancer compared with the average-risk women (12%). The risk of ovarian cancer incidence is also much higher in women with a *BRCA1/2* mutation than in the normal population (17%-44% vs 1.5%).[3] Today, female carriers of a *BRCA1* or *BRCA2* mutation (both affected and unaffected) are offered various choices of lifesaving preventive care, including prophylactic surgery, chemoprevention, and intensive surveillance, aimed at reducing their risk of developing breast or ovarian cancer.[4]Nonetheless, in reality, finding the right choice is far more complicated.

The limitation in risk quantification is one of the key areas of challenge. Currently, carriers of *BRCA* mutation variants known as "definitely pathogenic" are commonly offered full high-risk surveillance, whereas decision making for carriers of variants with little or unknown risk for breast cancer remains unanswered.[5,6]

Bilateral prophylactic mastectomy, which is known as the single most effective preventive option, reduces the risk of breast cancer by about 90%.[7] Similarly, prophylactic bilateral salpingo-oophorectomy (PBSO) has been estimated to substantially decrease the risk of ovarian cancer in *BRCA* carriers.[8] However, age is very critical for prophylactic surgery. It has been demonstrated that unaffected carriers younger than 50 years gain more benefit from prophylactic procedures such as mastectomy than the others.[9] Also, it has been estimated that PBSO in premenopausal *BRCA* carriers may reduce their risk of breast cancer by 50%.[4,10]

The effect of the inherited mutation on the overall survival of a breast cancer patient is also a challenging issue. While many studies have shown that prophylactic procedures will be beneficial and increase the long-term survival, a recent study called POSH (Prospective Outcomes in Sporadic versus Hereditary breast cancer) did indicate that there was no significant difference in survival between BRCA1/2 carriers and non-carriers with young age at onset and at the time points of 2, 5, and 10 years after the first diagnosis and concluded that immediate bilateral mastectomy had no advantage in the overall survival of patients in at least 10 years' time period from the first diagnosis.[11] Another study showed that *BRCA* carriers undergoing breast-conserving therapy had a higher risk of local recurrence after 5, 10, and 15 years compared with the carriers who underwent a mastectomy.[12] A cohort study also showed that early-stage (I or II) breast cancer patients with a *BRCA* mutation who received bilateral mastectomy had longer survival rates compared with those undergoing unilateral mastectomy.[13]

None of the risk-reducing strategies is fully eliminating the risk of developing cancer and yet comes with potential complications. Risk-reducing surgeries of a woman who is within her childbearing time period have implications for her fertility or breastfeeding and also body image. Oophorectomy also causes early menopause and imposes several issues including gain weight, osteoporosis and heart diseases.[6,14]

Intensive surveillance has been designed to facilitate early detection of breast cancer in high-risk

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women, however, adherence is commonly required which may impose regular expenditure. The false positive test result is also another issue coming with psychological costs adding more distress to the individual.[7]

Chemoprevention by estrogen modulators tamoxifen and raloxifene decreased the risk of breast cancer by up to 70% and 76%, respectively, but had no effects on estrogen-negative breast cancer patients.[15] While other chemoprevention agents are yet to be approved, existing cancer medications exert adverse effects including increased risk of endometrial cancer and venous thrombosis.[7]

Given these considerations, there is no straightforward task as the best risk-reducing practice for a *BRCA* mutation carrier. What is clear is that the risk of cancer in mutation carriers increases over time, but this does not mean to push patients to act immediately. Recent findings are emphasizing that carriers who have a pathogenic germline mutation in a susceptibility gene benefit from prophylactic surgeries; however, the best practice should be individualized and taken in to account according to each patient's type of mutation, age, tumor prognosis, consideration of the short-term and long-term risks, as well as the patient preferences.

**References**


1. Casaubon JT, Regan JP. BRCA 1 and 2. StatPearls. Treasure Island (FL). 2018.
2. Guo F, Hirth JM, Lin Y-l, Richardson G, Levine L, *et al.* Use of BRCA mutation test in the US, 2004–2014. American journal of preventive medicine. 2017;52(6):702-9.
3. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, *et al.* Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402-16.
4. Salhab M, Bismohun S, Mokbel K. Risk-reducing strategies for women carrying brca1/2 mutations with a focus on prophylactic surgery. BMC Women's Health. 2010;10:28.
5. Lindor NM, Goldgar DE, Tavtigian SV, Plon SE, Couch FJ. BRCA1/2 Sequence Variants of Uncertain Significance: A Primer for Providers to Assist in Discussions and in Medical Management. The Oncologist. 2013;18(5):518-24.
6. McCarthy AM, Armstrong K. The Role of Testing for BRCA1 and BRCA2 Mutations in Cancer Prevention. JAMA internal medicine. 2014;174(7):1023-4.
7. Padamsee TJ, Wills CE, Yee LD, Paskett ED. Decision making for breast cancer prevention among women at elevated risk. Breast Cancer Research : BCR. 2017;19:34.
8. Smith KL, Isaacs C. BRCA mutation testing in determining breast cancer therapy. Cancer J. 2011;17(6):492-9.
9. Giannakeas V, Narod SA. The expected benefit of preventive mastectomy on breast cancer incidence and mortality in *BRCA* mutation carriers, by age at mastectomy. Breast Cancer Res Treat. 2018;167(1):263-7.
10. Kauff ND, Domchek SM, Friebel TM, Robson ME, Lee J, *et al.* Risk-reducing salpingo-oophorectomy for the prevention of BRCA1-and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. Journal of Clinical Oncology. 2008;26(8):1331.
11. Copson ER, Maishman TC, Tapper WJ, Cutress RI, Greville-Heygate S, *et al.* Germline *BRCA* mutation and outcome in young-onset breast cancer (POSH): a prospective cohort study. The Lancet Oncology. 2018;19(2):169-80.
12. Nilsson MP, Hartman L, Kristoffersson U, Johannsson OT, Borg A, *et al.* High risk of in-breast tumor recurrence after BRCA1/2-associated breast cancer. Breast Cancer Res Treat. 2014;147(3):571-8.
13. Metcalfe K, Gershman S, Ghadirian P, Lynch HT, Snyder C, *et al.* Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: retrospective analysis. BMJ. 2014;348:g226.
14. Stan DL, Shuster LT, Wick MJ, Swanson CL, Pruthi S, *et al.* Challenging and Complex Decisions in the Management of the *BRCA* Mutation Carrier. Journal of Women's Health. 2013;22(10):825-34.
15. Liede A, Mansfield CA, Metcalfe KA, Price MA, Snyder C, *et al.* Preferences for breast cancer risk reduction among BRCA1/BRCA2 mutation carriers: a discrete-choice experiment. Breast Cancer Research and Treatment. 2017;165(2): 433-44.

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# Displaced Epithelium in Breast Pathology: A Review

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ABSTRACT

**Background:** Although iatrogenic displacement of epithelial cells after breast instrumentation is a well-documented phenomenon, it is usually underdiagnosed. Misinterpretation of this issue results in overtreatment of patients in some instances. Additionally, the hazard of tumor seeding and dissemination after needling is a concern to both clinicians and patients. Both issues are addressed in this narrative review.

**Methods:** We searched PubMed for abstracts of English-language publications using keywords "needle track/tract" and "displaced epithelium/epithelial displacement/iatrogenic displacement," which resulted in 439 records restricted to human subjects. We read all the abstracts and selected 27 manuscripts with the most relevance.

**Results:** There are some histopathologic features that can be useful in differentiating between epithelial displacement and real invasion/metastasis. The risk of seeding or metastasis after needling is shown to be trivial. Factors militating against the growth of dislodged cells are also discussed.

**Conclusion:** Epithelial displacement is an important issue in breast pathology that should be considered in every patient with a history of breast instrumentation.

## Introduction

Displacement of tissue may occur following any type of intervention or surgical procedure in different organs. Both epithelial and mesenchymal components can be displaced. Implantation of carcinoma cells in the needle tract during percutaneous biopsy has been reported in cancers such as renal cell carcinoma, thyroid carcinoma, hepatocellular carcinoma, small cell carcinoma of lung and breast carcinoma.[1-7]

In breast tissue, displacement of epithelial component, both benign and malignant, may result in a misdiagnosis of invasive carcinoma or metastasis. Therefore, pathologists and other practitioners in the field of breast diseases should be cognizant of this phenomenon.

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Displacement of epithelium is common after needling procedures, including percutaneous core needle biopsy that is commonly used for evaluation of suspected breast lesions.[8-11] It occurs in any type of breast lesion.[12] In one study, 22 out of 64 excised breast specimens showed displaced neoplastic cells in needle tracks.[13] In a recent systematic review, displacement rate in a total of 927 cases from nine studies on surgically excised breast specimens ranged from 2% to 63%.[13, 14] This wide range can be attributed to the type of breast lesion (more common in papillary lesions), time interval between needling and surgery, type of procedure, and needle gauge. Although both patients and clinicians may be concerned about the proliferation of displaced malignant cell resulting in tumor recurrence at needling site or distant organs, the risk of this so-called "seeding" is only 0.2% to 0.7%.[15-18]

Epithelial displacement is important from two points of view including correct histopathologic diagnosis and hazard of needle track seeding or even metastasis.[19] Therefore, both issues are addressed in this review.

## Methods

We searched PubMed for English-language publications related to human subjects using the following keywords: "needle track," "needle tract," "displaced epithelium," "epithelial displacement," and "iatrogenic displacement," which yielded 439 records. We read all the abstracts and selected 27 papers with the most relevance.[1, 2, 5-7, 12, 13, 15, 17, 20-37] The full texts of the selected papers were obtained. We used both the selected papers and our experience to write the narrative review. The images are all taken from our cases in the Cancer Institute of Tehran University of Medical Sciences.

## Results

*Definition of displaced epithelium and how it differs from real invasion or metastasis*

When the epithelium is dislocated mechanically by surgical or radiological interventions, it is called displaced epithelium (DE). This iatrogenic phenomenon should be distinguished from local invasion or metastasis. In the latter situations, the neoplastic cells that have gained the ability to invade the stroma or vascular channels are dislodged from the main bulk of in situ carcinoma without requiring any external mechanical force. In both situations, some atypical cells are evident in the stroma, regional lymph nodes, or even distant sites such as bone marrow. Therefore, distinguishing between these two entities may be a great challenge for the histopathologist.

*Procedures resulting in DE*

Any type of instrumentation can result in DE, including fine needle aspiration, core needle biopsy, wire localization of lesions, vacuum-assisted breast biopsy (VABB), injections for sentinel lymph node identification, and incisional or excisional biopsies.[22,37] DE has also been reported after liposuction in a male patient with gynecomastia.[35]

The least damaging method is fine needle aspiration, where a 22-G needle is employed for entering the tumor. Needles with a larger gauge, such as 11- or 14-G, used for tissue diagnosis, result in more frequent DE.[38]

Having a very low rate of false negative results, VABB has a sensitivity and specificity superior to core needle biopsy.[23,39-41] In three studies, no malignant cell displacement was identified after this procedure. In these studies, 28, 23, and 21 VABBs were performed using 11-G, 14-G, and 11-G needles, respectively.[31,42,43]

*Factors influencing the frequency of DE*

The number and volume of identified tumor cells in needle track is inversely related to the intervening time between core needle biopsy and excision of the lesion.[22] Two main determinants of neoplastic cell displacement along needle tracks are the short term between core needle biopsy and excisional surgery and the histology of the tumor.[38]

In benign and malignant papillary lesions, epithelial displacement occurs more commonly in comparison with other neoplasms of the breast because of the fragility of these lesions. In one study in 2005, 50 out of 53 cases with epithelial displacement had an underlying papillary lesion.[27] These epithelia were dislocated to the stroma surrounding the papillary lesions and adjacent lymph-vascular channels imitating invasion. These displaced epithelia can be even transferred to axillary lymph nodes.

*Clinical significance of DE*

The trivial risk of development of clinical tumor recurrence at the needle biopsy site despite the high frequency of DE suggests that DE has little clinical significance. Radiotherapy is probably sufficient for eradicating isolated tumor cells in the needle track. The study of Boutin *et al.* on mesothelioma patients revealed metastasis in the needle track in 8 out of 20 patients who had not received radiation, while none of the twenty patients receiving radiotherapy developed metastasis.[44] Thurfjell *et al.* showed local recurrence in 11% of patients with breast carcinoma who had undergone breast-conserving surgery (33/303). Recurrence due to seeding in the needle track was suspected in 3 cases (3/33), none of whom had received postoperative radiotherapy.[24] Therefore, radiation of breast tissue, which is often performed after lumpectomy, obviates the mentioned risk of local recurrence. Additionally, the needle track is often removed during the surgical excision of malignant tumors.[32] A study on a large number of patients showed that core needle biopsy or fine-needle aspiration, for diagnosis of a malignant breast tumor, does not result in an increased risk of sentinel lymph node metastasis.[45]

The major issue is the risk of misinterpretation of DE by the pathologist who reviews the patient's excised material.[30]

*Histopathologic features of the needle track*

Displaced epithelia are most commonly identified at the site of needle track. The salient histopathologic features of needle track are as follows:

- Old or recent hemorrhage, depending on the interval between biopsy and excision (Figure 1).
- Hemosiderin deposition, either within the macrophages or in the stroma
- Granulation tissue formation, fibrosis, and chronic inflammation (Figure 2)
- Fat necrosis
- Foreign body reaction
- The presence of a large number of macrophages as identified by immunostaining for CD68 (Figure 3)
- The inflammation, hemorrhage, and fibrosis are arranged in a linear/elongated fashion (Figure 4)

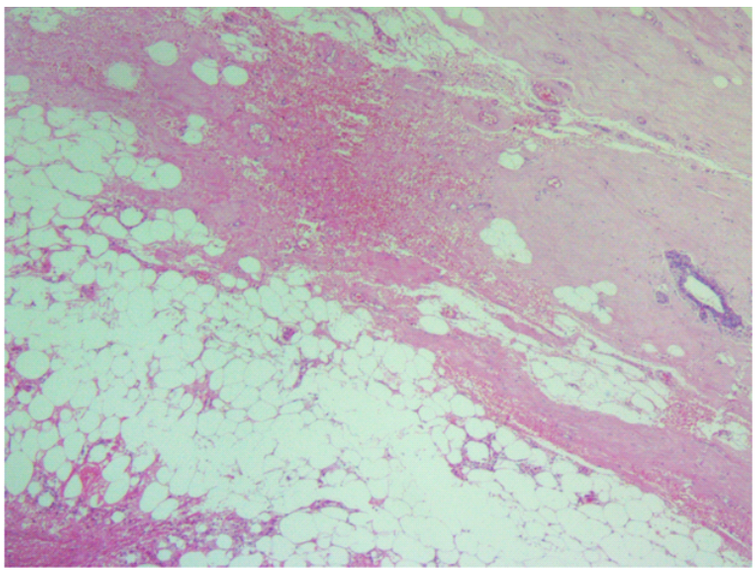

**Figure 1.** Hemorrhage at needling site (H&E, ×40).

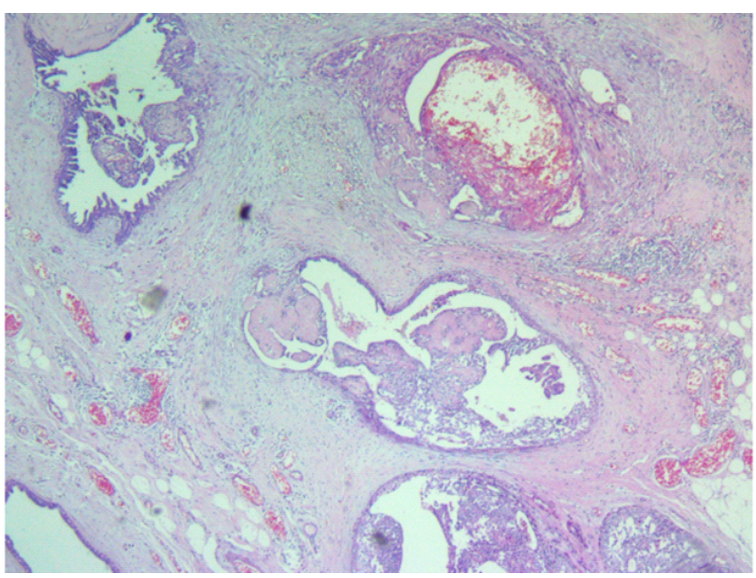

**Figure 2.** Intraductal papilloma with features of needle site.
Note the hemorrhage, granulation tissue, and fibrosis (H&E, ×40)

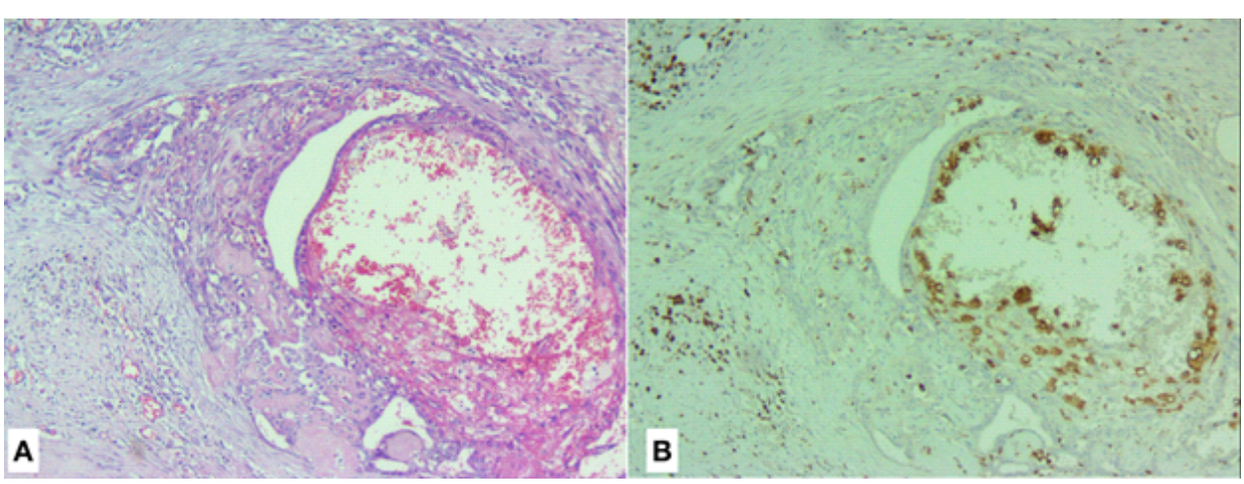


**Figure 3.** A. Intraductal papilloma in a case showing displaced epithelium. Note the hemorrhage at needle track site (H&E, ×100); B. Immunostaining for CD68 highlights the macrophages at needling site (×100).

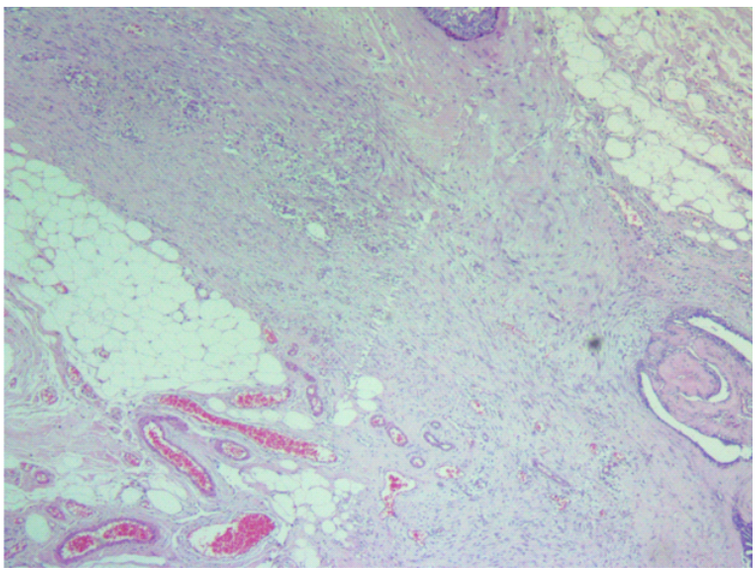

**Figure 4.** Needle track. A part of an intraductal papilloma is seen at the right side of the image. The elongated fibrosis and inflammation highlight the path of the needle biopsy performed a few weeks before (H&E, ×40).

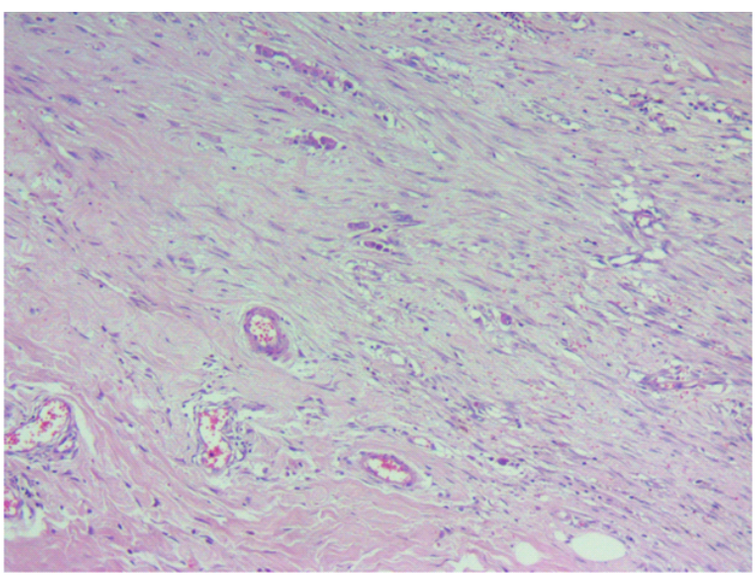

**Figure 5.** Displaced epithelium in a fibrotic stroma. Small cords or nests of displaced epithelium are evident in an extensively fibrotic stroma. The displaced epithelium is arranged in a rather linear fashion (H&E, ×100).

*Histopathologic features of DE and how it can be distinguished from authentic invasion or metastasis*

DE should be suspected when we observe a major intraductal component (particularly if this component is a papillary proliferation) or a small presumably invasive tumor.[27] The surgeon or radiologist should notify the pathologists, if there has been any history of prior biopsy or other instrumentations.

How can DE be differentiated from genuine invasive carcinoma? Apart from being located along needle track with aforementioned histopathologic features, the following characteristics may be helpful:

- The displaced epithelial cells are usually arranged in a linear pattern (Figure 5).
- The displaced cells show some degree of degeneration. It depends on the time interval between needling and excision. The longer this interval is, the more degenerative changes are identified. changes. The degenerated cells have pyknotic nuclei with increased intensity of cytoplasmic eosinophilia (Figure 6). If the interval between needling and biopsy is long enough, the displaced cells become necrotic or are completely removed by macrophages.
- The cells are morphologically similar to the intraductal component.
- Immunostaining for cytokeratin (Figures 7 and 8) and CD68 may be helpful in distinguishing between DE and epithelioid histiocytes (Figures 3 and 6).
- Immunostaining for myoepithelial markers and high–molecular weight cytokeratin may be utilized when the intraductal component is a benign proliferation with preserved myoepithelial cells.[46] However, the absence of staining for these markers does not preclude the

possibility of DE.

•Sometimes the displaced epithelia are seen in lymphatic channels. There are even reports about the transfer of the displaced epithelia to the lymph nodes along the lymphatic channels.[28, 33, 34, 36,37,47,48]

•Fibrosis related to needling, and not a desmoplastic reaction around invasive carcinoma, is very extensive. Therefore, the displaced epithelia usually constitute a small fraction of an extensive reaction (Figure 3).

•Some displaced epithelial cells may show squamous metaplasia, resulting in its being mistaken as adenosquamous cell carcinoma.

Displacement of the epithelium to regional lymph nodes and even remote organs such as bone marrow is on record.[37, 49] Since most of these cases are misdiagnosed as metastasis by pathologists, the exact frequency of these findings cannot be determined. Some features useful for distinguishing between DE and real metastasis include:

• The displaced cells are usually in the form of isolated cells or small clusters.

• They are usually evenly distributed in the lymph node sinus and do not form expansile masses or nodules.

• They are accompanied by red blood cells, macrophages, and giant cells.

• The invasive component is very small (for instance, when we have a microinvasive carcinoma).

• The grade of tumor and its type are less compatible with metastasis, e.g., a low-grade tumor or a papillary or mucinous carcinoma (in these situations, the likelihood of lymph node metastasis is very low, and if we see epithelial cells in lymph nodes, it should be interpreted cautiously).

• The biomarker results (ER, PR, and HER2) are different from the primary tumor.

• The tumor is morphologically different from the invasive carcinoma.

•DE is evident in lymphatic channels of the breast tissue.

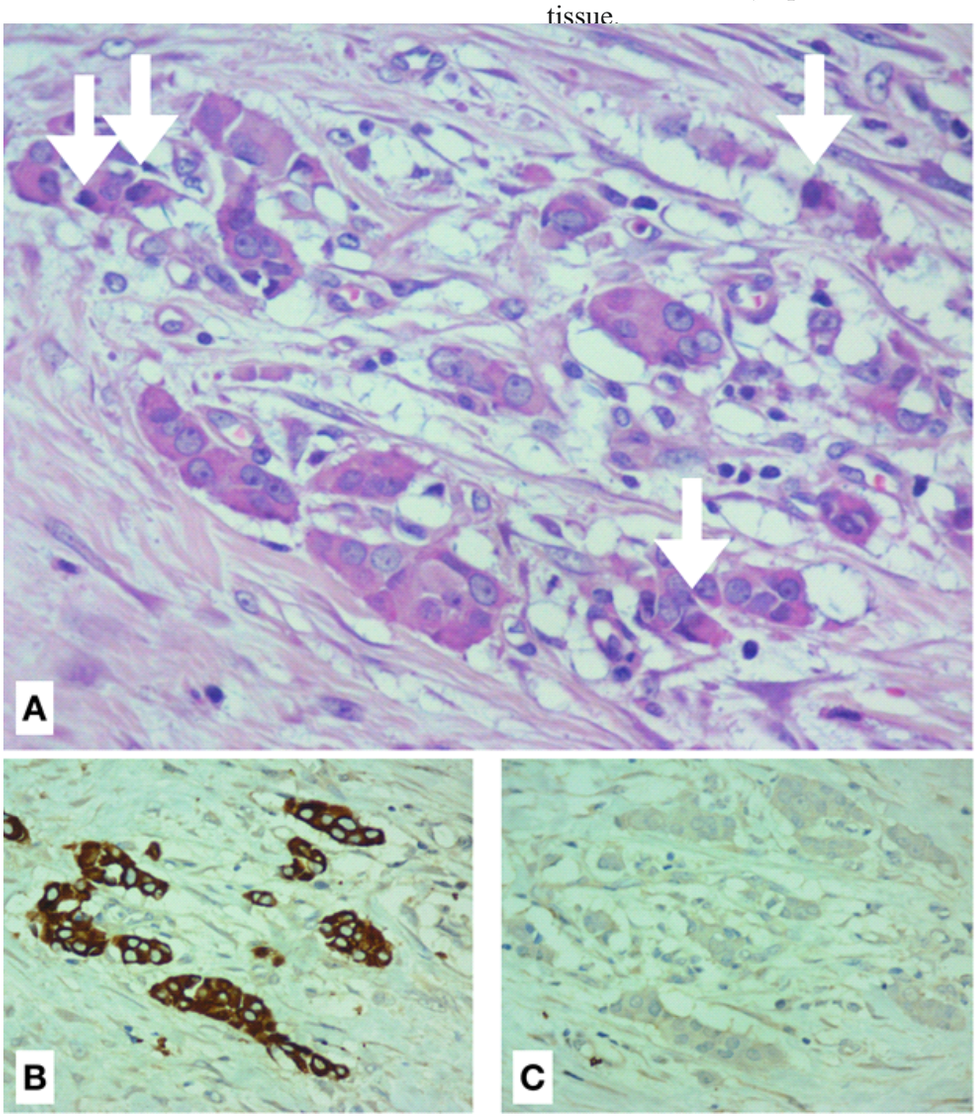


**Figure 6.** A. Displaced epithelium: some cells show degenerative changes characterized by pyknotic nuclei and increased eosinophilia of cytoplasm (white arrows); B. The displaced epithelium is highlighted by cytokeratin AE1/AE3; C. No staining for P63.

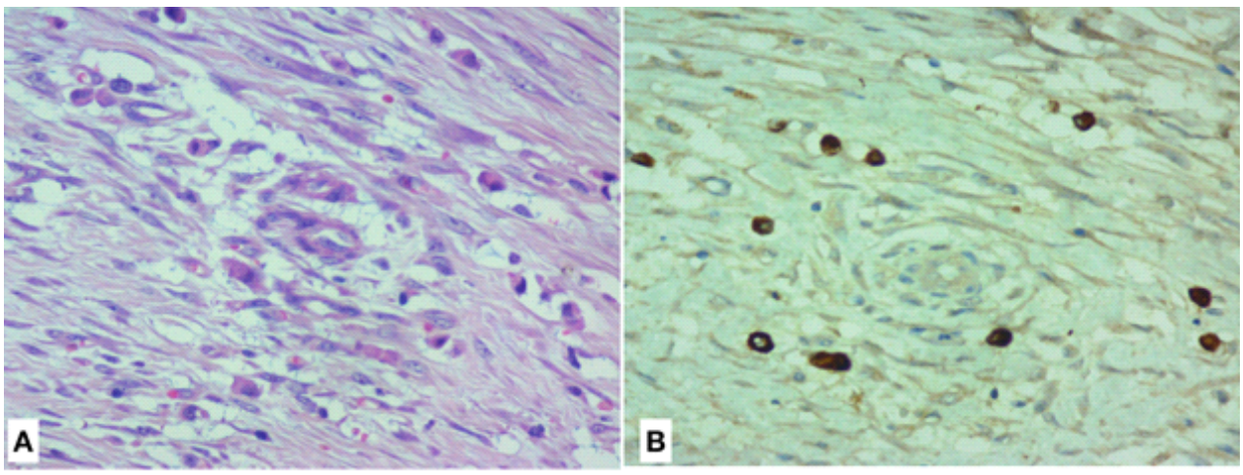


**Figure 7.** A. Scattered displaced epithelial cells are seen with marked degenerative changes. The degenerated cells have hyperchromatic pyknotic nuclei and densely eosinophilic cytoplasm; B. Because of the dispersion of displaced cells and degenerative changes, the epithelial nature of cells can be overlooked. In these situations, immunostaining for cytokeratin may be helpful in elucidating the nature of degenerated cells.

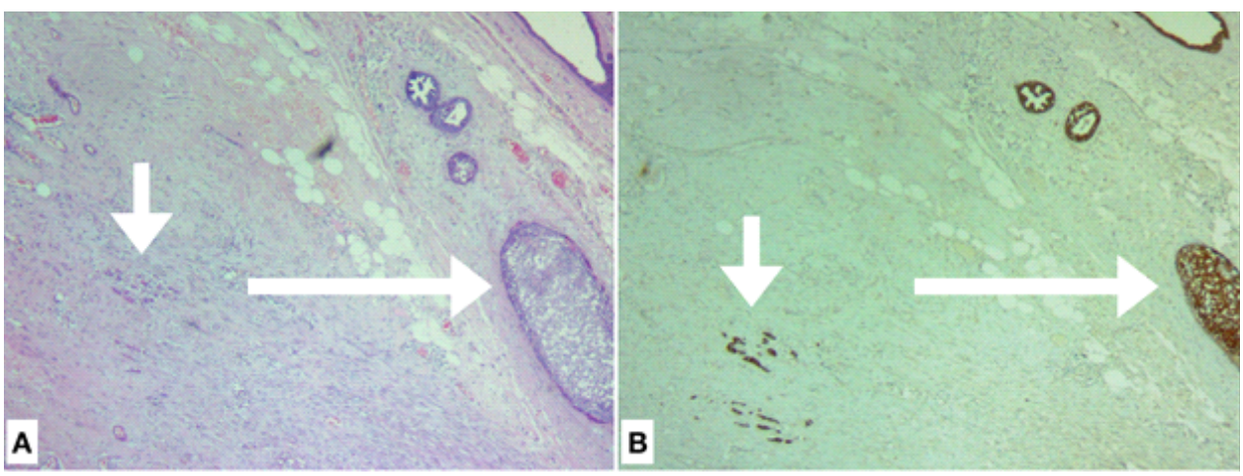


Figure 8. A. An atypical intraductal proliferation (the long arrow) and displaced epithelium (the short arrow) are depicted. Note the needle track features around the displaced epithelium (H&E stain, ×40); B. Cytokeratin AE1/AE3 staining confirms the epithelial nature of the displaced epithelium (the short arrow). Cytokeratin also highlights the intraductal component (the long arrow) (magnification ×40).

**Discussion**

Displacement of epithelium often occurs after needle biopsy of a breast lesion. Any epithelial cell can be displaced, including benign intraductal proliferations, in situ carcinoma, and invasive carcinoma.[10] The major diagnostic problem is related to the displacement of intraductal proliferative cells (both benign and malignant) to the stroma or lymphatic channels, which results in misdiagnosis as an infiltrating tumor.[8] Displacement of an invasive carcinoma along the needle track usually poses no diagnostic problem for the histopathologist. Its clinical significance has been discussed elsewhere in the manuscript. Occasionally, the displaced epithelium, dislodged into the lymph-vascular channels, may be carried to the regional lymph node, resulting in detection of isolated tumor cells in sentinel lymph nodes.[36,37,47]

Diagnosis of DE may be a great challenge for pathologists. Sometimes, it is overcalled as invasive carcinoma.

According to previous studies, the incidence of tumor seeding and recurrence at the site of needle track is low relative to the frequency of displaced tumor cells at this site.[50] This finding may be explained based on cancer stem cell theory and the characteristics of malignant tumors. All tumors have two basic components including parenchyma and stroma. The stroma is host-derived and crucial for the growth of neoplasms because it supplies blood and essential factors. In tumors, normal interactions between cells and extracellular matrix are altered and disrupted so that tumor cells can detach from each other easily. Tumor cells, as well as host-derived stromal cells, can secrete proteolytic enzymes that can degrade interstitial connective tissue, facilitating the movement of and, eventually, local invasion by tumor cells.[51]

During diagnostic procedures such as core needle biopsy or aspiration and excisional biopsy, tumor cells can be dislodged and displaced in needle track. Detached tumor cells can also enter lymphatic channels via these procedures and, at least theoretically,

colonize other sites far from the main lesion.[37,49] How can the low rate of local recurrence at biopsy site or lymph node metastasis be explained despite the presence of tumor cells in lymph nodes?

Cancer cells do not survive alone but recruit normal host-derived cells to serve as contributing members by producing tumor microenvironment. Tissue microenvironment is necessary for the growth of the tumor and also the development of other characteristics of malignancy such as invasion and metastasis. The cells that contribute to the production of tumor microenvironment are cancer-associated fibroblasts, angiogenic vascular cells, and infiltrating immune cells.[52]

Alternatively, according to cancer stem cell theory, all tumors contain a population of cells that show biologic properties similar to those of normal adult stem cells. These stem cells are responsible, if not crucial, for maintenance of malignant tumors.[53,54] Moreover, like normal stem cells, they require a specialized microenvironment named "stem cell niche" for regulation and progression of their growth. It represents a dynamic compartment by means of which additional components including endothelial, immune, and stromal cells as well as soluble factors help develop the environment necessary for both self-renewal and differentiation of stem cells.[52,55]

Almost all tumors, even at early phases, release cancer cells into blood, but a clinically evident metastatic disease occurs after a long period of latency. This observation suggests that metastatic colonization is an inefficient process and that most cancer cells die in blood. The investigations that show circulating tumor cells outnumber the overt metastatic lesion support this observation.[56]

Disseminated tumor cells need both stem cells and specialized microenvironment to survive. Experimental studies have provided evidence that signals from primary tumor can result in the development of a microenvironment in a distant homing organ. Thus, the so-called "premetastatic niche" is provided before the arrival of circulating tumor cells.

The low frequency of needle track seeding or metastasis can be due to the absence of cancer stem cells or appropriate microenvironment in the new location. However, this proposal should be confirmed by further investigations.

Although the frequency of seeding in needle track is very low, it is a well-documented entity.[26, 29, 57] The risk factors for the development of seeding in the track of breast needling were evaluated in a study by Santiago *et al.*[18] They showed that the major risk factors included grade 3 infiltrating ductal carcinomas, triple-negative carcinomas, use of non-coaxial needles, and multiple insertions. The frequency of seeding in this study was less than 0.2% (8 of 4010 core needle biopsies) and the mean time between core needle biopsy and development of seeding was 60.8 days.

Undoubtedly, a large number of cases of displaced epithelia are signed out as invasive carcinoma or metastasis by pathologists all over the world. Accordingly, the unexpectedly good prognosis in some cases of presumed invasive carcinoma with regional lymph node metastasis can be attributable to the overcalling of a noninvasive lesion.[33,58,59]

As conclusion, we should be aware of the possibility of epithelial displacement after needle aspiration or biopsy to differentiate dislodged epithelial cells from infiltrating tumor cells and lymphatic invasion. Degenerative alteration of neoplastic cell clusters and the absence of desmoplastic stroma around them indicate epithelial displacement.

**References**


1. Ito Y, Tomoda C, Uruno T, Takamura Y, Miya A, *et al.* Needle tract implantation of papillary thyroid carcinoma after fine-needle aspiration biopsy. World J Surg. 2005;29(12):1544-9.
2. Ito Y, Asahi S, Matsuzuka F, Nakamura Y, Amino N, *et al.* Needle tract implantation of follicular neoplasm after fine-needle aspiration biopsy: report of a case. Thyroid. 2006;16(10):1059-62.
3. Volpe A, Kachura JR, Geddie WR, Evans AJ, Gharajeh A, *et al.* Techniques, safety and accuracy of sampling of renal tumors by fine needle aspiration and core biopsy. J Urol. 2007;178(2):379-86.
4. Stokes ME, Thompson D, Montoya EL, Weinstein MC, Winer EP, *et al.* Ten-year survival and cost following breast cancer recurrence: estimates from SEER-medicare data. Value Health. 2008;11(2):213-20.
5. Horn T, Seidl S, Gschwend JE, Kubler H. Implantation metastasis of prostate cancer in a suprapubic cystostomy tube needle tract. Prostate Cancer Prostatic Dis. 2010;13(3):292-4.
6. Scotti V, Di Cataldo V, Falchini M, Meattini I, Livi L, *et al.* Isolated chest wall implantation of non-small cell lung cancer after fine-needle aspiration: a case report and review of the literature. Tumori. 2012;98(5):126e-9e.
7. Carlin SP, Garcia-Botella A, Diez-Valladares L, Perez-Aguirre E, Ortega L, *et al.* Dissemination of hepatocellular carcinoma in subcutaeous tissue after fine needle aspiration cytology (FNAC). Hepatogastroenterology. 2013;60(128):1839-40.
8. International Breast Cancer Consensus C. Image-detected breast cancer: state of the art diagnosis and treatment. International Breast Cancer Consensus Conference. J Am Coll Surg. 2001;193(3):297-302.
9. Perry NM, Party EW. Quality assurance in the diagnosis of breast disease. EUSOMA Working Party. Eur J Cancer. 2001;37(2):159-72.

10. Clarke-Pearson EM, Jacobson AF, Boolbol SK, Leitman IM, Friedmann P, *et al.* Quality assurance initiative at one institution for minimally invasive breast biopsy as the initial diagnostic technique. J Am Coll Surg. 2009;208(1):75-8.
11. Gutwein LG, Ang DN, Liu H, Marshall JK, Hochwald SN, *et al.* Utilization of minimally invasive breast biopsy for the evaluation of suspicious breast lesions. Am J Surg. 2011;202(2): 127-32.
12. Torous VF, Schnitt SJ, Collins LC. Benign breast lesions that mimic malignancy. Pathology. 2017;49(2):181-96.
13. Hoorntje LE, Schipper ME, Kaya A, Verkooijen HM, Klinkenbijl JG, *et al*. Tumour cell displacement after 14G breast biopsy. Eur J Surg Oncol. 2004;30(5):520-5.
14. Liebens F, Carly B, Cusumano P, Van Beveren M, Beier B, *et al*. Breast cancer seeding associated with core needle biopsies: a systematic review. Maturitas. 2009;62(2):113-23.
15. Chao C, Torosian MH, Boraas MC, Sigurdson ER, Hoffman JP, *et al.* Local recurrence of breast cancer in the stereotactic core needle biopsy site: case reports and review of the literature. Breast J. 2001;7(2):124-7.
16. Cho E, Kim MH, Cha SH, Cho SH, Oh SJ, *et al.* Breast cancer cutaneous metastasis at core needle biopsy site. Ann Dermatol. 2010;22(2): 238-40.
17. Brenner RJ, Gordon LM. Malignant seeding following percutaneous breast biopsy: documentation with comprehensive imaging and clinical implications. Breast J. 2011;17(6):651-6.
18. Santiago L, Adrada BE, Huang ML, Wei W, Candelaria RP. Breast cancer neoplastic seeding in the setting of image-guided needle biopsies of the breast. Breast Cancer Res Treat. 2017; 166(1):29-39.
19. Ansari TZ, Zaidi AA, Parekh A, Iqbal O, Masood N, *et al.* Factors influencing the opinion of individuals in determining tumour spread after biopsy. BMC Res Notes. 2011;4:548.
20. Youngson BJ, Cranor M, Rosen PP. Epithelial displacement in surgical breast specimens following needling procedures. Am J Surg Pathol. 1994;18(9):896-903.
21. Youngson BJ, Liberman L, Rosen PP. Displacement of carcinomatous epithelium in surgical breast specimens following stereotaxic core biopsy. Am J Clin Pathol. 1995;103(5): 598-602.
22. Diaz LK, Wiley EL, Venta LA. Are malignant cells displaced by large-gauge needle core biopsy of the breast? AJR Am J Roentgenol. 1999;173(5):1303-13.
23. Liberman L, Vuolo M, Dershaw DD, Morris EA, Abramson AF, *et al.* Epithelial displacement after stereotactic 11-gauge directional vacuum-assisted breast biopsy. AJR Am J Roentgenol. 1999;172(3):677-81.
24. Thurfjell MG, Jansson T, Nordgren H, Bergh J, Lindgren A, *et al.* Local breast cancer recurrence caused by mammographically guided punctures. Acta Radiol. 2000;41(5):435-40.
25. Douglas-Jones AG, Verghese A. Diagnostic difficulty arising from displaced epithelium after core biopsy in intracystic papillary lesions of the breast. J Clin Pathol. 2002;55(10):780-3.
26. Knight R, Horiuchi K, Parker SH, Ratzer ER, Fenoglio ME. Risk of needle-track seeding after diagnostic image-guided core needle biopsy in breast cancer. JSLS. 2002;6(3):207-9.
27. Nagi C, Bleiweiss I, Jaffer S. Epithelial displacement in breast lesions: a papillary phenomenon. Arch Pathol Lab Med. 2005; 129(11):1465-9.
28. Bleiweiss IJ, Nagi CS, Jaffer S. Axillary sentinel lymph nodes can be falsely positive due to iatrogenic displacement and transport of benign epithelial cells in patients with breast carcinoma. J Clin Oncol. 2006;24(13):2013-8.
29. Fitzal F, Sporn EP, Draxler W, Mittlbock M, Taucher S, *et al.* Preoperative core needle biopsy does not increase local recurrence rate in breast cancer patients. Breast Cancer Res Treat. 2006;97(1):9-15.
30. Phelan S, O'Doherty A, Hill A, Quinn CM. Epithelial displacement during breast needle core biopsy causes diagnostic difficulties in subsequent surgical excision specimens. J Clin Pathol. 2007;60(4):373-6.
31. Michalopoulos NV, Zagouri F, Sergentanis TN, Pararas N, Koulocheri D, *et al.* Needle tract seeding after vacuum-assisted breast biopsy. Acta Radiol. 2008;49(3):267-70.
32. Uematsu T, Kasami M. Risk of needle tract seeding of breast cancer: cytological results derived from core wash material. Breast Cancer Res Treat. 2008;110(1):51-5.
33. van Deurzen CH, Bult P, de Boer M, Koelemij R, van Hillegersberg R, *et al.* Morphometry of isolated tumor cells in breast cancer sentinel lymph nodes: metastases or displacement? Am J Surg Pathol. 2009;33(1):106-10.
34. Koo JS, Jung WH, Kim H. Epithelial displacement into the lymphovascular space can be seen in breast core needle biopsy specimens. Am J Clin Pathol. 2010;133(5):781-7.
35. McLaughlin CS, Petrey C, Grant S, Ransdell JS, Reynolds C. Displaced epithelium after liposuction for gynecomastia. Int J Surg Pathol. 2011;19(4):510-3.
36. Tvedskov TF, Jensen MB, Kroman N, Balslev E. Iatrogenic displacement of tumor cells to the sentinel node after surgical excision in primary breast cancer. Breast Cancer Res Treat. 2012;131(1):223-9.

37. Nayak A, Bleiweiss IJ. Iatrogenically false positive sentinel lymph nodes in breast cancer: Methods of recognition and evaluation. Semin Diagn Pathol. 2018;35(4):228-35.
38. Loughran CF, Keeling CR. Seeding of tumour cells following breast biopsy: a literature review. Br J Radiol. 2011;84(1006):869-74.
39. Pisano ED, Fajardo LL, Tsimikas J, Sneige N, Frable WJ, *et al.* Rate of insufficient samples for fine-needle aspiration for nonpalpable breast lesions in a multicenter clinical trial: The Radiologic Diagnostic Oncology Group 5 Study. The RDOG5 investigators. Cancer. 1998;82(4): 679-88.
40. Altomare V, Guerriero G, Giacomelli L, Battista C, Carino R, *et al.* Management of nonpalpable breast lesions in a modern functional breast unit. Breast Cancer Res Treat. 2005;93(1):85-9.
41. Dhillon MS, Bradley SA, England DW. Mammotome biopsy: impact on preoperative diagnosis rate. Clin Radiol. 2006;61(3):276-81.
42. Liberman L, Hann LE, Dershaw DD, Morris EA, Abramson AF, *et al.* Mammographic findings after stereotactic 14-gauge vacuum biopsy. Radiology. 1997;203(2):343-7.
43. Stolier A, Skinner J, Levine EA. A prospective study of seeding of the skin after core biopsy of the breast. Am J Surg. 2000;180(2):104-7.
44. Boutin C, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. Chest. 1995;108(3):754-8.
45. Peters-Engl C, Konstantiniuk P, Tausch C, Haid A, Hoffmann B, *et al.* The impact of preoperative breast biopsy on the risk of sentinel lymph node metastases: analysis of 2502 cases from the Austrian Sentinel Node Biopsy Study Group. Br J Cancer. 2004;91(10):1782-6.
46. Yeh IT, Mies C. Application of immunohistochemistry to breast lesions. Arch Pathol Lab Med. 2008;132(3):349-58.
47. Diaz NM, Cox CE, Ebert M, Clark JD, Vrcel V, *et al*. Benign mechanical transport of breast epithelial cells to sentinel lymph nodes. Am J Surg Pathol. 2004;28(12):1641-5.
48. Tada K, Ogiya A, Kimura K, Morizono H, Iijima K, *et al.* Ductal carcinoma in situ and sentinel lymph node metastasis in breast cancer. World J Surg Oncol. 2010;8:6.
49. Shyamala K, Girish HC, Murgod S. Risk of tumor cell seeding through biopsy and aspiration cytology. J Int Soc Prev Community Dent. 2014;4(1):5-11.
50. Allawi Z, Cuzick J, Baum M, investigators AL. Does trauma or an intercurrent surgical intervention lead to a short-term increase in breast cancer recurrence rates? Ann Oncol. 2012;23(4):866-9.
51. Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell. 2012;21(3): 309-22.
52. Decker AM, Cackowski FC, Jung Y, Taichman RS. Biochemical Changes in the Niche Following Tumor Cell Invasion. J Cell Biochem. 2017;118(8):1956-64.
53. Jones DL, Wagers AJ. No place like home: anatomy and function of the stem cell niche. Nat Rev Mol Cell Biol. 2008;9(1):11-21.
54. Huch M, Rawlins EL. Cancer: Tumours build their niche. Nature. 2017;545(7654):292-3.
55. Melzer C, von der Ohe J, Lehnert H, Ungefroren H, Hass R. Cancer stem cell niche models and contribution by mesenchymal stroma/stem cells. Mol Cancer. 2017;16(1):28.
56. Massague J, Obenauf AC. Metastatic colonization by circulating tumour cells. Nature. 2016; 529(7586):298-306.
57. Kopans DB, Gallagher WJ, Swann CA, McCarthy KA, White G, *et al.* Does preoperative needle localization lead to an increase in local breast cancer recurrence? Radiology. 1988; 167(3):667-8.
58. Giuliano AE, Hawes D, Ballman KV, Whitworth PW, Blumencranz PW, *et al.* Association of occult metastases in sentinel lymph nodes and bone marrow with survival among women with early-stage invasive breast cancer. JAMA. 2011;306(4):385-93.
59. Weaver DL, Ashikaga T, Krag DN, Skelly JM, Anderson SJ, *et al.* Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med. 2011;364(5):412-21.

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# Recurrent multiple fibroadenomas: History of a case presented in MDT meeting with clinical discussion and decision making

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ABSTRACT

**Background:** Fibroadenoma is a common benign breast disorder in young women which has a low risk of malignant transformation. Most fibroadenomas present as a single mass, but the presence of multiple fibroadenomas can be seen in 15–20% of patients, with average number of 3–4 masses in one breast. In different studies and reports, various treatment modalities-including observation and follow up, surgery, radiofrequency ablation, etc- have been proposed, though the best management for these patients are not determined yet.

**Case presentation:** We present the case of 33-year-old female with history of multiple bilateral benign breast lesions with a presumptive diagnosis of fibroadenomas. She had three previous surgical excisions in the past 14 years. Her case was presented to a breast MDT meeting to obtain a recommendation on appropriate management.

**Question:** The proposed a question in MDT concerned the best and most appropriate management plan for the patient; Does she require further surgical excisions? And if not, how should she be followed?

**Conclusion:** After reviewing past medical history, physical examination, and all documents regarding the patient, MDT members recommended that the patient should be managed with close follow up with physical examination and ultrasound every 6 months. The necessity of further surgical intervention would be determined according to any new findings.

## Introduction

Fibroadenoma is a common benign breast disorder occurring in almost 20% of women. It mostly occurs in women of child-bearing age, especially those under 30.[1-3] The risk of malignant transformation is very low in fibroadenomas; but epithelial hyperplasia, atypical hyperplasia (0.81%), invasive and insitu ductal and lobular carcinoma has been seen rarely in fibroadenomas.[1-3] Patients with strong positive family history of breast cancer and complex fibroadenomas need greater attention, as the risk of malignant transformation is higher in these subgroups of patients.[3]

Ultrasound is a reliable diagnostic test for fibroadenomas. Generally, when clinical and ultrasound features are consistent with diagnosis of fibroadenoma, no tissue biopsy is needed and it is managed either conservatively or excised;[1, 3] but if there is no certainty, biopsy -often core needle biopsy- is helpful in making definite diagnosis. Fibroadenomas are often managed by observation with clinical control and imaging (usually ultrasound), or surgical excision according to the size and features of the lesion and its risk of malignant transformation, and patient characteristics and preferences.[4]

When considering a patient with presumed fibroadenoma based on clinical and imaging findings, one important thing to deal with is how to accurately differentiate it from phyllodes tumor. Phyllodes tumor

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of the breast is an uncommon fibroepithelial neoplasm which is classified into benign, borderline, and malignant types according to histologic features.[5] Although in some studies special features of imaging modalities (like size, shape, and margin of the mass in mammography; size, shape, margin, echo pattern, and vascularization of the mass in ultrasound; internal cystic areas on MRI) are reported to be helpful to ascertain imaging-histological concordance and guide clinicians to make appropriate decisions about correct follow-up or the necessity of biopsy or excision, differentiating fibroadenoma from phyllodes tumor based on clinical, radiologic and even pathologic findings is not always easy.[5,6]

Most fibroadenomas present as a single mass, but the presence of multiple fibroadenomas can be seen in 15–20% of patients. Average number of masses in cases of multiple fibroadenomas has been reported to be 3–4 in one breast, and occurrence of more than five fibroadenomas is reported to be much less common.[2] Unlike women with a single fibroadenoma, most of the patients with multiple fibroadenomas have a strong family history of these lesions.[2] The etiology of this entity has not been clearly known yet. Possibilities like taking oral contraceptive pills, imbalance of estrogen levels in the body, hypersensitivity of local breast tissue to estrogen, dietary factors, or inherited predisposition has been proposed in different studies.[7]

Patients with multiple fibroadenomas usually undergo several diagnostic imaging, tissue biopsies and surgical excisions during their life, all showing same benign results. Therefore, this disorder poses a conundrum for the surgeon, as it is difficult to avoid unnecessary imaging and procedures while not missing any malignant lesions. In different studies and reports, various treatment modalities -including observation and follow up, surgery, radiofrequency ablation, …- have been proposed, though the best management for these patients has not been determined yet.

Herein, the medical records of a 33-year old woman discussed in Multidisciplinary Team Discussion (MDT), is presented. The patient had the history of multiple bilateral benign type breast lesions in favor of fibroadenoma and three previous excisions during the past 14 years. She was suffering from the recurrence of lesions in the same area of the breast, as well as the other quadrants of both breasts. The medical records of the patient are presented in MDT session for clinical discussion and decision making concerning appropriate management.

**Case presentation**

A 33-year-old female was referred to our breast clinic with complaint of multiple bilateral breast masses for the past 14 years. She had no positive family history of breast or ovarian cancer, she was married and nulliparous. In her physical examination a 25mm mobile mass was palpated in UIQ of the right breast. She had undergone multiple previous imaging tests (including 6 ultrasound exams and two breast MRIs). All the imaging modalities reported multiple benign looking masses in both breasts. She had three surgical excisions, two with pathology of fibroadenoma, and the last one (which had been done 2 years before the current presentation) with pathology of benign fibroepithelial lesion reported to be benign phyllodes tumor in pathology review. On her recent ultrasound, multiple hypoechoic lesions with benign features in both breasts was reported, five masses in the left breast (the biggest one 20 mm in 7 o'clock), and three in the right (the biggest one was 21mm in 1 o'clock). The report of core needle biopsy for the recent lesions in both sides was compatible with fibroadenoma. She did not take oral contraceptive pills or any other medications. Her menstrual cycles were regular and there were no findings on gynecologic exam. The patient's history was presented in multidisciplinary team meeting of breast unit in the surgery department, Tehran University of medical sciences to decide appropriate management.

**Question**

The proposed question was about the most appropriate management for the patient as the further step: Does she need further surgical excisions? And if not, how should she be followed up?

**Discussion**

Fibroadenoma is a common benign breast disorder mostly seen in young women under 30. They rarely progress into malignant lesions.[1-3] There are several treatment options for fibroadenomas including observation with clinical and imaging control and surgery.[4] It is postulated that fibroadenomas may be safely followed, if volume growth rate is less than 16% in those younger than 50 years and less than 13% per month in those 50 years or older. A mean size change of 20% for a 6-month interval reported to be acceptable for all ages.[8] It was concluded that non-operative management of fibroadenomas seems to be safe.[9, 10] Surgical resection is another effective and appropriate treatment, but the permanent surgical scar can cause psychological issues for the patients, especially younger ones.[1] The surgical treatment of choice for fibroadenoma is breast lumpectomy, however, multiple fibroadenomas may pose a particular challenge.[2] Other proposed treatments include minimally invasive treatment such as vacuum assisted breast biopsy applied for mass resection and thermal ablation treatment with radiofrequency ablation (RFA), microwave ablation, and laser ablation.[1]

Most fibroadenomas present as a single mass; however, the presence of multiple fibroadenomas can be seen in 15–20% of patients, with average

number of 3-4 masses in each breast.[2] The best management for patients with multiple fibroadenomas is not determined yet. Most patients undergo several imaging and diagnostic procedures, as well as surgical excisions during their life which causes psychologic and cosmetic distress for them. In different studies and reports, various treatment modalities have been proposed for this group of patients.

Pasta et al. have reported a case of a 22-year-old woman undergone surgical treatment many times to remove multiple mammary fibroadenomas. They proposed that the periodic radiological exams would be the proper management, and the surgical treatment should be reserved only for rapidly growing lesions.[11] Based on natural history of fibroadenomas, the method of observation, follow-up and implementing surgical resection only under certain conditions -such as large tumor size and inability to rule out malignancy- has been claimed to be the most common advice in other studies.[1,12]

As mentioned above, the treatment of choice for fibroadenoma is the surgical excision, but multiple fibroadenomas may pose a particular challenge and necessitate more extensive surgeries e.g. oncoplastic techniques for reconstruction of the breast shape. In one study by Camara *et al.*, Riberi technique of reduction mammaplasty modified by Rezai was used for selective resection of more than seventy fibroadenomas on two patients. In this technique, remodeling of the breast like a mastopexy through the inferior pedicle technique was done. The authors concluded that multiple fibroadenomas of the breast can be removed safely with these techniques.[4] In another study by Lai HW *et al.*, 20 patients with multiple fibroadenomas (average number of 3.3 masses in each patient) underwent surgical excision with round block technique; they reported low complications rate and good aesthetic results and concluded that the round block technique is a useful oncoplastic procedure for the management of multicentric fibroadenomas excised at the same time.[13]

The effect of some new non-surgical techniques in treatment of multiple fibroadenomas has been investigated in some studies. In one report by Povoski, a female patient with 16 breast lesions (eight within each breast), presumed on ultrasound to be fibroadenomas, underwent ultrasound-guided vacuum-assisted breast biopsy of 14 of these 16 lesions during a total of 11 separate procedures performed during seven separate sessions over a ten and fifteen days. The patient discontinued taking OCP after the third treatment session. In addition, two of these 16 breast lesions were removed by surgical excision. A pathologic diagnosis of fibroadenoma and/or fibroadenomatosis was confirmed for all lesions. The rate of recurrence in this study was extremely low; with an interval follow-up ultrasound at least 8 months following treatment, showing the absence of any residual lesions or recurrences at the site of the 16 original breast lesions. The authors finally concluded that this approach is highly recommended in similar appropriately selected patients.[14]

In another study by Li *et al.* the safety and efficacy of ultrasound (US)-guided percutaneous radiofrequency ablation (RFA) for multiple breast fibroadenomas was evaluated. Sixty-five patients with multiple breast fibroadenomas underwent US-guided percutaneous RFA under general anesthesia. Contrast-enhanced US (CEUS) was used immediately after operation to determine whether the tumor was ablated completely or not. The complete ablation rate (CAR) and the change of focal volume were evaluated by CEUS at the first and third months after operation. The number of lesions in all patients was reported as high as 256 nodules. Complete ablation was achieved for 251 nodules (98.04%) after the first month. The volume reduction rate was 39.06% and 75.99% at the first and the third month after operation, respectively, of which 45 nodules were completely absorbed (17.58%). The authors reported no complications such as skin burns, hemorrhage, hematoma, or nipple discharge during and after RFA. They concluded that regarding the advantages of high CAR, mild injury, rapid recovery, and cosmetic outcome, RFA has the potential to become the preferred method in the treatment of breast fibroadenoma, especially for multiple fibroadenomas.[1]

In a study by Dhar *et al.* the effect of Centchroman (Ormeloxifene) -a novel non-steroidal selective antiestrogen- on the treatment of mastalgia and fibroadenoma was evaluated. Sixty patients with mastalgia or breast fibroadenoma (42 and 18 patients, respectively) who were 35 years old and younger were included in this study. They received centchroman 30 mg on alternate days for 3 months and were followed up for 6 months. Results of clinical examination, visual analog scale (VAS) for pain relief, and ultrasonography for the size of breast mass were recorded. Fibroadenoma size ranged from 1.5 to 5 cm, single or multiple in one or both breasts. In the fibroadenoma group, there was a mixed response, with complete disappearance in 40%, partial regression in 20%, and no response in the remaining 40%. There were very few side effects. The authors concluded that Centchroman is safe for the treatment of fibroadenoma.[7]

In conclusion, management of multiple fibroadenomas can be a complicated clinical situation especially for recurrent lesion, and there is no universal consensus about the best management yet. More prospective investigation is needed to reach a standard management plan. It seems that consideration of history, physical examination, imaging and any previous pathologies of each patient and making decision individually, probably with help

of a MDT discussions, is the best option for now.

**Multidisciplinary team (MDT) Recommendation**

The patient history, imagings, and pathologic reports was presented to MDT. The imaging and pathology reports was reviewed by two other pathologists and radiologists. According to the expert opinion of the breast radiologists, all masses seen in the last ultrasound and MRI were looking to be benign and neither malignant features nor significant changes in the recent masses were found in the follow up MRI and Ultrasonography exams. After review of all documents, MDT members recommended thet close follow up could be continued by means of physical examination and ultrasound every 6 months. The necessity of further surgery would be determined according to the possible new findings or mass enlargements in the future.

**Ethical Consideration**

Medical ethics considerations were fully observed according to the protocol delivered by ethics committee of surgery department at Tehran University of Medical Sciences (TUMS).

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**


1. Li P, Xiao-Yin T, Cui D, Chi JC, Wang Z, et al. Evaluation of the safety and efficacy of percutaneous radiofrequency ablation for treating multiple breast fibroadenoma. J Cancer Res Ther. 2016;12(Supplement):C138-C42.
2. Panda SK, Patro B, Mishra J, Dora RK, Subudhi BS. Multiple fibroadenomas in bilateral breasts of a 46-year-old Indian woman - A case report. Int J Surg Case Rep. 2014;5(5):262-4.
3. Rao S, Latha PS, Ravi A, Thanka J. Ductal carcinoma in a multiple fibroadenoma: diagnostic inaccuracies. J Cancer Res Ther. 2010;6(3):385-7.
4. Camara O, Egbe A, Koch I, Herrmann J, Gajda M, et al. Surgical management of multiple bilateral fibroadenoma of the breast: the Ribeiro technique modified by Rezai. Anticancer Res. 2009;29(7):2823-6.
5. Zhang Y, Kleer CG. Phyllodes Tumor of the Breast: Histopathologic Features, Differential Diagnosis, and Molecular/Genetic Updates. Arch Pathol Lab Med. 2016;140(7):665-71.
6. Duman L, Gezer NS, Balcı P, Altay C, Başara I, et al. Differentiation between Phyllodes tumors and fibroadenomas based on Mammographic Sonographic and MRI features. Breast Care. 2016;11(2):123-7.
7. Dhar A, Srivastava A. Role of centchroman in regression of mastalgia and fibroadenoma. World J Surg. 2007;31(6):1178-84.
8. Gordon PB, Gagnon FA, Lanzkowsky L. Solid breast masses diagnosed as fibroadenoma at fine-needle aspiration biopsy: acceptable rates of growth at long-term follow-up. Radiology. 2003;229(1):233-8.
9. Cant P, Madden M, Coleman M, Dent D. Non-operative management of breast masses diagnosed as fibroadenoma. British journal of surgery. 1995;82(6):792-4.
10. Carty NJ, Carter C, Rubin C, Ravichandran D, Royle GT, et al. Management of fibroadenoma of the breast. Ann R Coll Surg Engl. 1995;77(2): 127-30.
11. Pasta V, Tintisona O, Vergine M, Martino G, Torcasio A, et al. [Multiple repetitive mammary fibroadenomas. Case report]. G Chir. 2007;28(5):209-12.
12. Williamson ME, Lyons K, Hughes LE. Multiple fibroadenomas of the breast: a problem of uncertain incidence and management. Ann R Coll Surg Engl. 1993;75(3):161-3.
13. Lai H-W, Kuo Y-L, Su C-C, Chen C-J, Kuo S-J, et al. Round block technique is a useful oncoplastic procedure for multicentric fibroadenomas. the surgeon. 2016;14(1):33-7.
14. Povoski SP. The utilization of an ultrasound-guided 8-gauge vacuum-assisted breast biopsy system as an innovative approach to accomplishing complete eradication of multiple bilateral breast fibroadenomas. World journal of surgical oncology. 2007;5(1):124.

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# Implementation of a Discharge Planning to Improve Quality of Life in Breast Cancer Patients: A Quasi-Experimental Study

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ABSTRACT

**Background:** Breast surgery for women newly diagnosed with breast cancer is associated with poor postoperative quality of life (QOL). The aim of this study was to determine the effectiveness of a programmed discharge planning in improving overall QOL and its physical, emotional, social, and spiritual domains.

**Method:** In this quasi-experimental study, we evaluated the newly diagnosed breast cancer women undergoing breast-conserving therapy in two groups, an experimental group (n = 35) and a control group (n = 34). The experimental group received programmed discharge planning at the time of hospital admission until six weeks after discharge. The control group received routine hospital care. Participants completed the QOL questionnaires before and after the intervention. The data were analyzed using the independent-samples t test, Fisher exact test, and Mann-Whitney U.

**Results:** Before the intervention, there were no significant differences between the control and experimental groups in overall QOL or its physical, emotional, social, and spiritual domains. The data analysis after intervention showed significant improvement in QOL in the experimental group as compared with the control group. The changes in the scores of various domains of QOL were statistically significant ($P < 0.01$).

**Conclusion:** This study emphasizes that programmed discharge planning is useful for improving QOL after breast-conserving surgery. Our finding could be applied to breast cancer patients with radiation therapy or chemotherapy.

## Introduction

Cancer is a major public health problem worldwide. According to statistics, the most frequent type of cancer in women is the cancer of the breast.[1] It is also the most prevalent cancer diagnosed among Iranian females, accounting for 24.4% of all malignancies.[2] A treatment choice for breast cancer is surgery. Surgical treatment of breast cancer, aimed at facial and breasts areas, have deep psychological impacts on women's body image, quality of life, and sexual life.[3]

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Anxiety, worry, stress, fear, depression, and social isolation are the most experienced problems during the course of breast cancer diagnosis and surgical procedures. These psychological problems lead to the progression of cancer, as well as a slowed treatment process.[4-7]

Despite these problems, the average length of stay after surgical procedures has been decreasing for a variety of reasons, including advances in medical technology and financial problems.[8, 9] Shorter stays in hospital after the operation for breast cancer are suitable for patients who recover quickly from surgery.[10] Nevertheless, it is essential to establish appropriate follow-up services for women with breast cancer after discharge.[11]

An essential element in delivering health care is continuity of care. This is particularly important for people with chronic diseases.[12] The associations

between continuity of care and patient satisfaction,[13] health-related quality of life,[14] reduced readmission rate, urgent care use,[15] and health care costs have been demonstrated previously.[16]

Discharge planning is an essential component of continuity of care.[17] Planning the discharge has demonstrated positive outcomes for hospitalized patients, including decreased early unplanned readmissions and costs for providing health services.[18,19]

Recent data suggest that newly diagnosed breast cancer patients who are discharged early from the hospital need an effective follow-up plan. Although early discharge is safe and feasible, postoperative follow-up plan should be initiated as soon as possible after surgery. It also could help improve patients' quality of life (QOL). Quality of life is now considered an important end point in the treatment of breast cancer patients. These patients might benefit from programmed discharge planning.

The aim of this study was to determine the effectiveness of a programmed discharge planning in improving overall QOL and its physical, emotional, social, and spiritual domains in breast cancer patients undergoing breast-conserving therapy (BCT). The findings of this investigation can provide the basic information required for the development of a systematic discharge planning service.

**Methods**

This quasi-experimental study was conducted at Imam Khomeini Hospital of Tehran University of Medical Sciences between December 2010 and May 2011.

All subjects of the study were identified at diagnosis through the results of the histopathological reports. Inclusion criteria were as follows: being a female aged ≥ 20 years, having a newly diagnosed stage I/II breast cancer, being an initial BCT candidate, having no history of mental or physical illness, being reachable via telephone, living in Tehran, have not participated in a patient education program, have not undergone immediate mastectomy after BCT.

Patients were contacted after being referred to the breast cancer clinic. The data were collected through interviews with patients and the review of their medical records. The patients were invited to participate in the study if they met the inclusion criteria.

Demographic and medical data for the participations were recorded. This questionnaire contained items such as age, marital status, employment, education (illiterate, able to read and write, primary, high school, college, and above), cancer stage, and axillary lymph node dissection (removed nodes).

Two measurements of quality of life were obtained, the first after the diagnosis and the second at the end of the study period.

The sample size for the study was calculated based on QOL end points from previous studies. Using a 95% confidence interval and 80% power, we calculated a sample size of n = 36 in each group. Patients were randomly assigned to 2 groups. The approval by the institutional ethics committee (approval No. S/624/130) and the informed consent from participants were obtained.

Quality of life was assessed using a 51-item questionnaire comprising physical (16 items), emotional (17 items), social (11 items), and spiritual (7 items) domains. The overall QOL was computed by calculating the scores of all the questions. We used the SF-36 questionnaire for physical domain, and the Quality of Life Instrument-Breast Cancer Patient Version(QOL-BC) for emotional, social and spiritual domians. The total score ranged between 0 and 204, with lower scores corresponding to better QOL.

The questionnaire content validity was determined by 10 experts in the breast cancer field, and its reliability was determined by calculating Cronbach's alpha, which was 0.77. Internal consistency and validity were assessed by a pilot study on 15 patients with newly diagnosed breast cancer not included in the study.

The participants in the experimental group completed the patient care needs assessment checklist, telephone consultation form, and home visit form during the intervention. These forms were developed by researchers based on the information in the literature and after interviewing 5 experts in the area of breast cancer.

The patients in the discharge-planning program were provided with preoperative education, postoperative education, two home visits, and telephone consultations. Individual patients' needs were considered in all consultations.

A nursing instruction and counseling were provided in every step based on the patients' individual needs. After patients were discharged, we provided appropriate support and instruction for each patient during two home visits. On each visit, the specific patient needs were identified using the checklist, and then the first author gave instructions on such matters as changing the dressing, managing drains, exercise interventions for upper limb, etc. The first visit was made within the first week after discharge, the second in the sixth week after discharge. Telephone consultations were performed on six occasions with 1-week intervals to address potential problems at times other than during home visits.

Patients in the control group received the hospital routine discharge plan. Two interviews were done in this group: the first one was held upon their admissions to collect data about demographic and medical characteristics, and the second took place 6 weeks after discharge to complete the QOL questionnaire.

**Table 1.** Baseline characteristics of study participants

| Characteristics | Experimental group (n = 36) | Control group (n = 36) | P value |
|---|---|---|---|
| Age | | | |
| < 35 | 3 (8.6) | 6 (17.6) | |
| 35-55 | 26 (74.3) | 26 (76.5) | |
| > 55 | 6 (17.1) | 2 (5.9) | 0.39* |
| Mean (SD) | 46.2 (8.7) | 44.3 (9.2) | |
| Marital status | | | |
| Married | 27 (77.1) | 29 (85.3) | |
| Single | 3 (8.6) | 3 (8.8) | 0.71** |
| Divorced | 4 (11.4) | 1 (2.9) | |
| Widowed | 1 (2.9) | 1 (2.9) | |
| Employment | | | |
| Employed | 9 (25.7) | 10 (29.4) | 0.73*** |
| Housewife | 26 (74.3) | 24 (0.6) | |
| Education | | | |
| Illiterate | 6 (17.1) | 4 (11.8) | |
| Able to read and write | 4 (11.4) | 4 (11.4) | |
| Primary | 16 (45.7) | 14 (41.2) | 0.46**** |
| High school | 6 (17.1) | 10 (29.4) | |
| Collage and above | 3 (8.6) | 2 (5.9) | |
| Cancer stage | | | |
| Stage I | 14 (40.0) | 13 (38.2) | 0.88** |
| stage II | 21 (60.0) | 21 (61.8) | |
| Axillary lymph node dissection | | | |
| Yes | 27 (77.1) | 24 (70.6) | 0.53*** |
| No | 8 (22.9) | 10 (29.4) | |
| Missing | 1 | 2 | |

*Independent *t* test, ** Fisher exact test, *** Chi-square test, **** Mann-Whitney U test

*Data analysis*

The Statistical Package for the Social Sciences was used for data analysis. Descriptive statistics were used to summarize the demographic and medical characteristics. The Independent t test was used to compare the mean scores on QOL domains between the groups. A significance level of $\alpha = 0.05$ was used in statistical analyses.

## Results

A total of 72 women with breast cancer met the inclusion criteria for the study, with 36 in each group. One woman in the experimental group and 2 in the control group withdrew from the study because of mastectomy and moving to another city, respectively.

Table 1 presents descriptive data. Most participants aged 35-55 years. The average age of each group was 44.3 ± 9.2 (control group, mean ± SD) and 46.2 ± 8.7 (experimental group, mean ± SD).

Twenty-nine women (85.3%) in the control group and 27 (77.1%) in the experimental group were married. Most participants had secondary education in both groups (41.2% in the control group, 45.7% in the experimental group). Twenty-four patients (70.6%) in the control group and 26 (74.3%) in the experimental group were unemployed.

Many of the patients in this study had stage II breast cancer (61.8% in the control group, 60% in the experimental group).

Most participants also had axillary lymph node management (65.7% in the control group, 62.8% of the experimental group). There were no significant differences between the groups in age at diagnosis, marital status, employment, education, cancer stage, and axillary lymph node dissection.

Women in the experimental group were followed up for six weeks according to their discharge plan. Table 2 shows the comparison of before- and after-intervention QOL scores between the groups.

There was no significant difference in physical, emotional, social, spiritual domain scores or in overall QOL between the groups before the intervention. All QOL domains significantly improved in the experimental group after the intervention compared with the control group (overall QOL: 101.48 vs 46.6; physical domain: 31.8 vs 12.8; emotional domain: 38.1 vs 17.8; social domain: 24.3 vs 11.9; and spiritual domain: 7.1 vs 4.1; $P < 0.01$ for all variables).

## Discussion

The global burden of breast cancer continues to increase largely. This issue is a threat to public health throughout the world. However, breast cancer and its treatment can also result in a wide range of physical and psychological problems that exert a negative impact upon patients' QOL.

In general, length of stay in hospital after breast cancer surgery has decreased during the past decades.[9]

**Table 2.** Pre- and post-intervention scores for quality of life and its domains in the groups

| QOL domains | Time | Experimental group (n = 36) | Control group (n = 36) | P value* |
|---|---|---|---|---|
| Physical Domain | Before | 13.0 (8.2) | 10.8 (7.4) | 0.25 |
| | After | 12.8 (6.7) | 31.8 (6.8) | **<0.01** |
| Emotional Domain | Before | 44.5 (5.9) | 45.6 (4.2) | 0.40 |
| | After | 17.8 (4.9) | 38.1 (6.0) | **<0.01** |
| Social Domain | Before | 26.7 (4.5) | 27.9 (3.3) | 0.21 |
| | After | 11.9 (3.2) | 24.3 (5.1) | **<0.01** |
| Spiritual Domain | Before | 8.8 (3.9) | 9.2 (3.3) | 0.66 |
| | After | 4.1 (1.8) | 7.1 (3.2) | **<0.01** |
| Overall QOL Score | Before | 93.1 (10.4) | 93.5 ( 6.9) | 0.83 |
| | After | 46.6 (7.3) | 101.38 (11.1) | **<0.01** |
| Missing | | 1 | 2 | |

Appropriate follow-up is necessary after early discharge from hospital following surgery for breast cancer. Nursing care planning for patients with breast cancer undergoing surgery can continue after being discharged from hospital. One of the main objectives of continuity of care is to keep the relationships between patients and health care provider.[20] Early discharge from hospital in breast cancer patients needs special follow-up. This may help the patient to complete her long treatment process.

In the current study, we examined the effect of programmed discharge planning including telephone consultation and home visits after breast-conserving surgery on QOL. Before the intervention, both groups had almost the same levels of physical, emotional, social, and spiritual well-being. However, mean scores of all domains of QOL improved significantly in the experimental group 6 weeks after discharge from the hospital, indicating the effectiveness of discharge planning and continuity of care in promoting QOL of women after breast cancer surgery.

No significant changes were found in QOL of the patients in the control group at the end of the study. A reason for this could be that the patients in the control group were discharged after BCT without receiving special nursing cares except for some brochures. As a result, the QOL scores in the control group did not improve by the end of the study.

In a study of patients with coronary artery bypass graft, QOL subscales improved when the patients were provided with postoperative training and counseling sessions over 6 weeks after discharge from the hospital.[21] In other study conducted in Egypt by Mounir *et al.*, a discharge-planning program had a very significant effect on QOL and knowledge of geriatric patients with acute myocardial infarction.[22]

Our finding is especially important for directing the attention toward initiating discharge planning in hospitals. An important element in this study was that the intervention was developed to address the individual needs of the participants. In contrast to the usual patient discharge plan, which was the same for all breast cancer patients after surgery, this intervention focused on the individual's needs. We found that the focus of the discharge plan on physical, emotional, social, and spiritual well-being of individual patients was an essential factor contributing to success in this population.

In conclusion, effective discharge planning can play an essential role in improving QOL in newly diagnosed breast cancer patients after discharge from the hospital. Supporting patients during hospitalization and after discharge has a positive effect on postop-erative patient QOL.

Addressing specific patient needs through an individualized discharge plan may be particularly cost-effective as it increases the self-care knowledge and patient satisfaction and reduces hospital readmission rate and complications after discharge.[23,24]

Discharge planning is important for clinicians and women with breast cancer to optimize long-term QOL.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

**References**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA: a Cancer Journal for Clinicians. 2016;66(1):7-30.
2. Sharifian A, Pourhoseingholi MA, Emadedin M, Nejad MR, Ashtari S, *et al.* Burden of breast cancer in Iranian women is increasing. Asian Pac J Cancer Prev. 2015;16(12):5049-52.
3. Akça M, Ata A, Nayır E, Erdoğdu S, Arıcan A. Impact of Surgery Type on Quality of Life in Breast Cancer Patients. The Journal of Breast Health. 2014;10(4):222-8.
4. Baqutayan SMS. The effect of anxiety on breast cancer patients. Indian Journal of Psychological

Medicine. 2012;34(2):119.
5. Gokgoz S, Sadikoglu G, Paksoy E, Guneytepe U, Ozcakir A, *et al.* Health related quality of life among breast cancer patients: a study from Turkey. Global Journal of Health Science. 2011;3(2):140.
6. Ohsumi S, Shimozuma K, Kuroi K, Ono M, Imai H. Quality of life of breast cancer patients and types of surgery for breast cancer--current status and unresolved issues. Breast cancer (Tokyo, Japan). 2007;14(1):66-73.
7. Peerawong T, Phenwan T, Supanitwatthana S, Mahattanobon S, Kongkamol C. Breast conserving therapy and quality of life in Thai Females: a mixed methods study. Asian Pac J Cancer Prev. 2016;17(6):2917-21.
8. Kalra AD, Fisher RS, Axelrod P. Decreased length of stay and cumulative hospitalized days despite increased patient admissions and readmissions in an area of urban poverty. Journal of General Internal Medicine. 2010;25(9):930-5.
9. Downing A, Lansdown M, West RM, Thomas JD, Lawrence G, *et al.* Changes in and predictors of length of stay in hospital after surgery for breast cancer between 1997/98 and 2004/05 in two regions of England: a population-based study. BMC Health Serv Res. 2009; 9(1):202.
10. Naraynsingh V, Rambally R, Maharaj R, Dan D, Hariharan S. Early Hospital Discharge Following Breast Cancer Surgery in the West Indies: a Trinidad Study. Journal of the National Medical Association. 2011;103(8):754-6.
11. Cindy D, Philippa W, Sally R. Early Discharge Following Breast Surgery: Assessing Care, Support, And Informational Needs Of Women With Early Breast Cancer In Australia. Australian and New Zealand Journal of Surgery. 2000;70(8):569-72.
12. Napolitano F, Napolitano P, Garofalo L, Recupito M, Angelillo IF. Assessment of continuity of care among patients with multiple chronic conditions in Italy. PloS one. 2016;11(5):e0154940.
13. Adler R, Vasiliadis A, Bickell N. The relationship between continuity and patient satisfaction: a systematic review. Family practice. 2010;27(2): 171-8.
14. Bayliss EA, Ellis JL, Shoup JA, McQuillan DB, Steiner JF, *et al.* Association between Continuity of Care and Health-Related Quality of Life. The Journal of the American Board of Family Medicine. 2017;30(2):205-12.
15. Barker I, Steventon A, Deeny SR. Association between continuity of care in general practice and hospital admissions for ambulatory care sensitive conditions: cross sectional study of routinely collected, person level data. bmj. 2017;356:j84.
16. Bayliss EA, Ellis JL, Shoup JA, Zeng C, McQuillan DB, *et al.* Effect of continuity of care on hospital utilization for seniors with multiple medical conditions in an integrated health care system. The Annals of Family Medicine. 2015;13(2):123-9.
17. Shepperd S, Lannin NA, Clemson LM, McCluskey A, Cameron ID, *et al.* Discharge planning from hospital to home. The Cochrane database of systematic reviews. 2013(1):Cd000313.
18. Zhu QM, Liu J, Hu HY, Wang S. Effectiveness of nurse-led early discharge planning programmes for hospital inpatients with chronic disease or rehabilitation needs: a systematic review and meta-analysis. Journal of Clinical Nursing. 2015;24(19-20):2993-3005.
19. Nakanishi M, Niimura J, Tanoue M, Yamamura M, Hirata T, *et al.* Association between length of hospital stay and implementation of discharge planning in acute psychiatric inpatients in Japan. International journal of mental health systems. 2015;9(1):23.
20. Alazri M, Heywood P, Neal RD, Leese B. Continuity of Care: Literature review and implications. Sultan Qaboos University Medical Journal. 2007;7(3):197-206.
21. Akbari M, Celik S. The effects of discharge training and postdischarge counseling on quality of life after coronary artery bypass graft surgery. Nursing and Midwifery Studies. 2018;7(3):105-10.
22. Mounir EH, Elhameed SHA, Shrief WI, El-Safty EE. Effect of implementing a nursing discharge plan on quality of life of geriatric patients with acute myocardial infarction. IOSR Journal of Nursing and Health Science (IOSR-JNHS). 2016;5(2):20-9.
23. Mazloum SR, Heidari-Gorji MA, Bidgoli-Gholkhatmi M, Agayei N. Effectiveness of discharge-planning on physical quality of life of patients with ischemic heart disease. Int J Appl Basic Med Res. 2016;6(2):129-33.
24. Hesselink G, Zegers M, Vernooij-Dassen M, Barach P, Kalkman C, *et al.* Improving patient discharge and reducing hospital readmissions by using Intervention Mapping. BMC Health Serv Res. 2014;14:389.

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# Risk Assessment and Anesthesia Classification in Breast Cancer Surgery

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ABSTRACT

**Background:** There are various factors affecting the effectiveness of the treatment of breast cancer patients. Although the disease pathology, along with surgery and other therapeutic modalities, plays the principal role in patient outcomes, anesthesia still plays an important role in the success of treatment. This study was designed to show the effects of anesthetic plans on risk classification and assessment in breast cancer surgeries.

**Methods:** Two hundred sixty patients receiving different types of breast cancer surgery for therapeutic and reconstructive purposes were enrolled in this study. They were divided into three groups according to the anesthesia risk assessment. Group 1 consisted of low-risk patients (ASA I) who received small surgeries such as lumpectomy. Patients with intermediate risk of anesthesia (ASA II) or those who underwent breast cancer and axillary surgery with overnight admission (ASA I or II) were considered as group 2. Group 3 comprised the patients with higher risk for anesthesia (ASA class III) regardless of the surgery type or those in any ASA class who were about to undergo advanced and prolonged surgeries such as breast reconstruction with free or pedicle flaps.

**Results:** Two hundred sixty-eight surgical interventions were done in 260 patients. There were 106, 107, and 47 patients in groups 1, 2, and 3, respectively. In group 1, five patients out of 106 were admitted in the hospital for 24 hours after surgery and the remaining 101 patients were discharged from the hospital in a few hours after the operation when they were fully conscious and could tolerate the diet completely. All 107 patients in group 2 were admitted in the hospital for a few days after the operation, though the vast majority of them (98 patients) discharged from the hospital the day after surgery. In the last group, 6 out of 47 patients showed the signs of surgical complications such as partial flap ischemia in the postoperative period, mostly after TRAM or DIEP flap breast reconstruction surgery.

**Conclusion:** The findings of this study support the idea that breast surgeries can be done in an ambulatory situation with no considerable risk. In contrast, all medical and anesthetic considerations should be taken into account in more complex surgeries, especially when they are applied in high-risk patients.

## Introduction

All patients who undergo anesthesia must have a preanesthetic evaluation by an anesthesia clinician to assess the patient's perioperative risk and readiness for the planned procedure and to create an anesthetic plan.[1] Different factors can affect anesthetic outcomes, e.g., underlying systemic disease,

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especially those affecting the respiratory, cardiac, or immune system. Also, the type of disease is important in anesthesia risk of the patients. Surgery for the treatment of cancer is a good example demonstrating the importance of the type of disease in peroperative care of the patients. Cancer patients may have a higher risk in the perioperative period compared with other patients. As an example, cancer patients have higher-than-normal numbers of platelets and clotting factors in their blood. On the other hand, some treatment modalities applied in the management of breast cancer patients may increase the risk of postoperative complications such as developing a blood clot. Chemotherapy, with or without targeted therapy, and tamoxifen can increase the risk of thromboembolic events.[2,3] Research indicates that there is an association between thrombosis and malignancy.[3]

Reoperation can independently increase the risk of anesthesia. One of the most common reasons for reoperation in breast cancer patients is thrombotic events in autologous breast reconstruction. The pattern of early thrombosis is variable and is governed by the complex interplay between tumor factors, cancer treatment medications, and patient factors. The trauma of major surgery and extensive surgical dissections in the trunk may itself play animportant role in increasing thrombotic events after autologous breast reconstruction.[4]

In the modern era, with the intensive preioperative monitoring of the patients, the risk of anesthesia and preioperative complications has decreased considerably. Early postoperative mobilization and the earlier discharge of the patient from the hospital are important in the prevention of thromboembolic events and the complications.[5]

Among all cancers that need surgery, breast cancer has the most varied extent of the surgery—from small, short-duration surgeries to extensive, long operations affecting a considerable area of the trunk with microscopic vascular anastomoses.

This study was designed to show the anesthesia complications in three study groups.

## Methods

Two hundred sixty patients receiving different types of breast cancer surgery for therapeutics and reconstructive purposes were enrolled in this study from April 2017 to July 2018 in Imam Khomeini referral hospital. Patients who were candidates for surgery were referred to preoperative anesthesia clinic of the hospital as part of the surgery preparation process. They were assessed in the anesthesiology clinic and the anesthesia risk assessment sheets were filled up for every individual patient.

The patients were divided into three groups according to the protocol of the study. The study protocol was approved by the ethics committee of the Surgery Department of the university. Group 1 consisted of the patients who were planned for small breast surgeries such as lumpectomy. The patients in this group had low anesthesia risks (ASA I). Patients with intermediate risk of anesthesia (ASA II) and those who underwent breast cancer and axillary surgery, except for sentinel LN biopsy, and needed overnight admission (whether ASA I or II) were considered as group 2. Group 3 was comprised of patients who had a high risk of anesthesia (ASA III) or were going to receive advanced and prolonged surgeries such as autologous breast reconstruction regardless ASA classification (I, II, or III).

Anesthesia was induced by intravenous infusion of propofol 1% and remifentanil (total intravenous anesthesia) in 70 cases, and 95 patients were anesthetized with inhaled anesthetics sevoflurane and isoflurane with intermittent inhalation of fentanyl and sufentanil. In all the cases, muscle relaxation was induced by atracurium besilate or cisatracurium. Optimal ventilation and oxygenation along with the monitoring of blood gases, acid-base balance, and metabolic balance, i.e., blood sugar and osmolality, temperature monitoring, and avoidance of hypothermia in both groups were monitored. Depth of anesthesia was controlled using a bispectral index (BIS) monitoring system. Because of the particular importance of proper perfusion of the flaps and their vascular anastomosis, inotropic drugs and crystalloid fluids were used in some cases as required. Postoperative care including hemodynamic monitoring, urinary output record, and postoperative pain management with opiate and non-opiate drugs were done.

## Results

Two hundred sixty-eight surgical interventions were done in 260 patients. Age distribution of the patients is presented in Table1. The most frequent operation was breast-conserving therapy with axillary staging. Table 2 shows the distribution of patients in different study groups and the different types of surgeries.

There were 106, 107, and 47 patients in groups 1, 2, and 3 respectively. In group 1, five patients out of 106 stayed in the hospital for the next 24 hours after surgery, and the remaining 101 patients were discharged from the hospital within a few hours after the operation when they were fully conscious and could tolerate the PO diet completely. All the 107 patients in group 2 were admitted to the hospital for a few days after the operation, though the vast majority of them (98 patients) were discharged from the hospital the day after surgery. Three patients were hospitalized more than 1 day because of insurance and administrative issues, and the remaining 6 patients stayed at the hospital for more prolonged monitoring and analgesic medications. There were no anesthesia complications in group 1 or 2.

In the last group, 6 out of 47 patients showed signs

**Table 1.** Distribution of breast cancer patients by age

| age | N (%) |
|---|---|
| <20 | 12 (4.8%) |
| 20-30 | 27 (10.8%) |
| 31-40 | 46 (18.5%) |
| 41-50 | 81 (32.6%) |
| 51-60 | 51 (20.5%) |
| 61-70 | 19 (7.6%) |
| >70 | 12 (4.8%) |
| total | 248 (100.0%) |

**Table 2.** Surgery type and study classification

| Type of Surgery | Number of interventions (N = 268) | Study group 1* (N = 106) | Study group 2* (N = 107) | Study group 3* (N = 47) |
|---|---|---|---|---|
| Lumpectomy | 66 | 61 | 5 | 0 |
| BCS** ± OBS*** ± ASLNB | 50 | 15 | 29 | 6 |
| BCS ± OBS + ALND | 26 | 0 | 22 | 4 |
| Mastectomy ± ALND/SLNB | 40 | 0 | 27 | 13 |
| Nipple-areola complex reconstruction | 7 | 7 | 0 | 0 |
| Revision of the previous breast reconstruction | 9 | 6 | 3 | 0 |
| Mastectomy and early reconstruction with implant/expander | 28 | 0 | 25 | 3 |
| Autologous breast reconstruction ± mastectomy | 17 | 0 | 0 | 17 |
| Bilateral Mastectomy ± implant reconstruction | 9 | 0 | 4 | 5 |
| Other | 17 | 17 | 0 | 0 |

* Number of patients

** Breast-conserving surgery

*** Oncoplastic breast surgery

of surgical complications such as partial flap ischemia in the postoperative period mostly after TRAM or DIEP flap breast reconstruction surgery. Although 4 patients recovered with conservative management, two patients were reoperated and discharged after 8 to 10 days of intensive medical and anesthesia care. There was one mortality in the third group due to comorbidity in a patient who underwent mastectomy without axillary lymph node dissection. She suffered from recurrent ulcerative breast cancer lesions that were not responsive to systemic chemotherapy. She has been diagnosed with breast cancer 4 years before and treated with surgery followed by chemotherapy, radiotherapy, and hormonal therapy in 2013. Despite the use of appropriate anticoagulation in the preoperative period, the patient showed the signs of diffuse pulmonary thromboembolism, confirmed with CT angiography, which resulted in cardiac arrest. The patient was not responsive to cardiopulmonary resuscitation. Another patient had progressive respiratory distress and tachycardia on the first day after surgery. She was rechecked for flap perfusion and vascular grafts circulation, and perfusion scan was done in order to rule out diffuse emboli. The result was diffuse thromboembolism and arterial gas disturbance. The patient immediately received respiratory support treatment using anticoagulants so that her life, as well as the flap, would be saved. However, the revascularization for DIEP flap failed, and the second operation ended up with flap resection. the other cases had skin color changes and coldness due to hypoperfusion but were restored with conservative treatment.

## Discussion

Preoperative evaluation and risk assessment are essential to anesthesia management.[6-8] In this study, we categorized the patients who were candidates for any kind of breast surgery into three groups. While there was no complication in group 1 and 2, group 3 had a different outcome because the patients in this group were at a greater risk of morbidity and mortality compared with group 1 and 2. The patients were categorized in this group according to one or more of the following conditions: 1. suffering from an underlying disease which made comorbidity; 2. undergoing more complex and longer surgeries, which cause higher physiologic stress during the surgery; and 3. receiving chemotherapy before treatment. One mortality in the study group occurred in a patient with severe morbidity, although all other morbidities were in the subgroup of TRAM or DIEP flap reconstructions. For example, DIEP flap, which is used for breast reconstruction in a selected number of patients, is a prolonged procedure involving microvascular anastomoses. Furthermore, the extent of the dissection in this operation causes hypothermia in the patient. These patients are at greater risk, especially when the blood flow of the flap is questionable. The ischemia in the flap induces

cytotoxic products in the ischemic tissue, which then enter the systemic circulation and negatively affect the cardiovascular function of the patients who are already under considerable physiologic stress after a long surgery.[9] On the other hand, the tissue perfusion is crucial in these patients in the postoperative period. The mean arterial pressure should be maintained within ±20 to ±30 mm Hg of the baseline. Sufficient fluid therapy, electrolyte balance, normothermia, and correction of anemia with blood transfusion are the basic strategies to maintain the physiologic status of the patient in a stable condition and to establish flap perfusion.

In the recent decade, the indications and use of preoperative chemotherapy have been developed considerably. Because of vascular toxicity, chemotherapy leads to endothelial dysfunction, with loss of vasodilatation effects and suppressed anti-inflammatory and vascular reparative functions. Those changes exacerbate ischemia, and hypothermia worsens the situation of the patients.[10]

The extent of surgical dissection also plays an important role in increasing postoperative complications and morbidity. Dissection of the extensive surface areas of the trunk, including chest, abdomen, and -in some situations- thighs, would increase insensible loss and lead to hypothermia during surgery as well as in the postoperative period. These factors increase the risk of thrombosis in vascular grafts and diffuse thromboembolism in some cases. Sufficient oxygenation, perfect ventilation with acid-base balance during surgery, and monitoring the electrolytes are necessary.[11-14] We had two thromboembolic events in our series, and one of them led to mortality. Prophylactic anticoagulant therapy should be considered in the surgical and anesthetic plan.[15,16] There were one morbidity and one mortality in this study. These complications happened despite risk assessment and appropriate preparation of the patients. It should be always taken into consideration that these kinds of complications can be life-threatening. We recommend considering ICU care for the patients at higher risk of complications, especially when the operation is long and complex with extensive dissection.

There were no complications in groups 1 and 2. Taking enough care of the hemodynamic function and tight monitoring of ideal oxygenation helped us to avoid further complications. Six patients remained hospitalized for more than one day in group 2 because of severe pain in the site of operation. It seems that enough analgesic medication can also prevent the hospitalization of patients. Opiate and non-opiate medications should be advised meticulously in the early postoperative period.[17-19]

It seems that most breast surgeries can be done in an ambulatory situation with no considerable risk. In contrast, all medical and anesthetic considerations should be taken into account in more complex surgeries, especially when they are performed on high-risk patients

**Conflict of Interest**

The authors have none to disclose.

**References**


1. Rafiemanesh H, Salehiniya H, Lotfi Z. Breast Cancer in Iranian Woman: Incidence by Age Group, Morphology and Trends. Asian Pac J Cancer Prev. 2016;17(3):1393-7.
2. Akbari ME, Sayad S, Sayad S, Khayamzadeh M, Shojaee L, et al. Breast Cancer Status in Iran: Statistical Analysis of 3010 Cases between 1998 and 2014. International journal of breast cancer. 2017.
3. Otaghvar HA, Hosseini M, Tizmaghz A, Shabestanipour G, Noori H. A review on metastatic breast cancer in Iran. Asian Pacific Journal of Tropical Biomedicine.2015;5(6):429-33.
4. Bucknor A, Syed M, Gui G, James S. Thrombosis of the internal mammary artery during delayed autologous breast reconstruction: A manifestation of occult residual cancer. JPRAS Open. 2016;8:6-8.
5. Westbrook AJ, Buggy DJ. Anaesthesia for breast surgery. Continuing Education in Anaesthesia, Critical Care & Pain. 2003;3(5):151-4.
6. Böhmer AB, Wappler F, Zwissler B. Preoperative risk assessment—from routine tests to individualized investigation. Deutsches Ärzteblatt International. 2014;111(25):437.
7. Cohn SL, Fleisher L, Saperia GM. Evaluation of cardiac risk prior to noncardiac surgery. UpToDate, Waltham, MA Accessed. 2017;6:13-8.
8. Kramer J, Graf B, Zausig Y. Preoperative risk evaluation from the perspective of anaesthesiology. Der Chirurg; Zeitschrift fur alle Gebiete der operativen Medizen. 2011;82(11): 1037-50; quiz 51-2.
9. Eltzschig HK, Eckle T. Ischemia and reperfusion--from mechanism to translation. Nat Med. 2011;17(11):1391-401.
10. Cameron AC, Touyz RM, Lang NN. Vascular complications of cancer chemotherapy. Canadian Journal of Cardiology. 2016;32(7):852-62.
11. Mastectomy Risks 2013 [Available from: https://www.breastcancer.org/treatment/surgery/mastectomy/risks.
12. TRAM Flap Surgery Risks 2015 [Available from: https://www.breastcancer.org/treatment/surgery/reconstruction/types/autologous/tram/risks.
13. Breast reconstruction with flap surgery 2018 [Available from: https://www.mayoclinic.org/tests-procedures/breast-reconstruction-flap/about/pac-20384937.
14. Selber JC, Kurichi JE, Vega SJ, Sonnad SS,Serletti JM. Risk factors and complications in free TRAM flap breast reconstruction. Ann Plast Surg. 2006;56(5):492-7.

15. Kim EK, Eom JS, Ahn SH, Son BH, Lee TJ. The efficacy of prophylactic low-molecular-weight heparin to prevent pulmonary thromboembolism in immediate breast reconstruction using the TRAM flap. Plastic and reconstructive surgery. 2009;123(1):9-12.
16. Pan XL, Chen GX, Shao HW, Han CM, Zhang LP, et al. Effect of heparin on prevention of flap loss in microsurgical free flap transfer: a meta-analysis. PLoS One. 2014;9(4):e95111.
17. Chen C, Nguyen M-D, Bar-Meir E, Hess PA, Lin S, et al. Effects of vasopressor administration on the outcomes of microsurgical breast reconstruction. Annals of plastic surgery. 2010;65(1):28-31.
18. Hiltunen P, Palve J, Setala L, Mustonen PK, Berg L, et al. The effects of hypotension and norepinephrine on microvascular flap perfusion. J Reconstr Microsurg. 2011;27(7):419-26.
19. Jeong W, Lee S, Kim J. Meta-analysis of flap perfusion and donor site complications for breast reconstruction using pedicled versus free TRAM and DIEP flaps. The Breast. 2018;38:45-51.

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# Patient Satisfaction and Body Image Following Mastectomy, Breast-Conserving Therapy, and Mastectomy With Reconstruction: A Study in Iran

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ABSTRACT

**Background:** Breast cancer is considered a chronic disease owing to the increases in survival rate. Thus, better body image and patient satisfaction with the surgery have become more important factors to be considered when choosing the surgical approach. The aim of this study was to compare body image and patient satisfaction following three different approaches.

**Methods:** We evaluated 183 consecutive patients who had undergone three different surgeries including breast-conserving surgery (BCS), mastectomy, or mastectomy followed by reconstruction (M-R). Body image was evaluated using the BICI questionnaire, and patient satisfaction was rated using a multiple-choice question and a scale ranging from 1 to 10.

**Results:** A significantly better body image was observed in the M-R and BCS groups compared with mastectomy (P = 0.02). In body image subscale analysis, social functioning scores were higher in the M-R and BCS groups than in the mastectomy group (P = 0.01), but no differences were obtained between surgery groups in appearance dissatisfaction subscale. Patients were more satisfied with BCS than the other two surgeries (P = 0.008).

**Conclusion:** Based on the results of this study, it could be proposed that both oncoplastic BCS and implant reconstruction could provide patients with acceptable body image, while BCS could bring about better satisfaction with the surgery. Reconstruction may be an alternative for the patients to improve body image and satisfaction when BCS is not applicable.

## Introduction

Breast cancer is diagnosed at a more advanced stage in developing countries,[1, 2] and the incidence is also increasing.[1, 3] More and more patients will need breast surgery in the near future in low- and middle-income countries including I.R. Iran.[4] Nowadays, the most frequent surgery for breast cancer patients, especially at early stages, is breast-conserving surgery (BCS).[5] Although surgical approach toward breast cancer favors more conserving procedures, mastectomy is sometimes inevitable and is performed in 20%-30% of cases.[6] It was shown that survival rates were not different between mastectomy and other less invasive approaches.[7, 8] In spite of these findings, some studies demonstrated increasing rates of mastectomy,[9-12] mostly chosen by the patients.[13] This may be due to the fear of recurrence or perception of

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improved survival.[14] Breast reconstruction, a proper alternative for patients who are candidates for mastectomy, was first described in the 1970s, and multiple surgical techniques are now available,[15] making interactive decision making for reconstruction essential for patients and doctors.[16]

Why perform breast reconstruction? Improved appearance satisfaction,[17] positive effects on body image,[18] better sexual function,[19] and better long-term health[20] may be among the reasons to opt for breast reconstruction. With improved breast cancer survival rates, breast cancer is classified as a chronic disease. Thus, other factors such as quality of life, satisfaction, body image, and sexuality become important besides the treatment of the disease itself.[21,22]

Body image, which is defined as a multidimensional construct that extends beyond the evaluation of an individual's appearance[23] and entails an individual's perception of his or her body, may be altered postoperatively and affect patients' psychosocial functioning.[24]

Patient satisfaction is influenced by different factors such as overall outcome and specific breast features (size, shape, and symmetry).[25] Also, factors other than the procedure itself, including personality traits,[26] appearance investment,[27,28] pain,[29] scars, missing a nipple,[30,31] and recovery time,[32] may cause dissatisfaction.

Breast reconstruction is thought to be a coping strategy to prevail over body image changes after mastectomy.[15, 33-35] Whether patient satisfaction is higher with reconstruction or breast conservation is still a question.[36-49] The goal of this study was to compare patient satisfaction and body image of patients undergoing mastectomy, BCS, or mastectomy followed by reconstruction. To our knowledge, this is the first study to compare satisfaction and body image among these techniques in I.R. Iran.

## Methods

*Subjects*

A series of 183 consecutive patients who had undergone breast cancer surgery between August 2016 and September 2017 at Breast Cancer Research Center (BCRC; Motamed Cancer Institute, Tehran, Iran) or Imam Khomeini Hospital Complex (IKHC; Tehran, Iran) were enrolled . The decision to choose the type of surgery had been taken through an interactive process involving a multidisciplinary team of physicians and the patients, with the final decision remaining with the patient. Patients were eligible to enter the study if they had undergone mastectomy, oncoplastic BCS, or mastectomy followed by implant reconstruction (M-R, either immediate or delayed) and had finished the treatment at least 3 months before enrollment in the study. The end of the treatment was marked by the last session of radiotherapy if applicable. Otherwise, the time of completing the treatment and the start of follow-up was considered the treatment completion time. Written informed consent was obtained from each patient, and the data were collected anonymously. This was an observational study and researchers made no controlled or randomized intervention. Patients completed the Persian version of Body Image Concern Inventory (BICI) during a follow-up visit. Demographic and clinical data were extracted from patients' records in BCRC and IKHC. The local ethics committee approved all the study protocols (IR.ACECR.IBCRC.REC.1394.7).

*Questionnaire*

The BICI questionnaire is a 19-item multiple-choice, self-report instrument to evaluate the patient's body image. Patients were asked to rate each item about how often they had the described behavior or feeling on a 5-point Likert scale from 1 (never) to 5 (always). The total score ranged from 19 to 95, with higher scores corresponding to greater concern regarding body image (12 of 86). During answering the questionnaire, the patient was supervised by a research assistant to provide any additional information and make sure that no item was left unrated or rated twice. Six patients were illiterate, so a research assistant read the questions and marked the answers for them. This questionnaire consists of two subscales, namely, appearance dissatisfaction (items 1,3,5,8,9,14-19) and social functioning interference (items 2,4,6,7,10-13). The mean Spearman-Brown coefficient was calculated 0.62 and Cronbach's alpha was 0.93.[50] Sajadinejad *et al.* reported an overall Cronbach's alpha coefficient of 0.84, and alpha coefficients of 0.84 and 0.74 for appearance dissatisfaction and social functioning interference, respectively, in the Persian version of BICI.[51]

*Patient Satisfaction With the surgery*

We used a multiple-choice question to evaluate patients' satisfaction with the surgery: how satisfied are you with the cosmetic result of your operation? The patients could choose from among very satisfied, moderately, slightly, and not satisfied at all. This was used in a similar study.[33] We also asked the participants to rate their satisfaction with the surgery on a scale of 0 (least satisfaction) to 10 (most satisfaction).

*Data Analysis*

Distributions of body image and satisfaction score were not normal based on the Kolmogorov-Smirnov test. Quantitative data were presented as mean and standard deviation. The one-way ANOVA test was used to show differences in scale variable between groups. The Fisher exact test was used to represent differences in categorical variables between the three surgery groups. Statistical comparisons for body image score and satisfaction (scale score) were made using Kruskal-Wallis one-way

**Table 1.** Comparison of patients' characteristic between surgery groups

| | | BCS[a] N (%) | Mastectomy N (%) | M-R[b] N (%) | P[1] |
|---|---|---|---|---|---|
| Marital status | Married | 62 (88.6) | 56 (83.6) | 37 (88.1) | 0.669 |
| | Single[2] | 8 (11.4) | 11 (16.4) | 5 (11.9) | |
| Educational level | University | 21 (30.0) | 15 (23.1) | 16 (41.0) | 0.158 |
| | ≤ Diploma | 49 (70.0) | 50 (76.9) | 23 (59.0) | |
| Economic status[3] | Low | 6 (9.5) | 8 (11.8) | 21 (48.8) | < 0.001 |
| | Moderate | 57 (90.5) | 60 (88.2) | 22 (51.2) | |
| Employment status | Clerk | 17 (24.3) | 26 (37.1) | 11 (25.6) | 0.218 |
| | Housewife[4] | 53 (75.7) | 44 (62.9) | 32 (74.4) | |
| Age | Mean | 43.8 | 46.5 | 41.5 | 0.006 |
| | (SD) | (7.7) | (8.5) | (7.2) | |
| Time after treatment[5] | Mean | 41.3 | 50.2 | 35.3 | 0.146 |
| | (SD) | (39.0) | (44.3) | (29.3) | |

*Abbreviations: a, breast-conserving surgery; b,* mastectomy *followed by reconstruction*

ANOVA, and differences between each pair of groups were shown using the Dunn's post hoc test. We then used a multiple linear regression model to predict satisfaction score (scale score) and body image score based on surgery groups and adjusted the model for age, time after treatment, education, and socioeconomic status. Breast-conserving surgery was assumed as the reference group. We used binary logistic regression to predict satisfaction (categorical score) based on the type of surgery ("very satisfied" and "moderately" were grouped as satisfied and "slightly" and "not satisfied at all" were grouped as unsatisfied). Tests were two-tailed and P values ≤ 0.05 was considered significant. All analyses were performed on SPSS v.16.

## Results

We enrolled 183 consecutive females with breast cancer who had undergone mastectomy, breast-conserving surgery (BCS), or mastectomy followed by reconstruction (M-R) and were seen post operative as their routine follow-up. Seventy patients (38.3%) had undergone mastectomy, 70 (38.3%) BCS, and 43 (23.5%) reconstruction. The mean (SD) age of the participants at the time of surgery was 44.31 ± 8.12 years (range: 25-62 y). The mastectomy group was significantly older than the M-R group (46.5 vs 41.5 y, P = 0.005). The mean follow-up was 43.52 (Range: 3-288) months. The characteristics of the three groups are presented in Table 1.

Description: 1, P value is calculated using the Fisher exact test for parametrical variable and ANOVA for age and time after treatment; 2, includes both single and widowed patients; 3, classified according to income; 4, includes housewives and retired patients; 5, time after treatment is the time after the last treatment in month

*Body image*

Body image (BI) was evaluated with the BICI questionnaire. We report three scores for body image: total body image, appearance dissatisfaction, and

**Table 2.** Comparison of body image score and satisfaction in surgery groups

| | | BCS[a] | Mastectomy | M-R[b] | P[1] |
|---|---|---|---|---|---|
| Body image | Median ($1^{st}$, $3^{rd}$ $Q^3$) | 32 (23-41.25) | 36.5 (29-45.25) | 30 (26-42) | 0.027 |
| | Mean (SD) | 33.80 (11.93) | 38.57 (12.78) | 33.30 (11.25) | |
| | Mean rank | 84.66 | 105.30 | 82.30 | |
| Social function | Median ($1^{st}$, $3^{rd}$ Q) | 16 (11-20.25) | 17 (14-22) | 15 (11-19) | 0.013 |
| | Mean (SD) | 15.87 (6.09) | 18.21 (5.71) | 15.30 (5.54) | |
| | Mean rank | 84.36 | 106.51 | 80.81 | |
| Appearance dissatisfaction | Median ($1^{st}$, $3^{rd}$ Q) | 17 (11.75-22) | 18 (14-25) | 17 (13-23) | 0.098 |
| | Mean (SD) | 17.93 (6.82) | 20.36 (7.89) | 18.00 (6.44) | |
| | Mean rank | 84.41 | 102.61 | 87.08 | |
| Satisfaction with surgery | Median ($1^{st}$, $3^{rd}$ Q) | 10 (10-10) | 10 (8.75-10) | 10 (7.5-10) | 0.008 |
| | Mean (SD) | 9.49 (1.34) | 9.08 (1.65) | 8.89 (1.63) | |
| | Mean rank | 104.19 | 87.38 | 79.69 | |

*Abbreviations: a, breast-conserving surgery; b,* mastectomy *followed by reconstruction*

social functioning score. The mean total BI score of patients was 33.61 (18-70). The mean body image score in the BCS was 33.80 (11.93), in the mastectomy group was 38.57 (12.78), and in the M-R group was 33.30 (11.25). A significant difference was seen among the three groups in BI (P = 0.027), with the lowest BI score being seen in the mastectomy group. The difference in social functioning was also significant, with the mastectomy group scoring lower than the other two groups (P = 0.013). No statistical difference, however, was observed in appearance dissatisfaction among the three groups (P = 0.098). The information regarding body image scores is shown in Table 2. Pairwise differences are presented in Figures 2 and 3.

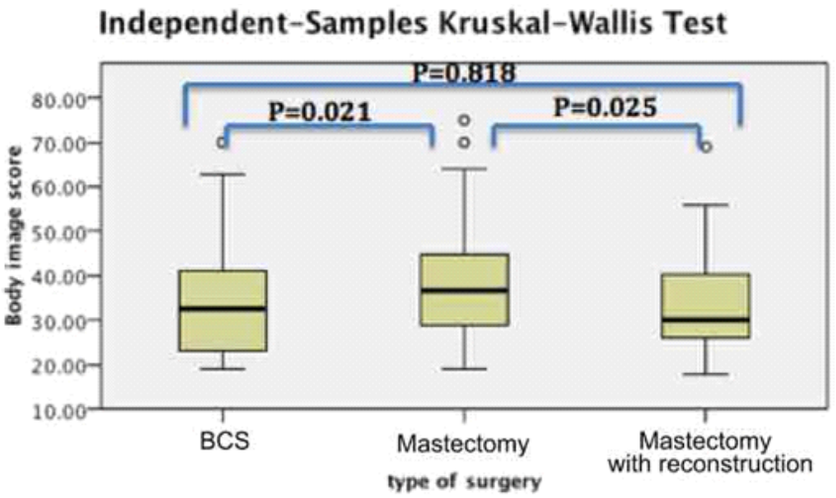


**Figure1.** Comparison of body image scores between surgery groups

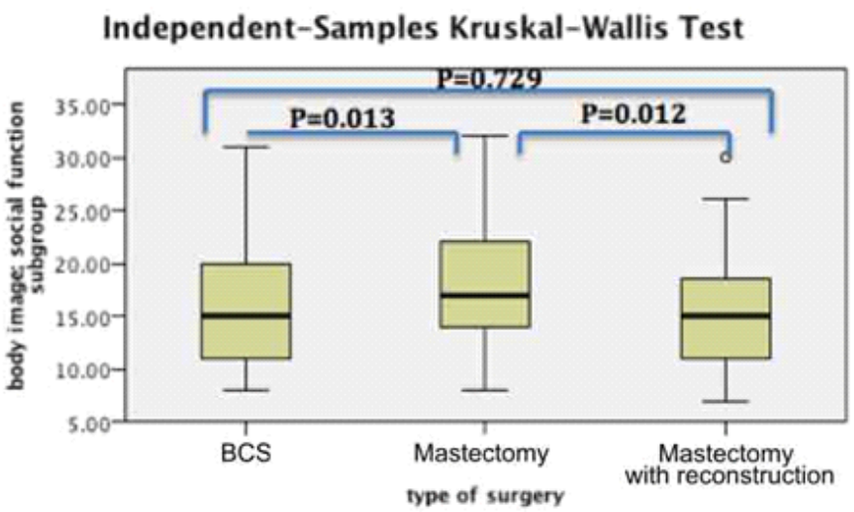


**Figure 2.** Comparison of social function score between surgery groups

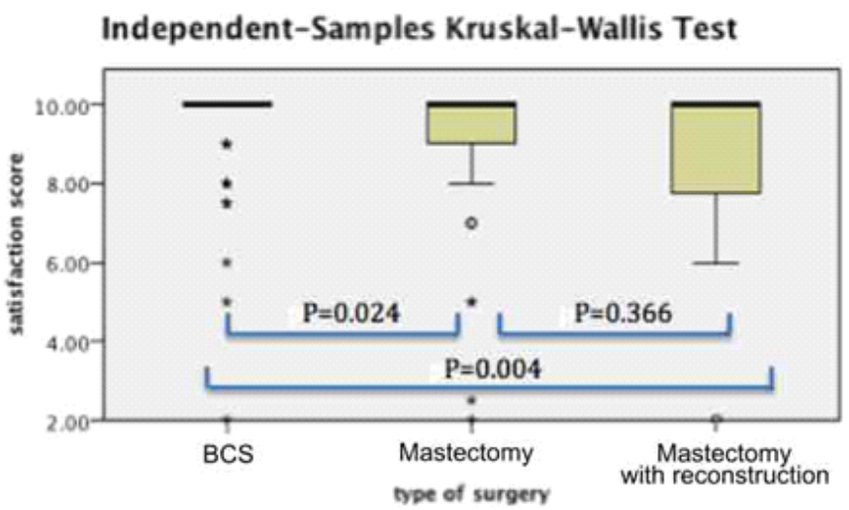


**Figure 3.** Comparison of satisfaction score between surgery groups

**Table 3.** Information regarding linear regression for predicting body image and satisfaction

| Type of surgery | Body image | Appearance dissatisfaction | Social function |
|---|---|---|---|
| Mastectomy | | | |
| B | 4.684 | 2.425 | 2.259 |
| βeta | 0.189 | 0.164 | 0.189 |
| Significance | 0.036 | 0.069 | 0.034 |
| M-R | | | |
| B | -1.806 | -0.502 | -1.303 |
| βeta | -0.064 | -0.030 | -0.096 |
| Significance | 0.514 | 0.762 | 0.324 |
| $R^2$ | 0.045 | 0.029 | 0.58 |

*Breast-conserving surgery is assumed as the reference group. The regression models are adjusted for age, marital status, education, economic status, and employment status. M-R, mastectomy followed by reconstruction.*

We then performed a multivariable linear regression and adjusted the regression for age, marital status, education, employment, and economic status. Breast-conserving surgery was assumed as the reference group. The results are shown in Table 3. The mastectomy group had significantly lower scores on body image and social function. However, scores on BI and its subscales showed no significant difference between the BCS and M-R groups.

As a supplementary analysis, we divided the patients into two groups; the first was patients who were surveyed within 6 months after the last treatment, and the second included those who were surveyed after 6 months. There was no significant difference in the mean body image score between the two groups (P = 0.30).

*Patient satisfaction*

We evaluated patient satisfaction with the surgery in two ways. First on a scale of 1-10, and second using a multiple-choice question. The satisfaction score was significantly different between the three groups (P = 0.008). That was the highest in the BCS group (9.49 ± 1.34) and the lowest in the M-R group (8.89 ± 1.63). There was no significant difference in satisfaction score between the mastectomy and M-R groups (P = 0.36). However, the difference was significant between the BCS and the other two groups (P = 0.024 for the mastectomy and P = 0.004 for the M-R group). These results are illustrated in Figure 3. In the multiple-choice question on satisfaction, there was a significant difference between the groups (P = 0.049). The BCS group had the highest number of "very satisfied" answers (91.4%), and in pairwise comparisons, there was a significant difference just between the BCS and M-R groups (91.4% vs 74.4%, P = 0.015). However, when considering "very satisfied" and "moderately" answers as satisfied and the other ones as dissatisfied, there was no significant difference in the percentage of satisfied patients between the surgery groups (BCS: 97.2%; mastectomy: 94.2%; and M-R: 95.3%). In the binary logistic model, none of the surgical techniques could increase the risk of dissatisfaction (BCS assumed reference; OR: 0.413 and 0.620; 95% CI: 0.08-2.74 and 0.08-4.46 for Mastectomy and M-R, respectively). In the supplementary analysis, there was no statistical difference in satisfaction score between patients who were surveyed within 6 months after the last treatment and those surveyed after 6 months (P = 0.32).

**Discussion**

The results of this study showed that among the three frequent surgeries for breast cancer, mastectomy was associated with the highest dysmorphic appearance concern, while BCS and mastectomy followed by reconstruction led to the same BI score. Mastectomy patients scored significantly lower on the social functioning subscale of the BICI compared with the other two groups; however, appearance dissatisfaction was not significantly different among the three groups. At the same time, BCS was associated with a greater satisfaction with surgery in comparison with mastectomy or M-R.

Breast cancer surgery approach has changed during recent years. As the number of breast cancer survivors increases, we should consider breast cancer a chronic disease. Chronic disease may potentially worsen the overall health of patients by limiting their functional status, productivity, and quality of life.[52] Thus, factors besides treatment options will bear importance for these patients, including body image and satisfaction after surgery.

The findings of our study indicated that the mastectomy group had a lower body image score compared with the BCS or M-R group. The latter groups were identical regarding BI. This finding is contrary to that of Fang *et al.*, who found that women receiving BCS had a significantly better overall body image. They declared that losing a breast could cause loss of body integrity. Thus, patients with reconstruction perceive themselves as deficient despite satisfaction with shape and appearance. Moreover, it was shown that reconstruction would contribute to a better body image than mastectomy alone, which is consistent with our finding.[15] Another study, by Al-Ghazal *et al.*, showed a significantly better body image and less psychosocial problems after BCS compared with breast reconstruction. The

rationale behind this finding was that BCS is less extensive and disfiguring, and as the most important factor in determining the type of treatment is the concern about adverse effects such as disfigurement,[53] BCS brought better body image.[33]

Previous studies comparing reconstruction and mastectomy have reported different results. Some studies found no significant differences between reconstruction and mastectomy in body image,[54-56] while others, in line with our findings, reported better body image after reconstruction.[33, 57, 58] There are several possible explanations for this inconsistency. The scale to measure body image differs widely in these studies. Some studies measure satisfaction with body image,[59,60] while others designed their own scale.[58, 61] Another explanation is that different women choose different surgery types, i.e. patients choosing reconstruction might differ from others in terms of preoperative body image and perception of their appearance.[22] Preoperative body image was a predictor of a better general body image in the long term.[62] Another important factor in body image is the conservation of nipple-areola complex, which was shown to improve body image score.[63]

Another variable that has been suggested to influence BI is the time after treatment. It was shown that if BI was evaluated during the first 6 months after treatment, the problems with body image would increase,[62, 64] although there are studies that point to the contrary. The mean follow-up time in our study was 43 months and we found no difference in body image of patients with less than <6 months versus >6 months of follow-up.

In addition, we should consider radiotherapy after BCS and the complications such as fibrosis, infection, and skin edema[65,66] as factors which may be associated with body image. The effects of age, marital status, and socioeconomic status on body image were investigated in previous studies, with conflicting results.[67] Nevertheless, we controlled for them in the linear regression model and matched the three groups based on these variables.

Our study showed that mastectomy patients had significantly low scores on overall BICI scale and social functioning subscale. However, no significant difference was observed between the surgery groups in appearance dissatisfaction. We should be aware of a particular domain of body image called body stigma, which emphasizes the loss of body integrity. Although breast appearance may be acceptable to a woman, the integrity may be considered lost. Therefore, none of these surgeries may solve this perception of integrity loss, and we saw that the reconstruction group had a better body image in the domain of body concern but not in body stigma than the mastectomy group,[15] which means losing a part of the body may be considered suffering to the patients even though they regain that lost part of the body in another shape and also with good appearance.

We found that the BCS group had the highest satisfaction with surgery. Satisfaction evaluation is believed to be completely different from the point of view of patients and physicians.[68] In our study, we just evaluated satisfaction from the patients' point of view. Although radiotherapy was reported to have the greatest impact on the cosmetic outcome, the BCS group had the highest satisfaction in our study. Our findings are consistent with a study by Al-Ghazal *et al.*[33] who performed oncoplastic BCS, which uses the reconstructive technique simultaneously. This may increase satisfaction and should be considered. A study by Kaviani *et al.* showed no differences in QoL between BCS and oncoplastic breast surgery (OBS).[69] However, OBS was considered cosmetically more acceptable in one study with acceptable oncologic outcomes.[70] Nicholson *et al.* showed higher satisfaction in patients receiving reconstruction versus BCS. They inferred that it is because the reconstruction patients are highly motivated individuals for whom cosmetic outcome is important and also the level of choice they had in the nature of their treatment.[71,72]

We didn't evaluate patients' preoperative satisfaction with their breast appearance. However, it has been shown that patients with higher satisfaction prior to surgery were more likely to be satisfied with reconstructed breast.[73]

Although the reconstruction group had the lowest satisfaction score among the three groups in our study, there was no statistically significant difference. A study by Ng *et al.* reported a significant difference in satisfaction between mastectomy and reconstruction groups.[74] A majority (64%) of their reconstructions were autologous, while all of our participants had received implant reconstruction. The type of reconstruction may account for this difference. In the binary logistic model, there were no differences between the surgery groups when dichotomizing the satisfaction outcome as satisfied or unsatisfied. The difference between this dichotomous result and the multiple-choice satisfaction measure may show that a yes/no question may not be a good scale to measure satisfaction and that further scales should be designed to measure satisfaction.

A limitation of the present study is that we did not perform a preoperative evaluation of body image and satisfaction, and preoperative status may have altered postoperative results. As we know, the grouping of patients is not randomized in such studies, and a multidisciplinary team decides the surgery approach. Thus, the use of propensity score may help to group the patients by demographic and clinical factors without randomization.[77] However, we were unable to use this score in our analysis. There are other factors apart from those we considered in our study that can influence body image. These factors, including self-esteem,[62] may be confounding, and we were unable to control them.

We cannot generalize these conclusions to all breast cancer patients. Another limitation was the lower number of reconstruction patients because of limitations for this type of surgery, such as lack of insurance coverage and higher costs.

As Conclusion, based on the results of this study, it could be proposed that BCS and mastectomy with reconstruction are associated with better body image and social functioning compared with simple mastectomy. Breast-conserving surgery could bring about better patient satisfaction with the surgery. Time is an important factor in determining satisfaction; however, evaluation of satisfaction should be made in different time points during follow-up.

**Conflict of Interest**

The authors have none to declare.

**References**


1. Harirchi I, Karbakhsh M, Montazeri A, Ebrahimi M, Jarvandi S, Zamani N, *et al.* Decreasing trend of tumor size and downstaging in breast cancer in Iran: results of a 15-year study. Eur J Cancer Prev. 2010;19(2):126-30.
2. Harirchi I, Kolahdoozan S, Karbakhsh M, Chegini N, Mohseni SM, Montazeri A, *et al.* Twenty years of breast cancer in Iran: downstaging without a formal screening program. Ann Oncol. 2011; 22(1):93-7.
3. Asadzadeh Vostakolaei F, Broeders MJ, Mousavi SM, Kiemeney LA, Verbeek AL. The effect of demographic and lifestyle changes on the burden of breast cancer in Iranian women: a projection to 2030. Breast. 2013;22(3):277-81.
4. Sinaei F, Zendehdel K, Adili M, Ardestani A, Montazeri A, Mohagheghi MA. Association Between Breast Reconstruction Surgery and Quality of Life in Iranian Breast Cancer Patients. Acta Med Iran. 2017;55(1):35-41.
5. Olfatbakhsh A, Mehrdad N, Ebrahimi M, Alavi N, Hashemi E, Kaviani A, *et al.* Evaluation of factors impacting cosmetic outcome of breast conservative surgery--a study in Iran. Asian Pac J Cancer Prev. 2015;16(6):2203-7.
6. Schmauss D, Machens HG, Harder Y. Breast Reconstruction after Mastectomy. Front Surg. 2015;2:71.
7. Veronesi U, Saccozzi R, Del Vecchio M, Banfi A, Clemente C, De Lena M, *et al.* Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. N Engl J Med. 1981;305(1):6-11.
8. Fisher B, Fisher ER, Redmond C. Ten-year results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trial evaluating the use of L-phenylalanine mustard (L-PAM) in the management of primary breast cancer. J Clin Oncol. 1986;4(6):929-41.
9. Gomez SL, Lichtensztajn D, Kurian AW, Telli ML, Chang ET, Keegan TH, *et al.* Increasing mastectomy rates for early-stage breast cancer? Population-based trends from California. J Clin Oncol. 2010;28(10):e155-7; author reply e8.
10. Mahmood U, Hanlon AL, Koshy M, Buras R, Chumsri S, Tkaczuk KH, *et al.* Increasing national mastectomy rates for the treatment of early stage breast cancer. Ann Surg Oncol. 2013;20(5):1436-43.
11. Katipamula R, Degnim AC, Hoskin T, Boughey JC, Loprinzi C, Grant CS, *et al.* Trends in mastectomy rates at the Mayo Clinic Rochester: effect of surgical year and preoperative magnetic resonance imaging. J Clin Oncol. 2009;27(25):4082-8.
12. Tuttle TM, Habermann EB, Grund EH, Morris TJ, Virnig BA. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. J Clin Oncol. 2007;25(33):5203-9.
13. Morrow M, Jagsi R, Alderman AK, Griggs JJ, Hawley ST, Hamilton AS, *et al.* Surgeon recommendations and receipt of mastectomy for treatment of breast cancer. JAMA. 2009;302 (14):1551-6.
14. Huang J, Chagpar AB. Quality of Life and Body Image as a Function of Time from Mastectomy. Ann Surg Oncol. 2018;25(10):3044-51.
15. Fang SY, Shu BC, Chang YJ. The effect of breast reconstruction surgery on body image among women after mastectomy: a meta-analysis. Breast Cancer Res Treat. 2013;137(1):13-21.
16. Mayor S. NICE updates guidance on early and advanced breast cancer. BMJ. 2009;338:b815.
17. Oiz B. [Breast reconstruction and psychological benefit]. An Sist Sanit Navar. 2005;28 Suppl 2:19-26.
18. Wilkins EG, Cederna PS, Lowery JC, Davis JA, Kim HM, Roth RS, *et al.* Prospective analysis of psychosocial outcomes in breast reconstruction: one-year postoperative results from the Michigan Breast Reconstruction Outcome Study. Plast Reconstr Surg. 2000;106(5):1014-25; discussion 26-7.
19. Filiberti A, Tamburini M, Murru L, Lovo GF, Ventafridda V, Arioli N, *et al.* Psychologic effects and esthetic results of breast reconstruction after mastectomy. Tumori. 1986;72(6):585-8.
20. Atisha D, Alderman AK, Lowery JC, Kuhn LE, Davis J, Wilkins EG. Prospective analysis of long-term psychosocial outcomes in breast reconstruction: two-year postoperative results from the Michigan Breast Reconstruction Outcome Study. Ann Surg. 2008;247(6):1019-28.
21. Golshan M, Cirrincione CT, Sikov WM, Berry DA, Jasinski S, Weisberg TF, *et al.* Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation.

rates: surgical results from CALGB 40603 (Alliance). Ann Surg. 2015;262(3):434-9; discussion 8-9.Outcomes Study. Ann Surg2008;247(6):1019-28.
22. Lee C, Sunu C, Pignone M. Patient-reported outcomes of breast reconstruction after mastectomy: a systematic review. J Am Coll Surg. 2009;209(1):123-33.
23. Pruzinsky T. Enhancing quality of life in medical populations: a vision for body image assessment and rehabilitation as standards of care. Body Image. 2004;1(1):71-81.
24. Fingeret MC, Nipomnick SW, Crosby MA, Reece GP. Developing a theoretical framework to illustrate associations among patient satisfaction, body image and quality of life for women undergoing breast reconstruction. Cancer Treat Rev. 2013;39(6):673-81.
25. Klassen AF, Pusic AL, Scott A, Klok J, Cano SJ. Satisfaction and quality of life in women who undergo breast surgery: a qualitative study. BMC Womens Health. 2009;9:11.
26. Urcuyo KR, Boyers AE, Carver CS, Antoni MH. Finding benefit in breast cancer: relations with personality, coping, and concurrent well-being. Psychol Health. Psychol Health. 2005;2(20):175-92.
27. Carver CS, Pozo-Kaderman C, Price AA, Noriega V, Harris SD, Derhagopian RP, *et al.* Concern about aspects of body image and adjustment to early stage breast cancer. Pschycosom Med.1998; 60(2):168-74.
28. Moreira H, Silva S, Canavarro MC. The role of appearance investment in the adjustment of women with breast cancer. Psychooncology. 2010;19(9):959-66.
29. Kulkarni AR, Pusic AL, Hamill JB, Kim HM, Qi J, Wilkins EG, *et al.* Factors Associated with Acute Postoperative Pain Following Breast Reconstruction. JPRAS Open. 2017;11:1-13.
30. Gopie JP, Timman R, Hilhorst MT, Hofer SO, Mureau MA, Tibben A. The short-term psychological impact of complications after breast reconstruction. Psychooncology. 2013;22(2):290-8.
31. Andrade WN, Baxter N, Semple JL. Clinical determinants of patient satisfaction with breast reconstruction. Plast Reconstr Surg. 2001; 107(1):46-54.
32. Murray CD, Turner A, Rehan C, Kovacs T. Satisfaction following immediate breast reconstruction: Experiences in the early post-operative stage. Br J Health Psychol. 2015; 20(3):579-93.
33. Al-Ghazal SK, Fallowfield L, Blamey RW. Comparison of psychological aspects and patient satisfaction following breast conserving surgery, simple mastectomy and breast reconstruction. Eur J Cancer. 2000;36(15):1938-43.
34. Gopie JP, ter Kuile MM, Timman R, Mureau MA, Tibben A. Impact of delayed implant and DIEP flap breast reconstruction on body image and sexual satisfaction: a prospective follow-up study. Psychooncology. 2014;23(1):100-7.
35. Zhong T, Hu J, Bagher S, Vo A, O'Neill AC, Butler K, *et al.* A Comparison of Psychological Response, Body Image, Sexuality, and Quality of Life between Immediate and Delayed Autologous Tissue Breast Reconstruction: A Prospective Long-Term Outcome Study. Plast Reconstr Surg. 2016;138(4):772-80.
36. Beckmann J, Johansen L, Richardt C, Blichert-Toft M. Psychological reactions in younger women operated on for breast cancer. Amputation versus resection of the breast with special reference to body-image, sexual identity and sexual function. Dan Med Bull. 1983;30 Suppl 2:10-3.
37. Steinberg MD, Juliano MA, Wise L. Psychological outcome of lumpectomy versus mastectomy in the treatment of breast cancer. Am J Psychiatry. 1985;142(1):34-9.
38. Ganz PA, Lee JJ, Sim MS, Polinsky ML, Schag CA. Exploring the influence of multiple variables on the relationship of age to quality of life in women with breast cancer. J Clin Epidemiol. 1992;45(5):473-85.
39. Yurek D, Farrar W, Andersen BL. Breast cancer surgery: comparing surgical groups and determining individual differences in postoperative sexuality and body change stress. J Consult Clin Psychol. 2000;68(4):697-709.
40. Schain WS, d'Angelo TM, Dunn ME, Lichter AS, Pierce LJ. Mastectomy versus conservative surgery and radiation therapy. Psychosocial consequences. Cancer. 1994;73(4):1221-8.
41. Taylor KL, Lamdan RM, Siegel JE, Shelby R, Hrywna M, Moran-Klimi K. Treatment regimen, sexual attractiveness concerns and psychological adjustment among African American breast cancer patients. Psychooncology. 2002;11(6):505-17.
42. Arora NK, Gustafson DH, Hawkins RP, McTavish F, Cella DF, Pingree S, *et al.* Impact of surgery and chemotherapy on the quality of life of younger women with breast carcinoma: a prospective study. Cancer. 2001;92(5):1288-98.
43. Polivy J. Psychological effects of mastectomy on a woman's feminine self-concept. J Nerv Ment Dis. 1977;164(2):77-87.
44. Wolberg WH, Romsaas EP, Tanner MA, Malec JF. Psychosexual adaptation to breast cancer surgery. Cancer. 1989;63(8):1645-55.
45. Ashcroft JJ, Leinster SJ, Slade PD. Breast cancer--patient choice of treatment: preliminary communication. J R Soc Med. 1985;78(1):43-6.
46. Penman DT, Bloom JR, Fotopoulos S, Cook MR, Holland JC, Gates C, *et al.* The impact of mastectomy on self-concept and social function: a combined cross-sectional and longitudinal study with comparison groups. Women Health. 1986;11(3-4):101-30.

47. Goldberg JA, Scott RN, Davidson PM, Murray GD, Stallard S, George WD, *et al.* Psychological morbidity in the first year after breast surgery. Eur J Surg Oncol. 1992;18(4):327-31.
48. Holmberg L, Omne-Ponten M, Burns T, Adami HO, Bergstrom R. Psychosocial adjustment after mastectomy and breast-conserving treatment. Cancer. 1989;64(4):969-74.
49. Lee MS, Love SB, Mitchell JB, Parker EM, Rubens RD, Watson JP, *et al.* Mastectomy or conservation for early breast cancer: psychological morbidity. Eur J Cancer. 1992; 28A(8-9):1340-4.
50. Littleton HL, Axsom D, Pury CL. Development of the body image concern inventory. Behav Res Ther. 2005;43(2):229-41.
51. Mohammadi N, Sajadinejad MS. The evaluation of psychometric properties of Body Image Concern Inventory and examination of a model about the relationship between body mass index, body image dissatisfaction and self-esteem in adolescent girls. Psychological Studies. 2007; 3:85-101.
52.Devins GM, Binik YM, Hutchinson TA, Hollomby DJ, Barre PE, Guttmann RD. The emotional impact of end-stage renal disease: importance of patients' perception of intrusiveness and control. Int J Psychiatry Med. 1983;13(4):327-43.
53. Margolis GJ, Goodman RL, Rubin A, Pajac TF. Psychological factors in the choice of treatment for breast cancer. Psychosomatics. 1989;30(2):192-7.
54. Noyan MA, Sertoz OO, Elbi H, Kayar R, Yilmaz R. Variables affecting patient satisfaction in breast surgery: a cross-sectional sample of Turkish women with breast cancer. Int J Psychiatry Med. 2006;36(3):299-313.
55. Rowland JH, Desmond KA, Meyerowitz BE, Belin TR, Wyatt GE, Ganz PA. Role of breast reconstructive surgery in physical and emotional outcomes among breast cancer survivors. J Natl Cancer Inst. 2000;92(17):1422-9.
56.Harcourt DM, Rumsey NJ, Ambler NR, Cawthorn SJ, Reid CD, Maddox PR, *et al.* The psychological effect of mastectomy with or without breast reconstruction: a prospective, multicenter study. Plast Reconstr Surg. 2003; 111(3):1060-8.
57. Janz NK, Mujahid M, Lantz PM, Fagerlin A, Salem B, Morrow M, *et al.* Population-based study of the relationship of treatment and sociodemographics on quality of life for early stage breast cancer. Qual Life Res. 2005; 14(6):1467-79.
58. Pusic A, Thompson TA, Kerrigan CL, Sargeant R, Slezak S, Chang BW, *et al.* Surgical options for the early-stage breast cancer: factors associated with patient choice and postoperative quality of life. Plast Reconstr Surg. 1999;104(5): 1325-33.
59. Mock V. Body image in women treated for breast cancer. Nurs Res. 1993;42(3):153-7.
60. Reaby LL, Hort LK, Vandervord J. Body image, self-concept, and self-esteem in women who had a mastectomy and either wore an external breast prosthesis or had breast reconstruction andwomen who had not experienced mastectomy. Health Care Women Int. 1994;15(5):361-75.
61. Cocquyt VF, Blondeel PN, Depypere HT, Van De Sijpe KA, Daems KK, Monstrey SJ, *et al.* Better cosmetic results and comparable quality of life after skin-sparing mastectomy and immediate autologous breast reconstruction compared to breast conservative treatment. Br J Plast Surg. 2003;56(5):462-70.
62.den Heijer M, Seynaeve C, Timman R, Duivenvoorden HJ, Vanheusden K, Tilanus-Linthorst M, *et al.* Body image and psychological distress after prophylactic mastectomy and breast reconstruction in genetically predisposed women: a prospective long-term follow-up study. Eur J Cancer. 2012;48(9):1263-8.
63. Levy J, Bosc R, Warren N, Rebecca S, Dao TH, Hersant B, *et al.* Nipple-Sparing Mastectomy and Immediate Breast Reconstruction With a Deep Inferior Epigastric Perforator Flap: A Study of Patient Satisfaction. Ann Plast Surg. 2018;80(6):639-43.
64. Brandberg Y, Sandelin K, Erikson S, Jurell G, Liljegren A, Lindblom A, *et al.* Psychological reactions, quality of life, and body image after bilateral prophylactic mastectomy in women at high risk for breast cancer: a prospective 1-year follow-up study. J Clin Oncol. 2008;26(24):3943-9.
65.Gross E, Hannoun-Levi JM, Rouanet P, Houvenaeghel G, Teissier E, Ellis S, *et al.* [Evaluation of immediate breast reconstruction and radiotherapy: factors associated with complications]. Cancer Radiother. 2010;14(8): 704-10.
66.Carnevale A, Scaringi C, Scalabrino G, Campanella B, Osti MF, De Sanctis V, *et al.* Radiation therapy after breast reconstruction: outcomes, complications, and patient satisfaction. Radiol Med. 2013;118(7):1240-50.
67. Hopwood P. The assessment of body image in cancer patients. Eur J Cancer. 1993;29A(2):276-81.
68. Juhl AA, Christensen S, Zachariae R, Damsgaard TE. Unilateral breast reconstruction after mastectomy - patient satisfaction, aesthetic outcome and quality of life. Acta Oncol. 2017;56(2):225-31.
69. Kaviani A, Mir M, Daryani A, Bonyadi M, Ebrahimi M, Neishaboury M, *et al.* Quality of Life after Breast Conservation versus Oncoplastic Surgery. Archives of Breast Cancer. 2015;2(2).
70. Kaviani A, Safavi A, Mohammadzadeh N, Jamei K, Ansari-Damavandi M, Salmon RJ.

Oncoplastic surgery in breast conservation: a prospective evaluation of the patients, techniques, and oncologic outcomes. Am J Surg. 2014;208(5):727-34.
71. Deadman JM, Leinster SJ, Owens RG, Dewey ME, Slade PD. Taking responsibility for cancer treatment. So6c Sci Med. 2001;53(5):669-77.
72. Nicholson RM, Leinster S, Sassoon EM. A comparison of the cosmetic and psychological outcome of breast reconstruction, breast conserving surgery and mastectomy without reconstruction. Breast. 2007;16(4):396-410.
73. Schmidt JL, Wetzel CM, Lange KW, Heine N, Ortmann O. Patients' experience of breast reconstruction after mastectomy and its influence on postoperative satisfaction. Arch Gynecol Obstet. 2017;296(4):827-34.
74. Ng SK, Hare RM, Kuang RJ, Smith KM, Brown BJ, Hunter-Smith DJ. Breast Reconstruction Post Mastectomy: Patient Satisfaction and Decision Making. Ann Plast Surg. 2016;76(6): 640-4.
76. Gopie JP, Mureau MA, Seynaeve C, Ter Kuile MM, Menke-Pluymers MB, Timman R, *et al.* Body image issues after bilateral prophylactic mastectomy with breast reconstruction in healthy women at risk for hereditary breast cancer. Fam Cancer. 2013;12(3):479-87.
77. Dauplat J, Kwiatkowski F, Rouanet P, Delay E, Clough K, Verhaeghe JL, *et al.* Quality of life after mastectomy with or without immediate breast reconstruction. Br J Surg. 2017;104(9): 1197-206.

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# The Relationship Between Health Literacy and Patient Participation in Medical Decision Making Among Breast Cancer Patients

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ABSTRACT

**Background:** Patient participation in medical decisions is essential and requires sufficient knowledge and awareness. Thus, the aim of this study was to investigate the relationship between health literacy and the participation of breast cancer patients in their medical decisions in Shiraz, Iran.

**Methods:** This was a descriptive-analytical study conducted on 196 women with breast cancer in 2016-2017. Data were collected using the standardized Health Literacy for Iranian Adults (HELIA) and the Decisional Conflict Scale. The data were analyzed using descriptive statistics and inferential methods (t test, Pearson correlation, ANOVA, and Kruskal-Wallis) on SPSS 21.

**Results:** The mean age of participants was 46.7 years. Their health literacy was inadequate (18.7) and their decisional conflict was average (51.79). There was also an inverse and significant relationship between health literacy and decisional conflict ($P < 0.001$, $r = -0.81$)

**Conclusion:** Increasing health literacy could reduce decisional conflict. It requires training individuals be able to access credible and reliable sources of information. This training can be provided through doctors, treatment staff, and public and social media.

## Introduction

Clinical governance is one of the tools used to improve the quality of health care in different countries. One of the goals of establishing clinical governance is to promote the participation of patients and communities in therapeutic processes.[1] In fact, patient participation is considered a legal right and an international standard for health care.[2] During the past 30 years, the concept of patient participation in medical decision making has developed from informed consent to the exchange of information between physicians and patients, which not only includes the benefits and risks of treatment options, but also includes the preferences and values of patients and physicians.[3] Recently, patient participation has become a necessary policy in many countries and health systems all over the world.[4]

Collaborative decision making is considered the key to the quality of patient-centered care, resulting in better health outcomes for patients.[5] In general, the goal of informed and coordinated participation of patients and physicians in treatment decision making is to involve the patients and physicians in the knowledge, values, preferences, and intentions of each other. As a result, the decisions taken will be more consistent with the patients' values, conditions, and preferences, which in turn may increase the quality of life and access to health objectives.

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Several studies have also shown that shared decision making would lead to a more effective physician-patient relationship and a common understanding of the treatment objectives, as well as reducing the decisional conflicts,[3] and bringing about better psychological adjustment, and higher levels of satisfaction.[6] Cuevas *et al.* mentioned the lower costs of treatment as one of the benefits of patient participation in decision making.[7] Furthermore, patient participation in decision making was reported to increase their commitment to health behaviors.[8] Ghiasvandyan *et al.*, too, concluded that the participation of patients in medical decision making would improve their awareness and confidence to start their treatment.[9]

In this regard, behavioral changes through health literacy to have an active role in medical decision making are possible.[10] In fact, health literacy is a prerequisite for making informed health care decisions.[11] The World Health Organization considers health literacy a major health determinant.[12] By definition, health literacy is a broad range of cognitive and social skills that empower people to accept, understand, and use information to enhance their health, well-being, and participation in their health-care decision making.[5,13] Hence, health literacy is one of the influential factors in guiding patients in terms of the information they need for their health care. Besides, since health literacy addresses all aspects of health care such as prevention, screening, diagnosis, and treatment, it is considered the basis for health care delivery systems.[14] According to reports, nearly 80 million Americans do not have adequate health literacy.[15] In Iran, according to the results of the national survey of 20 571 Iranian citizens, about half of the people had limited health literacy.[16]

On the other hand, the level of health literacy can affect cancer outcomes.[17] Today, the cause of over 12% of deaths in all countries is cancer.[18] Iran has an annual incidence of 70 000 new cancer cases, which can potentially double in the next two decades due to aging.[19] Of these cancers, breast cancer is the most common one and the second leading cause of death in women.[20, 21] According to the World Health Organization, this rate is increasing by 1.8% to 2%.[19] In Iran, breast cancer is the most common cancer in women, with an incidence rate increase of about 28.3 new cases per 100 000 women a year.[22] Considering the issues raised and insufficient studies in this field in Iran, the present study aimed to investigate the relationship between health literacy and the rate of patient participation in medical decision making among patients with breast cancer in the city of Shiraz, Iran, in 2016-2017.

## Methods

*Participants*

This was a descriptive-analytical study with a cross-sectional design that was conducted on women with breast cancer in Shiraz, Iran, in 2016-2017. The inclusion criteria were being 18 to 65 years old, being a newly diagnosed case, having the ability to communicate (lack of mental, hearing, visual, or speech disorders), willing to answer the questions, giving informed consent to participate in the study, and having visit with their doctors on how to treat their disease. At first, because of lack of similar articles, a sample of 40 cases was considered as a pilot. Then, based on a type I error of 0.05, a type II error of 0.2, and the correlation between the patients' health literacy and participation in their medical decisions obtained from the pilot study ($r = 0.122$), the sample size was determined to be 160 patients. The calculated sample size was increased to 196 to account for an estimated non-response rate of 20%. Due to the lack of cooperation of the private sector, the patients were selected only from public centers. There were two public centers dealing with breast cancer counseling and treatment in the city of Shiraz. One of the centers was excluded from the study because it provided only outpatient visits, and the patients would be referred to another center if the diagnosis of breast cancer was confirmed. The other center was for hospitalized patients where surgeries were done two days a week. Using the inclusion criteria, three trained interviewers interviewed the patients one day prior to their surgery and completed the questionnaire.

*Instruments*

Health literacy was measured using the Health Literacy for Iranian Adults (HELIA) questionnaire. The questionnaire consists of two sections including demographic characteristics and 33 questions in five domains of reading (4 questions), access (6 questions), comprehension (7 questions), assessment (7 questions), and decision making (12 questions). The validity and reliability of the questionnaire were determined by Montazeri et al (Cronbach's alpha coefficient range: 0.72 to 0.89).[23] Izadirad and Zareban, too, evaluated its validity and reliability (Cronbach's alpha coefficient: 0.92).[24] The items were rated on a 5-point scale (1 = totally disagree, and 5 = totally agree). The scores were then transferred to 0-100 scale so that scores 0-50 indicated inadequate health literacy, 50.1-66 indicated almost inadequate health literacy, 66.1-84 represented sufficient health literacy, and 84.1-100 represented excellent health literacy.

Patient participation in medical decision making was evaluated using the Decisional Conflict Scale, which has been identified in various studies as a standard for assessment of the uncertainty and factors influencing the decision-making process in health care.[25, 26] The questionnaire measures an individual's uncertainty about a course of action and the factors contributing to uncertainty through 16 questions on a scale from 0 (totally agree) to 4

(totally disagree). The uncertainty factors comprise five groups: a feeling of awareness, individual values, support, uncertainty, and effective decision making. Total score ranges from 0 (the highest certainty about the best decision taken) to 100 (the highest uncertainty about the best decision taken). The questionnaire was translated and validated by Mousavizadeh *et al.*, with the Cronbach's alpha being 0.94.[9]

*Data Analysis*

Descriptive statistics (percentage, frequency distribution, mean, and standard deviation) were used to provide a summary of participant characteristics, and nonparametric (Kruskal-Wallis) and parametric (t test, ANOVA, and Pearson correlation) tests were used to analyze the differences between groups. The nonparametric test was used if the data on a particular variable had not a normal distribution. Analyses were performed using SPSS 21.

## Results

*Demographic Information*

A total of 196 breast cancer patients with the mean age of 46.7 ± 9.92 years were enrolled in the study. In terms of education, 37.5% had elementary, 30.5% had a middle school degree, 18.5% had a high school certificate, and 13.5% had a university education. The majority of patients (81%) were housewives, with retired and employed patients making up the remaining 6.5% and 12.5% of the study sample, respectively. Regarding the access of the study population to the sources of health and illness information, 36% got information from doctors and health-care staff, 21.4% used radio and television, 17% used the Internet, 12.46% got information from their friends and acquaintances, 6.07% used booklets, pamphlets, and brochures, 3.8% used newspapers and magazines, and 0.32% used the interactive voice dialer (IVR)(a technology that allows a computer to interact with humans through the use of voice and DTMF (Dual-tone multi-frequency signaling) tones input via a keypad), and 2.88% did not know how to get the information they needed.

*Health Literacy*

The mean health literacy score of the patients under study was 18.70 ± 7.34. The mean scores on health literacy subscales were 33.45 ± 14.5 (decision making), 19.59 ± 9.8 (comprehension), 16.76 ± 7.1 (access), 11.72 ± 5.5 (reading), and 11.54 ± 4.7 (evaluation). The results of the Kruskal-Wallis test did not show a significant relationship between health literacy and education levels (P = 0.06). Furthermore, the ANOVA test did not show any significant relationships between health literacy and employment status (P = 0.8), the t test showed that general health literacy had no significant relationship with information-gathering methods (P = 0.98). No significant relationship was observed between health literacy and age (P = 0.09).

*Decisional Conflict*

The overall mean decisional conflict score was 51.79 ± 29.1, with the scores on subscales being 53.72 ± 32.1 (uncertainty), 53.3 ± 34.9 (support), 52.77 ± 35.8 (effective decision making), 50.67 ± 30.7 (value), and 49.64 ± 29.0 (awareness). There was no significant relationship between decisional conflict and age, job, education, and information-gathering methods (P = 0.3, P = 0.81, P = 0.95, P = 0.3).

*Health Literacy and Decisional Conflict*

There was a significant inverse relationship between health literacy and decisional conflict in general (r = -0.81, P < 0.001). Pairwise analyses of the correlations between the dimensions of health literacy and decisional conflict are shown in Table 1. A similar inverse relationship was observed for each pairwise comparison at a 99% confidence level.

## Discussion

The main objective of the present study was to investigate the relationship between health literacy and the rate of participation in one's medical decisions making among breast cancer patients in Shiraz, Iran. The results of this study showed an inadequate level of health literacy in the women with breast cancer (18.70), which was consistent with the results of a study by Sahrayi *et al.* on adults in Karaj (24.2%)[27] and that of Izadirad and Zareban carried

**Table 1.** Correlations between health literacy dimensions and decisional conflict dimensions

| Health literacy / Decisional conflict | Reading | Access | Comprehension | Assessment | Decision making and behavior |
|---|---|---|---|---|---|
| Awareness | R = -0.661a | R = -0.534a | R = -0.66a | R = -0.549a | R = -0.594a |
| Personal values | R = -0.655a | R = -0.536a | R = -0.726a | R = -0.513a | R = -0.668a |
| Support | R = -.0678a | R = -0.516a | R = -0.787a | R = -0.504a | R = -0.724a |
| Uncertainty | R = -0.665a | R = -0.516a | R = -0.771a | R = -0.554a | R = -0.723a |
| Effective decision making | R = -0.696a | R = -0.537a | R = -0.825a | R = -0.553a | R = -0.793a |

*P < 0.001*

out in Baluchestan (34%).[24] However, it was inconsistent with the results of a research by Haghighi *et al.* on women with breast cancer in Tehran (38.8%).[28] The reason for this inconsistency can be the difference in the populations studied. The participants in our study were newly diagnosed patients, while in the study of Haghighi *et al.*,[28] the participants were patients living with breast cancer and were more likely to have obtained knowledge during the treatment period.

In the present study, nearly one-third of the participants received their health and disease information from doctors and health-care staff (36%), and through radio and television (21%). In the studies by Sahrayi *et al.* and Izadirad and Zareban, radio and television (42.5% and 19%) and health-care staff (37% and 49.8%) were the most important sources of getting health information, which is consistent with the results of the present study.[24,27] In a systematic review, Hur *et al.* concluded that learning and health literacy could be improved by using multimedia tools and teaching in a simple language.[29] Another study suggested that a simple and understandable language used by the providers could be useful for patients' effective communications and better understanding.[30] The aforementioned issues indicate the importance of knowledge and awareness of the providers about health information and how to transfer them to patients, and also the importance of the mass media. In this regard, policy makers can plan to increase health literacy through the use of popular technologies.

The decisional conflict was reported at a moderate level (51.79) in this study, indicating the patients' uncertainty about their medical decision making. In a study by Essink *et al.* in 2016 to assess decision making knowledge and awareness of the patients with colon cancer, a low decisional conflict was reported (21.12).[31] Besides, in the study by Jukkala *et al.* in 2013 on women with breast cancer, decisional conflict was 48.5% and at a moderate level,[32] which is consistent with the present study. The conflict and hesitation could be due to the patients' uncertainty about their best medical decisions.[32] Uncertainty might also be due to the patients' inadequate awareness and knowledge of the disease and therapies, and it is recommended that service providers spend more time counseling their patients in order to reduce this uncertainty.

Finally, there was an inverse and significant relationship between decisional conflict and health literacy ($r = -0.81$, $P < 0.001$), which is consistent with the study done by Tagai on patients with colon cancer ($P < 0.001$),[26] the one by Doyle *et al.* on patients with AIDS ($P = 0.05$),[33] that of Essink *et al.* in colon cancer screening ($P = 0.05$), and also the study by Jukkala *et al.* on women with breast cancer ($P < 0.001$).[32]

High levels of uncertainty and concern for decision making can be caused by inadequate health literacy.[34] Low health literacy can be due to the patients' inadequate knowledge of their disease. This inadequate knowledge might lead to uncertainty in the patients and they might feel that the treatment was imposed on them and was not based on their preferences. In fact, they may think they made a useless choice that would ultimately lead to regret over the decision.[35]

Given that low health literacy causes conflict and uncertainty in patient decision making, it can be concluded that factors such as low ability to read, understand, and evaluate health information, the lack of access to reliable information, the lack of adequate knowledge of the benefits, risks, and side effects of the treatment, a perceived lack of support or the feeling of being under pressure, and the lack of attention paid to the patients' personal preferences and values are matters of concern and regret of the patients about their choice. Therefore, health literacy increases the ability of the patient, and subsequently the patient participation in decision making.[36] Hence, in order to increase the patients' health literacy and reduce their doubts in decision making, and considering patient-centeredness of the health care, it is suggested that required information along with methods of access to reliable information be provided to patients by the medical staff, and that patients be counseled about the disease and the treatment methods in a simple and understandable language, especially when there are more than one choice. This can lead to a better patient-doctor communication and mutual trust between them, increased patient commitment to health-care and treatment outcomes, increased quality of life, increased satisfaction, reduced decisional conflict, and reduced costs of the health care system.

The present study showed that increased health literacy could lead to reduced decisional conflict. Given the low level of health literacy observed in this study and the role of health-care providers and media in providing health information, it is suggested that these sectors should receive incentives to provide more comprehensive information to patients. Also, the use of mass media programs a simple and understandable way can help.

One limitation of this research was the lack of acess to patients in private clinics, which reduced the study generalizability to some extent. It is suggested to consider the socioeconomic conditions that can affect patient decision-making, and take into account the use of educational packages and assess the patients' health literacy before and after using the packages.

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**Conflict of Interests**

The authors declare no competing interest.

**References**


1. ebrahimpour h, khalili h, pourali M. The Relationship between Clinical Governance and Hospital Performance: Evidence of Ardabil. Hospital. 2014;13(3):59-68.
2. Rafii F, M. Soleimani, N. Seyed-Fatemi. Concept Analysis of Participation of Patient with Chronic Disease: Use of Hybrid Model. Iran Journal of Nursing. 2010;23(67):35-48.
3. Gionfriddo MR, Leppin AL, Brito JP, LeBlanc A, Boehmer KR, *et al.* A systematic review of shared decision making interventions in chronic conditions: a review protocol. Systematic reviews. 2014;3(1):38.
4. Vahdat S, Hamzehgardeshi L, Hessam S, Hamzehgardeshi Z. Patient involvement in health care decision making: A review. Iranian Red Crescent Medical Journal. 2014;1 6(1) :e12454.
5. Smith SK, Nutbeam D, McCaffery KJ. Insights into the concept and measurement of health literacy from a study of shared decision-making in a low literacy population. Journal of health psychology. 2013,18(8):1011-22.
6. Tariman JD, Doorenbos A, Schepp KG, Singhal S, Berry DL. Older adults newly diagnosed with symptomatic myeloma and treatment decision making. Oncol Nurs Forum. 2014;41(4):411-9.
7. De las Cuevas C, Peñate W. To what extent psychiatric patients feel involved in decision making about their mental health care? Relationships with socio-demographic, clinical, and psychological variables. Acta neuropsychiatrica. 2014;26(06):372-81.
8. AsadiJanati N, Vahdat S, Yazdan Panah A. Studying patient participation in controlling postoperative infection in orthognathic surgery in BouAli Hospital, Tehran in 2012-2013. Medical Sciences Journal. 2014; 24(3):189-93.
9. Ghiyasvandian S, Mousavizadeh Sn, Dehghan Nayeri N, Haghani H. The Effect of Decision Aid's Pakage in Selected Treatment by Patients with Early Stage Breast Cancer and Decision making Outcomes. Journal of Fasa University of Medical Sciences. 2013;3(3):271-9.
10. Khosravi A, Ahmadzadeh Kh, Arastoopoor Sh, R. T. Health Literacy Levels ofDiabetic Patients Referred to Shiraz Health Centers and Its Effective Factors. Health Inf Manage. 2015; 12(2):194-205.
11. Malloy-Weir LJ, Charles C, Gafni A, Entwistle VA. Empirical relationships between health literacy and treatment decision making: A scoping review of the literature. Patient education and counseling. 2015;98(3):296-309.
12. Reisi M, Mostafavi F, Hasanzade A, Sharifirad GR. The Relationship between Health Literacy, Health Status and Healthy Behaviors among Elderly in Isfahan, Iran. Health System Research. 2011;7(4):469-80.
13. Tavousi M, Ebadi M, Azin A, Shakerinejad G, Hashemi A, *et al.* Definitions of health literacy: a review of the literature. Journal of the Iranian Institute for Health Sciences. 2014;13(1):119-24.
14. Torres RY, Marks R. Relationships among health literacy, knowledge about hormone therapy, self-efficacy, and decision-making among postmenopausal health. Journal of health communication. 2009;14(1): 43-55.
15. Yee LM, Simon MA. The role of health literacy and numeracy in contraceptive decision-making for urban Chicago women. Journal of community health. 2014;39(2):394-9.
16. Tavousi M, Haeri MA, Rafiefar S, Solimanian A, Sarbandi F, *et al.* Health literacy in Iran: findings from a National study. Journal of the Iranian Institute for Health Sciences Research. 2016;15(1):95-102.
17. Busch EL, Martin C, DeWalt DA, Sandler RS. Functional health literacy, chemotherapy decisions, and outcomes among a colorectal cancer cohort. Cancer control: journal of the Moffitt Cancer Center. 2015;22(1):95-101.
18. Khdemi N, Khassi K. the study of cancer incidence and cancer registration in kermanshah province between 2009-2010 in women. 2. 2014;6(24):32-9.
19. Hatam N, Keshtkar V, Salehi A, Rafei H. The financial cost of preventive and curative programs for breast cancer: a case study of women in Shiraz-Iran. International journal of health policy and management. 2014;2(4):187.
20. Salesi M, Khoshneshin Ghashghaee Z, Daryanoosh F, Tahmasebi S, Taleie A. The effect of eight weeks aerobic exercise on cardiovascular and hormonal risk factors in breast cancer patients. Razi Journal of Medical Sciences. 2015;22(131):35-43.
21. Gohari MR, Abolghasemi J, Mohammadi M. Prognostic factors of metastases in breast cancer patients using the recurrent Andersen-Gill model. Koomesh. 2013; 14(4):483-9.
22. Sharifian A, Pourhoseingholi MA, Emadedin M, Rostami Nejad M, Ashtari S, *et al.* Burden of Breast Cancer in Iranian Women is Increasing. Asian Pacific journal of cancer prevention : APJCP. 2015;16(12):5049-52.
23. MONTAZERI A, Tavousi M, RAKHSHANI F, Azin SA, Jahangiri K, *et al.* Health Literacy for Iranian Adults (HELIA): development and psychometric properties. 2014.
24. Izadirad H, Zareban I. The Relationship of

Health Literacy with Health status, Preventive Behaviors and Health services Utilization in Baluchistan, Iran. J Educ Community Health. 2015;2(3):43-50.
25. O'Connor AM. Validation of a decisional conflict scale. Medical decision making. 1995;15(1):25-30.
26. Tagai EK. The relationship between health literacy and indicators of decision making for colorectal cancer screening among African Americans: University of Maryland, College Park; 2016.
27. Sahrayi M, Panahi R, Kazemi S-s, GoliRostami Z, Rezaie H, *et al.* The study of Health Literacy of adults in Karaj. Journal of Health Literacy. 2017;1(4):230-8.
28. Haghighi ST, Lamyian M, Granpaye L. Assessment of the level of health literacy among fertile Iranian women with breast cancer. Electronic physician. 2015;7(6):1359.
29. Hur I, Lee R, Schmidt J. How Healthcare Technology Shapes Health Literacy? A Systematic Review. 2015.
30. Wigfall LT, Tanner AH. Health Literacy and Health-Care Engagement as Predictors of Shared Decision-Making Among Adult Information Seekers in the USA: a Secondary Data Analysis of the Health Information National Trends Survey. Journal of cancer education : the official journal of the American Association for Cancer Education. 2016.
31. Essink-Bot ML, Dekker E, Timmermans DR, Uiters E, Fransen MP. Knowledge and informed decision-making about population-based colorectal cancer screening participation in groups with low and adequate health literacy. Gastroenterology research and practice. 2016.
32. Jukkala A, Walker DK, Krontiras H, Azuero A, Meneses K. Readiness to engage in treatment decision-making during initial surgical oncology consultation for early stage breast cancer. Clinical Nursing Studies. 2013;1(2):69.
33. Doyle KL, Woods SP, Morgan EE, Iudicello JE, Cameron MV, *et al.* Health-related decision-making in HIV disease. Journal of clinical psychology in medical settings. 2016;23(2):135-46.
34. Bergeron CD, Friedman DB, Spencer SM, Miller SC, Hilfinger Messias DK, McKeever R. An Exploratory Survey of Older Women's Post-Fall Decisions. Journal of applied gerontology. 2018;37(9):1107-32.
35. LeBlanc A, Kenny DA, O'Connor AM, Légaré F. Decisional conflict in patients and their physicians: a dyadic approach to shared decision making. Medical decision making. 2009;29(1):61-8.
36. Brabers AE, Rademakers JJ, Groenewegen PP, van Dijk L, de Jong JD. What role does health literacy play in patients' involvement in medical decision-making? PloS one. 2017;12(3):e0173316.

Case Report Open Access

Archives Of Breast Cancer

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# Warfarin Induced Necrosis of The Breast: A Case Report

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ABSTRACT

**Background:** Warfarin induced breast necrosis is a rare complication of oral anticoagulant therapy. Although it can be related to protein C, S, and antithrombin III deficiency; the pathogenesis of necrosis is still unknown.

**Case presentation:** We report a case of a 38-year-old woman with extensive left breast necrosis after receiving warfarin for treatment of deep vein thrombosis. Simple mastectomy was performed and the wound was closed secondarily with an abdominal advancement flap. Rivaroxaban was prescribed after discontinuation of warfarin.

**Conclusion:** Although breast necrosis following warfarin usage is uncommon, it should be considered in women presenting with breast symptoms after initiation of warfarin. Early diagnosis and appropriate management are essential to prevent extensive loss of breast tissue.

## Introduction

Warfarin is one of the most commonly prescribed oral anticoagulant medications, and it is used for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); and for thrombo-embolism prophylaxis in patients with valvular heart disease, mechanical heart valves, and atrial fibrillation.[1]

The most common complication of warfarin is bleeding,[1] which can be prevented by adjusting international normalized ratio (INR). Necrosis, osteoporosis, calcification, and purple toe syndrome are other side effects. Skin and subcutaneous tissue necrosis is an extremely rare and serious complication of warfarin with a prevalence of 0.1- 0.01 percent.[2] It was first described by Flood *et al*. in 1943.[3] Since then, there has been more than 300 reported cases in the literature,[2] but less than 40 of the reported cases involved the breast tissue.[4]

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We present a case of warfarin induced necrosis of the breast in a 38-year-old patient, treated with simple mastectomy.

## Case presentation

A 38-year-old female presented to the breast clinic of Imam Khomeini Hospital with the complaint of a necrotic ulcer on her left breast for 10 days. She had a history of admission for deep vein thrombosis (DVT) of the left lower limb one month earlier. The deep vein thrombosis occurred following long-term use of oral contraceptive pills (OCP). She received intravenous heparin followed by warfarin. She was discharged from the hospital with a daily dose of 10 mg of warfarin and with an INR of 2.1.

On admission for breast necrosis, no fever was detected but the patient had a foul-smelling necrosis involving most of her left breast (Figure 1). Blood work showed INR, activated thromboplastin time (aPTT), and platelets of 1.32, 38 seconds, and 460,000 per cubic milliliter, respectively. Hematology consultation recommended discontinuation of warfarin and administration of Rivaroxaban.

Considering the extent of breast necrosis (Figure 1), mastectomy was recommended. Before surgery, Rivaroxaban was discontinued, and heparin and

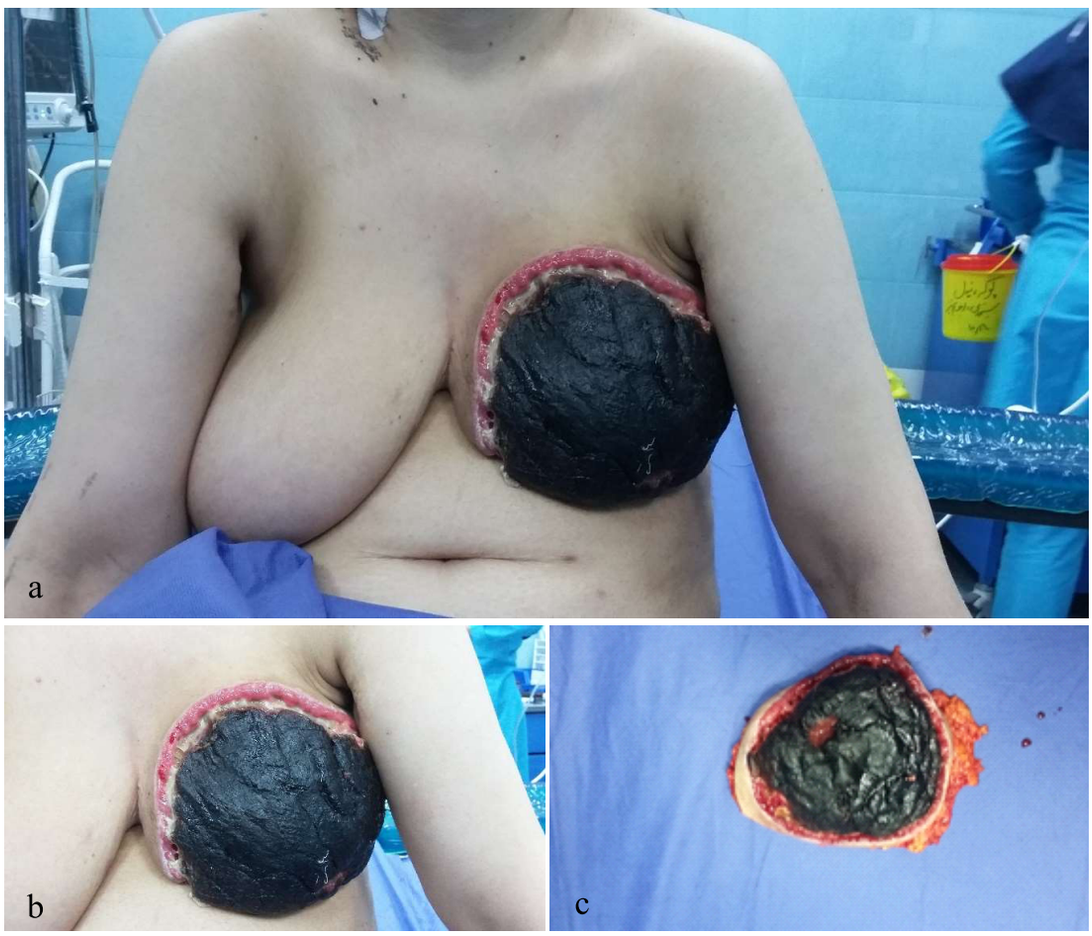


**Figure 1.** A, B: Left breast necrosis, C: Removed specimen

broad-spectrum antibiotics were started. The patient underwent left mastectomy. There were purulent secretions under the necrotic tissue and the wound was left open. Intravenous antibiotics were continued for 7 days. The wound irrigation and dressing were performed daily. The patient was discharged from the hospital with Rivaroxaban 7.5 mg/ twice a day for 21 days, then 20 mg/ day, and daily irrigation of the wound was arranged at a local clinic. Healing of the wound was monitored by the surgeon on a weekly basis. After one month, the wound was closed with abdominal advancement flap. Anticoagulation was continued for 6 months.

Further hematologic evaluation showed protein C deficiency. Pathology report confirmed breast parenchyma with diffuse and extensive necrosis and acute inflammation**.**

## Discussion

Skin and subcutaneous tissue necrosis is a rare complication of warfarin, occurring in 0.1-0.01% of patients receiving oral anticoagulation.[2] Women are more commonly affected with a female to male ratio of 3:1.[5] The areas with increased subcutaneous fat (abdomen, thighs, buttocks, legs, and breasts) are more susceptible to necrosis.[6-9] Breast is affected in about 10-15% of the patients.[4] It usually affects one breast, but bilateral breast necrosis is also reported.[4,10]

The symptoms start 1 to10 days after initiation of warfarin, and the majority of cases occur within 3 to 6 days.[4,6] However, there are reports of late-onset symptoms several years after commencement of therapy.[11-13] The initial manifestations of breast necrosis are paresthesia, pressure, and discomfort in the affected area. Later, erythematous or hemorrhagic skin lesions appear and will develop in to blisters and bullae, leading to skin necrosis and scar formation.[4,8]

It is important to consider other conditions that can mimic warfarin necrosis in differential diagnosis, such as micro-embolization (septic emboli, cholesterol emboli), heparin-induced skin necrosis as a result of the thrombocytopenia and thrombosis syndrome, disseminated intravascular coagulation, purpura fulminans, necrotizing fasciitis, cryoglobulinemia, inflammatory breast cancer, decubitus ulcers, snake venom induced skin necrosis, cellulitis, venous gangrene, necrotizing fasciitis, calciphylaxis, and hematoma.[1,14]

The exact pathogenesis of necrosis following warfarin usage is still unclear, however protein C deficiency, hypersensitivity, and direct toxic effect of warfarin are possible mechanisms of necrosis.[1,6] The most popular pathogenesis is acute protein C deficiency. Warfarin blocks vitamin K epoxide reductase enzyme and inhibits synthesis of clotting factors II, VII, IX, and X. It also inhibits synthesis of

anticoagulant protein C and protein S. Protein C and protein S have shorter half-life than vitamin K dependent clotting factors. Consequently, the patient develops a transient hypercoagulable state at the beginning of warfarin therapy and needs another form of anticoagulation, such as heparin, for 48-72 hours to prevent clot formation.[1,7,8,15]

Management of breast necrosis following oral anticoagulation therapy with warfarin, starts with discontinuation of warfarin. However, withdrawing warfarin will not affect the course of the established skin lesions.[4, 5, 16] Vitamin K and fresh-frozen plasma are administered to replenish protein C levels,[8] and anticoagulation should be continued by administering intravenous heparin or the non-vitamin K antagonist oral anticoagulants (NOACs) such as Dabigatran or Rivaroxaban.[17] The necrotic lesions should be managed surgically with debridement and appropriate wound care.

In conclusion, fulminant painful purpura and erythematous skin lesions in patients receiving warfarin should be suspected as warfarin induced necrosis. Immediate discontinuation of warfarin, administration of vitamin K, and fresh-frozen plasma is recommended. The skin lesion should be managed with appropriate surgical debridement and wound care.

**Ethical Consideration**

The patient announced her consent for using her data for this case report.

**Conflict of Interest**

The authors have no conflict of interest to disclose.

**References**


1. Simman R, Gould N, Jackson S. Warfarin-Induced Tissue Necrosis (WITN): Case Report and Literature Review. J Surg Oper Care. 2015;1(1):101.
2. Chan YC, Valenti D, Mansfield AO, Stansby G. Warfarin induced skin necrosis. Br J Surg. 2000;87(3):266-72.
3. Flood E. Thrombophlebitis migrans disseminata: report of a case in which gangrene of abreast occurred: observations on the therapeutic use of dicumarol (3, 3'methylenebis (4-hydroxy-coumarin)). NY State J Med. 1943;43:1121-4.
4. Ejzenberg D, Neusquen LP, Rolnik DL, Lozinsky AC, Piato JR. Breast necrosis induced by the use of coumadin: case report and review of literature. Einstein (Sao Paulo). 2015;13(3):417-9.
5. Fred HL. Skin Necrosis Induced by Coumarin Congeners. Tex Heart Inst J. 2017;44(4):233-6.
6. Nazarian RM, Van Cott EM, Zembowicz A, Duncan LM. Warfarin-induced skin necrosis. J Am Acad Dermatol. 2009;61(2):325-32.
7. Khalid K. Warfarin-induced necrosis of the breast: case report. J Postgrad Med. 2004;50(4):268-9.
8. Au AF, Fosnot J, Wu LC. Coumadin-induced skin necrosis of the breasts: case report. Ann Plast Surg. 2012;69(1):109-10.
9. Davis CE, Jr., Wiley WB, Faulconer RJ. Necrosis of the female breast complicating oral anticoagulant treatment. Ann Surg. 1972;175(5):647-56.
10. Lopez Valle CA, Hebert G. Warfarin-induced complete bilateral breast necrosis. Br J Plast Surg. 1992;45(8):606-9.
11. Essex DW, Wynn SS, Jin DK. Late-onset warfarin-induced skin necrosis: case report and review of the literature. Am J Hematol. 1998; 57(3):233-7.
12. Goldberg SL, Orthner CL, Yalisove BL, Elgart ML, Kessler CM. Skin necrosis following prolonged administration of coumarin in a patient with inherited protein S deficiency. Am J Hematol. 1991;38(1):64-6.
13. Sorensen DM, Eilbert W. Images in emergency medicine. Man with painful skin lesion. Warfarin sodium skin necrosis. Ann Emerg Med. 2010;55(3):302, 5.
14. Eby CS. Warfarin-induced skin necrosis. Hematol Oncol Clin North Am. 1993;7(6):1291-300.
15. Fawaz B, Candelario NM, Rochet N, Tran C, Brau C. Warfarin-induced skin necrosis following heparin-induced thrombocytopenia. Proc (Bayl Univ Med Cent). 2016;29(1):60-1.
16. Gelwix TJ, Beeson MS. Warfarin-induced skin necrosis. Am J Emerg Med. 1998;16(5):541-3.
17. Bakoyiannis C, Karaolanis G, Patelis N, Maskanakis A, Tsaples G, *et al.* Dabigatran in the Treatment of Warfarin-Induced Skin Necrosis: A New Hope. Case Rep Dermatol Med. 2016;2016:3121469.

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# 1. Open Access

*Archives of Breast Cancer* (*ABC*) provides immediate open access to its contents with the goal of contributing to a greater global exchange of knowledge. Through open access publication of *ABC*, we aim to broaden the free and full-access reach of the users all over the world to the published articles.

All the published material in *ABC* are, under a Creative Commons license, free to view and reuse with attribution by anyone in the world via the internet.

# 2. What do we publish?

## 2.1 Aims & scope

*ABC* is an open access, peer-reviewed journal that publishes articles on all aspects of breast cancer research, including the pathophysiology, prevention, early detection, diagnosis, treatment, molecular and cellular biology, genetics, epidemiology, psychological issues, rehabilitation, and quality of life. Although the main focus of the journal is breast cancer, important topics on benign breast diseases and breast health, such as breastfeeding, will be considered for publication.

## 2.2 Article types

- ***Original article***

These are reports of original experiment/research conducted by the authors. Original research must add to the body of knowledge on the subject and should adhere to ethical principles throughout the procedure. Studies

Original articles should not exceed 5,500 words including abstract, references, figure legends, and tables. The number of tables, figures, and references should be appropriate to the manuscript content. Authors whose first language is not English are advised to have their manuscripts checked carefully before submission.
Abbreviations of standard SI units of measurement should be used.
Sections of an original article are: (1) title page, (2) abstract, (3) keywords, (4) introduction, (5) methods, (6) results, (7) discussion, (8) acknowledgments, (9) conflicts of interest, (10) references, (11) figure and video legends, (12) tables, (13) figures, and (14) videos whenever applicable.

- ***Short communication***

A small-scale study that includes important new information may be published as a short communication. It usually carries an abstract of up to 150 words, a body of up to 800 words, up to 2 tables or figures, and essential references.
Sections of a short communication paper are: (1) title page, (2) abstract, (3) keywords, (4) introduction, (5) methods, (6) results, (7) discussion, (8) acknowledgments, (9) conflicts of interest, (10) references, (11) figure and video legends, (12) tables, (13) figures, and (14) videos whenever applicable.

- ***Commentary***

Commentaries discuss the findings, implications, and/or outcomes of specific research or wider research on a general topic. They elaborate on or offer original ideas about a specific paper or a widely-researched subject. Commentaries differ from reviews in that they represent the author's original ideas and suggestions instead of reporting and comparing the previous research.
Sections of a commentary include (1) title page, (2) keywords, (3) text, (4) acknowledgments, (5) conflicts of interest, and (6) references.

- ***Editorial***

Editorials are usually written by the editor in chief, deputy editor in chief, an associate editor, or a guest editor and are intended to represent the official opinion of the journal (or the guest editor) or introduce supplements, special issues, or new ideas relevant to the journal. In limited circumstances, individuals other than the individuals listed here may propose an editorial topic if they wish.
Sections of an editorial include (1) title page, (2) keywords, (3) main manuscript (4) acknowledgments, (5) conflicts of interest, (6) references.

- ***Letter to the editor***

Letters commenting on, questioning, or criticizing articles recently (within the past 4 issues) published in *ABC* or expressing views on relevant topics will be considered for publication.
Sections of a letter to the editor are (1) title page, (2) keywords, (3) text, (4) acknowledgments, (5) conflicts of interest, and (6) references.

- ***Case report and case series***

Case reports include case report/studies of patient(s) and describe a novel approach or add important insights into mechanisms, diagnosis, or treatment of a disease. Case reports are limited to 1,500 words including references. A case report manuscript should include (1) title page, (2) structured abstract (including background, case presentation, and conclusion), (3) keywords, (4) introduction, (5) case presentation, and (7) discussion. It should also contain discussion, acknowledgments, references, and illustrations (if applicable) as explained for the original articles.
All ethical considerations according to the Committee on Publication Ethics (COPE) guidelines, especially the informed consent in case reports, should be included at the end of the text just before the references.

- ***Review article***

A review article provides a detailed, thorough examination and summary of the literature on a specific topic. Authors are encouraged to contact the editor in chief (akaviani@archbreastcancer.com) before preparing an unsolicited review article to avoid duplication of other works already in progress. Review articles are limited to 7,000 words, including references, and should include the following sections: (1) title page, (2) structured abstract, (3) keywords, (4) introduction, (5) methods (search strategy), (6) results, (7) discussion, (8) acknowledgements, (9) conflicts of interest, (10) references, (11) figure legends, (12) tables, and (13) figures, whenever applicabe.

- ***Clinical experience***

In this type of manuscripts, the authors explore a debate in the clinical dilemma by presenting one or more

patients whose records are presented in the tumor board or multidisciplinary team (MDT) session of the hospital. The clinical decision which is made in the sessions are argued in this type of the manuscripts according to the scientific evidence.
Section of review article: (1) title page, (2) abstract, (3) keywords, (4) introduction, (5) case presentation, (6) question, (7) discussion, (8) acknowledgments, (9) conflicts of interest, (10) references, (11) figure legends, (12) tables, and (13) figures whenever it would be applicable.

## 2.3 Writing your paper

### 2.3.1 General format

All manuscripts should be prepared using MS Word (in .doc or .docx format). Submissions in the form of PDF files are not accepted. Manuscripts should be double-spaced, including text, tables, legends, and references.
Number each page and avoid footnotes; instead, and as sparingly as possible, use parentheses within the text. Use the Tab key once for paragraph indents, *Times New Roman typeface* for the text and *Symbols* for Greek and special characters.

### 2.3.2 Main sections of the manuscript

Papers can be divided into the following sections:

**Introduction**
- State clearly the main objectives of the study.
- Indicate the main reasons for doing the work.
- A detailed review of the literature is not recommended.
- The content should be accompanied by relevant references.

**Methods**
- Mention the type of study.
- Describe the methods, tools, and procedures employed with sufficient details to allow others to reproduce the results without the need to communicate with the authors.
- Describe the intervention and control groups, when relevant.
- Mention the type of statistical tests used.
- The rationale for using specific statistical tests, if applicable.
- State statistical significance when appropriate.

*ABC* complies with the COPE guidelines; therefore, all researchers are asked to read these guidelines to avoid cases of suspected research and publication misconduct (e.g., falsification, fabrication, plagiarism, inappropriate image manipulation, and redundant publication). For more information about COPE, please visit http://www.publicationethics.org.
Also, the authors should state that their study complies with the Declaration of Helsinki, that the locally appointed ethics committee has approved the research protocol, and that informed consent has been obtained from the subjects (or their guardians).

**Results**
- State findings of the study in the text, tables, or figures, and do not repeat the same findings in tables and figures and the text.
- Be precise and do not include material that is appropriate for the discussion, e.g., explanation of findings.
- Use the metric system/SI units to report scientific quantities and measurements.

**Discussion**
- State the original and important features of the study. Do not repeat the findings presented in the results section.
- Contain the significance of the findings and the relevance to previously published studies.
- State only the conclusions that are supported by the data.
- Mention the limitations and applications of the results.

### 2.3.3 Making your article discoverable

From the moment you set about writing the first draft of your manuscript, think about how you can make it more discoverable. The title, keywords and abstract are key to ensuring readers find your article through search engines.

# 3. Editorial policies

## 3.1 Peer review policy

Peer review is an integral part of scientific publishing that confirms the validity of the science reported. Peer-reviewers are experts who volunteer their time to help improve the journal manuscripts they review—they offer authors free advice.

Key characteristics of the peer review process are listed below:

All research articles are reviewed by at least two qualified experts.

All publication decisions are made by the journal's editor in chief on the basis of the reviews.

Members of the editorial board lend insight, advice, and guidance to the editor in chief generally and assist decision making on specific submissions.

- *Initial manuscript evaluation*

All manuscripts submitted to *ABC* are read by the editorial staff. To save time for authors and reviewers, only those papers that seem most likely to meet our editorial criteria are sent for formal review. Those papers judged by the editors to be of insufficient general interest or otherwise inappropriate are rejected promptly without external review (although these decisions may be based on informal advice from specialists in the field).

- *Type of peer review*

*ABC* employs a double-blind review process, where both the reviewer and author remain anonymous throughout the process.

- *Selecting peer reviewers*

Reviewer selection is critical to the publication process, and we base our choice on many factors, including expertise, reputation, specific recommendations, and our own previous experience of a reviewer's characteristics.

Reviewers should strive to observe the principle of confidentiality with regard to materials submitted to them.

- *How long does the review process take?*

Typically the manuscript will be reviewed within 4 weeks.

- *Final report*

A final decision to accept or reject the manuscript will be sent to the author along with any recommendations made by the reviewers and may include verbatim comments by the reviewers.

## 3.2 Authorship

Only when all the contributing authors give consent should a manuscript be submitted to a journal. The corresponding author should make sure that everyone whose work contributed to the manuscript is acknowledged as a contributing author. Only those who can legitimately claim authorship should be listed as authors. This consists of (a) contributions to the conception or design of the work; or the acquisition, analysis, and interpretation of data for the work; (b) drafting the work or revising it critically; and (c) final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

When a study is conducted by a large, multicenter group, the group must identify the individuals who can take direct responsibility for the manuscript. These individuals should meet all the criteria mentioned above.

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All contributors who do not meet the criteria for authorship as defined previously should be listed in the Acknowledgment section. Examples include a department chairperson who provided only general support, a person who provided purely technical help, or writing assistance.

## 3.4 Funding

Authors should provide detailed information regarding the source of financial and material support (grant number, etc.) for the research under a separate heading. If no funding is provided for the research, include the

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This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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State all funding sources and the names of companies, manufacturers, or external organizations providing technical or equipment support.
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Manuscripts should conform to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. All manuscripts reporting animal or human studies should state in the Methods section that ethical approval has been obtained from (or waived by) an ethics committee or institutional review board. Please make sure of providing the full name of the review committee as well as the approval number.
For research articles, a statement should be included in the Methods section indicating that informed consent, written or verbal, was obtained from participants. Case reports and case series, too, should provide an informed consent statement in the manuscript text. Also, manuscripts are required to state whether written informed consent was obtained for publication of patient information and images.
Do not submit the patient's actual written informed consent with your article, as this in itself is a violation of the patient's confidentiality. It suffices to submit a confirmatory letter along with the manuscript that written informed consent has been obtained from the patient and that the forms are kept by the authors/investigators themselves, for example in a patient's hospital record. See the ICMJE Recommendations for the Protection of Research Participants for more information.
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In accordance with the ICMJE requirements,*ABC* requires clinical trials to be registered in a WHO-approved public trials registry at or before the time of first patient enrolment to be considered for publication. The trial registry name and URL and the registration number must be included at the end of the abstract.

## 3.8 Reporting guidelines

Authors are encouraged to use the relevant research reporting guidelines for the study type provided by the EQUATOR Network. This will ensure that you provide enough information for editors, peer reviewers, and readers to understand how the research was performed and to judge whether the findings are likely to be reliable.
The key reporting guidelines are:
Randomized controlled trials (RCTs): CONSORT guidelines
Systematic reviews and meta-analyses: PRISMA guidelines and MOOSE guidelines
Observational studies in epidemiology: STROBE guidelines and MOOSE guidelines
Diagnostic accuracy studies: STARD guidelines
Quality improvement studies: SQUIRE guidelines

# 4. Publishing policies

## 4.1 Publication ethics

### 4.1.1 Plagiarism

*ABC* is powered by the iThenticate software, which is a plagiarism detection service that verifies the originality of the submitted content before publication. If plagiarism is identified, we will follow COPE guidelines.
Plagiarism includes (but is not limited to):
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If plagiarism is detected during the peer review process, the manuscript may be rejected. If plagiarism is detected after publication, we reserve the right to issue a correction or retract the paper, as appropriate.

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Any manuscript submitted to *ABC* must be original, and the manuscript, or substantial parts of it, must not be under consideration by any other journal.
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# 5. Preparing your manuscript

## 5.1 Word processing formats

We prefer Microsoft Word format (.DOC or .DOCX) for the submitted manuscripts, although PDF files are also accepted.

## 5.2 Artwork, figures, and other graphics

### 5.2.1 Figures

Figures should be limited to the number necessary for clarity and must not duplicate data given in tables or in the text. Submissions should have no more than a total of 8 figures and tables. Any number exceeding this should be designated as supplementary material for online access only. Figures must be suitable for high-quality reproduction and should be submitted in the desired final printed size so that the quality of the figure would not be affected after being printed. Figures should be no larger than 125 (height) × 180 (width) mm (5 × 7 inches) and should be submitted as separate files. Figures should be saved in TIFF format at a resolution of at least 300 pixels per inch at the final printed size for color figures and photographs, and 1200 pixels per inch for black-and-white line drawings. Although some other formats can be converted into TIFF format by the publisher, the conversion may alter the tones, resolution, and contrast of the image. Therefore, PDF is not acceptable as a source file for figures and illustrations.

### 5.2.2 Videos

Authors can submit videos and computer-generated graphics as well as a slide presentation if they think it is a part of their manuscript. The videos will be refereed as well, and the editors and reviewers may suggest changes. It is essential that the patient be not identifiable in the video unless he or she has provided written permission.

The length of each video clip or computer graphic should not exceed 40 MB. The authors can submit up to 3 videos or computer graphics. A concise legend for each video must be included in the manuscript. Only the videos which are compatible with Windows Media Player and submitted in MPEG-1 or MPEG-2 (.mpg) or QuickTime (.mov) format can be accepted.

### 5.2.3 Tables

Tables should be presented in a separate file. Provide a short, descriptive title for each table. Please make sure that each table is cited in the text and is numbered using arabic numerals. For tables adopted from previously published works, indicate the original source in the form of a reference at the end of the table caption. Asterisks (*) for significance values and other statistical points should be included under the table.

## 5.2.4 Figure and video legends

Each figure should have a concise caption (legend) describing accurately what the figure depicts. Figure legends should be mentioned at the end of the manuscript file and not in the figure file. Figure legends should begin with the term **Fig.** in boldface, followed by the figure number also in boldface (e.g., **Fig. 1**).

## 5.3 Reference style

*ABC* follows the AMA reference style. Please review the guidelines on AMA to ensure your manuscript conforms to this reference style.

If you use EndNote to manage references, you can download the AMA output file here.

The accuracy of reference details is the responsibility of the authors.

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In the main text, references should be cited consecutively by superscript arabic numerals. The reference list should be organized in numerical order according to the order of appearing in the text.

*Examples of* acceptable reference formats are as follow:

1. Harris JR, Lippman ME, Morrow M, Osborne CK. Diseases of the Breast. 5th ed. china: Wolters Kluwer Health; 2014.

*Reference to a chapter in an edited book:*

1. Hirshaut Y, Pressman P, Brody J. Breast Cancer: The Complete Guide: 5thEdition: Random House Publishing Group; 2009. Chapter 11: Hormone therapy and chemotherapy;p. 186-234.

*Reference to a chapter in an edited book which has been written by authors in a book edited by others:*

1. Newman LA, Bensenhaver JM, eds. Ductal Carcinoma In Situ and Microinvasive/Borderline Breast Cancer. In: Kanumuri P, Chapgar BA. Epidemiology of Ductal Carcinoma In situ. 4th ed. Springer. New York; 2015, p. 1-12.

If there are 7 or more authors, list the first 6 ones and then insert "*et al.*"

## 5.4 English language editing services

*ABC* offers language editing services to assist authors with the preparation of their manuscripts. These services are offered by third parties and will be available at a charge; however, authors publishing with *ABC* will qualify for a 50% discount. The cost of the language editing for each manuscript of the journal will differ from 50 to 150 Canadian dollars (CAD) depending on the word count of the article.

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# 6. Submitting your manuscript

## 6.1 How to submit your manuscript

Manuscripts should be submitted and tracked to the final decision at www.archbreastcancer.com. Manuscripts that do not comply with the instructions for authors will not be sent for external review.

*ABC* considers the following types of articles for publication: original research articles, reviews, letters, clinical experiences, case reports, case series, and short communication.

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Please supply a title, short title, an abstract, and keywords to accompany your article. The title, keywords, and

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- The abstract should be self-explanatory without reference to the main text;
- Limit the use of acronyms and abbreviations;
- The structure of the abstract includes Background, Methods, Results, and Conclusions.

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## 7.5 Complaints procedure

The best way to reach us is by email. Complaints should ideally be made to the person the complainant is already in contact with over the matter being complained about. If that is not appropriate, please email our managing editor Dr. Mojgan Karbakhsh (mkarbakhsh@sina.tums.ac.ir ).
Whenever possible, complaints will be dealt with by the relevant member of the editorial staff. If that person cannot deal with the complaint, he or she will refer it to our managing editor.
All complaints will be addressed within three working days. If possible, a full response will be made within four weeks.
If the complainant is not happy with the resolution, he or she may ask for the complaint to be escalated to the *ABC* editor in chief, Dr Ahmad Kaviani.

# 8. Further information

Any correspondence, queries, or additional requests for information on the manuscript submission process should be addressed to *ABC* editor in chief, Dr Ahmad Kaviani (akaviani@archbreastcancer.com).


Archives Of
Breast
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2015 Yearbook


Archives Of
Breast
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2016 Yearbook


Archives Of
Breast
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2017 Yearbook

# Announcement

As of 2018, ABC will consider the publication of articles under a new category called "**Clinical Experience**" These articles are meant to present a discussion of a problematic clinical situation. The manuscripts should be organized under the following headings: Case Presentation, Questions on the Management of Patient, Multidisciplinary Team (MDT) Discussion, Conclusion, and References. ABC invites all the clinicians and MDT coordinators to share their invaluable clinical experiences with their colleagues.

All the manuscripts submitted in 2019 will be assessed and peer-reviewed for publication in every issues in couple of weeks .
For more information regarding the journal scope and style, please visit ABC website at:

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