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## 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 celebrating the fifth anniversary of the journal while we have lost one of our best colleagues, Professor Mohammad Safaei-Kashtgar. May his soul rest in peace.

Now, the difficult, hard and complex mission started from in 2014 has been flourishing by being indexed in some internationally renowned databases e.g. such as EBSCO, Index Copernicus, and DOAJ, with the process of being indexed in and some more databases being underwaywhich are on the way. This is the beginning of a way to expand the activities of the journal. Meanwhile, the scientific and executive teams of the journal are working hard to improve the quality and the quantity of the published manuscripts.



We are planning to optimize the journal's website technically to simplify the interaction with a broader field of audiences in all countries. We also emphasize the publication of high-quality scientific articles from all over the globe.

Furthermore, since the beginning of 2018, measures have been taken to increase the number of the published articles and dramatically reduce the manuscript processing time waiting time of publication of the submitted articles will be improved in the way that the duration of manuscripts processing for review and publication will be dramatically reduced. The first decision will be made in one week after submission. UponBy receiving the corrections and the final proofarticle, a DOI code will be assigned to the manuscript, and in the upcoming two weeks the article will be published electronically in the journal's website as "in press". within the next two weeks.

We plan strive to improve both the quality and the qualntity of published material the journal to be able to put the journal among the top specialized journals in the field of breast cancer in the near future.

Best rergards Ahmad Kaviani, MD Porfessor of Surgery Editor-in-Chief

## 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 2018 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:

### **ARCHBREASTCANCER.COM**

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Archives Of Breast Cancer

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# Dr. Mohammed-Reza Safaei Keshtgar— A Pioneer of Innovation in Medicine and Professional Ethics



The number of two eyes is a little tone Count the wisdom of thousands more

Roudaki (858-941 A.D)

It is the 2006 Breast Cancer Congress in Tehran. The invited guest speaker, a humble and amiable, not to mention brilliant, surgical oncologist at University College London, is delivering an exciting speech about a multicenter research project on intraoperative radiotherapy. He then goes on to thrill the audiences by introducing the thechnique and hosting a workshop on sentinel lymph node biopsy. At the end of his speech, he treated all participants with fascinating pictures of his hometown in Southeast Iran and explained how he still felt his roots in that part of country. He was no one but Dr Mohammed-Reza Safaei Keshtgar.

He was, no doubt, the pioneer of minimaly invasive breast procedures, including sentinel lymph node biopsy, in the UK. His genuine commitment to educate and improve his colleagues in Iran, and other developing countries, made him regularly participate in cancer conferences in these countries and share his knowledge and expertise with local specialists. In 2014, we were honored to have him aboard in editorial board of the Archives of Breast Cancer, and the journal enjoyed his invaluable counsel since then. His scholarly contributions has helped to constantly improve the scientific quality of the journal during the past four years.

Diligence, determination, innovation in surgery, as well as adherence to professional ethics and commitment to research and education, made him a prominent figure in the field of cancer internationally—so that The Lancet introduced him and acknowledged his efforts in a 2011 article.

It is beyond any doubt that the decease of this distinguished physician and scientist is a great loss to the international scientific community, as well as his patients, and will deeply affect his colleagues. The Archives of Breast Cancer sincerely regrets that it has lost one of the most effective members of its editorial board. May his soul rest in peace.





### DOI: 10.19187/abc.2017411-3 Optimal Timing of Surgery after Neoadjuvant Chemotherapy of Breast Cancer

Borna Farazmand<sup>a</sup>, Maisa Yamrali<sup>a</sup>, Reza Ghalehtaki<sup>a</sup>, Mehran Habibi<sup>\*<sup>b</sup></sup>

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During recent decades, our understanding of the characteristics of breast cancer has improved, leading to improvements in individualized treatment methods historically, neoadjuvant chemotherapy (NAC) was limited to inoperable breast cancer<sup>1</sup>, however, according to the results of several studies in some centers around the world this method has become the routine practice in almost all stages of breast cancer (except for the very early ones). Initially, theories suggested that NAC may result in more rapid eradication of micrometastatic disease increasing overall survival (OS). Although studies could not confirm this theory, NAC has led to an increase in the rates of breast conserving therapy (BCT), a decrease in the extent of local treatment (e.g. axillary dissection) and as a result, better cosmetic outcomes.<sup>2</sup> Other benefits of NAC that made this method popular include providing prognostic and therapeutic information based on in vivo tumor response, turning inoperable tumors into operable ones and providing enough time for genetic testing and breast reconstruction.

Not only has NAC been helpful in the treatment of patients but its use has led to major advances in the field of cancer research.<sup>4</sup>

As an example, if considering pathologic response as a surrogate for survival, compared to the past, we may wait shorter to witness the results of clinical trials on new systemic therapies. In contrast, we still need the very survival curves to assess outcomes in studies on locoregional treatments which require long-term follow-ups to show meaningful differences. Thus, it is not surprising that

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21224, USA Tel: +1-410-550-8282 Fax: +1-410-550-2011 Email: mhabibi2@jhmi.edu many guidelines of locoregional treatment are not based on recent and prospective clinical evidence, but often have roots in retrospective or earlier studies.

NAC, per se, has opened new questions and issues that have not existed before, some include the accuracy and timing of sentinel lymph node biopsy in this setting<sup>5</sup>, indications of radiotherapy and the extent of the radiation field<sup>6</sup>, and further adjuvant chemotherapy in patients with inadequate response. An important question that we would like to address here is the optimal timing of surgery after NAC and its impact on survival.

The time of surgery after NAC is an ongoing issue. Large randomized trials demonstrating benefits of NAC (NSABP B18 & B27, EORTC 10902) along with several following studies made no mention of the timing of surgery.<sup>7,8</sup> Moreover, many single institution studies addressing this issue did not evaluate its impact on treatment outcome. Although, according to an accepted unwritten rule and also the information extrapolated from adjuvant chemotherapy studies, in current practice, the operation is performed as soon as the patient is fit. This usually is possible around 6 to 8 weeks after the completion of NAC.

In contrast to neoadjuvant chemotherapeutic series, there is substantial data on optimal interval after surgery for adjuvant chemotherapy. A metaanalysis demonstrated that increasing the time window could lead to decreased survival especially in patients with advanced, triple negative (TNBC) or Her2+ breast cancer<sup>9</sup>. Although according to biologic models of preclinical studies, a shorter time period from surgery to adjuvant chemotherapy would result in better outcomes<sup>10</sup>, there is no such biologic model in the setting of NAC.

There are too few studies, all retrospective, addressing time interval after completion of neoadjuvant chemotherapy for breast cancer. In 2014, Gabordi *et al.*, presented results of a study at



the annual meeting of the American Society of Breast Surgeons, demonstrating that patients undergoing surgery within 40 days after completion of NAC show greater reductions in final Ki-67, a marker of proliferative activity, which was associated with decreased recurrence rates.<sup>11</sup> In this study, 83 patients undergoing NAC and surgery during 2012 and 2013 were evaluated retrospectively. The decline rate of Ki-67 in the group having surgery within 40 days of NAC was 41% compared to 23% in the group who underwent surgery later (P=0.038).

Recently, two other retrospective articles emerged on this topic. In a study by Sanford et al., published in 2015 in Annals of Surgical Oncology journal, 1101 patients with stage I-III breast cancer who were treated with NAC in MD Anderson Center during 1995-2007 were identified and divided into 3 groups according to the interval between chemo and surgery:  $\leq 4$  weeks, 4-6 weeks, and 6-24 weeks.<sup>12</sup> There was no difference in 5-year recurrence-free survival (RFS) or locoregional recurrence-free survival (LRFS). In multivariate analysis, compared with an interval of  $\geq 4$  weeks, patients who underwent surgery at 4-6 or >6 weeks had equivalent overall survival (OS), LRFS, and RFS; a sensitivity analysis suggested worse OS in patients who underwent surgery at >8 weeks. The authors concluded that patients with maximal 8-week neoadjuvant chemotherapy to surgery interval had equivalent OS, RFS, and LRFS.

In the study by Omarini et al., a study published recently in the European Journal of Surgical Oncology, 319 patients with breast cancer were evaluated Who were treated in an Italian institute from 1991 to 2015.13 The study consisted of two groups according to the timing of surgery after chemotherapy:  $\leq 3$  weeks, and >3 weeks. OS and RFS were significantly worse in the latter group, with a hazard ratio of 3.1 (95% CI, 1.1-8.6 P = 0.03) and 3.1 (95% CI, 1.3-7.1 P = 0.008), respectively. Multivariate analysis confirmed that time to surgery (TTS) was an independent prognostic factor in term of OS (P = 0.03) and RFS (P = 0.01). Interestingly, even in the subgroup of patients with pathologic complete response (pCR), TTS continued to be an independent prognostic factor for both OS and RFS (P=0.05 and P=0.03).

The retrospective nature of these studies makes interpretation of results difficult. In addition, the small sample size in both studies, heterogeneity of their patients and the fact that patients received different treatment protocols are all the reasons why we cannot make a firm conclusion. It is worth mentioning that some of the patients in these studies were treated more than 20 years ago. In the Sanford study, the <4weeks interval group compared to other two groups had higher percentage of stage III and high-grade tumors. Additionally, the reason for delayed surgery was not mentioned in this study. In Omarini's study the percentage of pCR in the group with TTS <3 weeks was higher than the other one (30% vs. 19%, although not statistically significant, P = 0.07) and a higher proportion of patients with TTS <3 weeks had positive hormonal receptors (48% vs. 35%). The total duration of chemotherapy in different groups of these studies was not mentioned, and the interval between diagnosis /initiation of chemotherapy and surgery is not clear. Although we know that the time from diagnosis to surgery in the adjuvant setting has an impact on survival, still there is no study evaluating the impact of this timing in the neoadjuvant setting.

It should be noted that in practice several factors could influence the timing of surgery after NAC leading to difficulties in performing the surgery in a preplanned schedule. These factors include complications of chemotherapy, age and comorbidities of patients, preference of both patient and surgeon, and the facilities of that center.

Overall, it seems that there cannot be a definite conclusion based on available evidence, however, this reminds us that it is prudent to be on the safe side and perform surgery as soon as the general condition and complications of chemotherapy allow us to do so. Defining the true impact of time to surgery after NAC needs randomized prospective trials, even though such studies have some practical and ethical issues. At present, there is a need for more prospective studies with larger sample sizes, and more thorough information about patients and treatments in order to better understand the impact of TTS after NAC in treatment outcomes.

#### **Conflict of Interest**

The authors declare no conflict of interests.

#### References

- 1. Kaufmann M, von Minckwitz G, Mamounas EP, Cameron D, Carey LA, Cristofanilli M, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. Ann Surg Oncol 2012; 19(5): 1508-16.
- 2. Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. Br J Surg 2007; 94(10): 1189-200.
- 3. Gradishar WJ, Anderson BO, Balassanian R, Blair SL, Burstein HJ, Cyr A, et al. Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016; 14(3): 324-54.
- 4. Kuehn T, Bauerfeind I, Fehm T, Fleige B, Hausschild M, Helms G, et al. Sentinel-lymphnode biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort

study. Lancet Oncol 2013; 14(7): 609-18.

- 5. Lemanski C DX. Which node area should be irradiated after neoadjuvant chemotherapy in breast cancer? Cancer Radiotherapy 2015; 19(4): 271-5.
- 6. Lemanski C, Druet X, Riou O, Ducteil A, Azria D, Bourgier C. Which node area should be irradiated after neoadjuvant chemotherapy in breast cancer? Cancer Radiother 2015; 19(4): 271-5.
- Rastogi P, Anderson SJ, Bear HD, Geyer CE, Kahlenberg MS, Robidoux A, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008; 26(5): 778-85.
- 8. Van Nes JG, Putter H, Julien JP, Tubiana-Hulin M, van de Vijver M, Bogaerts J, et al. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. Breast Cancer Res Treat 2009; 115(1): 101-13.
- 9. Raphael MJ, Biagi JJ, Kong W, Mates M, Booth CM, Mackillop WJ. The relationship between time to initiation of adjuvant chemotherapy and survival in breast cancer: a systematic review and meta-analysis. Breast Cancer Res Treat 2016; 160(1): 17-28.
- Segatto I, Berton S, Sonego M, Massarut S, Perin T, Piccoli E, et al. Surgery-induced wound response promotes stem-like and tumorinitiating features of breast cancer cells, via STAT3 signaling. Oncotarget 2014; 5(15): 6267-79.
- Melville NA. Surgery Within 4 to 6 Weeks of Neoadjuvant Chemotherapy for Breast Cancer Linked to Reduced Ki-67: Presented at ASBS. May 6 2014. http://www.firstwordpharma .com/node/1208509?tsid=17.
- 12. Sanford RA, Lei X, Barcenas CH, Mittendorf EA, Caudle AS, Valero V, et al. Impact of Time from Completion of Neoadjuvant Chemotherapy to Surgery on Survival Outcomes in Breast Cancer Patients. Ann Surg Oncol 2016; 23(5): 1515-21.
- 13. Omarini C, Guaitoli G, Noventa S, Andreotti A, Gambini A, Palma E, et al. Impact of time to surgery after neoadjuvant chemotherapy in operable breast cancer patients. Eur J Surg Oncol 2016; 43(4):613-8.





### DOI: 10.19187/abc.2017414-9 Implication of Intramammary Lymph Node Metastasis in the Breast: A Review of the Literature

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#### ARTICLE INFO

#### ABSTRACT

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**Background:** The impact of positive intramammary lymph node (IM LN) on the prognosis of patients with breast cancer has been debated for years; likewise, the standard management of patients with positive IM LN remains unclear, especially when it is identified by preoperative imaging or by sentinel lymph node biopsy. The present study aims at reviewing the level of concurrent involvement of IM LN and axillary nodes to clarify the management of patients with breast cancer with positive IM LN and clinically negative axilla or negative axillary sentinel lymph nodes.

**Methods:** We reviewed all published studies on IM LN metastasis in breast cancer from 1980 to 2016 in 4 major databases. Twenty-five studies containing data on pathologic examination of IM LN were included, in twenty- two of which, pathologic status of IM LN and axillary lymph nodes were exactly available.

**Results:** The incidence of positive IM LN is highly variable (0%-100%). Positive IM LNs were associated with positive axillary lymph nodes in more than half of patients, but isolated involvement of IM LN were documented in significant number of patients in various studies.

**Conclusions:** Although metastatic IM LN could often be associated with axillary nodal involvement, it could be the only site of breast cancer spread; hence, the concept stating that positive IM LN mandate further axillary dissection needs to be debated.

#### Introduction

Intramammary lymph node (IM LN) was first defined by Egan & Mc Sweeney in 1982 as a lymph node surrounded by breast parenchyma. They found an incidence of 28% by studying 158 total mastectomy specimens.<sup>1</sup> The prevalence of IMLNs has been reported in the range of 1% to 48.4%, according to the methodology of the study as well as

Address for correspondence: Ramesh Omranipour, MD Address: Cancer Institute, Imam Khomeini hospital, Keshavarz Blvd., Tehran 1419733141, Iran Tel: +98-21-61192509 +98-21-22668611 Fax:+98-21-66935063 Email: omranipour@sina.tums.ac.ir the specimen's characteristic which were examined.<sup>2,</sup>

<sup>3</sup> Rampaul *et al.* reported an incidence of 48.4% in a series of total mastectomy specimen's examination after breast conserving surgery, while Jadusingh reported only 5 IMLNs in 3 cases of 77 total mastectomy specimens.<sup>3,4</sup>

IM LNs can be located anywhere within the breast, but most of them are recognized in the upper outer quadrant (38%-72%).<sup>5</sup> Most of IM LNs are not clinically palpable and could be observed on mammography as a well-circumscribed, oval, or round density smaller than 1cm with a central lucent hilum. They were reported on 5% of normal mammograms in a review of 1500 mammography.<sup>6</sup> On ultrasonography, they are well defined circumscribed hypo-echoic masses with an

echogenic line representing the hilum. In a study conducted by Linfords *et al.* on 16000 mammographic examination, 4 metastasis to IM LN were found and all involved lymph nodes were larger than 1 cm (range 1.2-2 cm), since radiological differentiation was very difficult, they recommended the biopsy of every lesion larger than 1 cm unless associated with dermatitis or mastitis.<sup>7</sup>

IM LNs have no clinical importance until they are involved by breast cancer, but their clinical importance remains controversial. Patients with IM LN metastases were considered to be in stage II disease and had PN1 disease, yet in the lack of axillary node association. The presence of positive IM LN can upstage the disease and change the therapeutic decisions.

Considering the high incidence of axillary nodal involvement in patients with positive IM LN, an axillary lymph node dissection had been recommended, but now by increasing the improvement in sentinel lymph node mapping technique, the position of axilla could be forecast by the position of axillary sentinel node rather than the status of IM LN.

The proper management of patients with positive IM LN and negative axillary lymph nodes is still under debate; the aim of this review is to provide a summary of the published data on IM LN metastasis in breast cancer to clarify the prognostic importance of this entity and to help in optimal management of this subset of patients with breast cancer.

#### Methods

A comprehensive review was conducted among the published articles from 1980 to 2016 using 4 electronic databases (ISI web of science, Scopus, Google scholar, PubMed). The keywords for this search were "intra-mammary lymph nodes", "intramammary lymph nodes", "extra-axillary lymph nodes", and "sentinel lymph nodes". These

Author	No. of cases	No. of specimens with IMLN	No. of patients with positive IMLN	No. of positive Axilla & positive IMLN
Egan&McSweety 19	83 <sup>1</sup> 173	45	15 (33%)	NA
Lindfors 19867	16000	4	4 (100%)	1 (25%)
Jadusingh 1992 <sup>4</sup>	682	5	1 (20%)	NA
Spillane 1999 <sup>6</sup>	3	3	2	1
Rull 1999 <sup>7</sup>	1	1	1	
Cyrlak 1999 <sup>8</sup>	1	1	1	1
Schmidt 2001 <sup>2</sup>	4056	44	2 (4.5%)	NA
Upponi 2001 <sup>19</sup>	3	3	2	0
Gajdos 2001 <sup>20</sup>	1	1	1	1
Gunhan-Bilgen 2001 <sup>21</sup>	1655	16	16 (100%)	9 (56%)
Victorzon 2003 <sup>22</sup>		8	0	0
Tytler 2003 <sup>23</sup>	2	2	1	0
Shen 2004 <sup>8</sup>	196	196	36 (28%)	29 (81%)
Kouskos 2004 <sup>24</sup>	2	2	2 (100%)	1 (50%)
Matheline 2005 <sup>25</sup>	1	1	1	0
Guth 2006 <sup>26</sup>	3601	64	20 (31%)	13 (72%)
Van Rijk 2006 <sup>9</sup>	785	59	13 (22%)	1 (8%)
Rampaul 2008 <sup>3</sup>	157	76	25 (29%)	15 (60%)
Cox 2008 <sup>10</sup>	15000	91	29 (32%)	18 (62%)
Nasser 200811	116	116	15 (26%)	12 (80%)
Intra 2008 <sup>12</sup>	9632	22	6/15 (40%)	0
Kijima 2008 <sup>27</sup>	4	4	2 (50%)	0
Vijan 2009 <sup>13</sup>	9800	93	32 (34%)	22 (69%)
Pugliese 2009 <sup>14</sup>	7140	151	36 (24%)	22 (67%)
Hogan 2010 <sup>15</sup>	100	113	21 (21%)	14 (67%)

 Table 1. Studies With the Level of Positive IM LN and Positive Axilla + Positive IM LN

Abbreviations: IMLN: Intramammary lymph nodes; NA: Not Available

keywords and some other like "breast cancer" and "metastasis" were combined to execute the search. The full texts of all relevant studies were retrieved and all references were searched. Among 36 studies, 25 had mentioned the level of IM LN involvement and 22 studies had provided sufficient data on pathologic status of IM LN and axillary lymph nodes in the same patients.

#### Results

The results of the present research were highly variable; the level of IM LN metastasis was in a range of 0% to 100% in specimens with IM LNs (Table 1). Excluding the case report studies, the concurrent involvement of IM LN and axillary lymph nodes was between 0% to 84%.

In studies reporting more than 100 patients, more than half of the patients had concurrent IM LN and axillary lymph node involvement, meaning that approximately less than half of the patients with IM LN metastasis had no need further axillary dissections and the status of the axilla could be identified by sentinel node biopsy.<sup>3,7-15</sup>

#### Discussion

The biopsy of intramammary sentinel lymph node was first described by Rull in 1999.<sup>17</sup> Uren *et al.* found them as sentinel lymph nodes in about 12% of their patients.<sup>28</sup>

The reported incidence of intramammary sentinel lymph nodes ranged between 0.2% and 14%, but there were a few reported cases of positive intramammary sentinel lymph nodes in the literature.<sup>12,15,25,28</sup>

Generally, 50% of the metastatic IM LNs was in the same quadrant as the tumor in the Egan's studies.<sup>1,29</sup>The sensitivity of breast imaging study for the detection of IM LN before surgery was low. It was only 18.5% in a study by Shen on 196 specimens, which had IM LN in pathologic examination.<sup>15</sup> A histological study by Schmidt on cadaver breasts detected IM LNs in 7.5%, half of which was not known radiologically.<sup>2</sup>

In a research conducted by Vijan *et al.*, IM LN were identified in 93 breast specimens: in 23 patients, they were found on preoperative imaging studies (15 on mammography, 4 on MRI, and 4 on lymphoscintigraphy), and 70 IM LN were known incidentally (48 by surgeon intraoperative and 22 by pathologist).<sup>13</sup>

The patients and tumor characteristics correlated with IM LN metastasis were age, grade, tumor multifocality, the presence of lympho-vascular invasion, and axillary nodal involvement. The age of patients and tumor grade were not correlated with IM LN metastasis in other studies.<sup>9,12,14,25,28</sup>

Patients with IM LN metastases are considered to be in stage II disease and have PN1 disease, yet in the lack of axillary node association. This practice is based on Egan & Mc Sweeney's study in 1983, which reported outcomes of 15 positive IM LN patients with 13 to17 years follow-up.<sup>29</sup> Among 6 patients, who had isolated IM LN metastasis without axillary nodes involvement, only 2 patients survived for 10 years. The presence of IM LN metastasis was correlated with poor prognosis in patients with stage I, but in patients involved in stage II illness, the existence of IM LN metastasis was not correlated with a lesser prognosis in comparison with patients without IM LN metastasis. It was obviously was the first study that addressed the prognostic significance of IM LN metastasis in breast cancer.

Later studies have had small number of populations, but Shen et al. from MD Anderson Cancer Center, in 2004, reported the clinical and pathologic data of 186 patients who had IM LNs in their mastectomy specimens.<sup>15</sup> IM LN metastasis was found in 36 patients (28%). Most patients, who had IM LN metastasis (81%), had axillary metastasis as well. The presence of IM LN metastasis was associated with reduced disease free survival (DFS) and overall survival (OS) in patients with axillary metastasis as well as in those without axillary metastasis. In the multivariate analysis, IM LN metastasis was an independent predictor of poor outcome; hence, they recommended further axillary lymph node evaluation as well as an adjuvant systemic therapy for patients with positive IM LNs.

In a review of all kinds of breast cancer with IM LNs from 1991 to 2005 in their center, Guth *et al.* reported the same results.<sup>26</sup> Also, 75% of patients with IM LN metastases had axillary nodal metastasis; thus, they agreed with Shen *et al.* about further axillary dissection in the setting of positive IM LN.

Rampaul *et al.* claimed that 48% of patients, undergoing complete mastectomy after breast conserving surgery, had IM LNs.<sup>3</sup> They found 15 patients with positive IMLN in the presence of negative axillary sampling. In this study, 60% (15 from 25) of patients with IM LN metastasis had axillary nodal metastasis.

Nasser *et al.* examined 116 specimens contain IM LNs.<sup>11</sup> In these series, 57 specimens had primary breast cancer. Most patients (80%), who had IM LN metastasis, had axillary node metastasis, too. The patients with IMLN metastasis had a minor 4- year's overall and disease free survival compared with the patients with a negative IM LN, but in contrary with the Shen *et al.*, they did not find it as an independent predictor of poor outcome on their multivariate analysis.

Another study, which is in favor of axillary dissection in the presence of IM LN metastasis, belongs to Hogan *et al.* from the UK.<sup>15</sup> They found that 67% of patients with IM LN metastasis owned more axillary metastasis; likewise, 1 patient, who had an involved IM LN with a negative axillary

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sentinel node, found axillary nodal recurrence 19 month later; consequently, they concluded that IM LN metastasis is associated with poorer overall survival and predicts strongly for axillary metastasis and they recommended axillary node clearance in the setting of positive IM LN. In this study, IM LN metastasis was an independent predictor of poor outcome on multivariate analysis.

In a study conducted by Vijan *et al.* in 2009, the rate of axillary metastasis in the presence of positive IM LN was 69%, and they proposed axillary dissection in the setting of positive IMLN so that more investigations verified the validity of SLN decision making in such condition.<sup>13</sup> A systematic review and meta-analysis on 18 studies by Abdullgaffar *et al.* found positive IM LN reliable predictors of axillary nodal involvement and, consequently, a director for additional surgical administration of the axilla.<sup>30</sup>

Some studies do not agree to the necessity of axillary clearance in the presence of positive IM LN.<sup>10, 12, 14</sup> Cox *et al.* found that positive IM LN and negative axilla patients have better prognosis than negative IM LN and positive axilla patients.<sup>10</sup>

Intra et al. reported 15 patients with sentinel lymph nodes both in axilla and in breast parenchyma.<sup>12</sup> In this study, all 15 axillary SLN were reactive and 6 of intramammary sentinel nodes were involved. Three of these 15 patients (2 of whom had positive IM LN) had an axillary node clearance and all nodes were reactive. With an average follow up of twenty-four months, no regional or local or systemic failures had happened. In a study conducted by Pugliese et al., the status of IM LNs were compared with the status of axilla.<sup>14</sup> In general, 61% of IM LN patients had axillary node metastasis. No further axillary involvement was recognized when axillary separation was accomplished in 7 patients with positive IM LN and negative axillary sentinel node. No axillary recurrence had occurred in other 7 patients with IM LN metastases and negative axillary sentinel node, with a median follow up of seventy-five months. According to Intra and Pugliese's study, axillary sentinel node biopsy can be used to guide axillary decision making in the presence of IM LN metastasis. Tytler et al. introduced 2 cases of intramammary sentinel node, one of whome was metastatic and further axillary dissection in this patient identified 13 reactive lymph nodes.<sup>23</sup> Bat et al. introduced 2 cases of metastatic IMLN in patients with breast cancer with a negative axillary sentinel lymph node.<sup>31</sup> The results of complete axillary lymph node dissection in these 2 patients were negative.

Fujii *et al.* reported a 70-year-old woman with metastatic IM sentinel node and reactive axillary sentinel nodes, who had been alive 11months after surgery without any loco regional or systemic recurrence.<sup>32</sup> Similarly, Rivera *et al.* reported a

similar 78-year-old woman with positive IM sentinel node and negative axillary sentinel node who had not undergone axillary dissection.<sup>33</sup>

Lee *et al.* in a study performed on twenty-two patients with IM LN metastases, concluded that these patients had more aggressive tumors with more lymphovascular invasion and increased the rate of axillary node involvement, proposing axillary dissection by the status of IM LN itself.<sup>34</sup>

According to a review research by Troupis *et al.*, there is no consensus in the case that intramammary sentinel node is positive, but axillary sentinel node is not involved.<sup>35</sup>

In a literature review of 386 publications, published by Diaz *et al.* in 2012, twenty-three patients with positive IM LN and negative axillary SLN, who underwent a complete axillary lymph node dissection, were identified. In all twenty-three patients, the result of axillary dissection was negative.<sup>36</sup> They concluded that axillary lymph node separation may be eluded in the setting of a positive IM LN and a negative axillary sentinel lymph node.

In conclusion, it seems that further studies are needed to define the clinical and prognostic impact of IM LN involvement on disease outcome. Although metastatic IM LN can often be associated with axillary nodal involvement, it can be the only site of breast cancer metastasis and can be increasingly identified by sentinel node biopsy technique. Today, SLN biopsy has become the standard care in the evaluation of axillary status in patients with breast cancer. It seems that by increasing the experience in technique of sentinel node biopsy, decision about axillary node dissection in IM LN positive patients could be founded merely on the histopathologic status of axillary sentinel lymph node.

#### References

- 1. Egan RL, McSweeney MB. Intramammary lymph nodes. Cancer 1983; 51(10): 1838-42.
- 2. Schmidt WA, Boudousquie AC, Vetto JT, Pommier RF, Alexander P, Thurmond A, *et al.* Lymph nodes in the human female breast: a review of their detection and significance. Hum Pathol 2001; 32(2): 178-87.
- 3. Rampaul RS, Dale OT, Mitchell M, Blamey RW, Macmillan RD, Robertson JF, *et al.* Incidence of intramammary nodes in completion mastectomy specimens after axillary node sampling: implications for breast conserving surgery. Breast 2008; 17(2): 195-8.
- 4. Jadusingh IH. Intramammary lymph nodes. J Clin Pathol 1992; 45(11): 1023-6.
- 5. Svane G, Franzen S. Radiologic appearance of nonpalpable intramammary lymph nodes. Acta Radiol 1993; 34(6): 577-80.
- 6. Stomper PC, Leibowich S, Meyer JE. The prevalence and distribution of well circumscribed



nodules on screening mammography: analysis of 1500 mammograms. Breast Dis 1991; (4): 197-203.

- LindforsKK, Kopans DB, Googe PB, McCarthy KA, Koerner FC, Meyer JE. Breast cancer metastasis to intramammary lymph nodes. AJR Am J Roentgenol 1986; 146(1): 133-6.
- 8. Shen J, Hunt KK, Mirza NQ, Krishnamurthy S, Singletary SE, Kuerer HM, *et al.* Intramammary lymph node metastases are an independent predictor of poor outcome in patients with breast carcinoma. Cancer 2004; 101(6): 1330-7.
- 9. Van Rijk MC, Tanis PJ, Nieweg OE, Olmos RA, Rutgers EJ, Hoefnagel CA, *et al.* Clinical implications of sentinel nodes outside the axilla and internal mammary chain in patients with breast cancer. J Surg Oncol 2006; 94(4): 281-6.
- 10. Cox CE, Cox JM, Ramos D, Meade TL. Intramammary sentinel lymph nodes: what is the clinical significance? Ann Surg Oncol 2008; 15(5): 1273-4.
- 11. Nassar A, Cohen C, Cotsonis G, Carlson G. Significance of intramammary lymph nodes in the staging of breast cancer: correlation with tumor characteristics and outcome. Breast J 2008; 14(2): 147-52.
- 12. Intra M, Garcia-Etienne CA, Renne G, Trifiro G, Rotmensz N, Gentilini OD, *et al.* When sentinel lymph node is intramammary. Ann Surg Oncol 2008; 15(5): 1304-8.
- 13. Vijan SS, Hamilton S, Chen B, Reynolds C, Boughey JC, Degnim AC. Intramammary lymph nodes: patterns of discovery and clinical significance. Surgery 2009; 145(5): 495-9.
- 14. Pugliese MS, Stempel MM, Cody HS, 3rd, Morrow M, Gemignani ML. Surgical management of the axilla: do intramammary nodes matter? Am J Surg 2009; 198(4): 532-7.
- 15. Hogan BV, Peter MB, Shenoy H, Horgan K, Shaaban A. Intramammary lymph node metastasis predicts poorer survival in breast cancer patients. Surg Oncol 2010; 19(1): 11-6.
- 16. Spillane AJ, Donnellan M, Matthews AR. Clinical significance of intramammary lymph nodes. Breast 1999; 8(3): 143-6.
- 17. Rull M, Fraile M, Alastrue A, Castella E, Calatrava A, Riba J, *et al.* Histologically invaded intramammary sentinel node, but no metastases found on axillary dissection. Eur J Surg 1999; 165(11): 1100-2.
- Cyrlak D, Carpenter PM. Breast imaging case of the day. Intramammary and axillary lymph node metastases from infiltrating lobular carcinoma of the breast. Radiographics 1999; 19 Spec No: S73-9.
- 19. Upponi S, Kalra S, Poultsidis A, Bobrow L,Purushotham AD. The significance of intramammary nodes in primary breast cancer. Eur J Surg Oncol 2001; 27(8): 707-8.
- 20. Gajdos C, Bleiweiss IJ, Drossman S, Tartter PI.

Breast cancer in an intramammary sentinel node. Breast J 2001; 7(4): 260-2.

- 23. Gunhan-Bilgen I, Memis A, Ustun EE. Metastatic intramammary lymph nodes: mammographic and ultrasonographic features. Eur J Radiol 2001; 40(1): 24-9.
- 22. Victorzon M, Hamalainen E, Svartback M, Lantto A. Extra-axillary sentinel node biopsy in breast cancer staging--is it necessary? Eur J Surg Oncol 2003; 29(7): 604-6.
- 23. Tytler I, Hayes A, Kissin M. Intramammary sentinel nodes in early breast cancer: can we find them and do they matter? Eur J Surg Oncol 2003; 29(1): 6-8.
- 24. Kouskos E, Rovere GQ, Ball S, Koh DM, Freeman A. Metastatic intramammary lymph nodes as the primary presenting sign of breast cancer. Breast 2004; 13(5): 416-20.
- 25. Mathelin C, Tomasetto C, Rio MC, Chenard MP, Brettes JP, Guyonnet JL. Improvement in intramammary sentinel lymph node removal using a novel prototype hand held probe during breast conservative surgery. Breast Cancer Res Treat 2005; 89(3): 305-8.
- 26. Guth AA, Mercado C, Roses DF, Hiotis K, Skinner K, Diflo T, *et al.* Intramammary lymph nodes and breast cancer: a marker for disease severity, or just another lymph node? Am J Surg 2006; 192(4): 502-5.
- 27. KijimaY, Yoshinaka H, Uenosono Y, Funasako Y, Ehi K, Yanagita S, *et al.* Intramammary sentinel lymph node in patients with breast cancer: report of four cases. Surg Today 2008; 38(6): 536-40.
- Uren RF, Howman-Giles R, Renwick SB, Gillett D. Lymphatic mapping of the breast: locating the sentinel lymph nodes. World J Surg 2001; 25(6): 789-93.
- 29. McSweeney MB, Egan RL. Prognosis of breast cancer related to intramammary lymph nodes. Recent Results Cancer Res 1984; 90: 166-72.
- 30. Abdullgaffar B, Gopal P, Abdulrahim M, Ghazi E, Mohamed E. The significance of intramammary lymph nodes in breast cancer: a systematic review and meta-analysis. Int J Surg Pathol 2012; 20(6): 555-63.
- 31. Bats AS, Coutant C, Antoine M, Uzan S, Barranger E. Intramammary lymph node metastasis of breast cancer after sentinel node biopsy: two cases and a review of the literature. Eur J Surg Oncol 2009; 35(3): 331-2.
- 32. Fujii T, Yajima R, Matsumoto A, Yamaki S, Uchida N, Tsutsumi S, *et al.* Implication of an Intramammary Sentinel Lymph Node in Breast Cancer: Is This a True Sentinel Node? A Case Report. Breast Care (Basel) 2010; 5(2): 102-4.
- 33. Rivera AL, Diwan A, Muylaert S, Lucci A. Intramammary lymph node presenting as the primary breast mass in infiltrating lobular carcinoma. Curr Surg 2006; 63(2): 107-9.



- 34. Lee SK, Kim S, Choi MY, Kim J, Lee J, Jung SP, *et al.* The clinical meaning of intramammary lymph nodes. Oncology 2013; 84(1): 1-5.
- 35. Troupis T, Michalinos A, Skandalakis P. Intramammary lymph nodes: a question seeking for an answer or an answer seeking for a question? Breast 2012; 21(5): 615-20.
- 36. Diaz R, Degnim AC, Boughey JC, Nassar A, Jakub JW. A positive intramammary lymph node does not mandate a complete axillary node dissection. Am J Surg 2012; 203(2): 151-5.





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### Inherent Radiation Sensitivity of Lymphocytes of Triple Negative (TN) and Luminal A: A Comparison Between Patients with Breast Cancer and Normal Individuals as Assayed by the Micronucleus Test

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#### ABSTRACT

**Background:** About 83% of patients with breast cancer (BC) undergo radiation therapy. These patients show various degrees of mild to acute reactions during and after the completion of treatment. The aim of this study was to compare inherent radiosensitivity of gamma-irradiated G0-lymphocytes between BC patients and normal individuals using cytokinesis blocked micronucleous assay.

**Methods:** Three to 4 mL blood was drawn in heparinized syringes from patients and normal individuals. A portion of the sample was irradiated with gamma rays at a dose of 300 cGy. Irradiated and non-irradiated samples were cultured in complete RPMI-1640 culture medium. A standard cytokinesis-blocked micronucleus assay protocol was followed for the preparation of binucleate lymphocytes. Slides were prepared and stained in Giemsa. Thousand binucleate cells were scored for the presence of micronucleus (MN). Data were statistically analyzed using SPSS software.

**Results:** The results showed that the background frequency of micronuclei in both groups of control and Luminal A (LA) patients was nearly similar and relatively low but was significantly higher in triple negative BC (TNBC) patients Significantly different (P<0.01). The irradiation of lymphocytes led to a high frequency of MN in control and LA patients, relatively higher in LA patients (P<0.001); but the frequency of MN was considerably lower in TNBC patients after irradiation.

**Conclusions:** The results indicated radio-sensitivity of LA patients but radioresistance in TNBC patients. This different reaction of lymphocytes of patients with BC might be due to different status of genome instability in these patients.

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#### Introduction

Excluding skin cancers, breast cancer (BC) is the most common malignancy in women (29%). Likewise, this malignancy claims the death of 14% of all cancer-based cases. BC ranks second as a cause of cancer death in women following lung cancer.<sup>1</sup>

Approximately, 10% to 15% of breast cancers are triple negative, in which case cancerous cells lack estrogen (ER), progesterone (PR), and HER-2 receptors. Generally, preoccupation with this type of cancer is weaker than the other types, also, they are resistant to treatment.<sup>2</sup> More confusingly, there is a high probability that the cancer returns and causes metastasis. The majority of patients are categorized as Luminal. In such patients, cancerous breast cells resemble Luminal cells in mammary glands. Luminal A has the best prognosis and the lowest probability of recurrence. These patients are ER+ and can be treated by hormone therapy.<sup>3,4</sup>

The main treatments in breast cancer include surgery, radiotherapy, chemotherapy and hormone therapy. The radiotherapy usage rate for breast cancer is about 83%.<sup>5</sup> In radiotherapy using X or gamma rays, the effort is made to damage cancer cells while sparing the normal cells. Normally, the prescribed dose for each radiotherapy session depends on the radiobiological reaction of both tumor and normal cells to radiation.<sup>6</sup> It is generally believed that individual differences in the radiosensitivity of normal tissue among patients with breast cancer stem from individual genetic differences and innate cellular-sensitivity depending on the function of various genes responsible for regulating cell cycle and DNA repair.

Patients with BC show different biological reactions from mild to acute for ionizing radiation during radiotherapy.<sup>8</sup> Also, upon the completion of radiotherapy, there may be side effects, such as fibrosis or secondary cancers in the radiotherapy area.<sup>9</sup> In fact, the final result of radiotherapy depends on the tolerance dose of normal tissues around the tumor. The highest level of normal cells' tolerance has a one-to-one relation to the maximum dosage of tumor radiation.<sup>10</sup> Studies have shown that 10% of the general public are sensitive to radiation and that 15% of the patients treated by radiotherapy are also sensitive to ionizing radiation.<sup>6,11</sup> It was shown that approximately 40% of patients with BC are sensitive to radiation.<sup>11-13</sup>

The aim of this study was to examin inherent radio-sensitivity of triple negative patients with breast cancer compared with that in Luminal A, patients with BC, and control health individuals. To this end, cytochalasin-blocked micronucleus (MN) assay was done on gamma irradiated G0lymphocytes of patients with BC. MN, observed as discrete element with similar feature to nucleus in cytoplasm of binucleate lymphocytes, representing an acentric chromosomal fragment or lagging chromosome in anaphase, is a well approved method for the study of radio-sensitivity. Although there are other well established cytogenetic methods, such as G2 chromosomal assay for radiosensitivity assessment, MN assay is a faster and easier method compared to other cytogenetic techniques.<sup>14-16</sup>

#### Methods

#### Study subjects

Fifteen triple negative BC (TNC) patients with the mean age of  $53.3\pm10.39$  (age range 37-78), 15 patients with Luminal A with the mean age of  $45.8\pm10.9$  (age range 32-62), and 30 normal individuals including 20 females with mean age of  $39.6\pm11.6$  (aged 26-63) and 10 males with mean age of  $43.8\pm10.02$  (age range 35-55) were enrolled in the present study. This study was approved by the Ethical Committee of Cancer Institute of Tehran University of Medical Sciences.

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All donors completed a written questionnaire to obtain information related to their life style including their dietary habits, medical history and exposure to chemical and physical agents. Therefore, all samples were screened to exclude radiation exposure, smoker, antibiotic therapy and virus infection at least one month prior to sampling.

Patients with breast cancer were not under chemo- or radiotherapy at the time of sampling. Regarding blood sampling, written informed consent was obtained from the patients and normal individuals. Three to 5 mL blood was drawn in heparinized syringes via venipuncture from both normal and the patient individuals. Blood sample collected from each volunteer was aseptically transferred to 2 tubes; hence, one of them was used as control and the other irradiated with gamma rays.

#### Irradiation

Irradiation of samples was done with gamma rays generated from a cobalt-60 machine (Theratron 780C, Canada). Blood samples were irradiated with a dose of 300 cGy at ambient room temperature in an irradiation field of  $10 \times$  to  $10 \times$  cm and at a source to sample distance of 80 cm.

#### **MN** assay

Full details of this assay have been outlined elsewhere with minor modification.<sup>17,18</sup> Briefly, whole-blood culture was initiated for each blood sample. To each culture vessel 0.5 ml of the blood was added to 4.5 ml complete RPMI-1640 culture medium supplemented with 15% fetal calf serum, 1% L-glutamine, 100 U/mL penicillin and 100 µg/mL streptomycin (all materials from Gibco BRL). The lymphocytes were stimulated to proliferate with 1% phytohemagglutinin (PHA, Life Technologies GmbH, Frankfurter, Germany, final concentration 1 µg/mL). Vessels were incubated at 37°C. Forty-four hours later, cytochalasin B (Sigma) was added at a final concentration of 6  $\mu$ g/mL. After further incubation, cells were harvested at 72 h poststimulation. After centrifugation and removal of culture medium cell suspension was exposed to hypotonic shock with 0.075 M KCl, followed by fixation, three times, in methanol:acetic acid (3:1, v/v) solution. For preparation of slides, cells were

dropped on clean glass slides and stained with 5% Giemsa (in phosphate buffer) for 5 minutes. The slides were then coded and randomized for analysis. Overall 1000 binucleated cells (BNCs) per slide were scored for the presence of micronucleus (MN) based on the standard criteria described previously.<sup>16</sup>

Figure 1 shows example of binucleate cells with or without micronuclei observed in this study.

#### Statistical analysis

The data were analyzed using the SASS 16.0 statistical program for Windows (SASS Inc., Chicago, IL, USA). The results were statistically analyzed using Kolmogorov-Smirnov test for normal distribution, then analyzed using Student's t-test and analysis of variance (ANOVA). P<0.05 was considered as statistically significant.



Figure 1. Photomicrograph showing a cytokinesis blocked binucleate lymphocyte without MN (A) and with one micronucleous (B) (Magnification x1000)

#### Results

Results of the study is summarized in Table 1 and shown in Figure 2. The total background frequency micronuclei in the control group was 19.9 per 1000 binucleate lymphocytes. The frequency of background micronuclei in lymphocytes of LA breast cancer patients was significantly higher than in control group (P<0.01). However a significantly higher background level of MN was seen in lymphocytes of TNBC patients compared to both control and LA groups (P<0.001) (Table 1, Figure 2-A).

Irradiation of lumphocytes with 300 cGy gamma rays led to a considerable increase in the frequency of MN in lymphocytes of control and LA groups. The mean frequency of radiation induced MN for control group was 145.7 micronuclei per 1000 binuclei cells (87 to 280 for females and 112 to 260 micronuclei cells for males). There was no statistical difference between the frequency of MN induced in lymphocytes of females and males(P> 0.1). The Frequency of radiation induced MN in lymphocytes of Luminal A patients was higher than in control group which was statistically significant (P< 0.01).

However, in our surprise, the frequency of radiation induced MN in lymphocytes of TNBC patients was considerably lower than both control and Luminal A groups (Mean 100 MN/1000 binuclei) (Figure 2-B). Net induced MN was calculated by subtracting background frequency from radiation induced MN, as shown in Figure 2-C.

**Table 1.** The average frequency of MN per binucleate lymphocyte observed in 3 groups before and after irradiation with 3 Gy of gamma rays

Gender	Number of Samples	Age	Frequency of Background MN /cell	Frequency of IR induced MN/cell	P-value	Frequency of Net induced MN/cell	P-value
Control Group					>0.1		>0.1
Female	20	39.6 ±10.8	$0.02\pm0.01$	$0.15\pm0.06$		$0.13 \pm 0.06$	
Male	10	$43.8\pm7.5$	$0.02 \pm 0.01$	$0.14\pm0.04$		$0.13\pm0.05$	
Total	30	$41.0\pm9.77$	$0.02\pm0.01$	$0.15\pm0.05$		$0.15\pm0.06$	
TNBC					< 0.001		< 0.001
Female	15	$53.5 \pm 10.3$	$0.07\pm0.014$	$0.10\pm0.03$		$0.04\pm0.03$	
Luminal A					< 0.001		< 0.001
Female	15	$45.8\pm10.9$	$0.04\pm0.02$	$0.19\pm0.07$		$0.15\pm0.05$	



**Figure 2.** Box plots showing baseline micronucleus frequency (panel A), radiation induced MN (panel B) and Net induced MN frequency (panel C) for controls, TNBC, and Luminal A BC patients. The boxes extend from the 25th percentile to the 75th percentile, with a horizontal line at the median (50th). The whiskers present the 10th and the 90th of the data. Moreover, "\*" denote P<0.001 compared to control group; "\*\*" denote P<0.001 compared to control and LA group.

#### Discussion

The present study describes different status of inherent radio-sensitivity of 2 types of BC lymphocytes; ie. TNBC and LA compared to healthy individuals. MN is evaluated in cytochalisinblocked binucleate lymphocytes as an indicator of cytogenetic damage induced by gamma-radiation. Radio-sensitivity is a feature of some genetic conditions like ataxia telangiectasia expressed as elevated levels of background and radiation induced chromosomal abnormalities.

Previous studies have shown that lymphocytes of about 45% of breast cancer patients show hypersensitivity to ionizing radiation when irradiated at G2 phase of the cell cycle.<sup>19-21</sup> However, this value drops to about 25% when lymphocytes of breast cancer patients is irradiated at G0 phase of the cell cycle.<sup>13,19,20</sup> As shown in Figure 2, we found that the frequency of radiation induced MN in lymphocytes of Luminal A BC patients was much higher than normal individuals indicating the hypersensitivity of these patients to ionizing radiation.

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The reason behind hypersensitivity of lymphocytes of patients with BC might be due to inefficient repair capacity of damaged DNA. Patel et al. have shown inefficient DNA repair capacity in patients with BC, using G2 assay and counting the number of chromatid aberrations in several time intervals.<sup>22</sup> Similarly, other investigators have shown defective DNA repair capacity in cancer prone individuals.<sup>23,24</sup> Further research also indicated that genome of individuals with cancer susceptibility and patients with BC generate more DNA damage and increase radio-sensitivity because of defective DNA repair mechanisms compared to normal individuals.<sup>11, 25, 26</sup> The elevated radio-sensitivity may lead to complications during or after radiotherapy of these patients as well as recurrence of secondary cancers due to its damaging effect on normal surrounding tissues.

However, as shown in Figure 1-A, the background frequency of MN in TNBC patients was much higher than in other two studied groups (P<0.001). Surprisingly, after irradiating the lymphocytes of TNBC patients, a dramatic decrease in the frequency of MN was observed. This observation might be indicative of resistance of lymphocytes in these patients to ionizing radiation. This result might be a plausible reason for the resistance of these patients to conventional chemo-and radiotherapy. The mechanism by which this resistance is happening is not clearly understood, but it is much similar to the observation of adaptive response induced by low doses of ionizing radiation in radiation workers.<sup>17</sup>

It was previously shown that high background frequency of MN is observed in lymphocytes of radiation workers exposed to very low doses of ionizing radiation below dose limit. Exposure of these lymphocytes to higher doses of ionizing radiation led to a considerable reduction in frequency of MN compared to non-exposed lymphocytes.<sup>17</sup> This observation might indicate that the existence of high background chromosomal abnormalities expressed as MN in lymphocytes as well as other tissues including tumor in patients with BC might keep cellular repair machinery activated to respond further insult to DNA.

In conclusion, unlike other patients with BC, TNBC patients do not show inherent radiosensitivity and rather they somehow show radioresistance.

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#### **Conflicts of Interest**

The authors declare no potential conflicts of interests.

#### References

- 1. Breast Cancer Facts & Figures. 2013-2014. https://www.cancer.org/content/dam/cancerorg/research/cancer-facts-and-statistics/breastcancer-facts-and-figures/breast-cancer-factsand-figures-2013-2014.pdf (accessed January 10 2016).
- Ovcaricek T, Frkovic SG, Matos E, Mozina B, Borstnar S. Triple negative breast cancer prognostic factors and survival. Radiol Oncol 2011; 45(1): 46-52.
- 3. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol 2010; 28(10): 1684-91.
- Harris JR, Lippman ME, Osborne CK, Morrow M. Diseases of the Breast: Lippincott Williams & Wilkins; 2012.
- 5. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005; 104(6): 1129-37.
- 6. Torres-Roca JF, Stevens CW. Predicting response to clinical radiotherapy: past, present, and future directions. Cancer Control 2008; 15(2): 151-6.
- Hall EJ, Giaccia AJ. Radiobiology for the Radiologist. 7 ed: Lippincott Williams & Wilkins; 2012.
- Shapiro CL, Recht A. Side effects of adjuvant treatment of breast cancer. N Engl J Med 2001; 344(26): 1997-2008.
- Clarke M, Collins R, Darby S, Davies C, Elphinstone P, Evans V, *et al.* 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. Lancet 2005; 366(9503): 2087-106.
- 10. Yorke ED, Jackson A, Rosenzweig KE, Merrick SA, Gabrys D, Venkatraman ES, *et al.* Dose-volume factors contributing to the incidence of radiation pneumonitis in non-small-cell lung cancer patients treated with three-dimensional conformal radiation therapy. Int J Radiat Oncol Biol Phys 2002; 54(2): 329-39.
- 11. Shahidi M, Mozdarani H, Bryant PE. Radiation sensitivity of leukocytes from healthy individuals and breast cancer patients as measured by the alkaline and neutral comet assay. Cancer Lett 2007; 257(2): 263-73.
- 12. Ryabchenko N, Glavin O, Shtefura V, Anikushko M. Chromosomal Radiosensitivity in Ukrainian Breast Cancer patients and healthy

Individuals. Experimental Oncology 2012; 34(2): 121-4.

- 13. Mozdarani H, Mansouri Z, Haeri SA Cytogenetic radiosensitivity of g0-lymphocytes of breast and esophageal cancer patients as determined by micronucleus assay. J Radiat Res 2005; 46(1): 111-6.
- 14. Salimi M, Mozdarani H. Different aspects of cytochalasin B Blocked micronucleus cytome (CBMN cyt) assay as a comprehensive measurement tool for radiobiological studies, biological dosimetry and genome instability. Int J Radiat Res 2015; 13: 101-26.
- 15. Hagmar L, Bonassi S, Strömberg U, Brøgger A, Knudsen LE, Norppa H, *et al.* Chromosomal aberrations in lymphocytes predict human cancer: a report from the European Study Group on Cytogenetic Biomarkers and Health (ESCH). Cancer Research 1998; 58(18): 4117-21.
- 16. Fenech M. The in vitro micronucleus technique. Mutat Res 2000; 455(1-2): 81-95.
- 17. Gourabi H, Mozdarani H. A cytokinesis-blocked micronucleus study of the radioadaptive response of lymphocytes of individuals occupationally exposed to chronic doses of radiation. Mutagenesis 1998; 13(5): 475-80.
- Grover P, Rekhadevi PV, Danadevi K, Vuyyuri SB, Mahboob M, Rahman MF. Genotoxicity evaluation in workers occupationally exposed to lead. Int J Hyg Environ Health 2010; 213(2): 99-106.
- Scott D, Hu Q, Roberts SA. Dose-rate sparing for micronucleus induction in lymphocytes of controls and ataxia-telangiectasia heterozygotes exposed to 60Co gamma-irradiation in vitro. Int J Radiat Biol 1996; 70(5): 521-7.
- 20. Scott D, Barber JB, Levine EL, Burrill W, Roberts SA. Radiation-induced micronucleus induction in lymphocytes identifies a high frequency of radiosensitive cases among breast cancer patients: a test for predisposition? Br J Cancer 1998; 77(4): 614-20.
- Mozdarani H, Ziaee Mashhadi AH, Alimohammadi Z. G2 chromosomal radiosensitivity and background frequency of sister chromatid exchanges of peripheral blood lymphocytes of breast cancer patients. Internatuinal Journal of Radiation Research 2011; 9(3): 167-74.
- 22. Patel RK, Trivedi AH, Arora DC, Bhatavdekar JM, Patel DD. DNA repair proficiency in breast cancer patients and their first-degree relatives. Int J Cancer 1997; 73(1): 20-4.
- 23. Sanford KK, Parshad R, Gantt RR, Tarone RE. A deficiency in chromatin repair, genetic instability, and predisposition to cancer. Crit Rev Oncog 1989; 1(3): 323-41.
- 24. Helzlsouer KJ, Harris EL, Parshad R, Perry HR, Price FM, Sanford KK. DNA repair proficiency potential susceptibility factor for breast cancer. J Natl Cancer Inst 1996; 88(11): 754-5.

- 25. Mohseni-Meybodi A, Mozdarani H, Mozdarani S. DNA damage and repair of leukocytes from Fanconi anaemia patients, carriers and healthy individuals as measured by the alkaline cometassay. Mutagenesis 2009; 24(1): 67-73.
- 26. Shahidi M, Mozdarani H, Mueller WU. Radiosensitivity and repair kinetics of gammairradiated leukocytes from sporadic prostate cancer patients and healthy individuals assessed by alkaline comet assay. Iran Biomed J 2010; 14(3): 67-75.



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## The Effectiveness of Acceptance-Commitment Therapy (ACT) on Perceived Stress, Symptoms of Depression, and Marital Satisfaction in Women With Breast Cancer

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#### ABSTRACT

**Background:** Breast cancer is a completely heterogeneous disease caused by interaction of factors, such as genetic and environmental risks leading to a progressive accumulation of genetic and epigenetic changes in breast cancer cells. Moreover, it deeply affects patients' mental and social health. The present study aimed at examining the effect of group commitment-acceptance treatment on perceived stress, symptoms of depression, and marital satisfaction in women with breast cancer.

**Methods:** The present research was a Randomized Controlled Trial (RCT), the study population of which consisted of women with breast cancer referred to Avicenna Research Institute in Tehran, Iran. The participants were selected randomly using random sampling method and Morgan table, and they were assigned to 2 groups of trial (20 individuals) and control (20 individuals). The trial group underwent 8 sessions (each taking 2 hours) for 1 month and received therapy in mind empowerment clinic based on acceptance and commitment, but the control group received no therapy except the routine management. Both groups were examined in terms of psychology using standardized questionnaires. Afterwards, the collected data were analyzed using mean and standard deviation, *t*-test, univariate analysis of covariance, and multivariate analysis of covariance by employment of SPSS software.

**Results:** The results of analysis of covariance indicated that the performed therapy improved the level of perceived stress, symptoms of depression, and marital satisfaction in the trial group. The calculated eta-squared (0.40) indicated that 40% of individual differences in post test scores of perceived stress, marital satisfaction, and symptoms of depression is related to ACT. In addition, the results of univariate analysis of covariance indicated that 48% of individual differences in scores of perceived stress, 63% of individual differences in scores of symptoms of depression were related to ACT.

**Conclusions:** The results of the present study show that acceptance-commitment group therapy is effective and productive in reduction of psychological problems of women with breast cancer. The findings of this study, in general, provide an experimental support for ACT in terms of reduction of psychological problems of patients with cancer.

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#### Introduction

According to the global statistics, breast cancer is the most common type of cancer among women.<sup>1</sup> In addition, it has been reported to be the most common and the second disease causing death among Iranian women.<sup>2</sup> The results of the related studies indicate that some of the most common consequences of breast cancer are physical problems (pain and

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fatigue), psychological problems (depression and anxiety), and other socio-mental problems leading to lower life quality in women especially among young women.<sup>3, 4</sup> The incidence of breast cancer is an experience associated with stress and anxiety. Women whose breast cancer is diagnosed on time receive medical care and surgery that have side effects, such as hair loss, nausea, lymphatic, and sexual problems. Prolonged treatment disturbs women's abilities to play their social role as household or working women and to perform their roles in future status and the possibility to go back to work. High level of stress has a long-term negative effect on women's self-assurance and leads them to have negative impact on family and marital performance. Moreover, it could result in lower life quality.

About 10% to 30% of patients experience PTSD clinical signs at the time of diagnosis.<sup>5</sup> Depression and anxiety are common psychiatric disorders in women with breast cancer.<sup>6, 7</sup> Patients with cancer have high levels of psychiatric disorders, the scope of which consisted of depression, anxiety, lack of coping with illness, loss of self-confidence, emotional disorders, and fear of recurrence and death.8 In addition, due to surgery, women with breast cancer lose a part of their body representing their genders.' Such issues result in impairment in body image of oneself leading to the reduction of self-confidence and feminine charm and along with it, stress, depression, and disappointment may come through.<sup>10</sup> Moreover, some of the studies show that even 3 years after medical treatments, the patient may have stress and depression.<sup>11</sup> One of the most significant reasons resulting in the emergence of depression in such patients is the pain caused by metastasis, reduction in social activities, and disability.<sup>12, 13</sup> Depression is a dangerous factor in reduction of survival rate in patients with cancer and an important factor in lack of acceptance of treatment by such patients.<sup>14-16</sup> Recently, a meta-analysis of studies was carried out on prevalence of mood and anxiety disorders among patients with cancer. The results of this research indicated that 12.9% to 29.8% of patients and 5.1% to 17% of patients experienced depression and anxiety, respectively.<sup>17</sup> According to a study conducted by Mahdavi et al.18 there is a significant difference between patients with cancer and cardiovascular patients in terms of marital satisfaction, perceived stress, and depression; in patients with cancer, there is lower marital satisfaction, higher perceived stress, and depression. In addition, findings of their study indicated that perceived stress in patients with cancer and depression in cardiovascular patients predict the levels of marital satisfaction.

Within the past 2 decades, a number of psychotherapies have developed as a third wave, including Dialectical Behavior Therapy (DBT), Acceptance and Commitment Therapy (ACT), Schema Therapy, Cognitive Behavioral Analysis System psychotherapy (CBASP), Mindfulnessbased Cognitive Therapy (MBCT), and Metacognitive Therapy (MCT). More exactly, Cognitive-behavioral therapy is a comprehensive expression for a general set of therapies and ACT is one of the many forms of CBT.<sup>19</sup> The main difference between ACT and CBT is that ACT protocol focuses on the clarification of values and goals as well as emphasizing a desire for experiencing all emotions and situations (primary strategies based on acceptance).<sup>20</sup> ACT is associated with a research program called "Relational Frame Theory (RFT)". Obviously, this approach accepts function changes in thoughts and emotions instead of changes in form, meaning, or frequency.<sup>21</sup> The main purpose of this approach is to provide mental flexibility, i.e. providing the ability to make practical choices from different proper options in order to avoid thoughts, emotions, memories, or problematic intentions that dominate individuals.<sup>22</sup> In these types of therapies, it is initially tried to increase individuals' flexibility in terms of mental acceptance of intellectual experiences (thoughts and emotions) and to reduce ineffective control.

Patients are told that any effort to avoid or control these unexpected intellectual experiences is ineffective or has inverse effects, leading to an increase in them. We should accept these experiences without external or internal reactions to completely eliminate them. In the second step, individuals' psychological awareness increases, i.e. they become aware of all of their emotions. In the third step, they are trained to separate themselves from such intellectual experiences (cognitive separation), so that they can act irrespective of these experiences. In the fourth step, efforts to reduce excessive obsession with personal stories (like being a victim). In the fifth step, individuals are helped to identify their main personal values in order to turn them to special behavioral goals (clarification of values); finally, providing motivation to act committedly, i.e. activities towards clear values and goals together with acceptance of intellectual experiences. Such experiences can lead to depressive thoughts, obsessions, tension, and thoughts related to fears and different accidents.<sup>22</sup> In addition to the importance of third wave behavior-cognitive therapies, such as ACT approach as an important emerging field of psychotherapy, which indicated its effective impact on stress, depression, anxiety disorders, and other clinical conditions,<sup>23-25</sup> there are limited number of research studies on the application of ACT techniques in psychotherapy of patients with cancer. For instance, the investigation of Hulbert-Williams, Storey and Wilson<sup>26</sup> can be reviewed, in which the ACT approach was considered an effective and practical intervention in coping with cancer.

Having the aforementioned issues in mind, the aim of the present study was to inform the patient of their emotions, thoughts, and behaviors about the risk of breast cancer and make them experience it without refusal so as to motivate them to pursue their life goals and values as well as accepting cancer and maintaining mental health. Hence, the present research aimed at specifying whether ACT can amend the level of perceived stress, symptoms of depression, and marital satisfaction in women with breast cancer.

#### Methods

The present research was a Randomized Controlled Trial (RCT), in which the study population consisted of women with breast cancer referred to Avicenna Research Institute in Tehran. The participants were selected randomly using random sampling method and Morgan table and they were assigned to 2 groups of trial (20 individuals) and control (20 individuals). The inclusion criteria included patients aged between 25 and 50, spending at least 1 month and at most 8 months from the diagnosis time, being under chemotherapy or radiation therapy in the past or present, having enough motivation for participating in the research at the primary interview, and not participating in other psychological courses at the same time. Moreover, the exclusion criteria included absence for more than 2 sessions and physical problems. The trial group received therapy based on acceptance and commitment for 8 sessions (each taking 2 hours) within 1 month, but the control group received no therapy. Prior to implementation of the therapy and after that, all participants were tested using Enrich's short-form marital satisfaction questionnaire (35 items), Cohen's perceived stress questionnaire (14 items), and Beck's short-from depression questionnaire (13 items). Eventually, the collected data were analyzed using mean and standard deviation, *t*-test, univariate analysis of covariance, and multivariate analysis of covariance by employment of SPSS software.

#### Research Tools

A) Perceived stress questionnaire (14 items): this questionnaire was provided by Cohen *et al.* in 1983, consisting of 3 versions of 4, 10, and 14 items, which are used to measure general perceived stress in 1 month and evaluate thoughts and emotions about stressful events, control, dominance, and coping with psychological pressure and experienced stresses. Homology scale reliability coefficients were obtained through Cronbach's alpha in a magnitude of 84% to 86% in a group of university students and a group of smokers. Scoring style of the questionnaires was based on a 5-point Likert scale (0: never, 1: almost never, 2: sometimes, 3: often, and 4: most of the time). The lowest score was 0 and the highest score was 56. Higher marks showed higher

perceived stress.<sup>27</sup> In a study conducted by Mahdavi *et al.*<sup>18</sup> Two methods were used for the reliability of the perceived stress questionnaire including Cronbach's alpha method and split-half method. The reliability of the whole questionnaire was 0.84 and 0.85, which showed that the reliability coefficients were acceptable.

B) Enrich's marital satisfaction questionnaire (35 items): this shortened questionnaire is a 115-question list, which was developed by Fowers and Olson.<sup>28</sup> This questionnaire is a self-report tool for measuring the reliability of marriage and level of satisfaction in marriage. The revised scale consists of 4 sub-scales, each of which has 35 items that can be used as research tools for marital satisfaction, communications, problem solving, and ideal falsification. The questions of the questionnaire have 5 answer choices: 1(I totally agree), 2(I agree), 3(I neither agree nor disagree), 4(I disagree), and 5(I totally disagree); they were scored on a scale of 1 to 5. The questionnaire's alpha coefficient for subscales, such as marital satisfaction, communi-cations, problem-solving, and ideal falsification were 86%, 84%, 83%, and 86%, respectively. The retest validity of the questionnaire for each subscale was 81%, 90%, 92%, and 93%.<sup>28</sup> Alpha coefficient in Asoodeh's study (2010): sample size: 365 couples, respectively, 68% (by removing item 24, alpha will be 78%), 78%, 62%, and 77%.<sup>29</sup> In a study conducted by Mahdavi et al.<sup>18</sup>,2 methods were used to obtain the reliability of the questionnaire: Cronbach's alpha and split-half. For the whole questionnaire, the reliability was 0.72 and 0.71, respectively, which showed that the reliability coefficients were acceptable.

C) Beck's short-form depression questionnaire (13 items): this questionnaire consisted of 13 self-report items, which expressed certain depression signs. Each item of this questionnaire includes a 4-choice scale with a score range of 0 to 3. Maximum and minimum scores were 39 and 0, which were provided for measurements in different semiotics areas of depression, such as emotional depression, cognitive depression, motivational depression, and physiological depression. Lait, Fout and Elior<sup>30</sup> reported that Beck's short-form Cronbach's alpha coefficient (13 items) is 0.87; and they reported that the re-testability is 0.90 within 2 weeks. In addition, in a study, Rajabi<sup>30</sup> examined internal homology and the reliability of short-form items of the questionnaire for students in Shahid Chamran University, Ahvaz, Iran. Based on the analysis of the main components, 2 factors were obtained: the first factor was negative emotion towards oneself, which expressed 43.9% of the items' variance; and the second factor was lack of joy, which expressed 8.6% of the items' variance. Cronbach's Alpha Coefficient and Split Half were reported to be 0.89 and 0.82 for the whole questionnaire and correlation coefficient between the short-form and 21-item form of Beck's depression questionnaire was 0.67. Short-from split-half internal coordination coefficient of Beck's depression questionnaire, after applying Spearman-Brown corrected formula for the whole questionnaire, was 0.82; 0.82 for negative emotion towards oneself (first factor) and 0.76 for lack of joy (second factor). In a study conducted by Mahdavi *et al.*<sup>18</sup>, to determine the reliability of Beck's depression questionnaire, 2 methods (Cronbach's alpha and split-half) were used for the whole questionnaire and they were, respectively, 0.94 and 0.90, showing that reliability coefficients were acceptable.

#### Ethical considerations

Obtaining informed consent from the patients, who

participated in the sessions and stating that the patients can withdraw at each stage of the research. Ensuring that the information obtained from the participants will remain confidential (privacy and confidentiality). Respecting to the patients who involved in the research ethically and avoiding discrimination.

#### Therapy Plan

The protocol of the therapy sessions was held based on Strosal, Hiz, and Wilson's book (acceptance and commitment)<sup>31</sup> within 1 month.

The summary of the contents of each session is as follow:

Session 1 Meeting of group members and therapist, discussion on privacy, breast cancer, examination of negative thoughts and emotions, listing 6 of the most important problems in life, description of therapy approach, and implementation of pre-test.

- Session 2 Checking the activities of session 1, measuring patients' problems in ACT viewpoint, explaining creative hopelessness, introducing external and internal world in ACT therapy plan, providing a list of advantages and disadvantages and methods of controlling problems in everyday life.
- Session 3 Checking the activities of session 2, discussion over ineffectiveness of controlling negative events using metaphors and training the tendency to think and feel negative, recording cases where patients have managed to get rid of inefficient control methods.
- Session 4 Checking the activities of session 3, introducing values, goals, measures, and obstacles to therapy, training the separation of assessments from personal experiences and observing thoughts without judgment, recording cases where patients have managed to observe experiences and emotions without evaluating.
- Session 5 Checking the activities of session 4, discussing amalgamation and using metaphors and experimental practice, communicating with present and considering oneself as context, training mind-awareness techniques, recording cases where patients have not been able to observe thoughts, using mind-awareness techniques.
- Session 6 Checking the activities of session 5, identifying patients' life values and evaluating values based on their level of importance, introducing perceived self-distinctiveness, continuing to identify life areas, role of choice in actions, providing a list of obstacles to the realization of values.
- Session 7 Checking the activities of session 6, introducing fusion with life story, emphasizing living the moment, offering practical strategies for solving problems, using metaphors, planning for commitment to values, reporting steps taken for values, and thinking about the accomplishments of sessions.
- Session 8 Concluding the concepts taught during sessions, asking members to explain their accomplishments, planning for the rest of their lives, implementing post-test and finally appreciating respondents for participating in the research.

#### Table 1. Descriptive Information of Women With Breast Cancer in Trial and Control Groups

Variable	Trial Group	Control Group
Number of Participants	20	20
Average Age	48.11	46.08
Marital Status Bachelor Married	2 18	1 19
Education Status High school Diploma Bachelor Degree Master Degree	5 11 4 0	8 10 2

#### Results

The descriptive information of participants are shown in table 1. The data presented in table 2 show the mean and standard deviation of trial and control group before and after interventions. As can be seen, in the trial group, the mean of perceived stress in pretest (26.80) is greater than the mean of perceived stress in post-test (22.45). In addition, the mean score of marital satisfaction in pre-test (103.15) is lower than the mean score of marital satisfaction in post-test (116.90). The mean score of symptoms of depression in pre-test (20.50) is greater than the mean score of symptoms of depression in post-test (12.60). In order to perform couple comparison of

Variable/grous	Stage	Mean	Standard Deviation
Perceived Stress			
Trial	Pre-test	26.80	6.51
111d1	Post-test	22.45	5.79
Control	Pre-test	27.45	6.37
Control	Post-test	28.30	6.19
Marital Satisfaction			
Trial	Pre-test	103.15	17.08
11141	Post-test	116.90	16.43
Control	Pre-test	96.30	14.61
Control	Post-test	94.85	13.11
Symptoms of Depression			
Trial	Pre-test	20.50	7.36
11141	Post-test	12.60	5.90
Control	Pre-test	18.40	5.44
	Post-test	19.0	5.73

Table 2. Mean and Standard Deviation	n of Trial and Control Group	, Before and After Interventions
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 Table 3: Comparison of Perceived Stress, Marital Satisfaction, and Depression in Trial and Control Group

 Before and After Interventions

Variable	Groups	Mean Differences Before and After Interventions	Standard Deviation Differences Before and After Interventions	t-test	DF	P-value
Perceived Stress Trial Control		4.35 -0.85	3.70 2.25	5.25 -1.68	19 19	0.000 0.110
Marital Satisfaction Trial Control		-13.7 1.45	8.65 3.56	-7.11 1.82	19 19	0.000 0.084
Depression Trial Control		7.90 -0.60	5.12 1.78	6.88 -1.50	19 19	0.000 0.150

the effect of punctuations before and after interventions, we used *t*-test (table 3).

According to "t" and its significance, a significant difference was shown between the scores of perceived stresses in the trial group before and after interventions (*t*-test = 5.25, P<001). However, there is not a significant difference between the scores of perceived stresses of the control group (*t*-test = -1.68, P = 0.110). There is a significant difference between the scores of marital satisfactions in the trial group before and after interventions (*t*-test = -7.11, P<0.001). But, there is not a significant difference between the scores of marital satisfactions in the control group before and after interventions (*t*-test = -7.11, P<0.001). But, there is not a significant difference between the scores of marital satisfactions in the control group before and after interventions (*t*-test = 1.82, P = 0.084). A significant difference

was shown between the scores of symptoms of depression control group before and after interventions (*t*-test=6.88, P<0.001). But, there is not a significant difference between the scores of symptoms of depression in the control group before and after interventions (*t*- test = -1.50, P = 0.150). According to the effect of independent variable (ACT) on the scores of dependent variables (perceived stress, marital satisfaction, and symptoms of depression), we used multivariate covariance analysis (MANCOVA). First, tests such as Pillai's Trace, Wilks' Lambada, Hotelling's Trace, and Roy's Largest Root were administered at the same time to examine the effect of ACT factor on the 3 dependent variables.

Table 4.	Results (	of Multiva	riate Co	ovariance	Analysis	of Perceived	Stress,	Marital	Satisfaction,	and Syr	nptoms
of Depre	ession in	Control an	d Trial	Groups,	Controllin	ng the Effect	of Prete	est			

Test title	Value	F	Df hypothesis	Df error	P-value	eta square	Statistical competence
Pillalis Trace	0.407	8.24	3	36	0.000	0.407	0.98
Wilks' Lambada	0.593	8.24	3	36	0.000	0.407	0.98
Hotelling's Trace	0.687	8.24	3	36	0.000	0.407	0.98
Roy's Largest root	0.687	8.24	3	36	0.000	0.407	0.98

The data presented in the above table show that by controlling pretest, there is a significant difference between women with breast cancer in trial and control groups in terms of perceived stress, marital satisfaction, or symptoms of depression (P < 0.001).

 $\eta$  square, which was 0.40, shows that 40% of personal differences is in the post-test scores of perceived stress, marital satisfaction, and symptoms of depression relating to the ACT effect. In order to understand in which variable, the observed difference

Variable/change source	SS	DF	MS	F	P-value	η square
Perceived stress						
Pre-test	1061.47	1	1061.47	128.48	0.000	0.77
Group	281.97	1	281.97	34.13	0.000	0.48
Error	305.67	37	8.26			
Marital satisfaction Pre-test Group Error	6953.56 2509.04 1448.78	1 1 37	6953.56 2509.04 29.15	177.58 64.07	0.000 0.000	0.83 0.63
Symptoms of depression Pre-test Group Error	845.72 611.88 443.07	1 1 37	845.72 611.88 11.97	70.62 51.09	0.000 0.000	0.65 0.58

 Table 5. Results of Single-variable Covariance Analysis of Perceived Stress, Marital Satisfaction, and

 Symptoms of Depression in Control and Trial Groups, Controlling the Effect of Pretest

is significant, we used single-variable covariance analysis (ANCOVA) for each dependent variable. The results of this analysis have been presented in table 4.

As shown in table 5, the probability of accepting "zero" hypothesis for comparing trial and control groups in post-test of all variables (perceived stress, marital satisfaction, and symptoms of depression) is lower than 0.05; in other words, after adjusting the scores of pretests, there are significant interaction differences between groups' respondents in post-test of all variables.

The data presented in table 1 and 4 show that, according to the mean score of perceived stress of the trial group (22.45), compared to the mean score of perceived stress of the control group (28.30), ACT effect significantly reduces stress in post-test (F = 34/13, P<0.001); and 48% of personal differences in the score of perceived stress is associated with the effect of ACT. On the other hand, according to the mean score of marital satisfaction in the trial group (116.90), compared to the mean score of marital satisfaction has significantly increased marital satisfaction in the trial group (F = 64.07, P<0.001); and 63% of personal differences in the scores of marital satisfactions is associated with ACT. In addition, according to the mean score of depression in the trial group (12.60), compared to the mean score of depression in the control group (19.0), ACT has significantly reduced symptoms of depression in the trial group (F = 51.09, P<0.001); and 58% of personal differences in the scores of symptoms of depression is associated with ACT.

#### Discussion

The findings of the present study indicated that group therapy training based on acceptance and commitment significantly reduced perceived stress, symptoms of depression, and enhanced marital satisfaction in women with breast cancer. During the treatment, patients learned to neutralize negative thoughts (observation of simplified thoughts) and to practice acceptance.

These practices led the patients to adopt a more neutral attitude towards their social and psychological problems. Knowledge and awareness growth in their thoughts and reactions might help them be aware of negative reactions and make them avoid conflict with the old life patterns as well as not to choose conflicting behaviors. In fact, this psychological training helps them experience negative thoughts and reactions in a new way. In other words, by improvement of mental flexibility, change in perception of the person, acceptance of negative thoughts and feelings, reduction of experimental avoiding, comprehensive awareness and considering the observer himself, faulting individual roles and temporary features, recreation of values, and commitment to achieve them, ACT can reduce psychological problems of women with breast cancer. In general, the research results are in line with the findings of other investigations, such as Mojtabaie and Asghari<sup>32</sup> that demonstrated that ACT significantly reduce symptoms of depression in women with breast cancer. Mohabbat-Bahar et al.<sup>33</sup> indicated that ACT is an effective method to reduce anxiety and depression in women with breast cancer. Moreover, Feros *et al.*<sup>34</sup> concluded that ACT is as effective as other psychotherapy approaches, including behavioral-cognitive therapy approach on the improvement of quality of life in patients with cancer. Another study carried out by Najvani et al.<sup>35</sup> indicated that ACT can be introduced as an intervention approach in treatment of depression in women with breast cancer. In addition, the main purpose of ACT is increasing the acceptance rate of thoughts and feelings associated with cancer as well as enhancing the psychological flexibility which leads to such changes in patients. The results of other studies in the field of using ACT show that implementing such an intervention provides psychological flexibility in patients with cancer, leading to changes in stress level, life quality, pain, and behavior.<sup>34</sup> As was mentioned before, mindawareness is one of the basic concepts in the ACT model, whose findings have shown that managing stress, based on mind-awareness, can play an effective role in reducing psychological stress and enhancing life quality and spiritual health.<sup>36</sup> Since treatment of cancer requires strategies that help patients adapt to their therapy procedures, psychological trainings can play an effective role in realizing this goal, especially acceptancecommitment therapy approach which believes that patients are never considered to be losers, damaged, or hopeless. In fact, this approach is always a type of rehabilitation which believes that all individuals deserve a life based on values, wealth, and meaning. In addition, pain is considered a part of life not an external essence for getting rid of life; and advancement has not been defined as an absolute level of success, but it includes the moment and consideration of future in order to reach a valuable life.<sup>37</sup> Generally, the acceptance of main ACT processes makes commitment easy. Commitment processes include the use of experimental rehearsals and metaphors, helping patients verbally express goals (i.e. values) that they purposefully and meaningfully select in their lives, and make commitment to consistent behavior changes that are led by these values (i.e. committed action); in addition, the acceptance of personal thoughts, emotions, and feelings has been designed to make the process of navigated committed action easy.<sup>38</sup>

Finally, it can be said that implementing group therapy interventions based on acceptance and commitment not only provides the possibility to accept emotions but also helps patients get rid of their useless methods for controlling and eliminating negative emotions and experiences, leading them to commitment to action based on values; this process helps reduce stress and depression as well as increase the components of marital satisfaction in women with breast cancer. Hence, we can use ACT as a proper intervention to enhance patients' capabilities in order to adapt to cancer and reduce its psychological effects. This therapy could be used as a complementary psychotherapy and medicine therapy in order to reduce stress and symptoms of depression and enhance marital satisfaction in women with breast cancer.

According to the results of this and other studies on effectiveness of psychological interventions on chronic disease, it is suggested that oncology specialists not only rely solely on medical treatment but also refer the patients to consultation and psychotherapy centers to use psychological interventions based on ACT in line with the improvement of mental health and the use of effective strategies to deal with the pain caused by the disease.

Time interval between the stages of pretest and posttest as well as the lack of follow-up stage to assess the extent of education impacts (ACT) on patients with breast cancer were limitations of the study.

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#### References

- 1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69-90.
- Akbari ME, Khayamzadeh M, Khoshnevis SJ, Nafisi N, Akbari A. Five and ten years survival in breast cancer patients mastectomies vs. breast conserving surgeries personal experience. Iranian Journal of Cancer Prevention. 2008;1(2):53-6.
- 3. So WK, Marsh G, Ling WM, Leung FY, Lo JC, Yeung M, *et al.* The symptom cluster of fatigue, pain, anxiety, and depression and the effect on the quality of life of women receiving treatment for breast cancer: a multicenter study. Oncol Nurs Forum. 2009;36(4):E205-14.
- Spiegel D, Riba MB. Managing anxiety and depression during treatment. Breast J. 2015;21(1):97-103.
- 5. Luecken LJ, Compas BE. Stress, coping, and immune function in breast cancer. Ann Behav Med. 2002;24(4):336-44.
- 6. Wang F, Liu J, Liu L, Wang F, Ma Z, Gao D, *et al.* The status and correlates of depression and anxiety among breast-cancer survivors in Eastern China: a population-based, crosssectional case-control study. BMC Public Health. 2014;14:326.
- Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. BMJ. 2005;330(7493):702.
- 8. Lee SJ, Fairclough D, Parsons SK, Soiffer RJ, Fisher DC, Schlossman RL, *et al.* Recovery after stem-cell transplantation for hematologic diseases. J Clin Oncol. 2001;19(1):242-52.
- Khan MA, Sehgal A, Mitra AB, Agarwal PN, Lal P, Malik VK. Psycho-behavioral impact of mastectomy. Indian Journal of Applied Psychology. 2000;26 (1-2):65-71.
- 10. Weis J. Support groups for cancer patients. Support Care Cancer. 2003;11(12):763-8.
- 11. Shields CG, Rousseau SJ. A pilot study of an intervention for breast cancer survivors and their spouses. Fam Process. 2004;43(1):95-107.
- Ciaramella A, Poli P. Assessment of depression among cancer patients: the role of pain, cancer type and treatment. Psychooncology. 2001;10(2):156-65.
- 13. Lampic C, Thurfjell E, Bergh J, Sjoden PO. Short- and long-term anxiety and depression in women recalled after breast cancer screening. Eur J Cancer. 2001;37(4):463-9.
- 14. Pirl WF, Siegel GI, Goode MJ, Smith MR. Depression in men receiving androgen deprivation therapy for prostate cancer: a pilot study. Psychooncology. 2002;11(6):518-23.
- 15. Bowers L, Boyle DA. Depression in patients with
advanced cancer. Clin J Oncol Nurs. 2003;7(3):281-8.

- Nordin K, Berglund G, Glimelius B, Sjoden PO. Predicting anxiety and depression among cancer patients: a clinical model. Eur J Cancer. 2001;37(3):376-84.
- 17. Mitchell AJ, Chan M, Bhatti H, Halton M, Grassi L, Johansen C, *et al.* Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. Lancet Oncol. 2011;12(2):160-74.
- 18. Mahdavi A, Taghizadeh MA, Esazadeh S, Salehi S, Darabi R, Rafigh P. Relationship Between Depression and Perceived Stress With Marital Satisfaction In Individuals Suffering Cancer and Cardiovascular Diseases. Advances in Natural and Applied Sciences. 2015;9(2):50-8.
- 19. Twohig MP. Acceptance and Commitment Therapy: Introduction. Cognitive and Behavioral Practice. 2012;19(4):499-507.
- 20. Wetherell JL, Afari N, Ayers CR, Stoddard JA, Ruberg J, Sorrell JT, *et al.* Acceptance and Commitment Therapy for generalized anxiety disorder in older adults: a preliminary report. Behav Ther. 2011;42(1):127-34.
- 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. Forman EM, Herbert JD, O'Donohue W, Fisher J. New directions in cognitive behavior therapy: Acceptance-based therapies. General principles and empirically supported techniques of cognitive behavior therapy. 2009:77-101.
- 23. Kahl KG, Winter L, Schweiger U. The third wave of cognitive behavioural therapies: what is new and what is effective? Curr Opin Psychiatry. 2012;25(6):522-8.
- 24. Dionne F, Ngo TL, Blais MC. [The psychological flexibility model: a new approach to mental health]. Sante Ment Que. 2013;38(2):111-30.
- 25. Dionne F, Blais MC, Monestes JL. [Acceptance and commitment therapy in the treatment of chronic pain]. Sante Ment Que. 2013;38(2):131-52.
- 26. Hulbert-Williams NJ, Storey L, Wilson KG. Psychological interventions for patients with cancer: psychological flexibility and the potential utility of Acceptance and Commitment Therapy. Eur J Cancer Care (Engl). 2015;24(1):15-27.
- 27. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
- Fowers BJ, Olson DH. Enrich marital inventory: a discriminant validity and cross-validation assessment. J Marital Fam Ther. 1989;15(1):65-79.
- 29. Asoodeh MH. Factors affecting successful

marriage from the perspective of happy couples: Tehran University; 2010.

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- 30. Rajabi GR. Psychometric properties of Beck depression inventory short form items (BDI-13). Journal of Iranian Psychologists. 2005; 1(4):291–8.
- Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: An experiential approach to behavior change: Guilford Press; 1999;304.
- 32. Mojtabaie M, Asghari N. Effectiveness of acceptance and commitment therapy (act) to reduce the symptoms of depression in women with breast cancer. Indian Journal of Fundamental and Applied Life Sciences. 2014;4(2):522-7.
- 33. Mohabbat-Bahar S, Maleki-Rizi F, Akbari ME, Moradi-Joo M. Effectiveness of group training based on acceptance and commitment therapy on anxiety and depression of women with breast cancer. Iran J Cancer Prev. 2015;8(2):71-6.
- 34. Feros DL, Lane L, Ciarrochi J, Blackledge JT. Acceptance and Commitment Therapy (ACT) for improving the lives of cancer patients: a preliminary study. Psychooncology. 2013;22(2):459-64.
- 35. Najvani BD, Neshatdoost HT, Abedi MR, Mokarian F. The effect of acceptance and commitment therapy on depression and psychological flexibility in women with breast cancer. Zahedan Journal of Research in Medical Sciences. 2015;17(4).
- 36. Fish JA, Ettridge K, Sharplin GR, Hancock B, Knott VE. Mindfulness-based cancer stress management: impact of a mindfulness-based programme on psychological distress and quality of life. Eur J Cancer Care (Engl). 2014;23(3):413-21.
- 37. Hayes SC, Pistorello J, Levin ME. Acceptance and Commitment Therapy as a Unified Model of Behavior Change Ψ. The Counseling Psychologist. 2012;40(7):976-1002.
- 38. BrickerJ, Tollison S. Comparison of motivational interviewing with acceptance and commitment therapy: a conceptual and clinical review. Behav Cogn Psychother. 2011;39(5):541-59.



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# Archives Of Breast Cancer

## The Relationship Between Polymorphic Fibroblast Growth Factor Receptor (FGFR) Gene and Breast Cancer Risk

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#### ABSTRACT

**Background:** Genetic factors associated with cancer have been widely investigated and several polymorphisms have been connected with breast cancer. Breast cancer (BC) can be considered one of the most popular reasons of death among women. BC, likewise, is the second cause of death in Iran. The present research aims at determining the frequency of the fibroblast growth factor receptor (FGFR) gene polymorphism in patients with breast cancer.

**Methods:** The FGFR family is one of the tyrosine kinase receptors containing 4 members, whose pathway is activated in many tumors. We assessed, for the first time, these polymorphisms and their consequences on the breast cancer risk association in an Iranian sporadic population-based case-control study including 126 patients with breast cancer and 160 controls using a PCR-RFLP-based assay.

**Results:** The analyses of the experimental and control groups indicated that homozygote genotype FGFR4 Gly/Gly has the highest frequency in experimental and control groups (30.4% and 18.9%). The main genotype FGFR4 Gly/Gly risk factors in our population were: ArgGly /GlyGly, OR = 2.359, 95% CI = 0.208 - 4.621, P = 0.001; ArgArg/ArgGly, OR = 0.412, 95% CI = 0.082 - 0.547, P = 0.078, ArgArg/GlyGly, OR = 0.076, 95% CI = 0.030 - 0.189, P = 0.26.

**Conclusions:** A significant association was observed between breast cancer risk and FGFR4 GlyGly and ArgGly polymorphism.

#### Introduction

Of several types of tyrosine kinase receptors, stem cell factor, platelet derived growth factor, epidermal growth factor, macrophage colony stimulating factor, and insulin receptors could be named. The FGFR family is one of the tyrosine kinase receptors containing 4 members, which have a highly conserved structure: extracellular ligandbinding domain, transmembrane domain, and intracellular tyrosine-kinase domain.<sup>1</sup>

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There are 4 high-affinity tyrosine kinase FGF receptors (FGFR1-4).<sup>1,2</sup> The 4 FGFRs produce ligand-binding specific isoforms by tissue-specific alternative mRNA splicing of the genes.<sup>3-7</sup> FGFs play a critical role in cell signaling.<sup>8</sup> FGF-FGFR complex activates the intracellular tyrosine kinase, mediating signal transduction through the direct phosphorylation of adaptor proteins.<sup>9</sup> Complex FGF signaling networks are crucial in the multiple cell biological activities like proliferation, differentiation, mitogenesis, migration, and apoptosis, and are, hence, implicated in tumor genesis,<sup>10-12</sup> the development of solid tumors, cancers, and other malignancies. A germ-line polymorphism in the FGFR4 gene (rs351855), resulting in the expression of FGFR4 containing either glycine (Gly388) or arginine (Arg388) at codon 388, and a G to A conversion was discovered, resulting in the substitution of glycine by arginine at position 388 in the transmembrane domain of the receptor.

On the other hand, a few studies discussed its role and association with breast cancer risk.

Breast cancer is a progressively significant reason of death among women; hence, the present study aimed at clarifying the role of FGFR4 (rs1966265, rs376618, and rs351855) as a high-risk breast cancer using of PCR-RFLP method.

To the best of our knowledge, the present research is the first attempt to investigate the association between the polymorphisms of FGFR4 gene and the risk of breast cancer in an Iranian context.

#### Methods

#### Patients data

The analyses were performed for 126 patients and 160 controls genotyped for FGFR4 and aged between 35 to 55.

The Local Ethical Committee of Islamic Azad University approved the present study from patient and control group rights point of view.

Before the onset of the study, the blood samples were collected from patients and controls. The participants were genotyped for the FGFR4 SNP, using genomic DNA obtained from peripheral blood lymphocytes. DNA was separated from peripheral blood, using FelxiGene DNA extraction kit (Qiagen Germany).

#### Genotyping

The polymorphisms were distinguished utilizing a modified PCR-RFLP method.<sup>13,14</sup> The PCR primers were synthesized by TAG Copenhagen A/S. Primers for each polymorphism is as follow. The primers ofthe FGFR4 were forward 5'GACCGCAGCA GCGCCCGAG GCCAG-3' and revers 5'-AGAGGGAAGAGGGAGAGCTTCTG-3' .<sup>15</sup> The cycling conditions were 94°C, 30 sec; 60°C, 30 sec; 72°C, 60 sec (35 cycles). The PCR products were digested with 1 unit of BstNI (New England BioLabs); and the amplified fragment of 168-bp was cut into fragments, the Arg 388 allele by 2 distinctive fragments of 82 and 27 bp, and a single distinctive band of 109 bp was observed for the Gly388 allele and separated on a 6% acrylamide gel.

This method can detect all 3 possible genotypes for the polymorphism: homozygous wild type, heterozygous variant type, and homozygous variant type.

The genotypes and allelic frequencies of FGFR4 polymorphisms in the experimental and control groups were analyzed by  $\chi 2$  and Fisher's exact tests.

#### Results

The present study was the first attempt to clarify the role of FGFR4 as a high-risk breast cancer using PCR-RFLP method.

There was a significant association between FGFR4 polymorphism and breast cancer risk.

The analyses of the experimental (126 patients) and control groups (160 patients) indicate that homozygote genotype FGFR4 Gly/Gly has a high frequency (30.4%, 18.9%) in both groups.

On the other hand, the heterozygote genotype in FGFR4 Arg/Arg has an increase in frequency in control group compared with experimental group (2.1 in patients and 17.1 in control group).

Table 1 showed some information on the Genotype FGFR4 Gly/Gly most common risk factors: ArgGly /GlyGly, OR = 2.359, 95% CI = 0.208 - 4.621, P=0.001\*\*\*; ArgArg/ArgGly, OR = 0.412, 95% CL = 0.082 - 0.547, P=0.078\*\*; ArgArg /GlyGly, OR = 0.076, 95% CI = 0.030 - 0.189, P = 0.26.

In the present study, we found a significant relationship between the presences of FGFR4 Gly/Gly and breast cancer.

#### Discussion

The FGFR4, MTHFR, and HFE genes are related to neoplastic diseases development, particularly, FGFR4 or Fibroblast growth factor receptor 4, involved in cancer progression.<sup>16</sup>

The FGFR4 Gly388Arg polymorphism in the transmembrane domain of the receptor contributes to genetic susceptibility to cancer cell invasiveness and

Table 1. FOR K4 genotype nequencies in (70) in experimental and control groups									
Study group	Ν	Arg/Arg	Gly/Gly	Arg/Gly					
Experimental	126	6 (2.1%)	87 (30.4%)	33 (11.5%)					
Control	160	49 (17.1%)	54 (18.9%)	57 (19.9%)					
Total	286	55 (19.2%)	141 (49.3%)	90 (31.5%)					
Fable 2. Comparise	on of genotypes								
Genotype FGFR4		OR	95% CL	P-value					
ArgArg /ArgGly		0.412	0.082 - 0.547	$0.078^{*}$					
ArgGly /GlyGly		2.359	0.208 - 4.621	≤0.001					
ArgArg /GlyGly		0.076	0.030 - 0.189	0.26					

Table 1. FGFR4 genotype frequencies [n (%)] in experimental and control groups

\* P<= 0.05



clinical chemo-resistance in breast cancer.<sup>17</sup>

The FGFR4 Arg (388) allele was observed to be associated with a poor prognosis according to several studies that showed single nucleotide polymorphism (SNP) at codon 388 (Gly or Arg) of fibroblast growth factor receptor 4 (FGFR4) was related with prognosis in patients with colorectal carcinoma, head and neck SCC, and several types of cancer including breast cancer.<sup>17,18</sup>

In a study in 2011, appeal in the genetic susceptibility to cancers led to a rising attention to the study of polymorphisms of genes engaged in tumor geneses. We had already published a study, in which 2 common functional polymorphisms existed in the *MTHFR* gene, C677T (rs1801133) and A1298C (rs1801131).<sup>19</sup> Thus, we decided to select this SNP FGFR4, because we had already worked upon FGFR2, even interionic and FGFR1.<sup>20,21</sup>

As a matter of fact, they were enzymes playing a central role in the methyl group metabolic pathway, which were engaged in both DNA methylation and DNA synthesis.

Some scientists challenged the existence of an association between polymorphisms and different cancer; as an example, Nan *et al.*<sup>22</sup> could not find any evidence for associations among these 7 genetic variants and the risks of melanoma and nonmelanocytic skin cancer in Caucasian American women. Bange *et al.*<sup>15</sup> concluded that cancer evolution and tumor cell motility are associated with the FGFR4 Arg (388) allele in German population.

However, many studies discussing other types of cancers found significant association, for example: Marme et al.<sup>23</sup> found that FGFR4 Arg388Gly genotype strong context specific prognostic factor in patients with advanced ovarian cancer in German population. Xu et al.<sup>24</sup> proposed that the FGFR4 Gly388Arg polymorphism most likely contribute to susceptibility to cancer, particularly in Asians. Besides, Arg (388) allele might be associated with increased risks of prostate cancer. Tanuma et al.<sup>25</sup> discovered that the majority of patients with homozygous Arg388 FGFR4 and whereas >90% patients carrying homozygous Gly388 FGFR4 were excellent predictors of the prognosis for oral squamous cell carcinoma for (OSCC) in Japanese patients.

Da Costa Andrade *et al.*<sup>18</sup> demonstrated that the FGFR4 Arg (388) allele was associated with survival in head and neck squamous cell carcinoma in Brazilian population. Wang *et al.*<sup>26</sup> found that the FGFR-4 Arg388 allele was associated with both an increased incidence and clinical aggressiveness of prostate cancer in American population.

In a study conducted by Morimoto *et al.*<sup>27</sup> a significant correlation was found between FGFR4 Gly388 and prognosis in patients with soft tissue sarcoma in Japanese population. Wang *et al.*<sup>26</sup> conclude that Homozygosity for the FGFR-4 Arg

allele was strongly associated with prostate cancer in white men with pelvic lymph node metastasis.

Dutra *et al.*<sup>26</sup> found Arg388 genotype and expression, as a novel marker of prognosis in squamous cell carcinoma of the mouth and oropharynx in Brazilian population.

Finally, the results of a research suggested that FGFR-4 induced to breast cancer. Thussbas *et al.*<sup>27</sup> and Xu *et al.*<sup>24</sup> found that FGFR4 Arg388 genotype was a marker for breast cancer progression in German and Asian population. Findings of the Seitzer *et al.*<sup>30</sup> study indicated FGFR4 Arg388 allele as a functional prognostic marker for breast cancer progression in mouse.

In brief, other scholars found best association in FGFR4 Arg, and Arg/Gly, with breast cancer risk.

However, in my research studies, there were a strong association between FGFR4 Gly/Gly, and breast cancer risk.

Hence, in our study, it can be concluded that there is a relation between the presence of FGFR4 Gly/Gly and increase breast cancer risk.

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#### References

- Itoh N, Ornitz DM. Evolution of the Fgf and Fgfr gene families. Trends Genet 2004; 20(11): 563-9.
- 2. Ornitz DM, Itoh N. Fibroblast growth factors. Genome Biol 2001; 2(3): REVIEWS3005.
- Chellaiah AT, McEwen DG, Werner S, Xu J, Ornitz DM. Fibroblast growth factor receptor (FGFR) 3. Alternative splicing in immunoglobulin-like domain III creates a receptor highly specific for acidic FGF/FGF-1. J Biol Chem 1994; 269(15): 11620-7.
- Ornitz DM, Xu J, Colvin JS, McEwen DG, MacArthur CA, Coulier F, *et al.* Receptor specificity of the fibroblast growth factor family. J Biol Chem 1996; 271(25): 15292-7.
- Orr-Urtreger A, Bedford MT, Burakova T, Arman E, Zimmer Y, Yayon A, *et al.* Developmental localization of the splicing alternatives of fibroblast growth factor receptor-2 (FGFR2). Dev Biol 1993; 158(2): 475-86.
- 6. Peters KG, Werner S, Chen G, Williams LT. Two FGF receptor genes are differentially expressed in epithelial and mesenchymal tissues during limb formation and organogenesis in the mouse. Development 1992; 114(1): 233-43.
- Stark KL, McMahon JA, McMahon AP. FGFR-4, a new member of the fibroblast growth factor receptor family, expressed in the definitive endoderm and skeletal muscle lineages of the

mouse. Development 1991; 113(2): 641-51.

- 8. Johnson DE, Williams LT. Structural and functional diversity in the FGF receptor multigene family. Adv Cancer Res 1993; 60: 1-41.
- Klint P, Claesson-Welsh L. Signal transduction by fibroblast growth factor receptors. Front Biosci 1999; 4: D165-77.
- DmowskiWP, Ding J, Shen J, Rana N, Fernandez BB, Braun DP. Apoptosis in endometrial glandular and stromal cells in women with and without endometriosis. Hum Reprod 2001; 16(9):1802-8.
- Eswarakumar VP, Lax I, Schlessinger J. Cellular signaling by fibroblast growth factor receptors. Cytokine Growth Factor Rev 2005; 16(2): 139-49.
- 12. Taniguchi F, Harada T, Ito M, Yoshida S, Iwabe T, Tanikawa M, *et al.* Keratinocyte growth factor in the promotion of human chorionic gonadotropin production in human choriocarcinoma cells. Am J Obstet Gynecol 2000; 182(3): 692-8.
- 13. Artamonov VV, Liubchenko LN, Shabanov MA, Babenko OV, Nemtsova MV, Zaletaev DV. Association of polymorphism of genetic markers of CYP19 and CYP17 with sporadic breast cancer. Mol Biol (Mosk) 2003; 37(6): 975-82.
- 14. Shin MH, Lee KM, Yang JH, Nam SJ, Kim JW, Yoo KY, *et al.* Genetic polymorphism of CYP17 and breast cancer risk in Korean women. Exp Mol Med 2005; 37(1): 11-7.
- 15. Bange J, Prechtl D, Cheburkin Y, Specht K, Harbeck N, Schmitt M, *et al.* Cancer progression and tumor cell motility are associated with the FGFR4 Arg(388) allele. Cancer Res 2002; 62(3): 840-7.
- 16. Batschauer AP, Cruz NG, Oliveira VC, Coelho FF, Santos IR, Alves MT, et al. HFE, MTHFR, and FGFR4 genes polymorphisms and breast cancer in Brazilian women. Mol Cell Biochem. 2011;357(1-2):247-53.
- 17. da Costa Andrade VC, Parise O, Jr., Hors CP, de Melo Martins PC, Silva AP, Garicochea B. The fibroblast growth factor receptor 4 (FGFR4) Arg388 allele correlates with survival in head and neck squamous cell carcinoma. Exp Mol Pathol 2007; 82(1): 53-7.
- Spinola M, Leoni VP, Tanuma J, Pettinicchio A, Frattini M, Signoroni S, *et al.* FGFR4 Gly388Arg polymorphism and prognosis of breast and colorectal cancer. Oncol Rep 2005; 14(2):415-9.
- 19. Hosseini M, Houshmand M, Ebrahimi A. MTHFR polymorphisms and breast cancer risk. Arch Med Sci 2011; 7(1): 134-7.
- 20. Reintjes N, Li Y, Becker A, Rohmann E, Schmutzler R, Wollnik B. Activating somatic FGFR2 mutations in breast cancer. PLoS One 2013;8(3): e60264.
- 21. Jang M, Kim E, Choi Y, Lee H, Kim Y, Kim J,

*et al.* FGFR1 is amplified during the progression of in situ to invasive breast carcinoma. Breast Cancer Res 2012; 14(4): R115.

- 22. Nan H, Qureshi AA, Hunter DJ, Han J. Genetic variants in FGFR2 and FGFR4 genes and skin cancer risk in the Nurses' Health Study. BMC Cancer 2009; 9: 172.
- 23. Marme F, Hielscher T, Hug S, Bondong S, Zeillinger R, Castillo-Tong DC, *et al.* Fibroblast growth factor receptor 4 gene (FGFR4) 388Arg allele predicts prolonged survival and platinum sensitivity in advanced ovarian cancer. Int J Cancer 2012; 131(4): E586-91.
- 24. Xu W, Li Y, Wang X, Chen B, Wang Y, Liu S, et al. FGFR4 transmembrane domain polymorphism and cancer risk: a meta-analysis including 8555 subjects. Eur J Cancer 2010; 46(18):3332-8.
- 25. Tanuma J, Izumo T, Hirano M, Oyazato Y, Hori F, Umemura E, *et al.* FGFR4 polymorphism, TP53 mutation, and their combinations are prognostic factors for oral squamous cell carcinoma. Oncol Rep 2010; 23(3): 739-44.
- 26. Wang J, Stockton DW, Ittmann M. The fibroblast growth factor receptor-4 Arg388 allele is associated with prostate cancer initiation and progression. Clin Cancer Res 2004; 10(18 Pt 1): 6169-78.
- 27. Morimoto Y, Ozaki T, Ouchida M, Umehara N, Ohata N, Yoshida A, *et al.* Single nucleotide polymorphism in fibroblast growth factor receptor 4 at codon 388 is associated with prognosis in high-grade soft tissue sarcoma. Cancer 2003; 98(10): 2245-50.
- 28. Dutra RL, de Carvalho MB, Dos Santos M, Mercante AM, Gazito D, de Cicco R, *et al.* FGFR4 profile as a prognostic marker in squamous cell carcinoma of the mouth and oropharynx. PLoS One 2012; 7(11): e50747.
- 29. Thussbas C, Nahrig J, Streit S, Bange J, Kriner M, Kates R, *et al.* FGFR4 Arg388 allele is associated with resistance to adjuvant therapy in primary breast cancer. J Clin Oncol 2006; 24(23): 3747-55.
- 30. Seitzer N, Mayr T, Streit S, Ullrich A. A single nucleotide change in the mouse genome accelerates breast cancer progression. Cancer Res. 2010;70(2):802-12.

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### The Challenge of Distinguishing Cylindroma of the Breast from Adenoid Cystic Carcinoma: A Case Report and Review of this **Rare Tumor**

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lesions within the breast.

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#### ABSTRACT

Background: Cylindroma of the breast is a rarely described tumor that closely resembles its dermal counterpart.

finding of a left breast mass on screening mammography. On histologic examination, the tumor was found to be consistent with cylindroma of the breast.

such as solid type adenoid cystic carcinoma, and this uncertainty may lead to a

dilemma in treatment options. These patients should be followed closely, as long-

term outcome data is not available given the uncommon occurrence of these

Keywords: Breast cylindroma, adenoid cystic carcinoma, synchronous breast cancer

#### Introduction

Cylindroma of the breast (CB) is a particularly rare lesion. It has been considered to be a benign lesion, similar to its dermal counterpart, and is often referred to as a dermal analogue tumor. Dermal cylindromas are more common, usually found as a solitary lesion, but may occur as multiple lesions in patients with Brooke-Spiegler Syndrome (BSS). Individuals with BSS develop multiple skin tumors such as cylindromas, spiradenomas, and trichoepitheliomas due to a mutation in the CYLD1 tumor suppressor gene that results in an error in apoptosis regulation. These tumors usually originate in hair follicles or sweat glands and are most often benign but may be malignant.<sup>1-7</sup> While dermal cylindromas are usually found on the head and neck, CBs arise from the breast parenchyma without involvement of the overlying skin, which is not

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surprising as breast tissue originates from the primordium that gives rise to the cutaneous apocrine glands.<sup>1-7</sup> Cylindromas may also be found in the salivary glands, lungs and kidneys. We report an individual case of an asymptomatic breast tumor discovered on screening mammography and discuss the challenge of differentiating CB from adenoid cystic carcinoma. We review the current literature and the difficulty of establishing a definitive diagnosis and treatment plan.

#### **Case Presentation**

A 55-year-old female with a history of bilateral subglandular saline breast implants presented with an asymptomatic abnormal finding on initial screening mammography classified as BIRADS 4 (Figure 1-A). On exam, she was found to have a wellcircumscribed 8mm palpable mass located in the 10 o'clock position, approximately 5 cm from the nipple without involvement of the overlying skin. There was no lymphadenopathy.Ultrasound confirmed a 0.8 cm lobulated hypoechoic mass in the left upper inner quadrant with irregular borders and increased vascularity (Figure 1-B). An excisional

Case presentation: We report a case of a 55-year-old woman with an incidental **Conclusions:** Generally considered to be a benign lesion, cylindroma of the breast may be challenging to differentiate from morphologically similar tumors,

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biopsy was recommended due to the close proximity of the lesion to the implant.

The patient had a significant maternal family history of cancer, including a perimenopausal aunt with breast cancer. Her mother and other maternal aunts, uncles, and cousins were diagnosed with colon, lung, prostate, brain, and unknown primary cancers between the ages of 40-60 years. Hereditary risk and genetic testing were reviewed and genetic screening revealed a PMS2 gene mutation, which is linked to Lynch syndrome. This mutation results in dysfunction of a DNA mismatch repair gene that increases the lifetime risk of colorectal, gynecologic, gastrointestinal, brain, sebaceous and various other types of cancer.

An ultrasound guided excisional biopsy revealed a low grade basaloid tumor of uncertain malignant potential with an involved margin, consistent with but not definitively, a cylindroma (Figure 2). The receptor status was ER-neg, PR-neg, Her2/neu-neg. The cells stained positive for p63 at the periphery. Due to the histologic similarity to adenoid cystic carcinoma (ACC), the decision was made to return to the operating room for re-excision. No residual tumor was seen on pathology.

In considering evaluation and/or treatment of the axilla, a review of the literature describes CB as a benign lesion treated with wide local excision alone. However, some authors consider CB as a variant of low-grade ACC with relatively indolent behavior.<sup>8</sup> Reports of low-grade ACC noted lymph node involvement in less than 2% of patients, usually in tumors greater than 2 cm. Therefore, a sentinel lymph node biopsy was not performed. Medical and radiation oncology consultations were completed postoperatively. Further testing included a colonoscopy that was normal as well as a CT scan of the chest, abdomen and pelvis with no evidence of synchronous lesions or metastasis. Systemic therapy was not indicated. However, as decreased local recurrence with postoperative radiation in the ACC population has been demonstrated, and because recurrence may be difficult to detect early on mammography due to shielding from the breast implant, adjuvant radiation therapy was recommended in the face of the patient's gene mutation. The patient tolerated 50 Gy of external beam radiation to the tumor bed and remains well 4 months after treatment. Close follow-up is planned with physical examination and yearly mammogram.



Figure 1. A) Spot compression craniocaudal view shows a lobulated mass (arrow) in the upper inner quadrant adjacent to the silicon implant (double arrow) B) Ultrasound shows a lobulated hypoechoic solid mass (arrow) with irregular borders closely adherent to the implant capsule (double arrow)



Figure 2. A) Low power image shows the relatively well circumscribed nature of the tumor composed of small, uniform basaloid cells B) Jigsaw pattern of growth with focal infiltration into fat C) Prominent hyaline basement membrane material (arrow) surrounding nests of basaloid cells

#### Discussion

Cylindroma of the breast often has borderline histologic features similar to those of adenoid cystic carcinoma, posing a dilemma for the clinician in predicting the benign or malignant behavior of these tumors, resulting in the potential for under or overtreatment. The rare nature of these tumors makes it difficult to accumulate adequate clinical data for physicians to help patients make informed decisions on the best course of treatment<sup>8</sup>

A cylindroma originating in the breast is rare with only 15 reported cases in the literature. Accurate identification can be challenging. Distinguishing CB from solid variant ACC, basaloid type is paramount to guiding treatment. CB classically displays well circumscribed, non-encapsulated nests and trabeculae of central basaloid cells and peripheral myoepithelial cells arranged in a characteristic jigsaw pattern surrounded by a thick periodic acid Schiff positive basement membrane that is immunoreactive for collagen IV. Immunohistochemical analysis typically demonstrates central basaloid cells that stain positive for cytokeratin 7 (CK 7), eccrine ducts that stain positive for CEA, peripheral myoepithelial cells that stain positive for p63, and Langerhans cells that stain positive for S100 protein. ACC similarly demonstrates nests and trabeculae of basaloid cells, as well as negative receptor status for estrogen, progesterone and Her2/neu receptors. However, it lacks the thick, continuous basement membrane and Langerhans cells. It also shows nuclear atypia, mitotic figures, invasive growth patterns, and possible mucin production.<sup>1-8</sup>

While ACC has an excellent prognosis, it may manifest an aggressive and malignant course. Patients with local recurrence and distant metastasis have been reported; therefore, it is generally treated by mastectomy or lumpectomy with adjuvant radiation therapy. CB, however, is thought to be a benign tumor, treated with wide local excision alone.<sup>6</sup> Fusco et al. recently proposed an additional method for differentiating CB from ACC using molecular analyses in addition to histological and immunohistochemical evaluations. They utilized whole-exome sequencing to confirm a clonal somatic CYLD site mutation, solidifying the diagnosis of CB as opposed to ACC.9 This added diagnostic evaluation may play a key role in selecting the proper treatment for patients where tumor identification is in doubt, such as in our case where, after multi-specialist review and discussion with our patient, the tumor was treated as ACC by the radiation oncologist.

Most authors agree that cylindroma of the breast was first described by Gokaslan *et al.* in 2001.<sup>1</sup> Our review of this and all subsequent case reports found the mean follow up period was 22 months (6 months-5 years, although several (n=8) of the reported cases do not specify follow up data). Aside from a single report of a CB malignancy published in 1939 by Nayer (likely not a cylindroma), no metastasis or recurrence has been reported for confirmed CB.<sup>2,3,5-7,10</sup>

Interestingly, of the 15 cases reviewed, 5 women were found to have synchronous invasive breast cancer (2 invasive lobular, 3 invasive ductal), more than triple the population incidence for synchronous breast cancer. While the cylindroma was an incidental finding on final pathology in these cases, it does raise questions about a possible association of this rare tumor with other malignant lesions. Bilateral breast MRI screening was considered but in light of limited data in these uncommon cases and plans for close follow-up, it was not recommended in this setting.

In conclusion, breast cylindroma is a rare tumor, and there is limited data to predict the long-term behavior and malignant potential of this tumor. Similarities with adenoid cystic carcinoma make the correct diagnosis challenging in some cases. Further investigation and follow up of women with cylindroma of the breast will be necessary to provide the best treatment and prognosis for patients.

#### **Conflict of Interest**

We have no financial or personal relationships to disclose. There is no funding source. Consent was not required for this paper.

#### References

- Gokaslan ST, Carlile B, Dudak M, Albores-Saavedra J. Solitary cylindroma (dermal analog tumor) of the breast: a previously undescribed neoplasm at this site. Am J Surg Pathol 2001; 25(6): 823-6.
- 2. Albores-Saavedra J, Heard SC, McLaren B, Kamino H, Witkiewicz AK. Cylindroma (dermal analog tumor) of the breast: a comparison with cylindroma of the skin and adenoid cystic carcinoma of the breast. Am J Clin Pathol 2005; 123(6): 866-73.
- Mahmoud A, Hill DH, O'Sullivan MJ, Bennett MW. Cylindroma of the breast: a case report and review of the literature. Diagn Pathol 2009; 4: 30.
- Vujhini SK, Kolte SS, Sushma Y, Satarkar RN. Cytomorphology of solitary cylindroma of the breast. Indian J Pathol Microbiol 2011; 54(1): 204-5.
- 5. Taghipour S, Shiryazdi SM, Sharahjin NS. Cylindroma of the breast in a 72-year-old woman with fibrocystic disease first misdiagnosed as a malignant lesion in imaging studies. BMJ Case Rep 2013; 2013:
- 6. Aggarwal R, Gupta O, Yadav YK, Dogra S. Cylindroma of the breast: a rare case report. Int J Trichology 2013; 5(2): 83-5.
- 7. Nonaka D, Rosai J, Spagnolo D, Fiaccavento S, Bisceglia M. Cylindroma of the breast of skin

adnexal type: a study of 4 cases. Am J Surg Pathol 2004; 28(8): 1070-5.

- 8. Rakha EA, Badve S, Eusebi V, Reis-Filho JS, Fox SB, Dabbs DJ, *et al.* Breast lesions of uncertain malignant nature and limited metastatic potential: proposals to improve their recognition and clinical management. Histopathology 2016; 68(1): 45-56.
- 9. Fusco N, Colombo PE, Martelotto LG, De Filippo MR, Piscuoglio S, Ng CK, *et al.* Resolving quandaries: basaloid adenoid cystic carcinoma or breast cylindroma? The role of massively parallel sequencing. Histopathology 2016; 68(2): 262-71.
- 10. Nayer HR. Case report section; cylindroma of the breast with pulmonary metastases. Dis Chest 1957; 31(3): 324-7.

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### DOI: 10.19187/abc.20174132-36 Synchronous Idiopathic Granulomatosis Mastitis and Breast **Cancer: A Case Report and Review of Literature**

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#### ABSTRACT

Background: Idiopathic granulomatous mastitis (IGM) is a rare benign breast disease, which can mimic breast cancer. As the managements of IGM and breast cancer are entirely different and the initial clinical manifestations are similar in several cases, it is very important to differentiate them.

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Case presentation: We reported a 48-year-old female patient with IGM and breast cancer. She was referred to the outpatient clinic with bilateral large masses and clinical impression of bilateral breast cancer with inflammatory features in the right side. Through pathology, the diagnoses of invasive ductal carcinoma (IDC) for the left breast lesion and IGM for the right breast lesion were confirmed, respectively. Incisional biopsy was performed for the right breast lesion to rule out breast cancer and to make sure of the diagnosis of IGM.

Conclusion: To the best of our knowledge, breast cancer and IGM were reported only in two studies. Although IGM is not the underlying cause of breast malignancy, the diagnosis of breast cancer should always be kept in mind. Any other lesions in these patients should be assessed well to rule out breast cancer.

Introduction Idiopathic granulomatous mastitis (IGM) is a rare benign condition of the breast, which can mimic breast cancer.<sup>1</sup> The clinical presentation of IGM may range from a mass, thickening, nipple discharge, dimpling to nipple retraction and edema, which are usually accompanied by concurrent inflammatory signs, for instance, redness, peau d'orange, and skin edema. While the therapeutic options for the management of IGM are limited to medical therapy, mainly anti-inflammatory drugs, and no rule is found

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for chemotherapy, hormonal therapy, and radiation therapy. Breast cancer is mostly managed by surgery and chemoradiotherapy as well as hormonal therapy. Thus, while the managements of these two diseases are quite different, the initial presentations are identical in most cases; therefore, it is of utmost importance to differentiate IGM from breast cancer.<sup>2</sup> In the present study, a patient with IGM was presented as she was diagnosed with breast cancer, too.

#### **Case Presentation**

A 48-year-old female patient was referred to KBDI (Kaviani Breast Disease Institute) with the chief complains of bilateral large palpable masses in her both breasts and nipple retraction in her right breast during the last four months. She had no history of breast and ovarian cancer in her first and second degree relatives, and there were no important

Through the physical examination, a 50-mm hard, ill-defined, and fixed-to-skin mass was palpated in her right breast with marked diffused edema, redness, peau d'orange, and nipple retraction in the central part of the same breast. In her contralateral breast, there was also a 35-mm hard, illdefined movable mass in upper central part of the breast. Ultrasonography (US) revealed a large hypoechoic mass with irregular borders and multiple echcogenic foci and inflammatory changes, indicating mastitis, which had been spread between 7 o'clock to 11 o'clock as well as to the subareolar region in right breast. Likewise, right lymphadenopathy with cortical thickening with preserved fatty hilum (the largest lymph node 32\*11mm with 6mm cortical thickening) was reported in US. Moreover, a hypo-echoic speculated mass measuring 30\*50mm with foci of calcification and oval shape lymph node with compressed fatty hilum (16\*9mm) was observed in the left breast and axillary region. Mammography showed distortion and mass-like lesion in both breasts in the context of extremely dense breast; CNB was performed for both masses, and through pathology, the diagnosis of stromal fibrosis, ductal epithelial hyperplasia, and granulomatous inflammation with micro-abscess formation was confirmed for the right breast lesion (figure 1) and invasive ductal carcinoma with the presence of lobular cancerization in left breast mass.

(figure 2). The results of further bacterial (including mycobacterium tuberculosis, etc), and fungal cultures of right breast specimen were negative. Incisional biopsy was performed in the right breast lesion to confirm the diagnosis of IGM and to rule out of the malignancy in the right breast. Metastatic work-up including multi slice CT-scan of thorax, abdomen, pelvic and whole body bone scan were performed and there is no evidences of metastasis in other parts. After the reconfirmation of the diagnosis in open biopsy and based on multidisciplinary team discussion (MDT) recommendation, the treatment was started with neo-adjuvant chemotherapy (Adriamycin, Cyclophosphamide and Docetaxel regimen for 6 courses every 3 weeks). Two weeks after neo-adjuvant chemotherapy, no palpable masses were observed in neither of the breasts and only small thickening in upper central part of the left breast and in upper-medial part of the right breast without edema and peaud' orange were remained. (figure 3) Magnetic resonance imaging (MRI) results showed a single mass measured 20\*12mm without satellite lesions at the end of chemotherapyin left breast. A wire was placed under the guide of mammography to localize the small lesion in order to perform breast conservative therapy. (figure 4) Breast conserving surgery and oncoplastic repair (round block technique) and sentinel lymph node biopsy was performed on the



Figure 1. IIdioapthic granulomatous mastitis. A- Terminal duct lobular units are infiltrated by mixed inflammatory cells including many histiocytes (poorly-formed granulomas). The arrow shows residue of a ductule. (H&E, x100), B- Mixed inflammatory infiltrate is shown with higher magnification. (H&E, x400), C- This low power view confirms the lobulocentric distribution of inflammation. The arrows depict the terminal duct lobular units. (H&E, x40), D- A terminal duct is surrounded by inflammatory cells including epithelioid histiocyte, poorly formed granulomas. (H&E, x100)



Figure 2. Left lesion - Invasive ductal carcinoma



Figure 3. Patient before surgery with wire localization in left breast



Figure 4. Mammography of both breasts with wire placed for localization of the lesion before surgery: Craniocaudal views (Left), Mediolateral views (Right)

left breast cancer. Pathology results reported the remnant of invasive ductal carcinoma. The treatment was pursued by the radiation therapy and hormonal therapy with Tamoxifen.

#### Discussion

IGM was first recognized and described by Kessler and Wolloch in 1972 as a chronic, benign, and rare condition, being able to mimic a variety of inflammatory and malignant diseases of the breast.<sup>3</sup> Although the etiology and pathogenesis of IGM is not completely recognized, several studies have suggested that multiple factors might trigger IGM, including metabolic or hormonal alterations and imbalances (pregnancy, birth, breast-feeding, hyperprolactinemia, oral contraceptive pills, a1antitrypsin deficiency, autoimmune reactions, direct response to trauma, granulomatous inflammation of the some other endocrine glands (e.g. thyroid), smoking, chemical irritation, and unknown microbiological agents).<sup>3-6</sup> The disease often occurs in reproductive ages, particularly in postpartum or breast-feeding periods.<sup>5,7</sup> The case presented in this study had no history of pregnancy and lactation within preceding 10 years; she had only taken oral contraceptives for a short period of time. The other risk factors were all negative in the patient.

The diagnosis of IGM in most of the patients is

challenging and it can be made based on clinical, radiological, and pathological features. Thus, the diagnosis is often accompanied by marked delay Most of the patients are referred to breast clinics with painful and palpable breast masses, being usually ill-defined and firm. The symptoms often occur unilaterally and they are sometimes concomitant with inflammatory signs and symptoms, such as breast edema, breast erythema, peau d'orange, sinuses tracts, fistula formation, nipple retraction, skin changes, and skin hyperemia.<sup>4,6,7</sup> In most cases, the clinical presentation of IGM mimics breast cancer especially locally advanced or inflammatory breast cancer. Considering the patient presented in this study, the clinical presentation of the disease resembled bilateral breast cancer.

The radiological features of IGM are usually nonspecific and often mimic carcinoma.<sup>8</sup> Focal asymmetric density is the most common finding in mammography, which is similar to the findings of malignancies.<sup>9,10</sup>

The most common findings in ultrasound imaging are parenchymal heterogeneity, irregular hypoechoic mass, and abscess formation.<sup>11</sup> MRI cannot distinguish between IGM and inflammatory carcinoma in many patients.<sup>12</sup> The definitive diagnosis of IGM is determined by histological study. The radiologic findings in the presented patient were, likewise, in favor of bilateral breast cancer. Nevertheless, to confirm the diagnosis and based on high clinical suspicion, incisional biopsy was performed from the same breast and the diagnosis of IGM was confirmed.

Histologically, IGM is characterized by nonnecrotizing granuloma formation with a localized infiltrate of multi-nucleated giant cells and chronic inflammatory picture with epithelioid histiocytes, lymphocytes, plasma cells, and polymorph leukocytes.<sup>5, 6</sup> Our patient had bilateral masses, the right-side mass with IGM diagnosis was large, fixed, and ill-defined mass with breast edema and peaud' orange that helped diagnosis clinically alike inflammatory breast cancer; however, in histopathology, it was reported as IGM.

The management of IGM is controversial and ranging from observation (50% of patients healing spontaneously), surgical treatment (wide local excision, incisional biopsy, drainage, mastectomy, etc.), to medical treatment (corticosteroids, Methotrexate, non-steroidal anti-inflammatory drug, immunosuppressive agent, such as Azathioprine , antibiotics, and more recently, rifampin).<sup>6,13-17</sup> We selected observation for the right breast and neo-adjuvant chemotherapy for the left breast cancer.

Importantly, malignancy and all other possible causes of mastitis must be excluded before making the diagnosis of IGM. Once diagnosed, the treatment is often difficult and needs patients' information about the natural history of the disease and takes considerable time. Considering the scientific evidence showing that more than 50 percent of IGM cases are misdiagnosed for breast cancer, histopathological examination should be used for definitive diagnosis.<sup>5,18</sup>

Considering the relationship of breast cancer and mastitis, a cohort study was conducted in Sweden can be mentioned. In this large-scale study, the assessment was performed on 8411 patients with sign and symptoms of mastitis. Among them, 106 women were diagnosed with breast cancer, subsequently. They found no association between breast cancer and inflammatory disease of the breast.<sup>19</sup> There existed no evidence, in which IGM or any other types of mastitis could be considered a risk factor for breast cancer.

To the best of our knowledge, only two studies reported breast cancer and IGM together. In 2013, Limaiem *et al.*<sup>20</sup> presented a case of a 77-year-old female with coexisting lobular granulomatous mastitis and ductal carcinoma in a single lesion. They concluded that it is possible for a patient to have two separate pathologies of breast carcinoma and inflammatory disease of breast simultaneously. They also suggested that dysplasia due to chronic inflammation can cause breast carcinoma. In the patient reported in our study, breast cancer and IGM were revealed in two separate lesions in different breasts at same time.

In a study conducted by Mazlan *et al.* in 2012,<sup>21</sup> the authors reported a 34-year-old female who had recurrent episodes of IGM and breast abscess in her right breast for 8 years. She was treated by high-dose corticosteroid and antibiotics. Her disease was under good control in this period. Later, she was presented with the progressive loss of vision and, subsequently, the diagnosis of orbital tumor due to distant metastasis of an unknown primary tumor. Consequently, the biopsy of right breast showed infiltrating ductal carcinoma. The authors discussed the possibility of relationship between chronic granulomatous mastitis and malignancy as a risk factor. In our case, breast cancer appeared in contralateral breast in the same time.

In several studies, granulomatous mastitis was presented by multifocal or bilateral lesions.<sup>22,23</sup> When the main lesion is diagnosed as IGM, most of the surgeons consider all the lesions as IGM and do not proceed to have tissue diagnosis for each lesion. The results of the present report showed that it is possible for a patient with bilateral breast lesions to have breast cancer and IGM at the same time.

Although IGM is not the underlying cause of breast malignancy, based on the similar presentation at the first referral and in the follow up visits, the diagnosis of breast cancer should always be kept in mind. Any new lesions in these patients should be evaluated to rule out breast cancer at first and the treatment of IGM can be continued, thereafter.

#### **Conflict of Interest**

The authors have no conflict of interest in the content of this article.

#### References

- 1. Ergin AB, Cristofanilli M, Daw H, Tahan G, Gong Y. Recurrent granulomatous mastitis mimicking inflammatory breast cancer. BMJ Case Rep 2011:bcr0720103156.
- Lai EC, Chan WC, Ma TK, Tang AP, Poon CS, Leong HT. The role of conservative treatment in idiopathic granulomatous mastitis. Breast J 2005; 11(6): 454-6.
- Kessler E, Wolloch Y. Granulomatous mastitis: a lesion clinically simulating carcinoma. Am J Clin Pathol 1972; 58(6): 642-6.
- 4. Altintoprak F, Kivilcim T, Ozkan OV. Aetiology of idiopathic granulomatous mastitis. World J Clin Cases 2014; 2(12): 852-8.
- 5. Fazzio RT, Shah SS, Sandhu NP, Glazebrook KN. Idiopathic granulomatous mastitis: imaging update and review. Insights Imaging 2016; 7(4): 531-9.
- 6. Benson JR, Dumitru D. Idiopathic granulomatous mastitis: presentation, investigation and management. Future Oncol



2016; 12(11): 1381-94.

- Pereira FA, Mudgil AV, Macias ES, Karsif K. Idiopathic granulomatous lobular mastitis. Int J Dermatol 2012; 51(2): 142-51.
- Sripathi S, Ayachit A, Bala A, Kadavigere R, Kumar S. Idiopathic granulomatous mastitis: a diagnostic dilemma for the breast radiologist. Insights Imaging 2016; 7(4): 523-9.
- 9. Yilmaz E, Lebe B, Usal C, Balci P. Mammographic and sonographic findings in the diagnosis of idiopathic granulomatous mastitis. Eur Radiol 2001; 11(11): 2236-40.
- MemisA, Bilgen I, Ustun EE, Ozdemir N, Erhan Y, Kapkac M. Granulomatous mastitis: imaging findings with histopathologic correlation. Clin Radiol 2002; 57(11): 1001-6.
- 11. Kiyak G, Dumlu EG, Kilinc I, Tokac M, Akbaba S, Gurer A, *et al.* Management of idiopathic granulomatous mastitis: dilemmas in diagnosis and treatment. BMC Surg 2014; 14: 66.
- 12. Rieber A, Tomczak RJ, Mergo PJ, Wenzel V, Zeitler H, Brambs HJ. MRI of the breast in the differential diagnosis of mastitis versus inflammatory carcinoma and follow-up. J Comput Assist Tomogr 1997; 21(1): 128-32.
- 13. Kaviani A, Noveiry BB, Jamei K, Rabbani A. How to manage idiopathic granulomatous mastitis: suggestion of an algorithm. Breast J 2014; 20(1): 110-2.
- 14. Mizrakli T, Velidedeoglu M, Yemisen M, Mete B, Kilic F, Yilmaz H, *et al.* Corticosteroid treatment in the management of idiopathic granulomatous mastitis to avoid unnecessary surgery. Surg Today 2015; 45(4): 457-65.
- 15. Gurleyik G, Aktekin A, Aker F, Karagulle H, Saglamc A. Medical and surgical treatment of idiopathic granulomatous lobular mastitis: a benign inflammatory disease mimicking invasive carcinoma. J Breast Cancer 201215(1): 119-23.
- 16. Farouk O, Abdelkhalek M, Abdallah A, Shata A, Senbel A, Attia E, *et al.* Rifampicin for Idiopathic Granulomatous Lobular Mastitis: A Promising Alternative for Treatment. World J Surg 2017:
- 17. Sheybani F, Sarvghad M, Naderi HR, Gharib M. Treatment for and clinical characteristics of granulomatous mastitis. Obstet Gynecol 2015; 125(4): 801-7.
- Bani-HaniKE, Yaghan RJ, Matalka, II, Shatnawi NJ. Idiopathic granulomatous mastitis: time to avoid unnecessary mastectomies. Breast J 2004; 10(4): 318-22.
- 19. Lambe M, Johansson AL, Altman D, Eloranta S. Mastitis and the risk of breast cancer. Epidemiology 2009; 20(5): 747-51.
- 20. Limaiem F, Khadhar A, Hassan F, Bouraoui S, Lahmar A, Mzabi S. Coexistence of lobular granulomatous mastitis and ductal carcinoma: a

fortuitous association? Pathologica 2013;105(6): 357-60.

- 21. Mazlan L, Suhaimi SN, Jasmin SJ, Latar NH, Adzman S, Muhammad R. Breast carcinoma occurring from chronic granulomatous mastitis. Malays J Med Sci 2012; 19(2): 82-5.
- 22. Velidedeoglu M, Kilic F, Mete B, Yemisen M, Celik V, Gazioglu E, *et al.* Bilateral idiopathic granulomatous mastitis. Asian J Surg 2016; 39(1): 12-20.
- 23. Choi SH, Jang KS, Chung MS. Bilateral granulomatous mastitis with a different etiology. Cancer Biomark 2015; 15(3): 333-8.





### DOI: 10.19187/abc.20174237-38 Breast Cancer Screening: A New Era?

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By the time the initial clinical trials has started population screening with mammography, this technique has widely been used in many countries. The Health Insurance Plan (HIP) trial started in 1963 and was offered to women with an age ranging from 40 to 64. The participants was randomized in 2 groups: the first were followed up with clinical exploration and mammography, while clinical follow up was offered to the control group. Ten years later, the mortality of the intervention group was reduced by 30% compared to the control group. Other trials, like the Two-County, showed similar results.<sup>1</sup>

Despite these good results, some controversies about mammographic screening have arisen in the last decade. The arguments of the critics against mammography can be grouped in several categories: a) small, if any, reduction of mortality due to mammography (inadequate aleatorization of the participants in the clinical trials, which makes it impossible to calculate the real mortality decrease), b) the rate of locally advanced breast cancers has not significantly decreased despite the use of the mammographic screening, c) false positive results that generate anxiety and unnecessary biopsies, d) overdiagnosis and overtreatment (less aggressive cancers are diagnosed and treated, which would be unlikely to kill the patient), e) high risk women (bearing BRCA mutations) do not achieve benefit from mammographic screening, but from MRI follow-up, f) the sensitivity of mammography decreases to 50% in dense breasts, and g) radioinduced cancers.<sup>2</sup>

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In the last decade, new technologies have demonstrated to increase the sensitivity of mammography, especially in dense breasts. On one hand, Digital Breast Tomosynthesis (DBT), a new breast imaging technique capable of showing multiple slices of the breast parallel to the detector, is a well-established technique.<sup>3</sup> Multiple studies have reported an important increase in the sensitivity of mammography, up to 43%. The majority of the cancers detected by DBT were invasive cancers, which means that overdiagnosis should not be relevant.<sup>3</sup> On the other hand, ultrasound (US) is, nowadays, widely used as a complementary technique after mammography. In a recent Japanese study (J-START), US has demonstrated to significantly increase the sensitivity of mammography and to reduce the rate of interval cancers.<sup>4</sup> As reported with DBT, the vast majority of US-detected cancers were invasive. The Automated Breast Ultrasound System (ABUS) offers the technologists the possibility to perform a 3D US examination of both breasts, which can be later reviewed by the radiologist in a work station.<sup>3,4</sup>

Finally, Magnetic Resonance Imaging (MRI) is, nowadays, considered the technique of choice for the screening of high risk patients (mutations BRCA 1&2), because MRI shows the highest sensitivity compared to conventional techniques.<sup>5</sup>

Taking into account the referred controversies about screening and the new imaging techniques, the question is: How should the breast cancer screening be designed in this century? It is not easy to answer this question, but, in my opinion, the key is to classify the patients according to their risk to develop breast cancer in future. High risk patients do not achieve benefit from participating in screening programs based on mammography; therefore, these patients should undergo screening with MRI. Fortunately, these patients are only a minority of the female population.

Middle risk patients, including women with positive family history of breast cancer as well as



histologically proven risk lesions (atypical ductal hiperplasia, lobular carcinoma in situ) could benefit from adding DBT or even US after mammography. Finally, women with fatty breasts and no positive family history for breast cancer, likely the majority of women in a screening, could be studied with mammography alone (or combined with DBT at the most). By using these criteria, the sensitivity of breast cancer screening could increase and the interval cancers decrease; and this is the way to reduce the mortality due to breast cancer.

#### References

- 1. Strax P. Results of mass screening for breast cancer in 50,000 examinations. Cancer. 1976;37(1):30-5.
- Gotzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? Lancet. 2000;355(9198):129-34.
- Skaane P, Bandos AI, Gullien R, Eben EB, Ekseth U, Haakenaasen U, *et al.* Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology. 2013;267(1):47-56.
- 4. Ohuchi N, Suzuki A, Sobue T, Kawai M, Yamamoto S, Zheng YF, *et al.* Sensitivity and specificity of mammography and adjunctive ultrasonography to screen for breast cancer in the Japan Strategic Anti-cancer Randomized Trial (J-START): a randomised controlled trial. Lancet. 2016;387(10016):341-8.
- 5. Sardanelli F, Podo F, Santoro F, Manoukian S, Bergonzi S, Trecate G, et al. Multicenter surveillance of women at high genetic breast cancer risk using mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (the high breast cancer risk italian 1 study): final results. Invest Radiol. 2011;46(2):94-105.



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### An Overview on Positron Emission Mammography in Breast Cancer Detection and Follow up: Particular Concerns in Iran as a Developing Country

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Generally, about 2 million new patients with breast cancer are diagnosed annually.<sup>1</sup> Breast cancer is the most prevalent cancer among females and it causes a considerable burden on both patients and health system.<sup>2</sup> The screening and diagnostic procedures including staging, restaging, and evaluating the response to treatment are costly. Yet, the need for rapid detection and diagnosis of the tumor and its recurrence pushes the imaging methods to the edge of science for incremental accuracy. The currently available breast imaging methods cover most encountered clinical needs, but certain areas may still be in need of increasing accuracy and preciseness. The possible clinical use of positron emission mammography (PEM) was reviewed in the current study and cons and pros as well as indications for clinical use were compared with other imaging modalities. Clinical indications for any imaging of breast can be purified into 5 categories: screening, diagnosis and staging, restaging, evaluating the response to treatment, and directing the biopsy tools.<sup>2</sup> The advantages and drawbacks of routine available breast imaging are roughly addressed in the following lines for every available tool.

Mammography is the essential method for breast cancer screening and diagnosis. The sensitivity is highly variable ranging from optimal to modest (95%-40%) in different populations, while the specificity is not also favorable. Nevertheless, the risk benefit ratio of the mammography is obviously confirmed and mammography is documented as the

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only diagnostic tool to reduce the mortality.<sup>3</sup> Albeit, there are certain concerns regarding the cost effectiveness of the breast cancer screening.<sup>4</sup> The reports of accuracy of breast specific gamma imaging (BSGI), a newly revived functional imaging, for lesion detection and diagnosis are noticeable. The sensitivity is reported to be more than 90% and the specificity is seemingly superior to that of MRI.<sup>5</sup> Whatever the result of the debits would be, mammography is the milestone method for the detection and diagnosis of breast cancer.<sup>3</sup>

Ultrasonography (US) is a complementary diagnostic tool for mammography and clinical examination for detection and characterization of lesions. It is not expensive; it imposes no ionizing radiation to the patient or the operator. US is valuable for the diagnosis of primary lesion and recurrences, the evaluation of the axilla, and guiding the biopsy. US has perfect negative predictive value (i.e. 100%) in optimal operating condition for the diagnosis of malignancy in palpable mass; the diagnosis of ill-defined masses including invasive lobular carcinoma are the weak points. US has proved its sufficient accuracy to locate additional foci of malignancy.<sup>6,7</sup>

Although the mammography and US are the essential imaging tools for diagnosis, the MRI is required in particular populations including those with dense breasts and those with post-surgical scars as well as BRCA positive patients or their first relatives. MRI illustrates the extent of the tumor and detects the ipsilateral and contralateral tumors and assists determining the need for neo-adjuvant therapy.<sup>8</sup> The role of MRI is underscored for the detection of the invasive component of ductal carcinoma in situ, primary lesion in node positive patients without known primary, and in breast Paget's disease.<sup>9</sup> MRI is also used to follow up the patients under 50 years, who are at high risk (>20%)



for recurrence. MRI is, likewise, radiation free with perfect sensitivity (>90%) and moderate specificity (>70%).<sup>9</sup>

The detectors of conventional PET scanners are rings with trans-axial field of view of about 20 to 40 cm. These devices are designed to image the whole body and patient's bed; the detector may move to cover the bed length. The spatial resolution of the PET/CT state-of-art scanners are smaller than 10 mm.<sup>10</sup> The indication of <sup>18</sup>F-FDG-PET/CT is for the evaluation of distant metastases in high risk patients, restaging, and the assessment of response to treatment. Apparently, there is no place for <sup>18</sup>F-FDG PET/CT for screening or the diagnosis of primary lesion.<sup>11</sup> The physical limitations of PET scanners, which unfavorably reduce spatial resolution, are many comprising that the detected line of response (LOR) contains the annihilation, not the emission source, acollinearity effect, relatively large size of detector element, and the depth of interaction error (parallax effect). Despite the fact that the contrast of the PET/MR is better and the privileges of MR are added to those of PET, the technical issues are more concerning, because the attenuation correction cannot be done as perfectly as in PET/CT. PEM is a dedicated breast PET with smaller field of view and minimal distance between the detectors and detector to the breast. The smaller detector elements and reduced parallax effect provided better in-plane full width at half maximum (FWHM) and spatial resolution was improved to 2 to3 mm. The sensitivity is also optimal and scatter is low because the detectors are in proximity and even touching the breast.<sup>12 18</sup>F-FDG accumulates in the hypermetabolic areas, the specification of malignant tumor cells. The detection of ipsilateral malignant lesion by conventional PEM is superior to MRI. Furthermore, PEM is a perfect alternative to MRI with similar expenses when MRI is prohibited for a certain contraindication including small metallic clips and foreign bodies in the eye or brain, cardiac defibrillator, and spinal prostheses as well as in patients susceptible to renal failure or sensitive to Gadolinium.<sup>13,</sup>

There are 2 major types of dedicated positron emission breast scanners: 2 planar or curved separated detector heads integrated with compression paddles (i.e. conventional PEM) and rotating detectors or ring shaped detectors (i.e. fully tomographic). The major drawbacks of both designs are image in quality of degradation at the edge of field of view, radiation, and high operation cost. In conventional PEM, the detection of chest wall lesions is further hesitated. Conventional PEM is 2 dimensional with notable limitation for the deep breast near the chest wall. The only commercial PEM in US, Flex Solo II (Naviscan, San Diego, USA)<sup>15</sup>, has  $6 \times 16.4$  cm<sup>2</sup> paired moving detectors with  $24 \times 16.4$  cm<sup>2</sup> compression paddles. PEM tubes are position sensitive and lutetium yttrium oxyorthosilicate (LYSO) crystal is cutted at 2×2×13 mm,<sup>3</sup> making a construction of  $13 \times 13$  arrays of crystal. Scan time is about 7 to10 minutes, 60 to80 minutes after 5 to13 mCi <sup>18</sup>F-FDG injection. For bilateral craniocaudal and mediolateral oblique views, 28 to 40 minutes is required. The scanner enables direct biopsy of the lesion employing an isotope guiding rod. In Iran, MAMMI (OncoVision, Valencia, Spain)<sup>16</sup> is logistically available with less than a half of investment for a whole body PET scanner. The scanner has 1 or 2 moving complete LYSP rings and images are fully tomographic (transaxial  $\times$  long-axial field of view 17 $\times$ 4 cm<sup>2</sup>). Scan time is between 5 to 15 minutes; 1 hour after about 5 mCi<sup>18</sup> F-FDG injection. Because the injected dose and the device costs are half of those of <sup>18</sup>F-FDG PET/CT, the scan would plausibly cost 20% to 40% of  $^{18}$  F-FDG PET/CT scans.<sup>1,12</sup>

In the advent of <sup>18</sup>F-FDG production in Iran as a developing country, <sup>18</sup>F-FDG PET/CT and PEM would be more available in future. While the indication of the PET is well documented and its cost is radically high compared to US and MRI, about 10 times more expensive and not covered by the insurance, the PEM is expected to be available with more reasonable cost and possibly indication for lesion detection, characterization of the tumor, evaluation of the extent of the invasion, local recurrence and response to treatment, and guiding the biopsy.<sup>17</sup> The compound of <sup>18</sup>F-FDG PET/CT and <sup>18</sup>F-FDG PEM at a single visit may be the optimal diagnostic tool admixing the whole body advantages of <sup>18</sup>F-FDG PET/CT with high local resolution of PEM with reduced total cost. It is noteworthy that had the PET/MR passed its current technical problems including attenuation correction, it may become the standard procedure in future.<sup>18</sup> In the perspective of nuclear medicine, better diagnosis and follow up are expected for patients with breast cancer in the horizon of perfect screening in which the BSGI may play a role and optimal follow up of the patients with PET/MR and <sup>18</sup>F-FDG PET/CT in addition to PEM.

According to the meta-analysis by Caldarella *et al.*, PEM is specific and sensitive for the evaluation of suspicious breast lesion with device.<sup>19</sup> Eight studies were included in the meta-analysis comprising 873 women with early breast lesions. The sensitivity and specificity values of PEM using FDG were 85% (95% CI, 83%-88%) and 79% (95% CI, 74%-83%), respectively; however, high statistical heterogeneity was observed among the included studies.

To sum up, mammography is the gold standard for screening, concerning the sensitivity in particular populations.<sup>3</sup> US assists the screening, diagnosis, and confirmation of the findings in mammography and further assessments of the findings in other



imaging modalities and examinations at any stage through the follow up.<sup>6</sup> MRI, with its optimal spatial resolution, is a powerful tool for the evaluation of local extension, multiplicity, and multi-centricity at staging time. MRI can evaluate response to therapy after chemotherapy either adjuvant or neoadjuvant.<sup>8,9</sup> BSGI promotes lesion diagnosis.<sup>20</sup> PET overwhelming power is the ability to assess the metabolic activity and the nature of whole body imaging. <sup>18</sup>F-FDG PET/CT is optimal for metastasis workup, restaging, and the evaluation of response to treatment. PEM may fill certain gaps in this scenario. The drawback for <sup>18</sup>F-FDG PET/CT is its low spatial resolution; had the spatial resolution been improved,<sup>18</sup>F-FDG PET/CT would have been an optimal imaging modality. Even though the whole body imaging privilege is lost in PEM, it has become a potent scanner with high spatial resolution, which makes the method suitable for diagnosis, staging, the detection of local recurrence, and response to therapy. Not only the cost and availability of PEM has already hindered its clinical use, but also notable inherited drawbacks including the radiation remain to be addressed.

It may be concluded that simultaneous PEM and whole body FDG-PET with a single injection promise optimal staging and restaging diagnostic performance. The high spatial resolution of PEM for the evaluation of local recurrence and the strength of whole body PET for the detection of distant metastases add up to optimize the diagnostic performance. Also, PEM may be useful for the diagnosis of suspected breast lesions and future studies should be directed to evaluate the clinical cost benefit concerns for screening and diagnostic performance of PEM.

#### References

- 1. Miyake KK, Nakamoto Y, Togashi K. Current Status of Dedicated Breast PET Imaging. Current Radiology Reports. 2016;4(4):1-11.
- 2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.
- 3. Drukteinis JS, Mooney BP, Flowers CI, Gatenby RA. Beyond mammography: new frontiers in breast cancer screening. Am J Med. 2013; 126(6):472-9.
- 4. Aslund M, Cederstrom B, Lundqvist M, Danielsson M. Scatter rejection in multislit digital mammography. Med Phys. 2006;33(4):933-40.
- 5. Tadwalkar RV, Rapelyea JA, Torrente J, Rechtman LR, Teal CB, McSwain AP, *et al.* Breast-specific gamma imaging as an adjunct modality for the diagnosis of invasive breast cancer with correlation to tumour size and grade. Br J Radiol. 2012;85(1014):e212-6.
- 6. Gundry KR. Breast Ultrasound: Indications and Findings. Clin Obstet Gynecol. 2016;59(2):380-93.
- 7. Fornage BD. Local and regional staging of

invasive breast cancer with sonography: 25 years of practice at MD Anderson Cancer Center. Oncologist. 2014;19(1):5-15.

- Hylton N. MR imaging for assessment of breast cancer response to neoadjuvant chemotherapy. Magn Reson Imaging Clin N Am. 2006;14(3):383-9, vii.
- 9. Menezes GL, Knuttel FM, Stehouwer BL, Pijnappel RM, van den Bosch MA. Magnetic resonance imaging in breast cancer: A literature review and future perspectives. World J Clin Oncol. 2014;5(2):61-70.
- Glass SB, Shah ZA. Clinical utility of positron emission mammography. Proc (Bayl Univ Med Cent). 2013;26(3):314-9.
- 11. Muller FH, Farahati J, Muller AG, Gillman E, Hentschel M. Positron emission mammography in the diagnosis of breast cancer. Is maximum PEM uptake value a valuable threshold for malignant breast cancer detection? Nuklearmedizin. 2016;55(1):15-20.
- 12. Martins MV. Positron Emission Mammography. Mammography Techniques and Review2015. p. 69-32.
- 13. Lind P, Igerc I, Beyer T, Reinprecht P, Hausegger K. Advantages and limitations of FDG PET in the follow-up of breast cancer. Eur J Nucl Med Mol Imaging. 2004;31 Suppl 1:S125-34.
- 14. Vercher-Conejero JL, Pelegri-Martinez L, Lopez-Aznar D, Cozar-Santiago Mdel P. Positron Emission Tomography in Breast Cancer. Diagnostics (Basel). 2015;5(1):61-83.
- 15. MacDonaldL, Edwards J, Lewellen T, Haseley D, Rogers J, Kinahan P. Clinical imaging characteristics of the positron emission mammography camera: PEM Flex Solo II. J Nucl Med. 2009;50(10):1666-75.
- Moliner L, Gonzalez AJ, Soriano A, Sanchez F, Correcher C, Orero A, *et al.* Design and evaluation of the MAMMI dedicated breast PET. Med Phys. 2012;39(9):5393-404.
- 17. Kalles V, Zografos GC, Provatopoulou X, Koulocheri D, Gounaris A. The current status of positron emission mammography in breast cancer diagnosis. Breast Cancer. 2013; 20(2): 123-30.
- Zaidi H, Becker M. The Promise of Hybrid PET\/MRI: Technical advances and clinical applications. IEEE Signal Processing Magazine. 2016;33(3):67-85.
- Caldarella C, Treglia G, Giordano A. Diagnostic performance of dedicated positron emission mammography using fluorine-18-fluorodeoxyglucose in women with suspicious breast lesions: a meta-analysis. Clinical breast cancer. 2014;14(4):241-8.
- 20. Johnson N, Sorenson L, Bennetts L, Winter K, Bryn S, Johnson W, *et al.* Breast-specific gamma imaging is a cost effective and efficacious imaging modality when compared with MRI. Am J Surg. 2014;207(5):698-701.

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### **Exploring the Role of Self-Efficacy for Coping With Breast Cancer: A Systematic Review**

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#### ABSTRACT

Background: Self-efficacy is a psychological source for helping patients adjust with breast cancer. The aim of the present review was to synthesize the studies on self-efficacy of women with breast cancer, to determine important factors affecting the perception of self-efficacy in breast cancer as well as to describe the role of self-efficacy in the breast cancer.

Archives Of

Methods: "Self-Efficacy (SE), Cancer-Related Self-Efficacy, Symptom-Management Self-Efficacy, Women, Breast Cancer, and Breast Neoplasms", as keywords, were searched in PubMed, CINAHL, OVID, and Web of Science from 2000 to 2016. We included only original articles published in English language, measuring self-efficacy in women with breast cancer.

Results: Twenty-four articles were chosen based on the inclusion criteria. The results of this review revealed that demographic variables, breast cancer diagnosis and type of treatment, bio-psycho-socio-spiritual status, and physician-patient relationship affect cancer specific SE. SE impacts on physical and mental health, pain management, quality of life, body image, clinician-patient communication, and health information seeking behavior.

Conclusions: This review showed that breast cancer self-efficacy is a critical component for enhancement of goal-directed behaviors in patients and it should be supported by health care providers and family members. Findings of this review has some limitations, since great amount of findings were based on cross sectional data. Further research is needed to examine the impacts of breast cancer selfefficacy on health-related variables.

Keywords: Self-efficacy, symptom management, breast cancer, women

#### Introduction

Studies have shown that patients with higher selfefficacy (SE) could use an effective strategy to confront the illness and to arrive at an eligible psychological and medical consequence.<sup>1</sup> Cancer diagnosis, medical procedures, and treatment

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are stressful situations for patients with cancer. Research in psycho-oncology field indicates that self-efficacy is an important factor in patients' capability to manage situations related to their

Perceived self-efficacy is a judgment of own personal ability to manage challenging contexts and arrive at a desired outcome.<sup>3</sup> SE is an important concept in Bandura's social cognitive theory. In this theory, attention to interaction among cognition and other personal factors, behavior, and environment is important,<sup>4</sup> and they influence on each other directionally.5 Therefore, SE is the result of an individual's thought patterns and emotional

cancer diagnosis and treatment.<sup>2</sup>



reactions, which, then, gives shape to the person's behavior.

SE affects the environment and social system.<sup>6</sup> SE includes (a) estimation of difficult task, (b) generality (performing a task across various situations or only under limited circumstances), and (c) strength (high effort for completing a task and resiliency for attaining a goal).<sup>7</sup>

According to Social Cognitive Theory, SE is an individual's belief in own ability to succeed in own performance and this behavior will lead to certain outcomes.<sup>8</sup> People's opinions about their ability to control and superiority over challenging situations are the central mechanisms of human agency, which are the impacts on goal seeking and goal attainment.<sup>4</sup>

<sup>6</sup> The most influential sources which form SE include: mastery experience or performance outcome (past positive and negative experience in life), vicarious experience (other people's performances), social persuasion (including verbal persuasions), and physiological states (emotional arousal).<sup>9</sup>

In health context, SE affects health practices and for a patient, it is a cause of adaption to illness,<sup>10</sup> increased well-being,<sup>11</sup> less psychological stress,<sup>12</sup> and lower functional disorder from the illness.<sup>13</sup> Patients with higher SE experience lower challenges in their relationship with the health care team<sup>1</sup> and decreased SE related to physical dysfunction.<sup>14</sup>

Studies on patients with cancer have identified general SE as an individual factor for coping with cancer<sup>15,16</sup> improving wellness,<sup>17</sup> better quality of life<sup>18,19</sup> and decreasing depression and anxiety in patients with cancer<sup>14,19-22</sup> even in 1 year follow-up.<sup>18</sup>

Heitzmann *et al.*<sup>10</sup> believed that cancer-specific SE includes 4 factors which are as follow: 1)independence (for doing daily living tasks) and thinking positively (hopeful attitude for coping with cancer)<sup>23</sup>; 2) cooperating with a medical team (being self-confidence yourself by searching medical information and support); 3) coping with stress (patients' skill to be relaxed when facing with cancer diagnosis and treatment); and 4) managing emotions (patient's ability to express emotions and look for situations to share them).<sup>16</sup>

Patients with cancer with higher SE are better adjusted with cancer<sup>24, 25</sup> and perhaps live longer than those with low rate of SE.<sup>19</sup> They have higher self-care behaviors and lower physical symptoms of cancer.<sup>26</sup>

Women with high SE managed and controlled symptom of cancer much more better.<sup>27</sup> One of the most common cancers in women is breast cancer.<sup>28</sup> SE in breast cancer survivors acts as a mediator of symptom distress<sup>15</sup> and it has an influence on physical and psychological health.<sup>29, 30</sup> Women with breast cancer who have a higher SE have lower depression and anxiety.<sup>18</sup> Therefore, SE is a critical subject in oncology. Beliefs in individual efficacy impact on life choices, levels of motivation, quality

of functioning, persistence of severity , and dealing with distress.  $^{\scriptscriptstyle 31}$ 

Various studies have been conducted on selfefficacy in women with breast cancer. Mohajjel Aghdam *et al.*<sup>32</sup> studied self-efficacy in patients with breast cancer by a systematic method and synthesized 12 articles. They found that self-efficacy was related to quality of life, emotional wellness, and fatigue, though they did not determine the important factors affecting the perception of self-efficacy in women with breast cancer and did not examine the role of SE in the process of breast cancer (diagnosis, treatment, survivor and end stage). Therefore, the aim of this study, was to summarize and synthesize studies on self-efficacy for coping with breast cancer.

#### Methods

Articles examined in the present review were collected through a search in the following databases from 2000 to 2016: PubMed, CINAHL, OVID, Web of Knowledge, and Science Direct. We conducted a systematic search to obtain original studies relevant to self-efficacy for coping with breast cancer. In order to find MeSH keywords and entry terms, we used Medical Subject Heading and PubMed. We understood that self-efficacy is a MeSH heading and does not have any entry terms, and breast neoplasms is MeSH heading and have entry terms. Thus, keywords for the search included (("Self-efficacy" OR "Health selfefficacy" OR "Cancer-Related Self-Efficacy" OR "Symptom-Management Self-Efficacy") AND "Women" AND ("Breast Neoplasms" OR "Breast cancer").

Original articles published in English language measuring self-efficacy in women with breast cancer as an independent, mediator, and dependent variable were included. We included studies without any limitations about study design, sample size design, tools of measurement, stage of breast cancer, type of treatment, and demographic variables. The exclusion criteria were as follow: studies measuring another type of self-efficacy (for example physical activity self-efficacy), studies focusing on another cancer type, studies not focusing on self-efficacy for coping with breast cancer and studies which published before 2000.

A total of 8372 full text articles were found: 397 from PubMed, 1743 from CINAHL, 1299 from OVID, 866 from Web of Knowledge, and 4067 from the Science Direct. We screened the title of studies in database; duplicates were removed, some of those were about self-efficacy only or self-efficacy which was related to another type of cancer and some of those did not have any relation between self-efficacy and breast cancer. Therefore, we included 145 articles that were related to this study. Among full texts of selective studies, 121 of them did not meet the inclusion criteria; hence, those were excluded.

Finally, according to the inclusion criteria and the



aim of this study, 24 articles were included. Included studies based on these criteria were summarized in table 1. Recorded data included authors' name, aim of the research, country of the research, research sample size, participants' characteristics, research design, and as research findings shown in table 1.

The study design of these selected articles were as follow: 16 articles used cross sectional investigations<sup>14,15,29,30,33,35-45</sup> 5 articles were longitudinal studies,<sup>13, 18, 43, 46-48</sup> 1 article used qualitative explorations,<sup>49</sup> 1 article used a randomized controlled trial,<sup>16</sup> and 1 article used mixed method design.<sup>50</sup> Women participated in these studies suffered from breast cancer and were in the age range of 23 to 78 with stages I to IV breast cancer. Almost all participants had the history of breast cancer surgery, including breast conservation or mastectomy. Some of them received radiation therapy, chemotherapy or hormonal therapy, while they used mono or combined modality of treatments.

Fourteen studies were conducted in the United States of America, <sup>13-16,30,35-37,39,41,42,44,45,50</sup> 1 was conducted in Canada, <sup>49</sup>2 were carried out in the Europe, <sup>18,43</sup> 1 was done in Iran, <sup>40</sup> 1 was done in Turkey, <sup>46</sup> 3 were performed in Taiwan, <sup>33,38,48</sup> 1 in china, <sup>29</sup> and 1 was done in Hong Kong. <sup>47</sup>

Various assessment tools were used to measure self-efficacy in these studies. General self-efficacy

(GSE) scale (Cronbach's  $\alpha$ =0.82) was used in 5 studies the most common.<sup>18, 29, 43, 47, 50</sup> The Cancer Behavior Inventory (CBI) (Cronbach's range=0.69 to 0.90) was used in 3 studies.<sup>36,37,40</sup> The Symptom-Management Self-Efficacy Scale Breast Cancer (SMSES-BC) (coefficient  $\alpha$ =0.96 for the total scale) in 2 studies<sup>33, 38</sup>; the Breast Cancer Self-Efficacy Scale (Cronbach's  $\alpha$ =0.89) was used in 2 studies<sup>35,41</sup> and the Stanford Emotional Self Efficacy Scale Cancer (SESES-C) (Cronbach's  $\alpha$ =0.9) in 2 studies.<sup>14,30</sup>Other assessment tools were used only once in these reviewed studies, including the Strategies Used by Patients to Promote Health (SUPPH) (Cronbach's  $\alpha$ =0.92 for the overall scale),<sup>46</sup> the Self-efficacy (Cronbach's  $\alpha=0.93$ ),<sup>34</sup> Perceived Self-efficacy (Cronbach's  $\alpha=0.93$ ),<sup>39</sup> the Breast Cancer Survivor Self-Efficacy Scale (Cronbach's  $\alpha$ =0.93),<sup>15</sup> the Health self-efficacy (Cronbach's  $\alpha$ =0.76),<sup>42</sup> the Self-Efficacy to Maintain Quality of Life Scale (SEQOL) (Cronbach's  $\alpha$  range= 0.93 to 0.86),<sup>48</sup> the Modified Stanford Self-Efficacy Scale (Cronbach's  $\alpha$ =0.91),<sup>49</sup> and the Cancer self-efficacy (CSE) (Cronbach's  $\alpha$ =0.8).<sup>45</sup> In addition, 3 studies did not report the value of Cronbach's alpha for their used tools, which were the Stanford Inventory of Cancer Patient Adjustment,<sup>13</sup> the Strategies Used by Patients to Promote Health (SUPPH),<sup>16</sup> and the Perceived Efficacy in Patient–Physician Interactions (PEPPI).<sup>44</sup>

Authors and year of publication	Aim	Country	Sample size	Participant characteristics	Research design	Self-efficacy measure	Finding
Adams <i>et al.</i> <sup>35</sup> (2016)	To examine the relationship between social constraints and physical symptom among breast cancer survivors.	USA	n= 1127	Mean age 57 years. Average time since diagnosis breast cancer 5.9 years. Average years of education 14.5. 74.2% married, 9.2% widowed, 7.9% single, 7.1% divorced	Cross-sectional	Breast Cancer Self-Efficacy Scale	High levels of partner and health care provider social restriction were correlated with decrease breast cancer SE ( $P < 0.0001$ ). path analysis model showed that breast cancer self-efficacy mediated relationships between partner social restriction and physical symptom (fatigue, sleep disturbance, and attentional functioning)
Liang <i>et al.</i> <sup>38</sup> (2016) of medi mau betw	To determine relationship between symptom distress and quality life and to examine a iating role of symptom nagement self-efficacy ween symptom distress and quality of life.	Taiwan	n=201	Mean age 53.6 years. 70.6% Married, 48.8% stage I and 32.8% stage II, and III. 64.7% a diagnosis of metastatic disease.	Cross-Sectional	Symptom- Management Self-Efficacy Scale Breast Cancer (SMSES-BC)	Distress did not significantly correlate with symptom-management SE and patients' QOL. Significant positive correlation between Symptom-management SE and patients' QOL.Symptom-management self-efficacy was mediation role effect on the relationship between patients' symptom distressand QOL.
Nejad <i>et al.</i> <sup>40</sup> (2015) le se won	To determine the evel of cancer-related olf-officacy in Iranian nen with breast cancer.	Iran	n=91	<ul> <li>68.1% of patients under 50 years old.</li> <li>95.6% of them married,</li> <li>63.7% of patients</li> <li>had primary school education.</li> <li>56% at 2nd stage of the disease.</li> </ul>	Cross-Sectional	Cancer Behavior Inventory (CBI)	Education and time since diagnosis predicate SE. Patients who have high level of academic education had higher self-efficacy compared to those with non-academic educations.Self-efficacy in patients increased by passing of time. Age of patients did not correlate with self-efficacy.Marital status did not associate with self-efficacy.

Table 1. Characteristics of studies about self-efficacy for coping with breast cancer



Authors and ye	ar Aim	Country	Sample	Participant	Research	Self-efficacy	Finding
Zhang <i>et al.</i> <sup>29</sup> (2015)	To determine the role of self-efficacy in relationship between uncertainty and self-care behavior.	China	n=97	Mean age 51.76 years. 42.3% completed high School education. 92.8% married. 60.8% diagnosis of stage II breast cancer. 60.8% ecceive chemotherapy ar 39.2% chemotherapy and radiation therapy.	design Cross-Sectional Descriptive	General Self-Efficacy Scale (GSE)	Two demographic variables which decrease self-efficacy in breath cancer were: young age and no college education. Relationship between uncertainly and SE was not statistically significant. Both SE and uncertainty independently predicted self-care behavior. SE positively correlated with self-care behavior when controlling effect of uncertainty. SE did not mediate in relationship between uncertainty and self-care behavior.
Liang <i>et al.</i> <sup>33</sup> (2015)	To develop and evaluate the Psychometric of the Symptom- Management Self-Efficacy Scale Breast Cancer (SMSES-BC).	Taiwan	n=152	Mean age was 55 years old. 64.7% had a diagnosis of metastatic breast cancer. 65.2% receiving chemotherapy, 37.6% hormone therapy and 24.9% target therapy	Cross-Sectional	Symptom- Management Self-Efficacy Scale Breast Cancer (SMSES-BC) related to chemotherapy.	Exploratory factor analysis showed three factors as follow: Managing chemotherapy-related symptoms, acquiring problem solving and managing emotional and interpersonal disturbances were extracted from SMSES-BC scale. Reliability of SMSES-BC was accepted for measuring symptom- management self-efficacy related to chemotherapy for breast cancer.
Shelby <i>et al.</i> <sup>39</sup> (2014)	To evaluate correlation between physical symptoms, self-efficacy for coping with symptoms, and functional, emotional, and social well-being in women taking adjuvant endocrine.	USA	n=120	Average age 63.66 years old. (Range, 45-84years). 66.1 %married, 56.3 % had a college degree. 55.4 % of women underwent breast conserving surgery. 52.7 % chemotherapy and 75 % radiation therapy. 82.1 % aromatase inhibitor and 17.9 % of women took Tamoxifen	Cross-Sectional	Perceived Self-Efficacy	Older women had higher SE (P < 0.05). Women who had lower SE showed higher physical symptoms (P < 0.05). Interaction between physical symptoms and SE was significant ( $\beta = 0.05$ , P < 0.001). Patients who had lower SE reported that physical symptoms were associated with lower functional well-being (P < 0.001). Physical symptoms did not correlate with well-being among women with high SE (P < 0.05). SE for coping with symptoms had moderated relationship between physical symptoms and emotional well-being. physical symptoms in patients who have high SE, did not relate to functiona and emotional well-being.
Chang <i>et al.</i> <sup>48</sup> (2014)	To explore differences between women who delay and who do not delay for seeking cancer diagnosis, and understand key factors predicting self- efficacy over time.	Taiwan	n= 80	Mean Age 49 years (range: 35–71). 23.9% married. 60% senior/high school education. 49.3% employed. 64.2% Stage I, II. 23.9 % Stage III, IV.	Longitudinal	Self-Efficacy to Maintain Quality of Life Scale (SEQOL)	Patients who delay a breast cancer examination had a decrease in self-efficacy after surgery compared to women who did not delay. Hope at the first doctor visit was an important factor that predicted of self-efficacy. Anxiety negatively influenced on self-efficacy, especially for the patients who did not delay. Self-efficacy was developed over time (first physician visit for breast examination and biopsy (T1); 1 week after first visit to receive the diagnostic histology report (T2); 2 months after the first visit, when patients wanted to be informed of the surgical pathology report (T3).) Depression, anxiety, and neuroticism showed negative correlation with self-efficacy.



Authors and year of publication	ar Aim	Country	Sample size	Participant characteristics	Research design	Self-efficacy measure	Finding
García-Jimenez et al. <sup>45</sup> (2014)	To examine the relation between cancer self-efficacy and spiritual well- being with acculturation, and study the mediating role in the relationship between acculturation and Self-rated health.	USA	n =333	Mean age 58.25 years, 27% had completed 6th grade or less and 42% had completed 7th grade high school. 31% more than high school. 40% breast conserving surgery and 60% mastectomy.	Cross-sectional telephone survey	Cancer self-efficacy (CSE)	Greater cancer self-efficacy was one factor of this study that had positive correlation with English proficiency. Higher cancer self-efficacy and greate inner peace had significant correlation with better self-rated health. Cancer self-efficacy and inner peace reduces effect of English proficiency on self-rated health. Cancer self-efficacy impacted on the self-rated health by the means of spiritual well-being related to inner peace and meaning in one's life.
Griggs <i>et al.</i> <sup>44</sup> (2014)	To evaluate the impact of Hispanic ethnicity and patient self-efficacy on adjuvant chemotherapy.	USA	n= 397	Mean age 47.8 years Among blacks, 30.7% Non-Hispanic white, 5.3% Non- Hispanic black, 56.9% Hispanic and 7.1% Asian/Pacific islander. 45.8% had completed less than high school and 54.2% were high school graduate. 19.4% stage I, 56.2% stage II, and 24.4% stage III.	Cross-sectional	Perceived efficacy in patient–physician interactions (PEPPI)	Patient self-efficacy did not correlate with chemotherapy. Ethnicity or patient self-efficacy (in communicating with physician's team) did not effect on receiving adjuvant chemotherapy.
Champion et al. <sup>41</sup> (2013)	Descriptive develop and psychometric of breast cancer self-efficacy scale (BCSES).	USA	n=1,127	Average age 57.1, 75% married, 59% had completed high school or two years of colleges	Cross-sectional	Breast Cancer Self-Efficacy Scale (BCSES)	Breast cancer self-efficacy scale (BCSES) was reliable and factor analysis showed that the scale was unidimensional. Predictive validity showed that BCSES correlated with quality-of-life (including physical, psychological, and social dimensions) and overall well-being. BCSES was significantly correlated with lower fatigue and attentional function. Increased level of BCSES associated with lower level of depression, anxiety, and fear of recurrence.
Melchior et al. <sup>43</sup> (2013)	To determine relationship between fear of disease progression during the year following diagnosis of breast cancer and general self-efficacy (SE).	Germany	n= 118	Mean age 54.2 75% married, 53.9% had completed secondary general school. 41.4% were employed 89% sustained breast surgery, 34.7% received chemotherapy, 26.3% received radiotherapy, 9.3% received both chemotherapy and radiotherapy and 15.3% received hormone therap	Cross-sectional	General Self- Efficacy Scale	High general SE correlated with lower fear of disease progression (FoP). SE was an important factor for prediction of FoP. Prediction of SE by FoP was influenced by the relationship between demographic and medical characteristic of FoP.
Lam <i>et al.</i> <sup>49</sup> (2012)	To understand correlation between self-efficacy and obtain a post- mastectomy breast reconstruction (PMBR) surgery information.	Canada	n= 10	Age range 29-75 years Time from breast cancer diagnosis was 11.5 months.	Qualitative interview	Modified Stanford Self-Efficacy Scale And Semi-structured qualitative interview	<ul> <li>Women with lower self-efficacy had a passive role in receiving PMBR information.</li> <li>Women with higher self-efficacy had an active role in searching PMBR information. Physicians provided emotional support for women who had lower</li> <li>self-efficacy for coping with cancer and highest breast cancer knowledge.</li> </ul>



Authors and yea	ar Aim	Country	Sample	Participant	Research	Self-efficacy	Finding
of publication		2	size	characteristics	design	measure	
Ziner <i>et al.</i> <sup>15</sup> (2012)	To explore the role of self-efficacy for predicting a fear of recurrence breast cancer.	USA	n=1,128	45% were diagnosed at 45 or younger and 55% were diagnosed from age 55–70. 75% married, 64% had college educatio 47% received lumpectom 51% received mastector and about 2% had both lumpectomy and mastector	Cross-Sectional Survey on, 1y, 1y, 1 1 mmy.	Breast Cancer Survivor Self-Efficacy Scale	Age at diagnosis breast cancer had not significant correlation with survivor SE. Patients who had higher level of fear of recurrence disease, felt anxiety, and thought about breast cancer and recalled it had not high level self-efficacy. Breast cancer survivor SE, which was a mediator variable, affected the relation of fear of recurrence, anxiety and recall patents.
Mosher <i>et al.</i> <sup>37</sup> (2010)	To examine the association between self-efficacy with pain management and distress.	USA	n=87	Mean age 50 years (Age range28-72 years) 56.3% were inferior tha sophomore, 50.6% married or marria equivalent, 50.6% stages I-III and 49.4% stage IV, 89.7% receive chemotherapy, 43.7% received radiation, 50.6% mastectomy and 31.0% lumpectomy	Cross-Sectional n ge d	Cancer Behavior Inventory (CBI)	Greater level of SE for coping with cancer was not significantly correlated with obstacles to pain treatment. Patients with higher level of SE had not a misunderstanding about cancer-related pain and treatment. Patients with higher level of SE were searching and comprehending medical information and perceived barriers to pain management. Older age, loss of radiation history was predictor of higher SE for coping with cancer. Greater SE for coping with cancer was predictor of less distress.
Namkoong et al. <sup>42</sup> (2010)	To evaluate the role of health self-efficacy on related effects of attain treatment information within computer-mediated breast cancer support groups on emotional well-being,	USA	n=177	Mean age 51 years. 27.1% were college graduates. 9.6% stage 0, 16.4% stage I, 29.9% stage II, 15.3%stage III 5.1% stage IV, and 4.0% had Inflammatory breast cancer.	Cross-Sectional	Health Self-Efficacy	Transferring treatment information within computer- mediated breast cancer support groups significantly affected emotional well-being for the patients who had higher health self-efficacy, but they had negative influence on those with lower health self-efficacy. Giving treatment information within computer made emotional well-being by means of health self-efficacy.
Rottmann et al. <sup>18</sup> (2010)	To examine the role of perceived self-efficacy in predicting breast cancer patients' emotional, physical and social well-being and to study the role of mental adjustment styles in the relation.	Denmark	n =684	Mean Age 54.54 years. (range: 29–81), 21% stage I, 40% stage II and 23% stage III.	Longitudinal	Danish version of the general self-efficacy (GSE) scale	Women in Higher education had higher GSE (general self-efficacy) and better physical functioning. Higher GSE had significant correlation with 3mental adjustment styles. Greater self-efficacy had correlation with emotional well-being after 12 months. Fighting spirit, anxious preoccupation, and Helplessness-hopelessness nearly effect on self-efficacy. Self-efficacy had a direct effect on emotional functioning. Among of self-efficacy, physical and social well-being, there were no significant correlation. Significant correlation were seen among self-efficacy, education ,and time since diagnosis. Self-efficacy predicted active approach- oriented adjustment style and emotional well-being in patients with breast cancer for 1 year later.
Antle <i>et al.</i> <sup>50</sup> (2009)	To examine the effect of breast cancer support group on increasing spiritual well-being and self-efficacy for cancer management.	USA	n=41	Average age 58.16 years 44.4% married. 63.5% had completed high school 58% early stage, 4% locally advanced, 16% spread to lymph nodes, and 14% spread to another part of the bod	Mixed-Methods Design 1 ły.	General Self-Efficacy Scale	Spiritual well-being had a positive significant correlation with cancer management SE. Spiritual-based support group intervention effect on the well-being and cancer management SE. Women who participated in spiritual support group learned coping strategies, obtained positive thinking, and met other survivors.



Authors and ye	ear Aim	Country	Sample	Participant	Research	Self-efficacy	Finding
of publication	1		size	characteristics	design	measure	
Akin <i>et al.</i> <sup>46</sup> (2008)	To examine the relationship between quality of life and self-efficacy of breast cancer patients undergoing chemotherapy	Turkey	n=141 rec had	Average age 49 years (range 25–70); 29.1% breast-sparing surgical procedure, 47.5% evived mastectomy and 23 d no history of breast surg All of them received chemotherapy.	Longitudinal 6 .4% gery.	Strategies Used by Patients to Promote Health	Educational level and occupation were found to be significant factors in self-efficacy ( $P < 0.05$ ). Income level and employment statues were not significant factors in level of self-efficacy ( $P < 0.05$ ). BMI was a significant factor in self-efficacy ( $P < 0.05$ ). The type of breast surgery was not a significant factor in the level of SE. Age and marital statues were not significant factors in self-efficacy between Turkish women with breast cancer. Self-efficacy was found to have negative relationship with disease stage and duration of breast cancer. SE had positive effect on health behaviors. The chemotherapy protocol was found to have an effect on the level of self-efficacy ( $P < 0.05$ ). Difference between the pre-chemotherapy and post-chemotherapy self-efficacy was not found to be statistically significant. A negative relationship was found between self-efficacy and psychological symptoms (mood distress).
Lam <i>et al.</i> <sup>47</sup> (2007)	To study relationship between short-term post-surgical adjustment with self-efficacy.	HongKong	; n= 367 ; 13 a	Mean age51.1 years. 75% married, 58% had at least complete secondary education, 35% were employed full time.71% received radica mastectomy (MRM). 21% breast conserving therapy (BCT),6% had MRM followed by breast reconstruction, 55.7% current adjuvant therapy chemotherapy, % received radiation ther nd 34.4% hormonal therapy	Longitudinal Cohort d l l	Generalized self-efficacy The Chinese version of Generalized Self-Efficacy Scale	<ul> <li>Women with high SE had better self-image.SE did not directly influence psychological morbidity.</li> <li>Women with high SE had more vulnerable to E-OI.</li> <li>Women with higher SE expected fewer negative attitude to surgery compared to women with low SE.</li> <li>SE directly enhanced extra-familial relationships, and self-image.</li> <li>SE indirectly impacted on impairing self-image and sexuality.</li> </ul>
Manne <i>et al.</i> <sup>13</sup> (2006)	To study the developm of self-efficacy over time among women with early stage breas cancer and to evaluate the relation between self-efficacy and specific psychological relationship, and functional outcomes.	t	n= 95 h	Mean age 50.8 92% married. 68% ad completed college peri 14.7% were ductal carcinoma insitu, 35.8% stage 1, 47.4% stage2, and 2.1% stage 3 breast cance 24% received mastectom and 76% breast-conservin surgery. 68.6% received chemotherapy and 25% received radiation.	Cross- Sectional od, and Longitudinal rr. y, g	Stanford Inventory of Cancer Patient Adjustment (SICPA)	Cancer-specific SE consists of coping with medical procedures, communication, activity management, personal management, effective management, and self-satisfaction. Activity management and self-satisfaction significantly improves over time, but communication cancer SE decrease overtime. Cancer SE was stable, but 2 factor of efficacy, namely activity management and self-satisfaction showed significant increase over 1 year after participation follow up.
Palesh <i>et al.</i> <sup>30</sup> (2006)	To investigate the relationship between self-efficacy, satisfaction with social support, stressful life events, and mood disturbance in women recently diagnosed and living in rural communities.	USA	n=82 79 7.3 5 42.6 59.76	Mean age 57.4 years. 68.3% married. 43% received mastectomy, 9.27% received lumpector % had reconstructive surg 50% received chemotherag 8% received hormone Th 5% received radiation treat	Cross- Sectional ny, gery, yy, erapy, tment.	Stanford Emotional Self-Efficacy Scale–Cancer	High level of mood disturbance was related to lower emotional SE. No significant relation was found betweer mood disturbance and emotional SE. Higher emotional self-efficacy increased the persistence of patient against mood disturbance. Women living in rural communities had greater efficacy to manage their emotions, confront death, and present at the moment; they had experienced lower distress.



Authors and yea of publication	ar Aim	Country	Sample size	Participant characteristics	Research design	Self-efficacy measure	Finding
Collie <i>et al.</i> <sup>36</sup> (2005)	To examine the correlation between self-efficacy, coping, social support, and problematic interaction with health care team.	USA	n=89 3 1 44 51 65 48.7 5	Mean age 57 years . (Range, 31-82 years). 26.1% lived in rural towns or cities; 1.8% were 5 miles awa 9.3% were 10 miles awa 9.3% were 10 miles awa 9.3% received mastectom 8% received mastectom 8% received chemothera 4% received radiation, a % received hormone the 67.4% were married and 5.2% were not employe	Cross-Sectional y, ty s. ies, py, nd rapy t.	The Cancer Behavior Inventory (CBI)	Women who had higher level of self-efficacy for coping with cancer, were involved in seeking and understanding medical information and had fewer problematic communication with health care team (physician and nurse) Patients who had difficult interaction with physician team were found to be less emotional SE (P < 0.001)
Han <i>et al.</i> <sup>14</sup> (2005)	To investigate the correlation between patients' psychosocial characteristics and problematic interactions with physicians.	USA	n= 352	Mean age 49.7 years. (Range: 23–78), 76.7% were married, 44.3% stage I, 47.7% stage II and 6.1% stage III of breast cancer.54 % received mastectomy, and 46% received a lumpectomy. 67.2% received chemotherapy and 41.5% received hormone therapy.	Cross-Sectional	Stanford Emotional Self Efficacy Scale Cancer (SESES-C)	Women who had traumatic stress symptoms and less emotional self-efficacy showed problem in relationship with physician team. Problematic communication with physician team could decrease emotional self-efficacy in patients with breast cancer.
Lev <i>et al.</i> <sup>16</sup> (2001)	To evaluate the impact of self-efficacy intervention on patients' self-care self-efficacy.	USA	n=56 45	Mean age 50 years (Range, 30-72years). 79% were married. 38% had completed high school. 36% stage I, 47% stage. % experienced lumpecton surgery, and 8% received mastectom	Experimental research designs: random assignment my	Strategies Used By Patients to Promote Health (SUPPH)	Self-efficacy increased the quality of life and decreased symptom distress for women who were diagnosed with breast cancer. Womer who received chemotherapy showed increased SE and higher quality of life and perceived lower distress.

#### Results

This section includes an overview of studies based on their research questions.

1. What are the important factors affecting the perception of self-efficacy in women with breast cancer?

Age: Studies showed that SE is related to age. Based on the included studies, older women reported higher SE for coping with cancer<sup>37</sup> and showed higher levels of SE (P < 0.05).<sup>39,49</sup> Moreover, younger age was related to lower levels of SE in women with breast cancer.<sup>29,35</sup>

Education: education was a significant factor in different dimensions of SE (P < 005).<sup>18</sup> Women with academic education, compared to those who did not have any academic education, had higher SE. While, women without any college education reported lower SE.<sup>40</sup>

Socioeconomic status (SES): In this review, socioeconomic was one of the variables that had been investigated. Lam *et al.*<sup>49</sup> found that women who were employed full time or retired showed high SE (P < 0.01). They showed that occupation was an

effective factor on SE (P < 0.01), while income level was not a significant factor in the level of SE (P < 0.05).<sup>46</sup>

Palesh *et al.*<sup>30</sup> found that women who had recently been diagnosed with stage 0 through III breast cancer (43% of women had mastectomy, 79.27% had lumpectomy, 7.3% had reconstructive surgery, 50% received chemotherapy, 42.68% had hormone therapy, 59.76% had radiation treatment) lived in rural communities, had high level of self-efficacy, and lower distress.

Marital status: Family, as a component of social system and social support, is a source of SE. In the present review, marital status of Iranian<sup>40</sup> and Turkish<sup>46</sup> women with breast cancer did not have a significant relation with SE.

Breast cancer diagnosis and treatment: Some of the studies in this review examined the effects of diagnosis and diagnosis time, stage of breast cancer, treatment, and type of breast surgery on SE.

Chang *et al.*<sup>48</sup> examined the difference between women who sought cancer diagnosis with and without a delay; they found that a delay in seeking medical examination was related to an increase in SE



at the first physician visit for breast examination and doing biopsy ( $T_1$ ), while it decreased in SE at 1 week after the first visit and at a time when patients received the diagnosis ( $T_2$ ); it also increased SE during 2 months after the visit when patients returned to be informed of surgical pathology ( $T_3$ ). However, in non-delayers, SE increased significantly from  $T_1$  to  $T_3$  after surgery. Akin *et al.*<sup>46</sup> found that the duration of time

diagnosis was not a significant factor in a level of SE. In contrast, Nejad<sup>40</sup> found that time diagnosis was a predictor of SE in women with breast cancer; 13 months since diagnosis can be defined as a newly diagnosed associated with low SE. The chemotherapy protocol for patients also influences the level of SE (P < 0.05).<sup>46</sup> SE increased a little during the treatment compared to pre-treatment, though the authors have not found any difference between the pre-chemotherapy and postchemotherapy.<sup>46</sup> Mosher et al.<sup>37</sup> among 87 women who were in stages I-III (50.6 %) and in stage IV (49.4%)received chemotherapy (89.7%), radiation (43.7%), mastectomy (50.6%) and lumpectomy surgery (31.0%), showed that the absence of radiation therapy predicated SE.

Akin *et al.*<sup>46</sup> found that SE, among 141 women with breast cancer who had breast spring surgical procedure (29.1%), mastectomy, (47.5%) and those who did not have any history of breast cancer (23.4%), the type of breast surgery was not a significant factor in the level of SE, the history of breast cancer in the family member was not a significant factor.

Physical and psychosocial statues: In this study, we found that one of the health factors that affects SE is BMI (Body Mass Index). BMI was a significant factor in self-efficacy breast cancer (P<0.05).<sup>46</sup>

Studies reported psychosocial and spiritual variables affect the SE of women with breast cancer. Laing *et al.*<sup>33</sup> explored 4 factors affecting the Symptom-Management Self-Efficacy for breast cancer related to chemotherapy. They were: acquiring problem solving, management, chemotherapy-related symptom, managing emotional, and interpersonal disturbance. Manne *et al.*<sup>13</sup> also explored 6 factors affecting Cancer-specific SE. The factors were: coping with medical procedures, communication, activity management, and self-satisfaction.

Hope (P < 0.001) and extraversion (P < 0.05) were positively correlated with SE.<sup>48</sup> Antle *et al.*<sup>50</sup> showed a significant positive correlation between spiritual well-being and cancer management SE (P < 0.05). They examined the effects of a spiritual-based support group on breast cancer management SE among women, 58% of whom were at early stage, 4% of whom were locally advanced, and 16% of whom experienced cancer spread to lymph

nodes. They found that intervention was effective to increase SE among African American cancer survivors with the mean age of 58.16 years.

We found that among psychological statuses, depression, anxiety, and neuroticism were negatively correlated with lower SE (P < 0.001). Lower stress predicted SE for coping with cancer, and symptom distress did not significantly correlate with symptom-management SE.<sup>35</sup>

Finally, among environmental elements, higher level of partner social constraints had relationship with lower breast cancer SE (P < 0.001).<sup>35</sup>

Clinician-Patient communication: Physician communication behaviors with patient affect cancerrelated SE.<sup>51</sup> Chang *et al.*<sup>48</sup> in a longitudinal study on 80 women, in which 64% of whom were in stage I, II and 23.9% of whom were in stage III or IV breast cancer, found that hope at the first physician visit is a key factor that predicts the change of SE, but social constraints (experience criticism and avoidance in dialog) has a reversal effect on setting treatment. Adams et al.35 found that high levels of social constraints from health care provider (doctors and nurses) were correlated with decreased breast cancer SE (P < 0.001). Absolutely, self-efficacy in women leads to fewer communication difficulties with a health care team (physician and nurse).<sup>36</sup> Han et al.<sup>14</sup> found that women who had problems in interacting with medical team had less emotional SE (P < 0.001).

2. What is the impact of perceived self-efficacy on the process of breast cancer in female patients (diagnosis to treatment)?

Physical symptom: SE is a significant factor for understanding how women with breast cancer manage physical symptoms.<sup>51</sup> Shelby et al.<sup>39</sup> examined the correlation among physical symptoms, SE and functional, emotional, and social well-being in women taking adjuvant endocrine (82.1% received aromatase inhibitor, 17.9% were taking Tamoxifen, and 55.4% underwent conserving surgery). Interaction between physical symptom and SE was significant ( $\beta$ =0.05, P < 0.001). Women who had lower SE showed greater physical symptom (P <0.05). Physical symptom was associated with lower functional well-being (P < 0.001). Therefore, SE for coping with symptom moderated relationship between physical symptom and emotional wellbeing.

Adams *et al.*<sup>35</sup> found that SE mediated relationship between partner and health care social constraints and physical symptom. Breast cancer SE had a mediator role between social constraints and fatigue, sleep disturbance, and lower attentional functional.

Self-care and self-rated health: Self-care behavior helps patients to cope with symptoms of cancer.<sup>52</sup> Garcia- Jimenez *et al.*<sup>44</sup> reported that higher cancer SE and greater inner peace significantly

correlated with better self-rated health among women, 19.4% of whom were in stage I, 56.2% of whom were in stage II, and 24.4% of whom were in stage III of breast cancer.

García-Jimenez, *et al.*<sup>45</sup> also reported that cancer SE could influence the self-rated health by means of spiritual well-being related to inner peace and meaning in one's life among women, 40% of whom had experienced breast conserving surgery and 60% of whom had recieved Mastectomy. Zhang *et al.*<sup>29</sup> found that SE is positively correlated with self-care behavior, when it had controlled the effect of uncertainty. Since uncertainty and SE were not significantly correlated, they independently predicted self-care behavior.

Pain management: Self-efficacy for managing pain symptoms is a patient's main ability to manage physical and psychological symptoms of cancer.<sup>22</sup> Mosher et al.<sup>37</sup> examined the association of SE with pain management and distress among 87 women, among whom 50.6% were in stage I or II, and 49.4% were in stage III or IV breast cancer (89.7% received chemotherapy, 43.7% received radiation, 50.6% had mastectomy, and 31% had lumpectomy surgery). They found that SE does not have any relation with barriers to pain management (P < 0.05). Self-efficacy did not predicate barriers to pain management. Higher self-efficacy, lower average pain level, and fewer barriers to pain management together predicated less stress, accounting for 39% the variance.

Quality of life: SE plays an important role in the patient's quality of life.<sup>50</sup> Studies have demonstrated that SE has a significant correlation with quality of life among cancer survivors.<sup>54</sup> Lev et al.<sup>16</sup> examined the effect of SE intervention on patient's self-care self-efficacy among 56 women who were in stage I (36%) and stage II, III (47%) breast cancer (38% had mastectomy, 45% had lumpectomy surgery). They found that the increase of SE influences quality of life. SE was highly correlated with all the domains of quality of life. Symptom-management self-efficacy had a significant correlation with the symptomatic quality of life (P < 0.01). Symptom-management self-efficacy had a mediation effect on relationship between patient's symptom distress and quality of life.<sup>38</sup> Patients who had lower symptom distress through higher symptom-management self-efficacy were shown to have greater quality of life.

Wellbeing: studies showed that SE correlates with psychological health and well-being.<sup>13</sup> Rottmann *et al.*<sup>18</sup> found that SE correlates with an approachoriented adjustment style (more fighting spirit and less anxious preoccupation and helplessnesshopelessness), but it does not correlate with fatalism and cognitive avoidance. SE predicted emotional well-being.<sup>41</sup> Palesh *et al.*<sup>30</sup> found no significant correlation between SE and mood disturbance (P < 0.001). Greater mood disturbance was related to lower emotional SE (P < 0.001). Greater SE for coping with cancer was only a predictor of less distress.<sup>35</sup>

Fear of recurrence is one of the challenges of survivors.<sup>13</sup> Ziner *et al.*<sup>15</sup> evaluated the effect of age at diagnosis on fear of breast cancer recurrence and identified the predictor of fear of recurrence by using SE as a mediator among 1128 women, among whom 47% had lumpectomy and 51% had a mastectomy surgery. They showed that higher perceived risk of recurrence (P < 0.01), knowledge of someone with a recurrence (P < 0.001), and breast cancer reminders (P < 0.005) were related, inversely, to breast cancer survivor SE. Breast cancer survivor SE explained about 18% (P < 0.001) of the variance in the fear of recurrence.

Melchior *et al.*<sup>43</sup> found a negative correlation between fear of progression and SE (P < 0.001). SE significantly increased the explained variance of initial fear of progression. As SE increased, depression, anxiety, and fear of recurrence decreased.

Self-image: body image is one of the complex issues in patients with breast cancer.<sup>55</sup> Lam *et al.*<sup>47</sup> examined the relationship between SE with short-term post-surgical adjustment among 367 women who had radical mastectomy (71%) or conserving surgery (21%) and found that women who had high SE had higher self-image (P < 0.05), because SE enhanced the self-image. They showed that women with low SE overestimated the negative effects of surgery and were more disappointed, while patients with high SE underestimated surgical impacts.

Health Information Seeking Behavior: seeking health information is an active coping strategy for chronic illness.<sup>36</sup> Collie *et al.*<sup>36</sup> found that women with breast cancer who had self-efficacy for coping with cancer sought and understood medical information.

Lam *et al.*<sup>47</sup> in studies about access Post-Mastectomy Breast Reconstruction (PMBE) information and consultation with a reconstruction surgery, found that Patients with lower SE preferred passive absorption of PMBE information and women who had higher SE preferred a more active role in gathering processing information.

Namkoong *et al.*<sup>42</sup> found a moderating role of health self-efficacy for the relationship between exchanging treatment information and emotional well-being.

#### Discussion

This review is synthesizing the published literature of self-efficacy in women with breast cancer. The aims of this review article were to determine the important factors affecting the breast cancer-related self-efficacy and to investigate the outcome of perceived selfefficacy in women with breast cancer. The result of this review revealed that demographic variables (age, education, socioeconomic status, and marital statues),



breast cancer diagnosis and type of treatment, psychosocial and physical statues, and physicianpatient relationship affect cancer specific SE.

Findings showed that older women had enough SE for coping with breast cancer. It may be because they had a prior successful experience for handling difficult situations during their life; therefore, they had greater feeling of self-confidence for controlling the procedures of breast cancer diagnosis and treatment. Accordingly, to increase SE in young women with breast cancer, vicarious experiences should be used.<sup>9</sup> Watching women with breast cancer in a similar situation, and comparing their own ability with other individuals' competence may increase SE in young women. Moreover, studies showed that women who had college education and were employed had higher SE. It may be because these are important factors of independent life style for women who seek medical information and obtain social support.<sup>40</sup> One of the studies reported that women living in rural communities have higher levels of emotional SE; one possible reason is that women who live in rural communities have learned how to fight with problems due to their difficult lives.<sup>30</sup> However, further comparing studies on cancer self-efficacy between urban and rural women are needed.

Last demographic variable that was determined to have an effect on SE is marital status. Marital status did not have a significant relation with SE. It was also shown that husbands (partners) had only a trivial role in supporting women with breast cancer; however, studies found that the husband of a woman with breast cancer is the most critical supporting source in confronting with a chronic illness.<sup>14,40</sup>

Another factor affecting SE is the procedure of a cancer diagnosis and a treatment. Studies found that a delay in the diagnosis of breast cancer has an effect on SE. SE in non-delayers increased regularly from the first physician visit to after the surgery, but increasing trends in SE among women with delay were erratic. The time of diagnosis was also a predictor of SE in women with breast cancer. Women who were diagnosed recently had a lower SE. Likely, patients who experienced the side effects of a breast cancer treatment had challenges in coping competences.<sup>10</sup> Therefore, having a successful experience and a suitable social support may increase SE, especially in survivors.

Studies found that a chemotherapy protocol and a loss of radiation therapy predicted SE. Common physical side effects of chemotherapy (e.g. nausea, loss hair, weight gain, and fatigue)<sup>57</sup> and psychological symptoms (anxiety and depression)<sup>58</sup> are the most prevalent symptoms in patients with breast cancer. Patients coping with cancer also experienced a number of short- and long-term practical and emotional issues that increased their distress.<sup>13</sup>

We did not find any study regarding the stage of the breast cancer; the type of breast cancer surgery was a significant factor in the level of SE.<sup>46</sup> Studies showed that mastectomy, as a type of surgery, has negative effect on woman's body image,<sup>59, 60, 61</sup> and research indicated that one of the factor which affects SE is body image.<sup>62,63</sup> Women who have higher level of body image have better perceived SE compared with others.<sup>62</sup> Thus, it seems that mastectomy surgery, compared to conserving surgery, has a negative effect on cancer related SE, by means of body image of women with breast cancer. Therefore, it would be better if this subject would be examined in a separate study. On the other hand, studies have reported that patients with cancer who receive treatment, decreased self-care SE over time.<sup>64</sup> In such patients, SE changes over time in dealing with life stressor.<sup>65</sup> Accordingly, it seems patients who are in the advanced breast cancer stage have lower level SE; thus, we recommend that studying SE in patients be at different stages of breast cancer.

In this review, we found that physical status affects the breast cancer SE. BMI was a significant factor of physical health related to SE. Studies reported that health related to SE was not correlated with a higher BMI.<sup>66</sup> Because it may influence a body image of a woman with breast cancer. Regarding the psychological statues, this synthesis showed that acquiring problem solving skills, communication skills, emotional management,<sup>41</sup> attention to spirituality, and positive thinking (hopeful) affect breast cancer self-efficacy.<sup>50</sup>

We found that lower levels of stress predicated SE for coping with cancer, but anxiety and neuroticism negatively correlated with higher levels of SE. As was mentioned, emotional arousal is one of the sources of SE. People judged about the ability based on emotional state which experienced at a completion of an action. Fear about a recurrence of breast cancer may be the reason of emotional arousal. Fear of recurrence correlated with a higher level of anxiety and depression.<sup>58</sup> Based on Bandura's social cognitive perspective, forethought and anticipation of the recurrence influence patients' confidence in coping with cancer.<sup>5</sup> Also, fears about their competency was an important reason that people perceived lower self-efficacy.<sup>6</sup> It seems that one of the resources of emotional arousal in patients with breast cancer is a method of treatment. For example, studies showed that examples of the side effects of the used Tamoxifen in a hormone therapy could be psychological distress, anxiety, and depression.<sup>67,68</sup> As was previously discussed, general SE was negatively related to anxiety<sup>22</sup> and low levels of SE were associated with high levels of anxiety and depressive symptoms.<sup>69</sup> Therefore, the effect of this method should be examined in the next studies.

According to the literature of cancer related to the self-efficacy in women with breast cancer, social



support is another factor. Higher levels of partner social constrains (avoidance and criticism) reduces breast cancer SE. Such women feel that they cannot inform others about cancer related thoughts and feelings because they are confronted by avoidance and criticism; therefore, they perceive low level of SE.<sup>35</sup> A physician-patient relationship also affects breast cancer SE. A team of physicians, who pay attention to patients' thought and feeling, improves the self-confidence for symptom cancer management. Conversely, criticism and avoidance in a dialog of a healthcare provider decreases SE.<sup>70</sup> On the other hand, hope at the first clinician visit is a key factor that predicts the change of self-efficacy. Therefore, through decreasing criticisms and increasing hope in the dialog with women, cancer self-efficacy would be improved.

Second part of this synthesis examined the outcomes of breast cancer SE on the patient's life. SE affects mental and physical health, pain management, quality of life, body image, and health information seeking behavior.

SE is a psychological source that decreases the negative physical symptom.<sup>39</sup> Self-confidence and trust to the capability prepare female patients for dominance over physical symptoms of breast cancer.<sup>35</sup> By this synthesis, we found that breast cancer SE impacts on the self-caring and increases the self-rated health. Rohrer *et al.*<sup>71</sup> believed that patient with high self-confidence had a better health. They have suggested a good communication and have provided self-care tools which increase healthy behaviors in their patients. Patient-center in health setting may increase self-confidence of patients with breast cancer.<sup>72</sup>

Symptom-management SE had a mediation effect on relationship between a patient's symptom distress and quality of life. A high SE perception increased cancer patient's adaption to the disease, improved quality of life, and decreased psychological problems.<sup>46</sup> Women with high levels of SE who received the medical information were reported to have lower level barriers to pain management.<sup>37</sup> Overall, perceived self-efficacy did not associate with intensity of pain in daily life among patients with cancer.<sup>17</sup>

In this synthesis, studies showed that SE affects the mental health of patients with breast cancer. SE is associated with an adjustment<sup>73</sup> by increasing an fighting spirit and decreasing anxious preconceptions and helplessness-hopelessness in women and makes them have fewer difficulties in communications with a health care team. Therefore, SE predicts emotional well-being. Another outcome of SE is improving a self-image.<sup>47</sup> Patients, who have high SE, underestimate surgical impact and have high self-image.

Finally, this review showed that health self-efficacy had a moderating role in the relationship between

treatment information received and emotional wellbeing. Because patients with low self-efficacy were informed by treatment information, emotional wellbeing could be damaged. Positive medical information influences emotional well-being for women with higher health self-efficacy, but negatively influences patients who have lower health efficacy.<sup>42</sup>

Regarding the points which mentioned in the study, this review has some limitations. One limitation is that the major findings of this review article are based on the cross sectional studies (16 articles). Cross sectional data limit the interpretation of the evidences. Thus, we recommend that studies should perform and evaluate the breast cancer self-efficacy from the diagnosis of cancer to treatment in different group of survivor and end stage patients by longitudinal method. This synthesis showed that the findings, which were related to interventions for cancer-specific self-efficacy, are limited, as only 1 study examined an intervention in the literature review. Therefore, we recommend to evaluate the intervention strategies to enhance selfefficacy in patients with breast cancer by experimental studies method.

Another limitation related to this synthesis is the variation in assessment tools used to assess self-efficacy; a number of studies used a general self-efficacy scale and others used a specific cancer-related self-efficacy scale.

There was also diversity in the stage of breast cancer, method of treatment, and type of surgery among participants of these studies. These limitations cause the restriction for the better understanding of the cancer related self-efficacy in women with breast cancer. Therefore, additional research for exploring the important factors affecting SE is needed; for example, investigating the effects of the stage of breast cancer on the breast cancer SE, the difference between self-efficacy of women with a different surgery (mastectomy and conserving), the different treatment (chemotherapy, radiotherapy, and hormone therapy), the influences of clinician and partner characteristics on the SE in women, the difference of the breast cancer SE in women based on physicianpatient communication style, and further empirical studies on interventions, such as examining the effect of vicarious experience (women who have effective coping strategies for breast cancer) on increasing the self-efficacy or the effect of patients education on this field.

This review revealed that younger women with newly diagnosed breast cancer, who did not have higher education, were not employed, and had delay in seeking breast cancer examination, were a particularly high-risk group regarding coping with breast cancer due to lower levels of self-efficacy. As was previously discussed, women who have low level of SE are further exposed in anxiety and depression syndromes. Therefore, they need especial attentions for the reinforcement of their confidence for coping with



SE for coping with BC

breast cancer from health care providers and family members.

In the oncology setting, it seems that communication between clinicians and patients is very important for perceived cancer SE in women with breast cancer. Therefore, communication skills and medical ethics should be considered in a medical research. In this field, empowering patients by means of education and giving appropriate health information, and preparing them for a treatment may increase the confidence to cope with a cancer. Women with breast cancer who have conflicts with their family members require family therapy interventions to decrease the social constrain and obtain social supports.

As was stated, self-efficacy is a personality construct that prepares individuals to cope with difficult situations. In this study, we tried to explore the important factors affecting breast cancer SE and to determine the effects of SE on the process of breast cancer.

At the end, it is necessary to point out that SE affects the environment of the patient and environmental factors can effect to modify patient's self-efficacy. Therefore, if health care professionals and family members prepare supportive environment (such as social persuasion and vicarious experiences), fighting spirit in women with breast cancer will improve. On the other hand, as was previously mentioned, patients with high levels of SE have cooperation with a medical team and get themselves independent. Consequently, a great attention should be paid to studies and clinical implications.

#### References

- 1. Bandura A. Health promotion by social cognitive means. Health Educ Behav. 2004;31(2):143-64.
- Koopman C, Butler LD, Classen C, Giese-Davis J, Morrow GR, Westendorf J, et al. Traumatic stress symptoms among women with recently diagnosed primary breast cancer. Journal of traumatic stress. 2002;15(4):277-87.
- Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychol Rev. 1977;84(2):191-215.
- 4. Bandura A. Social cognitive theory: an agentic perspective. Annu Rev Psychol. 2001;52(1):1-26.
- 5. Bandura A. Social cognitive theory of selfregulation. Organizational behavior and human decision processes. 1991;50(2):248-87.
- 6. Bandura A. Human agency in social cognitive theory. Am Psychol. 1989;44(9):1175-84
- Champion V, Skinner CS, Menon U. Development of a self-efficacy scale for mammography. Res Nurs Health. 2005;28(4):329-36.
- 8. Wolf MS, Chang CH, Davis T, Makoul G. Development and validation of the Communication and Attitudinal Self-Efficacy scale

for cancer (CASE-cancer). Patient Educ Couns. 2005;57(3):333-41.

- Bandura A. Perceived self-efficacy in cognitive development and functioning. Educ Psychol. 1993;28(2):117-48.
- 10. Heitzmann CA, Merluzzi TV, Jean-Pierre P, Roscoe JA, Kirsh KL, Passik SD. Assessing selfefficacy for coping with cancer: development and psychometric analysis of the brief version of the Cancer Behavior Inventory (CBI-B). Psycho-Oncology. 2011;20(3):302-12.
- 11. Karademas EC. Self-efficacy, social support and well-being: The mediating role of optimism. Pers Individ Dif. 2006;40(6):1281-90.
- 12. Kuijer RG, De Ridder DT. Discrepancy in illness-related goals and quality of life in chronically ill patients: the role of self-efficacy. Psychol Health. 2003;18(3):313-30.
- 13. Manne SL, Ostroff JS, Norton TR, Fox K, Grana G, Goldstein L. Cancer-specific self-efficacy and psychosocial and functional adaptation to early stage breast cancer. Ann Behav Med. 2006;31(2):145-54.
- 14. Han WT, Collie K, Koopman C, Azarow J, Classen C, Morrow GR, et al. Breast cancer and problems with medical interactions: relationships with traumatic stress, emotional self-efficacy, and social support. psycho-oncology. 2005;14(4):318-30.
- Ziner KW, Sledge GW, Bell CJ, Johns S, Miller KD, Champion VL, editors. Predicting fear of breast cancer recurrence and self-efficacy in survivors by age at diagnosis. Oncol Nurs Forum, 2012, 1;39(3):287-95.
- 16. Lev EL, Daley KM, Conner NE, Reith M, Fernandez C, Owen SV. An intervention to increase quality of life and self-care self-efficacy and decrease symptoms in breast cancer patients. Sch Inq Nurs Pract. 2001;15(3):277-94.
- 17. Lin CC. Comparison of the effects of perceived self-efficacy on coping with chronic cancer pain and coping with chronic low back pain. Clin J Pain. 1998;14(4):303-10.
- Rottmann N, Dalton SO, Christensen J, Frederiksen K, Johansen C. Self-efficacy, adjustment style and well-being in breast cancer patients: a longitudinal study. Qual Life Res. 2010;19(6):827-36.
- 19. Graves, K.D., Social cognitive theory and cancer patients' quality of life: a meta-analysis of psychosocial intervention components. Health Psychol. 2003, 22(2):210-9.
- 20. Broome BA. The impact of urinary incontinence on self-efficacy and quality of life. Health Qual Life Outcomes. 2003;1(1):35.
- 21. Allen JD, Shelton RC, Harden E, Goldman RE. Follow-up of abnormal screening mammograms among low-income ethnically diverse women: findings from a qualitative study. Patient Educ Couns. 2008;72(2):283-92.



- 22. Boehmer S, Luszczynska A, Schwarzer R. Coping and quality of life after tumor surgery: personal and social resources promote different domains of quality of life. Anxiety Stress Coping. 2007;20(1):61-75.
- 23. Duggleby W, Cooper D, Penz K. Hope, selfefficacy, spiritual well-being and job satisfaction. JAdv Nurs. 2009;65(11):2376-85.
- 24. Lev EL, Eller LS, Kolassa J, Gejerman G, Colella J, Lane P, et al. Exploratory factor analysis: strategies used by patients to promote health. World J Urol. 2007;25(1):87-93.
- 25. Kreitler S, Peleg D, Ehrenfeld M. Stress, selfefficacy and quality of life in cancer patients. Psycho-Oncology. 2007;16(4):329-41.
- 26. Porter LS, Keefe FJ, Garst J, McBride CM, Baucom D. Self-efficacy for managing pain, symptoms, and function in patients with lung cancer and their informal caregivers: associations with symptoms and distress. Pain. 2008;137(2):306-15.
- 27. Porter LS, Keefe FJ, McBride CM, Pollak K, Fish L, Garst J. Perceptions of patients' selfefficacy for managing pain and lung cancer symptoms: correspondence between patients and family caregivers. Pain. 2002;98(1):169-78.
- 28. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Tenyear national cancer registry data report. Cancer Epidemiol. 2015;39(4):519-27.
- 29.Zhang Y, Kwekkeboom K, Petrini M. Uncertainty, Self-efficacy, and Self-care Behavior in Patients With Breast Cancer Undergoing Chemotherapy in China. Cancer Nurs. 2015;38(3):19-26.
- 30. Palesh OG, Shaffer T, Larson J, Edsall S, Chen XH, Koopman C, et al. Emotional Self-Efficacy, Stressful Life Events, and Satisfaction with Social Support in Relation to Mood Disturbance among Women Living with Breast Cancer in Rural Communities. Breast J. 2006;12(2):123-9.
- Bandura A. Regulation of cognitive processes through perceived self-efficacy. Dev Psychol. 1989;25(5):729.
- 32. Mohajjel Aghdam A, Sanaat Z, Hassankhani H, Kochaki Nejad Z. Self-efficacy in breast cancer patients: A systematic review. IRJABS; 2013;4(5):1007–13.
- 33. Liang SY, Wu WW, Kuo CY, Lu YY. Development and Preliminary Evaluation of Psychometric Properties of Symptom-Management Self-Efficacy Scale for Breast Cancer Related to Chemotherapy. Asian Nurs Res (Korean Soc Nurs Sci). 2015;9(4):312-7.
- Loprinzi PD, Cardinal BJ. Self-efficacy mediates the relationship between behavioral processes of change and physical activity in older breast cancer survivors. Breast Cancer. 2013;20(1):47-52.
- 35. Adams RN, Mosher CE, Cohee AA, Stump TE,

Monahan PO, Sledge GW, et al. Avoidant coping and self-efficacy mediate relationships between perceived social constraints and symptoms among long-term breast cancer survivors. Psycho-Oncology. 2017;26(7):982-90

- 36.Collie K, Wong P, Tilston J, Butler L, Turner-Cobb J, Kreshka M, et al. Self-efficacy, coping, and difficulties interacting with health care professionals among women living with breast cancer in rural communities. Psycho-Oncology. 2005;14(10):901-12.
- 37. Mosher CE, Duhamel KN, Egert J, Smith MY. Self-efficacy for coping with cancer in a multiethnic sample of breast cancer patients: associations with barriers to pain management and distress. Clin J Pain. 2010;26(3):227-34.
- 38. Liang S-Y, Chao T-C, Tseng L-M, Tsay S-L, Lin K-C, Tung H-H. Symptom-Management Selfefficacy Mediates the Effects of Symptom Distress on the Quality of Life Among Taiwanese Oncology Outpatients With Breast Cancer. Cancer Nurs. 2016;39(1):67-73.
- 39. Shelby RA, Edmond SN, Wren AA, Keefe FJ, Peppercorn JM, Marcom PK, et al. Self-efficacy for coping with symptoms moderates the relationship between physical symptoms and well-being in breast cancer survivors taking adjuvant endocrine therapy. Support Care Cancer. 2014;22(10):2851-9.
- 40. Nejad ZK, Aghdam AM, Hassankhani H, Jafarabadi MA, Sanaat Z. Cancer-Related Self-Efficacy in Iranian Women With Breast Cancer. Women. Health. Bull. 2015;2(2):e23248.
- 41. Champion VL, Ziner KW, Monahan PO, Stump TE, Cella D, Smith LG, et al., editors. Development and psychometric testing of a breast cancer survivor self-efficacy scale. Oncol Nurs Forum, 2013; 40(6): 403–10.
- 42. Namkoong K, Shah DV, Han JY, Kim SC, Yoo W, Fan D, *et al.* Expression and reception of treatment information in breast cancer support groups: How health self-efficacy moderates effects on emotional well-being. Patient Educ Couns. 2010;81:41-7.
- 43. Melchior H, Buscher C, Thorenz A, Grochocka A, Koch U, Watzke B. Self-efficacy and fear of cancer progression during the year following diagnosis of breast cancer. Psycho-Oncology. 2013;22(1):39-45.
- 44. Griggs JJ, Liu Y, Sorbero ME, Jagielski CH, Maly RC. Adjuvant chemotherapy dosing in low-income women: the impact of Hispanic ethnicity and patient self-efficacy. Breast Cancer Res Treat. 2014;144(3):665-72.
- 45. García-Jimenez M, Santoyo-Olsson J, Ortiz C, Lahiff M, Sokal-Gutierrez K, Nápoles AM. Acculturation, inner peace, cancer self-efficacy, and self-rated health among Latina breast cancer survivors. J Health Care Poor Underserved.



2014;25(4):1586.

- 46. Akin S, Can G, Durna Z, Aydiner A. The quality of life and self-efficacy of Turkish breast cancer patients undergoing chemotherapy. Eur J Oncol N u r s . 2 0 0 8 ; 1 2 (5) : 4 4 9 5 6.
- 47. Lam WWT, Fielding R. Is self-efficacy a predictor of short-term post-surgical adjustment among Chinese women with breast cancer? Psycho-Oncology. 2007;16(7):651-9.
- 48. Chang H-J, Chen W-X, Lin EC-L, Tung Y-Y, Fetzer S, Lin M-F. Delay in seeking medical evaluations and predictors of self-efficacy among women with newly diagnosed breast cancer: A longitudinal study. Int J Nurs Stud. 2014;51(7):1036-47.
- 49. Lam A, Secord S, Butler K, Hofer SO, Liu E, Metcalfe KA, et al. A breast reconstruction needs assessment: How does self-efficacy affect information access and preferences? Can J Plast Surg. 2012;20(1):37.
- 50. Antle B, Collins WL. The impact of a spiritualitybased support group on self-efficacy and wellbeing of African American breast cancer survivors: a mixed methods design. Social Work and Christianity. 2009;36(3):286.
- 51. Zachariae R, Pedersen CG, Jensen AB, Ehrnrooth E, Rossen PB, von der Maase H. Association of perceived physician communication style with patient satisfaction, distress, cancer-related self-efficacy, and perceived control over the disease. Br J Cancer. 2003;88(5):658-65.
- 52. Huang C-H, Ho M-Y, Tsai JC-R. A Study of Physical Activity, Uncertainty and Health Selfefficacy in the Patients After Percutaneous Coronary Intervention. Tzu Chi Nursing Journal. 2012;11(3):66-76.
- 53. Porter LS, Keefe FJ, Garst J, McBride CM, Baucom D. Self-efficacy for managing pain, symptoms, and function in patients with lung cancer and their informal caregivers: associations with symptoms and distress. PAIN. 2008;137(2):306-15.
- 54. Yeung N, Lu Q. Affect as a mediator between self-efficacy and quality of life among Chinese cancer survivors in China. Eur J Cancer Care. 2014;23(1):149-55.
- 55. Paterson CL, Lengacher CA, Donovan KA, Kip KE, Tofthagen CS. Body Image in Younger Breast Cancer Survivors: A Systematic Review. Cancer Nurs. 2016;39(1):E39-58.
- 56. Kim SC, Shah DV, Namkoong K, McTavish FM, Gustafson DH. Predictors of online health information seeking among women with breast cancer: The role of social support perception and emotional well-being. J Comput Mediat Commun. 2013;18(2):98-118.
- 57. Schofield P, Jefford M, Carey M, Thomson K, Evans M, Baravelli C, et al. Preparing patients

for threatening medical treatments: effects of a chemotherapy educational DVD on anxiety, unmet needs, and self-efficacy. Support Care Cancer. 2008;16(1):37-45.

- 58. So WK, Marsh G, Ling W, Leung F, Lo JC, Yeung M, et al. Anxiety, depression and quality of life among Chinese breast cancer patients during adjuvant therapy. Eur J Oncol Nurs. 2010;14(1):17-22.
- 59. 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.
- 60. McGaughey A. Body image after bilateral prophylactic mastectomy: an integrative literature review. J Midwifery Womens Health. 2006;51(6):e45-9.
- 61. Kocan S, Gursoy A. Body Image of Women with Breast Cancer After Mastectomy: A Qualitative Research. J Breast Health (2013). 2016;12(4):145-50.
- 62. Pikler V, Winterowd C. Racial and body image differences in coping for women diagnosed with breast cancer. Health Psychol. 2003;22(6):632-7.
- 63. Williams PA, Cash TF. Effects of a circuit weight training program on the body images of college students. Int J Eat Disord. 2001;30(1):75-82.
- 64. Lev EL, Paul D, Owen SV. Age, self-efficacy, and change in patients' adjustment to cancer. Cancer Pract. 1999;7(4):170-6.
- 65. Kang SY, Deren S, Andia J, Colon HM, Robles R. Effects of changes in perceived self-efficacy on HIV risk behaviors over time. Addict Behav. 2004;29(3):567-74.
- 66. Ovaskainen ML, Tapanainen H, Laatikainen T, Mannisto S, Heinonen H, Vartiainen E. Perceived health-related self-efficacy associated with BMI in adults in a populationbased survey. Scand J Public Health. 2015;43(2):197-203.
- 67. Bober SL, Hoke LA, Duda RB, Regan MM, Tung NM. Decision-making about tamoxifen in women at high risk for breast cancer: clinical and psychological factors. J Clin Oncol. 2004;22(24):4951-7.
- 68. Demissie S, Silliman RA, Lash TL. Adjuvant tamoxifen: predictors of use, side effects, and discontinuation in older women. J Clin Oncol. 2001;19(2):322-8.
- 69. Muris P. Relationships between self-efficacy and symptoms of anxiety disorders and depression in a normal adolescent sample. Pers Individ Dif. 2002;32(2):337-48.
- 70.Rollnick S, Miller WR, Butler CC, Aloia MS. Motivational interviewing in health care: helping patients change behavior. Taylor &



Francis; 2008.

- 71. Rohrer JE, Young R, Sicola V, Houston M. Overall self-rated health: a new quality indicator for primary care. J Eval Clin Pract. 2007;13(1):150-3.
- 72. Flocke SA, Miller WL, Crabtree B. Relationships between physician practice style, patient satisfaction, and attributes of primary care.(Original Research). J Fam Pract. 2002;51(10):835-41.

73. Curtis R, Groarke A, Sullivan F. Stress and self-efficacy predict psychological adjustment at diagnosis of prostate cancer. Scientific reports. 2014;4:5569.



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# Archives Of Breast Cancer

## Immunohistochemical Expression of B-Cell Lymphoma-2 Gene with Clinicopathological Correlation: A Comparative Analysis of Triple Negative and Non-Triple Negative Breast Cancers

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#### ABSTRACT

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Keywords: B-Cell Lymphoma-2 (BCL-2), Non-Triple Negative Breast Cancers (NTNBcs), Triple Negative Breast Cancers (TNBCs), Immunohistochemistry (IHC)

#### Introduction

Breast carcinoma is the most popular cancer affecting the females, worldwide. Globally, every year, 1.4 million new cases of breast cancer are

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**Background:** B-Cell Lymphoma-2 gene is an anti-apoptotic protein associated with favorable prognosis in patients with breast cancer. The present study focused on immunohistochemical expression of the aforementioned gene with clinicopathological correlation in non-triple negative breast cancers (NTNBCs) and triple negative breast cancers (TNBCs).

**Methods:** We investigated 258 cases of primary breast cancers; they were divided into 2 groups (NTNBCs and TNBCs) based on their expression of estrogen receptor (ER), progesterone receptors (PR), and Her-2/neu receptors. BCL-2 expression was correlated with age, tumor size, tumor grade, histological subtype, lymph node status, and lymphovascular invasion (LVI).

**Results:** Among NTNBCs, 68.2% of cases expressed BCL-2 as compared to 53.3% in TNBCs (P-value = 0.035). In both groups, BCL-2 expression was significantly higher in younger patients, without lymphovascular invasion and lower grade (borderline significant in TNBCs). The variable which was associated with higher BCL-2 expression only in NTNBCs was smaller tumor size. In contrast, in TNBCs invasive ductal carcinoma was significantly associated with BCL-2 expression.

**Conclusions:** BCL-2 showed association with various clinicohistopathological characteristics in TNBC and NTNBC breast cancer patients. Yet, some of these variables were potentially related to better prognosis (the lack of LVI, smaller tumor size, and lower grade). On the other hand, younger age, which is a feature generally associated with poorer prognosis, was significantly related to BCL-2 expression.

diagnosed.<sup>1</sup> Breast cancer incidence varies based on different regions of the world.

This difference is related to differences such as race, genetics, cultural differences, and environmental exposures in various parts of the world.<sup>2</sup> Some studies conducted in India and Pakistan showed increase in the incidence of breast cancer, which were mostly ER, PR negative.<sup>2</sup>

Moreover, this incidence has been shown to be increased during past decade. According to Karachi Cancer Data, the incidence of breast cancer
increased from 1995 to 1995 by 53.1% and more prominently as high as 69.1% from 1998 to 2002 in Asia.<sup>3</sup>

The patients with breast cancer, who lack the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (Her-2/neu), are called triple negative breast cancers (TNBCs).<sup>4</sup> Triple negative breast cancers account for 10% to 20% of all patients with breast cancer. The patients with breast cancer, who can express either the hormone receptors ER, PR, or Her-2/neu, are non-triple negative breast cancers (NTNBCs). Most of the TNBCs, but not all of them, are basal type on gene expression profiling.

The TNBCs have an aggressive behavior,<sup>5</sup> increased chance of metastasis,<sup>6,7</sup> and unfavorable prognosis as compared to NTNBCs.

Some prognostic and predictive elements have extensively been studied in patients with breast cancer. B-cell lymphoma-2 (BCL-2) is a significant prognostic indicator in patients with breast cancer, and its expression, likewise, can be used as targeted therapy for some new drugs.<sup>8</sup>

BCL-2 is an anti-apoptotic protein expressed in 25% to 50% of patients with breast cancer.<sup>9,10</sup> BCL-2, in some studies, was correlated with progressed rate of survival, and it was reported as a favorable prognostic factor.<sup>10-14</sup> On the contrary, the lack of BCL-2 expression was shown to be an independent indicator of poor prognosis.

The number of studies showing prognostic importance of BCL-2 expression in TNBCs and NTNBCs is very limited. Keeping in view its prognostic significance, it has been suggested in various studies to include BCL-2 expression in the Nottingham Prognostic Index.

The aim of the present study was to compare the expression of BCL-2 in TNBCs and NTNBCs as well as to correlate its expression with various clinicopathological parameters. The present study would help to improve patients' stratification and to provide clinicians with more management criteria.

## Methods

This cross-sectional study was conducted at Histopathology Department of Armed Forces Institute of Pathology, Rawalpindi, Pakistan. A total of 258 primary patients with breast carcinomas were diagnosed from 20th January 2014 to 20th July 2016; they were included since hormone receptor and Her-2 status was available.

Age and other histopathologic parameters, such as histologic grade, type, nuclear grade, and lymphovascular invasion (LVI) were obtained from patient pathology records. Nottingham Criteria of Bloom & Richardson was used for grading all the tumors.<sup>15</sup>

Immunohistochemistry (IHC) was applied on the most representatives and well preserved areas of

tissue blocks fixed with 10% buffered formalin.

The results of IHC were evaluated and scored semiquantitatively by 2 histopathologists.<sup>16</sup> A cut off value was given for each marker for positive or negative staining. Hormone receptors were taken as positive if at least 1% of tumor cells showed moderate to strong nuclear staining.<sup>17</sup>

For Her-2/neu, membrane staining would be scored 0, if there was no or faint incomplete staining in <10% cells; 1, if there was faint incomplete staining in >10% cells. Score 3 was perceived positive with complete chicken wire like staining in >10% cells.<sup>16,17</sup>

For BCL-2, cytoplasmic or membranous staining of 10% or more tumor cells were perceived positive.<sup>15</sup> Cases with moderate to strong staining for this marker was regarded as positive as shown in figure 1.<sup>18</sup> IHC analyses for BCL-2 was performed on all specimens.



Figure 1. Cytoplasmic positivity of BCL-2 protein

Statistical analysis was performed using SPSS version 19.0. The descriptive statistics were calculated for both quantitative and qualitative variables. Chi square test was used for analysis. A P-value of less than 0.05 was considered as statistically significant.

## Results

A total of 258 patients were included in the present study. They consisted of 217 (84%) invasive ductal carcinomas, 24 (9.3%) invasive lobular carcinomas, and 6 (2.3%) mixed ductal and lobular carcinomas. The others included 3 (1.2%) mucinous, 3 (1.2%) tubular, 2 (0.8%) papillary carcinomas, 2 (0.8%) metaplastic, and 1 (0.4%) medullary carcinoma. The patients' age ranged from 28 to 90 with the mean age of 49. All the patients were females. Out of 258 cases, 198 were NTNBCs and 60 were TNBCs.

BCL-2 expression and its further correlation with clinicopathological parameters were summarized in table 1 and table 2.



Clinicopathological	Cases (N)	Percentage (%)	BCL-2 E	xpression	P-value
variables			Positive	Negative	
Patients' age					0.01
< 50 Years	94	47.5	72 (76.6%)	22 (23.4%)	
$\geq$ 50 Years	104	52.5	63 (60.6%)	41 (39.4%)	
Tumor Size					0.002
<2 cm	29	14.7	22 (76%)	7 (24%)	
2-5 cm	108	54.5	82 (75%)	26 (25%)	
>5cm	61	30.8	31 (51%)	30 (49%)	
Histologic Type					0.68
IDC	164	82.9	110 (67%)	54 (33%)	
ILC	20	10.1	16 (80%)	4 (20%)	
Mixed	6	3	4 (66.7%)	2 (33.3%)	
Others	8	4	5 (62.5%)	3 (37.5%)	
Tumor Grade					0.001
Grade I	3	1.5	3 (100%)	0	
Grade II	153	77.3	112 (73.2%)	41 (26.8%)	
Grade III	36	18.2	16 (44.4%)	20 (55.6%)	
Not applicable	6	3	4 (66.7%)	2 (33.3%)	
Lymph Node Metastasis					0.26
Seen	119	60.1	78 (65.5%)	41 (34.5%)	
Not Seen	61	30.8	45 (73.8%)	16 (26.2%)	
Not Identified	18	9.1	12 (66.7%)	6 (33.3%)	
Lymphoyascular Invasion					< 0.002
Seen	94	47.5	54 (57.4%)	40 (42.6%)	
Not Seen	104	52.5	81 (77.9%)	23 (22.1%)	

Table 1. Correlation	of BCL-2 expression	and clinicopathological	variables in non-triple negative breast
cancers $(N = 198)$			

Table 2. Correlation of BCL-2 expression and clinicopathological variables in triple negative breast cancers (N=60)

Clinicopathological	Cases (N)	Percentage (%)	BCL-2 E	xpression	P-value
variables			Positive	Negative	
Patients' age					0.02
< 50 Years	35	58.3	23 (65.7%)	12 (34.3%)	
$\geq$ 50 Years	25	41.7	9 (36%)	16 (64%)	
Tumor Size					0.12
<2 cm	7	11.7	4 (57%)	3 (43%)	
2-5 cm	33	55	21 (63.6%)	12 (36.4%)	
> 5cm	20	33.3	7 (35%)	13 (65%)	
Histologic Type					0.07
IDC	53	88.3	31 (58.5%)	22 (41.5%)	
ILC	4	6.7	1 (25%)	3 (75%)	
Mixed	0	0	0	0	
Others	3	5	0	3 (100%)	
Tumor Grade					0.05
Grade I	1	1.6	1(100%)	0	
Grade II	41	68.3	26 (63.4%)	15 (36.6%)	
Grade III	16	26.7	5 (31.3%)	11 (68.7%)	
Not applicable	2	3.4	0	2 (100%)	
Lymph Node Mets					0.10
Seen	37	61.7	16 (43.2%)	21 (56.8%)	
Not Seen	18	30	12 (66.7%)	6 (33.3%)	
Not Identified	5	8.3	4 (80%)	1 (20%)	
Lymphovascular Invasion					0.01
Seen	24	40	8 (33.3%)	16 (66.7%)	
Not Seen	36	60	24 (66.7%)	12 (33.3%)	

BCL-2 expression was more common in patients aged less than 50 as compared to those with age more than 50 in both NTNBCs and TNBCs, and it was statistically significant with P-value of less than 0.05. There was higher expression of BCL-2 in tumors smaller than 5 cm, but the expression decreased in tumors more than 5 cm (51%). It was statistically significant (as shown in table 1), but such significance was not found in TNBCs. BCL-2 expression was higher (80%) in invasive lobular cancers as compared to invasive ductal carcinomas (67%) in NTNBCs, but its expression was higher in ductal carcinomas in TNBCs.

There was also an inverse relationship of BCL-2 expression with grade of tumor being higher in low grade tumors as compared to high grade tumors in both NTNBCs and TNBCs with P-value less than 0.05. Tumors with BCL-2 expression showed lower incidence of lymph node metastasis and LVI in both NTNBCs and TNBCs, which was statistically significant, as shown in table 1 and table 2.

Regarding the association between BCL-2 expression and TNBCs/NTNBCs, BCL-2 expression was observed in 32 out of 60 TNBCs (53.3%), while it was detected in 135 out of 198 NTNBCs (66.2%). This difference was statistically significant (Chi square=4.45, P-value=0.035).

#### Discussion

There are different proteins, which regulate cell cycle, involved in initiation, progression, and treatment response in various malignancies. Some studies have recently been performed to detect various genes and proteins involved in regulation of apoptosis.

BCL-2, an anti-apoptotic gene, is extensively examined in patients with breast cancer for disease progression, treatment response, radiation therapy, chemotherapy, and more recently targeted therapy.<sup>8</sup> It was previously proved that follicular lymphomas as anti-apoptotic protein was associated with worse outcome, but in patients with breast cancer, it was associated with favorable outcomes.<sup>19</sup>

Considering its prognostic and therapeutic importance, we have compared BCL-2 expression of NTNBCs and TNBCs immunohistochemically.

The results of the previous research have revealed that BCL-2 was associated with better prognosis in all types of breast cancers, correlating with previous studies, as well.<sup>11, 20-22</sup> It was also associated with disease-free survival and increased overall survival.<sup>10</sup> The study revealed that BCL-2 expression was directly associated with ER and PR expression, and inversely associated with Her-2/neu expression, correlating with previously published studies.<sup>13,23</sup>

Significant association of BCL-2 expression was found with age, which was compatible with the results of the study conducted by Thomadaki *et al.*<sup>24</sup>

BCL-2 expression was significantly associated

with tumor size in NTNBCs, but the finding was less significant in TNBCs, which is in line with some international studies.<sup>16</sup> Some other studies showed no relationship between size of tumor and BCL-2 expression.<sup>14,25</sup>

In the present study, poorly differentiated tumors showed less BCL-2 expression than low grade breast cancers in both TNBC and NTNBCs. This finding was similar with the results of the study conducted by Bhargava *et al.* and Park *et al.*<sup>18, 26</sup> It suggested that higher tumor grade was associated with the loss of BCL-2 expression.<sup>12</sup>

Lymph node metastasis has been shown as the most important prognostic and predictive factor in breast cancer along with LVI.<sup>27</sup> In our study, BCL-2 expression was more common in tumors without LVI. This was similar with the findings of another international study.<sup>28</sup>

As was already demonstrated,<sup>12</sup> in our study, TNBCs breast cancer was associated with less BCL-2 expression than NTBCs tumors.

The limitations of the study included the lack of access to follow up of the patients and relatively smaller sample size due to which multivariate analysis could not be performed.

TNBCs showed some differences in BCL-2 expression as compared to NTNBCs. These might be due to BCL-2 participation in various biological pathways with different subsequent effects on cell survival, which was further dependent on tumor phenotype. It is of importance if we can identify different prognostic groups in TNBCs, which one can benefit from newer lines of therapy. BCL-2 expression may be of importance in response to neoadjuvant chemotherapy in TNBCs.<sup>29</sup>

Such a large scale study has not already been performed in this region. Hence, this study will provide clinicians with a good insight for using BCL-2 as a part of prognostic workup; likewise, its high expression in both types of tumors will incite further workup for targeted therapy against BCL-2.

The present study is one of the few studies examining the prognostic role of BCL-2 in breast cancer in NTNBCs and TNBCs. BCL-2 can be combined to the well-accepted clinicohistopathologic prognostic factors to predict overall prognosis of invasive breast cancer and guide treatment. BCL-2 showed association with various clinicohistopathological characteristics in TNBC and NTNBC breast cancer patients.

Nevertheless, some of these variables were potentially related with better prognosis (lack of LVI, less tumor size and lower grade). On the other hand, younger age, which is a characteristic generally associated with poorer prognosis, was significantly related to BCL-2 expression.

Further research is necessary to elucidate this association with sample size in different sub-groups and follow up. Moreover, targeted therapies against



BCL-2, (like BH3 mimetics ABT-737 & ABT199)<sup>8</sup> which are currently in clinical trials, can be used in future, especially in TNBCs, where limited options are available for treatment.

## References

- 1. Formenti SC, Arslan AA, Love SM. Global breast cancer: the lessons to bring home. Int J Breast Cancer. 2012;2012:249501.
- 2. Kakarala M, Rozek L, Cote M, Liyanage S, Brenner DE. Breast cancer histology and receptor status characterization in Asian Indian and Pakistani women in the U.S. a SEER analysis. BMC Cancer. 2010;10:191.
- 3. Amin S, Wahid N, Wasim B, Tabassum S. Battling with breast cancer ... addressing the issues. J Pak Med Assoc. 2011;61(6):597-9.
- Pala EE, Bayol U, Cumurcu S, Keskin E. Immunohistochemical characteristics of triple negative/basal-like breast cancer. Turk Patoloji Derg. 2012;28(3):238-44.
- 5. Badve S, Dabbs DJ, Schnitt SJ, Baehner FL, Decker T, Eusebi V, *et al.* Basal-like and triplenegative breast cancers: a critical review with an emphasis on the implications for pathologists and oncologists. Mod Pathol. 2011;24(2):157.
- 6. Fulford LG, Reis-Filho JS, Ryder K, Jones C, Gillett CE, Hanby A, *et al.* Basal-like grade III invasive ductal carcinoma of the breast: patterns of metastasis and long-term survival. Breast Cancer Res. 2007;9(1):R4.
- Hicks DG, Short SM, Prescott NL, Tarr SM, Coleman KA, Yoder BJ, *et al.* Breast cancers with brain metastases are more likely to be estrogen receptor negative, express the basal cytokeratin CK5/6, and overexpress HER2 or EGFR. Am J Surg Pathol. 2006;30(9):1097-104.
- 8. Oakes SR, Vaillant F, Lim E, Lee L, Breslin K, Feleppa F, *et al.* Sensitization of BCL-2expressing breast tumors to chemotherapy by the BH3 mimetic ABT-737. Proc Natl Acad Sci U S A. 2012;109(8):2766-71.
- 9. Tsujimoto Y. Cell death regulation by the Bcl-2 protein family in the mitochondria. J Cell Physiol. 2003;195(2):158-67.
- CallagyGM, Webber MJ, Pharoah PD, Caldas C. Meta-analysis confirms BCL2 is an independent prognostic marker in breast cancer. BMC Cancer. 2008;8:153.
- 11. Dawson SJ, Makretsov N, Blows FM, Driver KE, Provenzano E, Le Quesne J, *et al.* BCL2 in breast cancer: a favourable prognostic marker across molecular subtypes and independent of adjuvant therapy received. Br J Cancer. 2010;103(5):668.
- 12.Kallel-Bayoudh I, Hassen HB, Khabir A, Boujelbene N, Daoud J, Frikha M, *et al.* Bcl-2 expression and triple negative profile in breast carcinoma. Med Oncol. 2011;28 Suppl 1:S55-61.

- 13. Lee KH, Im SA, Oh DY, Lee SH, Chie EK, Han W, et al. Prognostic significance of bcl-2 expression in stage III breast cancer patients who had received doxorubicin and cyclophosphamide followed by paclitaxel as adjuvant chemotherapy. BMC Cancer. 2007;7:63.
- 14. Nadler Y, Camp RL, Giltnane JM, Moeder C, Rimm DL, Kluger HM, *et al.* Expression patterns and prognostic value of Bag-1 and Bcl-2 in breast cancer. Breast Cancer Res. 2008;10(2):R35.
- 15. Elston CW, Ellis IO. Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology. 1991;19(5):403-10.
- 16. Callagy GM, Pharoah PD, Pinder SE, Hsu FD, Nielsen TO, Ragaz J, *et al.* Bcl-2 is a prognostic marker in breast cancer independently of the Nottingham Prognostic Index. Clin Cancer Res. 2006;12(8):2468-75.
- 17. Kreike B, van Kouwenhove M, Horlings H, Weigelt B, Peterse H, Bartelink H, *et al.* Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast Cancer Res. 2007;9(5):R65.
- Park SH, Kim H, Song BJ. Down regulation of bcl2 expression in invasive ductal carcinomas is both estrogen- and progesterone-receptor dependent and associated with poor prognostic factors. Pathol Oncol Res. 2002;8(1):26-30.
- 19. Dema A, Dragan S, Lazar E, Munteanu D, Taban S, Lazureanu C, *et al.* Bcl-2 expression in breast carcinomas in postmenopausal women. TMJ. 2008;58(3-4):155-61.
- 20. Hellemans P, van Dam PA, Weyler J, van Oosterom AT, Buytaert P, Van Marck E. Prognostic value of bcl-2 expression in invasive breast cancer. Br J Cancer. 1995;72(2):354-60.
- 21. Sirvent JJ, Aguilar MC, Olona M, Pelegri A, Blazquez S, Gutierrez C. Prognostic value of apoptosis in breast cancer (pT1-pT2). A TUNEL, p53, bcl-2, bag-1 and Bax immunohistochemical study. Histol Histopathol. 2004;19(3):759-70.
- 22. Kroger N, Milde-Langosch K, Riethdorf S, Schmoor C, Schumacher M, Zander AR, *et al.* Prognostic and predictive effects of immunohistochemical factors in high-risk primary breast cancer patients. Clin Cancer Res. 2006;12(1):159-68.
- 23. Gasparini G, Barbareschi M, Doglioni C, Palma PD, Mauri FA, Boracchi P, *et al.* Expression of bcl-2 protein predicts efficacy of adjuvant treatments in operable node-positive breast cancer. Clin Cancer Res. 1995;1(2):189-98.
- 24. Thomadaki H, Talieri M, Scorilas A. Prognostic value of the apoptosis related genes BCL2 and BCL2L12 in breast cancer. Cancer Lett. 2007;247(1):48-55.

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- 25. Cecka F, Hornychova H, Melichar B, Ryska A, Jandik P, Mergancova J, et al. Expression of bcl-2 in breast cancer: correlation with clinicopathological characteristics and survival. Acta Medica (Hradec Kralove). 2008;51(2):107-12.
- 26. BhargavaV, Kell DL, van de Rijn M, Warnke RA. Bcl-2 immunoreactivity in breast carcinoma correlates with hormone receptor positivity. Am J Pathol. 1994;145(3):535-40.
- 27. Munster PN, Norton L. Predictive factor for the response to adjuvant therapy with emphasis in breast cancer. Breast Cancer Res. 2001;3(6):361-4.
- 28. Neri A, Marrelli D, Roviello F, DeMarco G, Mariani F, DeStefano A, *et al.* Bcl-2 expression correlates with lymphovascular invasion and longterm prognosis in breast cancer. Breast Cancer Res Treat. 2006;99(1):77-83.
- 29. Tawfik K, Kimler BF, Davis MK, Fan F, Tawfik O. Prognostic significance of Bcl-2 in invasive mammary carcinomas: a comparative clinicopathologic study between "triplenegative" and non-"triple-negative" tumors. Hum Pathol. 2012;43(1):23-30.



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## The Study of Type D Personality and Cognitive Strategies of Emotion Regulation as Predictors of Happiness and Quality of Life in Women With Breast Cancer

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#### Introduction

The most common cancer in Iranian women, breast cancer, is among the 3 leading causes of death in Iran.<sup>1</sup> Based on a report of Ministry of Health

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ABSTRACT

**Background:** Various personality traits, like A and D, have a lot of stress, anxiety, and negative emotions that make the patients with breast cancer be susceptible to more stress and negative perception of events. Thus, the aim of the present study was to examine the association of type D personality and cognitive strategies of emotion regulation with happiness and quality of life (QOL) in women with breast cancer.

**Methods:** The present cross-sectional study included 100 women with breast cancer referred to Shiraz medical centers in summer 2015; the population of the study was chosen through purposive sampling method. Information was recorded through filling 4 questionnaires, including type D personality scale, cognitive emotion regulation questionnaire (CERQ), Oxford happiness inventory, and QOL questionnaire.

**Results:** A significant negative association was observed between type D personality and happiness, and there was a positive association between type D personality and QOL (P < 0.001), between positive cognitive strategies of emotion regulation and QOL(P < 0.001), positive cognitive strategies of emotion regulation and happiness (P < 0.001), but no significant relationship was found between negative cognitive strategies of emotion regulation and happiness (P = 0.08). No significant relationship between negative cognitive strategies of emotion regulation and QOL(P=0.25) was seen.

**Conclusions:** These results elucidate the associations between personality and illness perceptions, demonstrating their close interrelatedness. Therefore, we can increase the awareness and understanding of personality traits as well as emotional regulation strategies about the disease in order to enhance happiness and quality of life in such patients.

Center for Disease Management of Iran, the most widespread cancers in women included breast, skin, colon, rectum, stomach, esophagus, hematopoietic system, thyroid, ovary, and uterus.<sup>2</sup> Breast cancer ranks first in women with Age Standardized Incidence Rate (ASR) =28.25, higher than the reported rate of skin cancer.<sup>3</sup>

It is estimated that half of the new cases and 60% of the world's deaths belongs to the developing countries due to adopting western life style and also infections.<sup>4,5</sup>

Quality of life (QOL) is a multidimensional

notion engaging facets of individuals' physical, psychological, and social well-being.<sup>6</sup> The determinants of QOL in women with breast cancer include psychosocial factors, like coping style as well as socio-demographic and medical factors.<sup>7</sup> Some surveys have concentrated on the impact of psychological factors on cancer.<sup>8</sup> Studies have confirmed the influences of coping styles, optimism, and certain personality traits on cancer, <sup>9</sup> although others have found no association between personality traits and cancer risk.<sup>10</sup>

Described as a tendency to experience a high joint incidence of negative affectivity and social inhibition, type D (distressed) personality has become a significant research subject in the area of medical psychology in recent years.<sup>11</sup> Patients with personality traits D internally experience a large amount of stress and negative emotions; hence, they are at increased risk of cardiovascular disorders.<sup>12</sup> Studies have designated that type D personality disorder enhances the comorbidity and health burden in patients with cancer.<sup>13</sup>

Emotional self-regulation is a structured effort to regulate thoughts, feelings, and actions to achieve specific objectives. Although all goals in life are not the same, the ability to self-regulate creates harmony among objectives. In other words, self-regulation requires sacrificing one goal for other goals. A previously conducted study has shown that positive emotions facilitate self-regulation and negative emotions harm self-regulation.<sup>14</sup>

Cognitive emotion regulation is universal; individual differences exist in the particular thoughts or cognitions through which people regulate their emotions in response to life experiences. Cognitive emotion regulation is, hence, broadly supposed to be an imperative subject regarding mental health.<sup>15</sup> Cognitive emotion regulation is, likewise, correlated with depression and emotional problems that are linked with numerous diseases.<sup>15,16</sup>

Cancer is a crisis with which anyone may confront and it causes many problems for the affected patients, containing complex treatment protocols, long treatment duration, and resistance to treatment that cause great stress and despair.<sup>17</sup> These difficulties are particularly problematic in the case of breast cancer, in which mastectomy may additionally cause psychosocial problems for the affected patients, including occupational and sexual problems.<sup>18</sup> Furthermore, patients suffering from breast cancer have increased the rates of depression and anxiety in the first year after diagnosis.<sup>19</sup>

Therefore, these 2 factors may play a central role inprediction of the individual's happiness that interacts with the quality of life (QOL) in patients with breast cancer. Because of the disagreements, novelty, and significance of this issue, we aimed to investigate the association between type D personality and cognitive strategies of emotion regulation with happiness and quality of life in women with breast cancer.

#### Methods

#### Study design

The present cross sectional descriptive study included 100 women with breast cancer who referred to Mottahari Clinic affiliated to Shiraz University of Medical Sciences for chemotherapy during summer 2015; the participants were chosen based on purposive sampling. As a technique generally used in qualitative research, purposeful sampling is utilized for the classification and selection of informationrich cases for the most effective use of limited resources.<sup>20</sup> This involves recognizing and choosing individuals or groups of individuals based on special knowledge about or experience with a phenomenon of interest.<sup>21</sup> We included patients whose diagnosis was made during 1 to 5 years prior to the study and had not underwent mastectomy. Any patient diagnosed more than 5 years prior to the study or had concurrent underlying diseases, comprising physical and psychological comorbidities, like cardiovascular diseases, diagnosed general anxiety disorder, and bipolar and major depressive disorders was excluded. We excluded incomplete questionnaires from the study. The demographic data of patients were recorded and they were asked to complete the following questionnaires:

1. The questionnaire of quality of life (SF-36), designed by Ware and Sherbourne in 1992,<sup>22</sup> contains 36 items, representing 8 different domains, including general health, physical functioning, limitation in role playing due to physical and emotional reasons, body pain, social function, vitality, and mental health. The scores range from 0 to100 and higher scores show better QOL, internal consistency of scales measured by Cronbach's exceeded 0.80 and validity estimated 0.075. The Persian version of the questionnaire has been previously validated by Montazeri *et al.*<sup>23</sup> with estimated internal reliability of 77% to 90% in all aspects, except delight (65%). He, likewise, reported Cronbach's alpha coefficients for all subscales in the range of 0.70 to 0.85.<sup>23</sup>

2. Oxford happiness inventory, designed by Argyl, Martin, and Crossland in 1989,<sup>24</sup> contains 29 items in 5 domains, including satisfaction, positive mood, health, efficiency, and self-esteem. Each item has 4 choices, scored from 0 to 3, where never indicates 0, 1 shows few, 2 signifies moderate, and 3 shows very much. The total score ranges from 0 to 78, and scores less than 40 to 42 identify depression and dissatisfaction, while score greater than 42 show happiness. The Persian version of the questionnaire has previously been validated by Hadinezhad and Zareei,<sup>25</sup> reporting a Cronbach's alpha of 90% and test-retest reliability of 78%.

3. Type D personality scale, designed by Denollet,<sup>11</sup> evaluates the parameters of negative



affectivity (NA) and social inhibition (SL). Each domain has 14 items, scored as "never, sometimes, often, and always" and is scored from 0 to 28; scores greater than 10 show positive results and the total score ranges from 0 to 56. Reliability and validity of Persian version of Type D personality Questionnaire (DS14) has previously been evaluated by Fakhari *et al.* in patients with coronary artery disease.<sup>26</sup>

4. Cognitive emotion regulation questionnaire (CERQ), a multi-dimensional questionnaire designed by Garnefski *et al.*<sup>27,28</sup> in 2002, assesses the cognitive emotion regulation after an unpleasant event. These subscales include: 1) Non-acceptance of Emotional Response 2) Difficulties Engaging in Goal-directed Behavior 3) Impulse Control Difficulties 4) Lack of Emotional Awareness 5) Limited Access to Emotion Regulation Strategies 6) Lack of Emotional Clarity. These subscales are designed to assess a persons' behavioral reaction after experiencing a stressful life event. Some items are reverse-scored. Each subscale is scored on a 5point Likert scale ranging from "Almost Never" to "Almost Always." The total score ranges from 36 to 180. The Persian version of the questionnaire has previously been validated by Hasani,<sup>29</sup> reporting a Cronbach's alpha of 0.76 to 0.92.

The participants completed the questionnaires anonymously and under observation of the researcher who explained any vague item in the questionnaires to them.

#### Ethical considerations

The protocol of the present study was approved by Shiraz University of Medical Sciences. The design and objectives of the study were explained to all participants and written informed consent was obtained from those who were inclined to take part in the survey; they were informed that they were free not to participate in the study and this would not affect their treatment protocol. The participants were ensured that their information would be kept confidential and anonymous in all stages of the study.

#### Statistical analysis

Quantitative variables were presented as mean  $\pm$  standard deviation (SD) and categorical variables as

frequency (percentage). The associations between variables were defined by regression models and Pearson's coefficient. For the statistical analysis, the statistical software SPSS version 21.0 for windows (SPSS Inc., Chicago, IL) was used. P-values less than 0.05 were considered statistically significant.

#### Results

The mean  $\pm$  SD age of patients was  $50.39\pm1.23$  years. Educational status of patients is demonstrated in Table 1. Of all patients, 76% had personality type D, 80% had happiness, 93% used negative strategies and 15% used positive strategies for cognitive emotion regulation, and QOL was low in 53% of patients. In Table 2, mean and standard deviation of Type D personality, happiness, quality of life, and cognitive strategies of emotion regulation are demonstrated.

Table 1. Educational status

	N(%)
Illiterate	9 (7.65%)
Primary	23 (23. 24%)
Medium	21 (22 .27%)
Diploma	29 (31.54%)
Collegiate	18 (15.3%)

Table 2. Mean and standard deviation of main varia	bles
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	$Mean \pm SD$
Type D personality trait	$27.31\pm9.71$
Happiness	$51.5\pm14.49$
Quality of life	$49.19 \pm 1.35$
Positive cognitive strategies of emotion regulation	$69.5\pm13.52$
Negative cognitive strategies of emotion regulation	$48.5\pm10.74$

As shown in Table 3, happiness showed significant association with type D personality trait and with positive cognitive strategies. There were also significant association between quality of life and type D personality, negative cognitive strategies, and positive cognitive strategies of emotional regulation.

**Table 3.** The association of type D personality trait, negative and positive cognitive strategies of emotion regulation with happiness and quality of life in the study participants

	Type D personality trait	Negative cognitive strategies of emotion regulation	Positive cognitive strategies of emotion regulation
Happiness	r = -0.63, P = 0.0001	r = 0.11, P = 0.25	r = 0.63, P = 0.0001
Quality of life	r = 0.44, P = 0.0001	r = 0.17, P = 0.08	r = -0.36, P = 0.0001

 $(\cdot)$ 

#### Discussion

The QOL and happiness in patients suffering from cancer can have an important impact on their prognosis and general health.<sup>30</sup> Moreover, surveys have shown that patients with breast cancer have a worse social well-being than patients with other cancers;<sup>31</sup> consequently, considering the psychological factors in patients suffering from breast cancer is of great importance. The results of the present study signified important negative correlation between type D personality and happiness (r = -0.63, P = 0.0001). Besides, a positive association was found between type D personality and QOL (r = 0.63, P = 0.0001). There was also a significant positive association between positive cognitive strategies of emotion regulation and happiness (r = 0.63, P = 0.0001). Furthermore, a negative association was found between positive cognitive strategies of emotion regulation and QOL (r = -0.36, P = 0.0001), but the association between negative cognitive strategies of emotion regulation and QOL was not significant (r = 0.17, P = 0.08). Several studies have assessed the association between personality type D and diseases, but have seldom focused on patients with cancer. Personality is known as an independent factor in subjective wellbeing and happiness,<sup>32</sup> which was confirmed by the results of the present study. Individuals with type D personality trait require to be confirmed by others and may, hence, confront problems coping with diseases,<sup>33</sup> specifically diseases that influence their body image, like breast cancer, which may ultimately lead to mastectomy. These difficulties, intensely, affect patients suffering from breast cancer, particularly patients with type D personality trait, who encounter emotional problems and have negative emotions; therefore, type D personality trait is connected with social and emotional complications that predispose the patients to diseases.<sup>11,34</sup>

Considering the association between type D personality and QOL, studies have attained different findings that might be because of the different nature of the diseases studied. Pederson et al. have established a significant negative association between type D personality and impaired QOL in cardiac patients.<sup>35</sup> Similarly, have other researchers proven lower health-related QOL in cardiac patients with type D personality trait.<sup>36-38</sup> The results of the above-mentioned studies are inconsistent with the results of the present study, which might be due to the fact that patients with type D personality have difficulty in social relations and many choose loneliness.<sup>33</sup> Patients with breast cancer have additional problems in social relations;<sup>18</sup> hence, they appear less in the society and are less influenced by the negative responses of the society. Moreover, the majority of patients in the present study had breast cancer for 1 to 5 years, while social problems mainly emerge in early phases of disease after diagnosis<sup>19</sup> that could affect the results of the present study and cause higher QOL in patients with type D personality.

Some studies have also suggested that type D personality trait influences the neuro-endocrine system via stress.<sup>12</sup> Therefore, type D personality trait may not only have psychological effects on patients' health, but it may also induce physiological changes in the body that affect patients' health condition that need additional investigation in the area of breast cancer.

Few studies have considered cancer, but they have also not focused on type D personality in patients with breast cancer. Denollet have previously proposed type D personality and age as independent risk factors for cancer development in men.<sup>39</sup> Carver et al. have also associated optimism and psychological well-being to survival of patients with breast cancer.9 Similarly, Epping-Jordan et al. have evaluated psychological adjustment in patients suffering from breast cancer at 3 and 6 months' follow-up and have suggested optimism as a vital factor in such patients.<sup>40</sup> As long as pessimism is one of the characteristics of individuals with type D personality, the above-mentioned surveys also approve the results of the present study. Mols et al. have assessed patients with colorectal cancer and have reported that patients with type D personality trait have a significantly higher psychological distress and concern about the disease<sup>41</sup> that generally approves the results of the present study; although the above-mentioned studies have not focused on the variables argued in the present study.

Similar to the results of the present study, Giese-Davis et al. have reported changed emotion regulation strategies in patients with metastatic breast cancer and have proven the efficiency of emotion-focused therapy<sup>42</sup> that is consistent with the results of the present study, showing that positive cognitive strategies of emotion regulation predict patients' happiness. Additionally, emotion regulation strategies have also been associated to different diseases by other researchers. Kinnunen et al. have associated emotion regulation with metabolic syndrome<sup>16</sup> and Karademas et al. have associated emotion regulation strategies to illnessrelated emotions,43 suggesting that emotion regulation strategies have physiological impacts on the body that need greater attention, particularly in patients suffering from cancer. Thus, it is proposed that future studies evaluate the psychological and physiological effect of personality traits and emotion regulation strategies on patients suffering from breast cancer.

The strengths of the present study included evaluating this novel issue in patients with breast cancer that is the first most prevalent cancer in Iran and guiding the researchers to focus on the psychological state of patients suffering from breast cancer. But, it also had some limitations, such as not considering the prognosis of patients, which was not within the objectives of the study. Besides, as the results of the present study suggested, psychological treatment of patients with breast cancer may play a key role in the prognosis of the patients. Therefore, it is proposed that future studies assess the effect of psychotherapy in 2 aspects of personality traits and emotion regulation strategies on the prognosis and treatment of patients suffering from breast cancer.

Nowadays, due to changes in lifestyle, noncommunicable diseases including cancers are increasing. Among all kinds of cancers, breast cancer is the most common cancer and the most leading cause of death among women. Patients are severely damaged mentally and emotionally, because breast is a sensitive part of their body and is considered a sign of beauty and charm. Since the treatment of breast cancer in women is accompanied with complications, it may have high cultural and social psychological effects, as their health is closely associated with the health of the family and the community. Therefore, we need to increase our awareness and understanding of personality traits as well as emotional regulation strategies about this disease and develope strategies in order to enhance happiness and quality of life in such patients.

## **Conflict of Interest**

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

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## References

- Mousavi SM, Gouya MM, Ramazani R, Davanlou M, Hajsadeghi N, Seddighi Z. Cancer incidence and mortality in Iran. Annals of Oncology. 2008;20(3):556-63.
- 2. Alikhani S. A national profile of NCD risk factors in the IR Iran; Selected results of the first suvey of Iranian NCD risk factors surveillance system. Technical unit for noncommunicable disease risk factors surveillance. Center for Disease Control, Ministry of Health and Medical Education. 2005.
- Dahlui M, Ramli S, Bulgiba AM. Breast cancer prevention and control programs in Malaysia. Asian Pac J Cancer Prev. 2011;12(6):1631-4.
- 4. Ma J, Jemal A. Breast cancer statistics. Breast Cancer Metastasis and Drug Resistance: Springer; 2013. 1-18.

- 5. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiology Biomarkers & Prevention. 2010;19(8):1893-1907.
- 6. Cella DF. Quality of life: concepts and definition. J Pain Symptom Manage. 1994;9(3):186-92.
- 7. Mols F, Vingerhoets AJ, Coebergh JW, van de Poll-Franse LV. Quality of life among long-term breast cancer survivors: a systematic review. Eur J Cancer. 2005;41(17):2613-9.
- 8. Leshan LL, Worthington RE. Personality as a factor in the pathogenesis of cancer: A review of the literature\*. British Journal of Medical Psychology. 1956;29(1):49-56.
- 9. CarverCS, Smith RG, Antoni MH, Petronis VM, Weiss S, Derhagopian RP. Optimistic personality and psychosocial well-being during treatment predict psychosocial well-being among long-term survivors of breast cancer. Health Psychology. 2005;24(5):508.
- Temoshok L. Personality, coping style, emotion and cancer: towards an integrative model. Cancer surveys. 1986;6(3):545-67.
- Denollet J. DS14: standard assessment of negative affectivity, social inhibition, and Type D personality. Psychosomatic medicine. 2005;67(1):89-97.
- 12. Habra ME, Linden W, Anderson JC, Weinberg J. Type D personality is related to cardiovascular and neuroendocrine reactivity to acute stress. Journal of psychosomatic research. 2003;55(3):235-45.
- Mols F, Oerlemans S, Denollet J, Roukema JA, van de Poll-Franse LV. Type D personality is associated with increased comorbidity burden and health care utilization among 3080 cancer survivors. General hospital psychiatry. 2012;34(4):352-9.
- Myerberg L. Forgiveness as a mechanism of self-regulation: an ego-depletion model. 2011. Honors Theses. 112.
- 15. Garnefski N, Kraaij V. Relationships between cognitive emotion regulation strategies and depressive symptoms: A comparative study of five specific samples. Personality and Individual differences. 2006;40(8):1659-69.
- 16. Kinnunen M-L, Kokkonen M, Kaprio J, Pulkkinen L. The associations of emotion regulation and dysregulation with the metabolic syndrome factor. Journal of psychosomatic research. 2005;58(6):513-21.
- 17. Gonzalez-Angulo AM, Morales-Vasquez F, Hortobagyi GN. Overview of resistance to systemic therapy in patients with breast cancer. Breast Cancer Chemosensitivity: Springer; 2007. p. 1-22.
- 18. Avis NE, Crawford S, Manuel J. Psychosocial problems among younger women with breast

cancer. Psycho-Oncology. 2004;13(5):295-308.

- 19. Burgess C, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. Bmj. 2005;330(7493):702.
- 20. Patton MQ. Qualitative Research and Evaluation Methods, 3rd edn Sage. Thousand Oaks, California. 2002.
- 21. Creswell JW, Clark P. VL. Designing and conducting mixed methods research. London: Sage. 2007.
- 22. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. Medical care. 1992:473-83.
- Montazeri A, Goshtasebi A, Vahdaninia M, Gandek B. The Short Form Health Survey (SF-36): translation and validation study of the Iranian version. Quality of life research. 2005;14(3):875-82.
- 24. Argyle M, Martin M, Crossland J. Happiness as a function of personality and social encounters. Recent advances in social psychology: An international perspective. 1989:189-203.
- 25. Hadinezhad H, Zareei F. Reliability, validity, and normalization of the Oxford Happiness Questionnaire. 2009; 12(23):
- 26. Fakhari A, Norouzi S, Pezeshki MZ. Reliability and Validity of Type D Personality Questionnaires (DS14 Persian Version) in Coronary Artery Patients. Medical Journal of Tabriz University of Medical Sciences and Health Services. 2014;36(4):78-85.
- 27. Garnefski N, Kraaij V, Spinhoven P. Negative life events, cognitive emotion regulation and emotional problems. Personality and Individual differences. 2001;30(8):1311-27.
- Garnefski N, Kraaij V. Cognitive emotion regulation questionnaire–development of a short 18-item version (CERQ-short). Personality and Individual Differences. 2006;41(6):1045-53.
- 29. Hasani J. The psychometric properties of the cognitive emotion regulation questionnaire (CERQ). Journal of Clinical Psycology. 2010;2(3):73-84.
- 30 Stavrou D, Weissman O, Polyniki A, Papageorgiou N, Haik J, Farber N, *et al.* Quality of life after breast cancer surgery with or without reconstruction. Eplasty. 2009;9:e18.
- 31. Üstündag S, Zencirci AD. Factors affecting the quality of life of cancer patients undergoing chemotherapy: A questionnaire study. Asia-Pacific Journal of Oncology Nursing. 2015;2(1):17.
- 32. Steel P, Ones DS. Personality and happiness: a national-level analysis. Journal of Personality and Social Psychology. 2002;83(3):767.
- 33. Williams L, O'Connor RC, Howard S, Hughes

BM, Johnston DW, Hay JL, *et al.* Type-D personality mechanisms of effect: the role of health-related behavior and social support. Journal of Psychosomatic Research. 2008;64(1):63-9.

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- 34. Denollet J. Type D personality: a potential risk factor refined. Journal of psychosomatic research. 2000;49(4):255-66.
- 35. Pedersen SS, Denollet J. Type D personality, cardiac events, and impaired quality of life: a review. European journal of cardiovascular prevention & rehabilitation. 2003;10(4):241-8.
- 36. Pedersen SS, Holkamp PG, Caliskan K, van Domburg RT, Erdman RA, Balk AH. Type D personality is associated with impaired healthrelated quality of life 7 years following heart transplantation. Journal of psychosomatic research. 2006;61(6):791-5.
- 37. Denollet J, Vaes J, Brutsaert DL. Inadequate response to treatment in coronary heart disease adverse effects of Type D personality and younger age on 5-year prognosis and quality of life. Circulation. 2000;102(6):630-5.
- 38. Aquarius AE, Denollet J, Hamming JF, Henegouwen DPVB, De Vries J. Tpe-D personality and ankle brachial index as predictors of impaired quality of life and depressive symptoms in peripheral arterial disease. Archives of Surgery. 2007;142(7):662-7.
- Denollet J. Personality and risk of cancer in men with coronary heart disease. Psychological Medicine. 1998;28(04):991-5.
- 40. Epping-Jordan JE, Compas BE, Osowiecki DM, Oppedisano G, Gerhardt C, Primo K, *et al.* Psychological adjustment in breast cancer: processes of emotional distress. Health Psychology. 1999;18(4):315.
- 41. Mols F, Denollet J, Kaptein AA, Reemst PHM, Thong MSY. The association between Type D personality and illness perceptions in colorectal cancer survivors: a study from the populationbased profiles registry. Journal of Psychosomatic Research. 2012;73(3):232-9.
- 42. Giese-Davis J, Koopman C, Butler LD, Classen C, Cordova M, Fobair P, *et al.* Change in emotionregulation strategy for women with metastatic breast cancer following supportive-expressive group therapy. Journal of Consulting and Clinical Psychology. 2002;70(4):916.
- 43. Karademas EC, Tsalikou C, Tallarou M-C. The impact of emotion regulation and illness-focused coping strategies on the relation of illness-related negative emotions to subjective health. Journal of Health Psychology. 2011; 16(3):510-9.

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## Synchronous Invasive Lobular Carcinoma of Breast With Hodgkin Lymphoma: A Case Report

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## ABSTRACT

Background: Multiple Primary Malignant Neoplasms (MPMN) is a wellknown entity. Most of these tumors are metachronous. The treatment of Hodgkin lymphoma increases the risk of developing second malignancies including breast cancer. However, the synchronous occurrence of breast cancer and Hodgkin lymphoma is rare.

Archives Of

**Case presentation:** We presented a case of a 31-year-old woman with simultaneous diagnosis of lobular carcinoma of the breast and Hodgkin lymphoma. The patient underwent modified radical mastectomy followed by hormone therapy as adjuvant treatment of breast cancer and simultaneous chemotherapy for Hodgkin lymphoma.

Conclusions: To the best of our knowledge, this is the first report of coexistence of breast cancer and Hodgkin lymphoma. Synchronous cancers present therapeutic challenges to the clinicians, and the treatment planning should be discussed in a multidisciplinary team.

hodgkin lymphoma Introduction

synchronous tumor,

The first report of Multiple Primary Malignant Neoplasms (MPMN) was published by Billroth in 1889.<sup>1</sup> Since then, numerous reports of MPMNs have been published. MPMNs constitute 0.4% to 21% of all cancers<sup>2</sup> and the incidence is increasing.<sup>3</sup> MPMN is defined as "'two or more primary cancers located at different sites or at the same site, if histological characteristics are different".<sup>4</sup> MPMNs are considered synchronous, if the second primary tumor is diagnosed within 6 months of the first tumor

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diagnosis. If the time interval between diagnoses of the tumors is more than 6 months, the tumors are considered metachronous.<sup>2</sup> Synchronous primary tumors are rare.<sup>5</sup> They present a therapeutic challenge to the physician and should be treated by a multidisciplinary team with a patient-oriented approach.<sup>6</sup> We presented a rare instance of concurrent breast cancer and Hodgkin lymphoma.

## **Case presentation**

A 31-year-old woman was referred to the oncology clinic with the diagnosis of Hodgkin lymphoma. She was visited by her family physician a year earlier with night fever, chills, weight loss, and retrosternal pain. She was treated with antibiotics without any improvement. Gradually, a swelling developed over her sternum, and a biopsy of the lesion showed granuloma. Since she lived in an

endemic area for tuberculosis, the treatment of tuberculosis with Isoniazid, Rifampin, Ethambutol and Pyrazinamide was started for her and it was continued for 6 months. The size of sternal swelling decreased, but she noticed the development of new swellings in her lower neck and axillary areas. The biopsy of the right supraclavicular lymph nodes was performed and the pathology result showed Hodgkin lymphoma, nodular sclerosis with mixed cellularity nodule type.

While referring the patient to the oncology clinic, physical examination revealed bilateral supraclavicular and axillary lymphadenopathy, and 2 masses in the right breast at 12 and 7 o'clock measured 4 and 2 cm, respectively. No other organomegaly was detected. She had no significant medical or surgery history. She mentioned a family history of breast cancer in her 3 cousins. Her menarche was at 15 years of age and her first child birth was when she was twenty-one.

Considering her family history of breast cancer and no report of breast involvement in Hodgkin lymphoma, the possibility of a second primary malignancy was probable. The result of mammography showed 2 suspicious masses and skin thickening in the right breast (figure 1). Breast ultrasonography was performed and the result revealed 6 highly suspicious masses in the right breast. The masses ranged from 6 to 34 mm.

The result of MRI of the breast revealed 2 adherent large irregular shape enhancing masses in the right breast with multiple smaller masses around them in favor of multi-centric breast cancer (figure 2 and 3). In addition, there were multiple enlarged pathologic appearing lymphadenopathies in both axillae (figure 4). An irregular shape chest wall mass in medial deep part of the right side of chest wall was detected with the involvement of ribs and pleura and extension to the mediastinum (figure 5).



**Figure 1.** MLO mammography showing a large lobulated irregular shape mass with ill-defined border in the right breast upper part and another mass posterior to the main mass. Mild skin thickening of the central part of the right breast is also noted.



Figure 2. Breast MRI, T1 with contrast subtraction axial image, showing multiple irregular shaped enhancing masses in central and outer part of right breast



Figure 3. Breast MRI, T1 with contrast and subtraction in MIP axial image, showing 2 adherent large irregular shaped enhancing masses in the right breast with multiple smaller masses around them in favor of multi-centric breast cancer



**Figure 4.** Breast MRI, axial T1 image, Multiple enlarged pathologic appearing lymphadenopathies are seen in both axillae



Figure 5. Breast MRI, T1 with IV contrast and subtracted axial image, showing irregular shape chest wall mass in medial deep part of right side of chest wall with involvement of ribs and pleura and extension to the mediastinum

The biopsy of the masses of the right breast was performed and the pathology was multi-centric invasive lobular carcinoma. Estrogen and progesterone receptors were positive, HER-2 neu was negative, and Ki-67 was 15%. The FNA of left axillary lymph nodes was consistent with Hodgkin lymphoma, and there was no involvement with lobular carcinoma.

Blood work showed mild microcytic anemia, high platelet count, elevated ESR, and mildly elevated bilirubin. Liver function tests and LDH were within normal range. Bone marrow biopsy did not show involvement with Hodgkin lymphoma. Computed tomography scan of neck and thorax revealed numerous bilateral supraclavicular, infraclavicular, axillary, and mediastinal lymph nodes. Abdominal and pelvic CT scans were normal.

The patient was diagnosed with synchronous stage II Hodgkin lymphoma and locally advanced breast cancer. The management of each malignancy was discussed in the multidisciplinary oncology conference of the hospital. The multidisciplinary team agreed on the surgical treatment of breast cancer followed by simultaneous adjuvant treatment with tamoxifen for breast cancer and chemotherapy for Hodgkin lymphoma.

The patient underwent right modified radical mastectomy and axillary lymph node dissection. A small area of pectoralis major muscle, involved with one of the masses, was resected. The pathology report revealed multi-centric invasive mixed lobular and ductal carcinoma, histologic and nuclear grade II with angiolymphatic and perineural invasion. The smallest tumor was 7 mm and the largest one was 5 cm in diameter. All margins were free from tumor. Seven out of 8 axillary lymph nodes were involved with metastatic tumor. The microscopic examination of lymph nodes revealed lymph node tissue with the presence of sheets and nests of epithelial neoplastic cells. In some foci, there was diffuse obliteration of nodal architecture without capsular thickening or broad bands of parenchymal fibrosis. In addition, numerous classical Reed- Sternberg cells were present in a background of small lymphocytes, eosinophils, histiocytes, plasma cells, and occasional neutrophils (figure 6).



**Figure 6.** Histological analysis of the lymph node involved by Hodgkin lymphoma and breast carcinoma (magnification: A =x 40, B =x 100, C&D =x 400) A & B) Black arrow: Nodular Hodgkin lymphoma, red arrow: Invasive Ductal Carcinoma. C) Black arrow: Reed-Sternberg cell. D) Black arrow: Reed-Sternberg cell, red arrow: Invasive Ductal Carcinoma

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Following the surgery, she received 12 cycles of chemotherapy for Hodgkin lymphoma with Adriamycin, Bleomycin, Vinblastine, and Dacarbazine (ABVD) regimen. Concurrently, she received Tamoxifen and Diphereline as adjuvant therapy for breast cancer. A CT scan, after 8 cycles of chemotherapy, showed no evidence of disease in the neck, axillae, and mediastinum. A PET- CT scan, 3 months after the completion of chemotherapy, showed no metabolically active lesion throughout the body, indicating complete metabolic response to the treatment. She received adjuvant radiotherapy for breast cancer.

## Discussion

After the first report of MPMN by Billroth, Warren, and Gates collected 1259 cases from the literature and described the criteria for the diagnosis of MPMNs.<sup>7</sup> The criteria of Warren and Gates required: 1) the histologic confirmation of the malignant nature of each tumor, 2) the existence of tumors in geographically separate sites and 3) the lack of possibility of metastasis from another neoplasms. These criteria have been updated by an international working group in 2004.<sup>4</sup>

MPMNs are, likewise, categorized as synchronous or metachronous. Tumors diagnosed at the same time or within 6 months of the first tumor are considered synchronous and tumors diagnosed at more than a 6-month interval are considered metachronous. Metachronous MPMNs are more common than synchronous neoplasms<sup>8,9</sup> with a ratio of 2 to 2.7:1.<sup>2,6</sup>The present percentage of MPMNs is increasing <sup>3,10,11</sup> and this increase might be attributed to more successful treatment of the primary tumors.<sup>12</sup>

There are several explanations for the occurrence of MPMNs. One theory is increased survival of patients with cancer due to more effective therapies.<sup>13</sup> The cancer survivors have a 20% increase in their risk of new primary cancer development.<sup>14</sup> Another explanation is the effect of the therapies for the first cancer. Curtis reported Alkylating agents as a risk factor for developing acute non-lymphocytic leukemia and preleukemia following breast cancer treatment.<sup>15</sup> Patients treated with radiation therapy are predisposed to the development of a second cancer. One example is the development of breast cancer following radiation therapy for Hodgkin lymphoma<sup>16-19</sup> and contralateral breast cancer in patients who received radiotherapy for breast cancer.<sup>2</sup>

Furthermore, it has been suggested that during fetal life, cells with a predisposition to malignant transformation migrate to multiple organs. Later, exposure to environmental carcinogens could induce multiple primary neoplasms.<sup>21, 22</sup> In other cases of MPMNs, inherited mutations are responsible for multiple malignancies. The examples of these mutations are BRCA1 and 2, P53, PTEN, etc.

There are multiple reports of breast cancer occurring after radiation therapy for Hodgkin lymphoma.<sup>16, 17, 19, 23-25</sup> There are also reports of breast involvement by hematologic malignancies, but breast involvement by Hodgkin lymphoma has not been reported.<sup>26</sup> There has been numerous reports of synchronous occurrence of breast cancer and other malignancies, including bladder,<sup>5</sup> thyroid,<sup>27</sup> pancreas,<sup>28</sup> renal cell carcinoma,<sup>29</sup> thymoma,<sup>30</sup> lung, and melanoma,<sup>8</sup> etc. To the best of our knowledge, this is the first report of synchronous occurrence of breast cancer and Hodgkin lymphoma. The treatment of synchronous cancers presents a therapeutic challenge to both clinicians and patients. The treatment of these patients needs to be planned by a multidisciplinary team. Clinicians need to be aware of the chance of multiple primary cancers to prevent delayed diagnosis of the second cancer.

## References

- 1. Ghosh S, Rao PB, Sarkar S, Kotne S, Turlapati SP, Mishra A. A rare case of a synchronous anaplastic carcinoma thyroid with ductal carcinoma breast. Case Rep Oncol Med. 2014;2014:468159.
- Liu Z, Liu C, Guo W, Li S, Bai O. Clinical analysis of 152 cases of multiple primary malignant tumors in 15,398 patients with malignant tumors. PLoS One. 2015;10(5):e0125754.
- 3. Lopez ML, Lana A, Diaz S, Folgueras MV, Sanchez L, Comendador MA, *et al.* Multiple primary cancer: an increasing health problem. Strategies for prevention in cancer survivors. Eur J Cancer Care (Engl). 2009;18(6):598-605.
- 4. Working Group R. International rules for multiple primary cancers (ICD-0 third edition). Eur J Cancer Prev. 2005;14(4):307-8.
- 5. Wallace D, Arul D, Chitale S. Synchronous tumours of the breast and bladder. J Surg Case Rep. 2014;2014(7): rju066.
- 6. Testori A, Cioffi U, De Simone M, Bini F, Vaghi A, Lemos AA, *et al.* Multiple primary synchronous malignant tumors. BMC Res Notes. 2015;8:730.
- 7. Warren S. Multiple primary malignant tumors, a survey of the literature and statistical study. Am J cancer. 1932;16:1358-414.
- Kurul S, Akgun Z, Saglam EK, Basaran M, Yucel S, Tuzlali S. Successful treatment of triple primary tumor. Int J Surg Case Rep. 2013;4(11):1013-6.
- 9. Sakellakis M, Peroukides S, Iconomou G, Boumpoucheropoulos S, Kalofonos H. Multiple primary malignancies: a report of two cases. Chin J Cancer Res. 2014;26(2):215-8.
- 10.Dong C, Hemminki K. Second primary neoplasms in 633,964 cancer patients in Sweden, 1958-1996. Int J Cancer. 2001;93(2):155-61.



- 11. Filali K, Hedelin G, Schaffer P, Esteve J, Arveux P, Bouchardy C, *et al.* Multiple primary cancers and estimation of the incidence rates and trends. Eur J Cancer. 1996;32A(4):683-90.
- Hemminki K, Aaltonen L, Li X. Subsequent primary malignancies after endometrial carcinoma and ovarian carcinoma. Cancer. 2003;97(10):2432-9.
- 13. Yancik R, Ries LA. Aging and cancer in America. Demographic and epidemiologic perspectives. Hematol Oncol Clin North Am. 2000;14(1):17-23.
- 14. Luciani A, Balducci L. Multiple primary malignancies. Semin Oncol. 2004;31(2):264-73.
- 15. Curtis RE, Boice JD, Jr., Moloney WC, Ries LG, Flannery JT. Leukemia following chemotherapy for breast cancer. Cancer Res. 1990;50(9):2741-6.
- 16. van Leeuwen FE, Klokman WJ, Hagenbeek A, Noyon R, van den Belt-Dusebout AW, van Kerkhoff EH, *et al.* Second cancer risk following Hodgkin's disease: a 20-year follow-up study. J Clin Oncol. 1994;12(2):312-25.
- 17. Hilal T, Rudy DW. Radiation-induced breast cancer: the question of early breast cancer screening in Hodgkin's lymphoma survivors. Oxf Med Case Reports. 2016;2016(2):17-8.
- 18. Howell SJ, Searle C, Goode V, Gardener T, Linton K, Cowan RA, *et al.* The UK national breast cancer screening programme for survivors of Hodgkin lymphoma detects breast cancer at an early stage. Br J Cancer. 2009;101(4):582-8.
- 19. Sanna G, Lorizzo K, Rotmensz N, Bagnardi V, Cinieri S, Colleoni M, *et al.* Breast cancer in Hodgkin's disease and non-Hodgkin's lymphoma survivors. Ann Oncol. 2007;18(2):288-92.
- 20. Murakami R, Hiyama T, Hanai A, Fujimoto I. Second primary cancers following female breast cancer in Osaka, Japan--a population-based cohort study. Jpn J Clin Oncol. 1987;17(4):293-302.
- 21. Schwartz LH, Ozsahin M, Zhang GN, Touboul E, De Vataire F, Andolenko P, *et al.* Synchronous and metachronous head and neck carcinomas.Cancer. 1994;74(7):1933-8.
- 22. Bedi GC, Westra WH, Gabrielson E, Koch W, Sidransky D. Multiple head and neck tumors: evidence for a common clonal origin. Cancer Res. 1996;56(11):2484-7.
- 23. Allen SD, Wallis MG, Cooke R, Swerdlow AJ. Radiologic features of breast cancer after mantle radiation therapy for Hodgkin disease: a study of 230 cases. Radiology. 2014;272(1):73-8.
- 24. Horst KC, Hancock SL, Ognibene G, Chen C, Advani RH, Rosenberg SA, et al. Histologic subtypes of breast cancer following radiotherapy for Hodgkin lymphoma. Ann Oncol. 2014;25(4):848-51.
- 25. Tieu MT, Cigsar C, Ahmed S, Ng A, Diller L, Millar BA, *et al.* Breast cancer detection among

young survivors of pediatric Hodgkin lymphoma with screening magnetic resonance imaging. Cancer. 2014;120(16):2507-13.

- 26. Cox J, Lunt L, McLean L. Haematological cancers in the breast and axilla: a drop in an ocean of breast malignancy. Breast. 2005;14(1):51-6.
- 27. Zhong J, Lei J, Jiang K, Li Z, Gong R, Zhu J. Synchronous papillary thyroid carcinoma and breast ductal carcinoma: A rare case report and literature review. Medicine (Baltimore). 2017;96(7):e6114.
- 28. Castro M, Vierkoetter K, Prager D, Montgomery S, Sedgwick K. Synchronous Onset of Breast and Pancreatic Cancers: Results of Germline and Somatic Genetic Analysis. Case Rep Oncol. 2016;9(2):387-94.
- 29. Arjunan R, Kumar D, Kumar KV, Premlatha CS. Breast Cancer with Synchronous Renal Cell Carcinoma: A Rare Presentation. J Clin Diagn Res. 2016;10(10):XD03-XD05.
- 30. Athanasiou E, Michalopoulou-Manoloutsiou E, Bobos M, Hatzibougias DI, Zarogoulidis P, Katsikogiannis N, *et al.* Coincidence of thymoma and breast cancer and in a 56-year-old female patient. Ann Transl Med. 2016;4(22):446.





# ABC of Medical Ethics and Professionalism in the Breast Clinic

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Meeting the standards of medical ethics is one of the essential requirements of medical practice as it has a tremendous effect on the patients' lives in physical and psychological aspects.<sup>1</sup> However, depending on the nature of the disease, sometimes issues of medical ethics become very critical.

Breast cancer is the most common cancer among women throughout the world and is one of the most important causes of death.<sup>2</sup> The high prevalence of the disease, involvement of women, and the remarkable importance of the organ for a female patient from,' along with the medical and financial aspects of treatment, potential complications, and their influence on the individual, familial, and social life of patients have made this disease a unique and critical one, particularly in the field of professionalism and medical ethics. Medical literature in this field recognizes and emphasizes some aspects of the disease<sup>4</sup> including reaction of the patients to diagnosis, confidentiality and privacy, interactions with medical team, coping with the disease, treatment costs and conflict of interest, etc.

## **Ethical Considerations for Breast Cancer**

Confidentiality and Privacy

Confidentiality and privacy of patients are among the most important ethical principles, with a rich background in the history of medicine.<sup>5</sup> Protecting privacy of the patient maintains trust in doctorpatient relationship, which maintains respect for her autonomy, and avoids serious harms to the patient.<sup>6</sup> By having individual autonomy, on one hand, and social roles and needs, on the other, human beings

Address for correspondence: Ahmad Kaviani, MD Address: Kaviani Breast Disease Institute (KBDI), No 3, Tavaneer Sq., Tehran, 1434888483, Iran Tel: +98 21 88871785 Fax: +98 21 88871698 Email: akaviani@tums.ac.ir have a dual nature, and thus, maintaining privacy is of utmost importance and has a close relationship with human dignity. The patient needs confidence in the physician to express her pain and concerns and consequently, privacy and confidentiality becomes critical in this relationship.<sup>7,8</sup> Confidentiality and privacy should be a major concern in the following settings/aspects:

1) Arrangement of room and medical equipment: Arranging the equipment, the examination room and paying attention to the privacy of the examination site (e.g., whether the examination site is seen from the entrance door or from the window or front building) is of utmost importance. It is, even, necessary in the room design and setup that a fence covers the space between the examination site and the seat of the patient's companions so that if the patient does not want to be seen by the companions, it would be easily achievable.

2) How to take history: Talking about the breast symptoms and the points that are important in the patient history (such as menarche and menopause) can be embarrassing for some patients. It is necessary to pay special attention to the privacy of the environment and the way to ask such questions.

3) How to do examinations: Breast is a feminine organ and considered a private organ for many women. Evidence exists that at least in some countries, women use the word "chest" instead of "breast" when talking with a health care professional (especially with a male physician).<sup>9</sup> Embarrassment and shame of visiting a doctor for a breast problem are among psychosocial factors that potentially contribute to delay in seeking medical care.<sup>3</sup> Issues such as doctor's age, etc. may be important for the patient while performing examinations.

As with what mentioned above, patients may ask Chaperone while being examined; their request should be taken into consideration (someone with the same gender should be present during the examination).<sup>10,11</sup> Exposing the organ for the physical exam, however, is embarrassing for many women.<sup>12</sup> This issue is independent of the gender of the examiner, although if gender of the examiner and the patient is not the same, this situation will be even more inconvenient. Although, according to the medical standards, the examination should not be performed over cloths, patient's values and opinions should be considered to the extent that it does not undermine the examination standards. This is especially important in the clinics of teaching hospitals, where the learners are present. It is imperative to note that no one in the examination room must be present specially when the patients do not agree.

#### Telling the Truth and Giving Bad News

There have been many discussions about informing the patients about their incurable and severe disease. According to the principle of patient's autonomy, the patient should be informed of the diagnosis, treatment and prognosis of the disease, the cost and effectiveness of existing treatments. However, having this right, the patient faces several emotional, and psychological barriers in practice.<sup>13</sup>

Thus, one of the important codes of medical ethics is how to report bad news to the patient. Although some patients are unaware of their diagnosis and even have no idea about the presence of cancer in their bodies, most of them can guess to have cancer, and few of them are fully aware of their disease. Regardless of the above-mentioned cases, patients like, expect, and are entitled to hear the diagnosis from their doctors. Some questions that should be addressed in this regard appear below:

1) Does the patient need to know her diagnosis? Telling the truth may be interpreted as avoiding a lie (knowingly and intentionally talking about things that are not true), deception (including lying, concealing the truth, or telling the truth in a way that misleads the patient), and incomplete and misguiding information to the patients.<sup>14</sup> Therefore, the patient needs to know her diagnosis undoubtedly. Knowing the truth helps the patient accept the challenges through the treatment steps and better cope with the problems. Studies have also shown that most patients want to know the truth about their disease.<sup>15</sup> However, some studies, in Iran, have shown that the health care team was reluctant to tell the truth to the patient, and even assumed it to be wrong; they were worried that it might despair the patients and could interfere with the therapeutic process;<sup>16,17</sup> this process needs be addressed and modified.

Furthermore, the need for having enough information to sign the informed consent for the necessary treatments requires knowing the truth. It is clear that deception leads to further deceptions, and there would be a possibility for the third person to, inappropriately, disclose the facts at the wrong time and place without taking the professional steps. This will pose more harm to the patient; thus, hearing the truth in appropriate conditions is recommended.

Only if telling the truth would result in potentially serious harms to the patients such as depression, isolation, or suicide, concealing all or part of the truth could be justified.<sup>18</sup>

2) How should the patient be informed? There are various techniques for telling the truth to patients. Most of the authors have suggested that this unpleasant news should be told to patients during counseling sessions with allocating adequate time.<sup>19</sup>

<sup>20</sup> Thus, the physicians have to plan for informing the patient about the bad news and consider a quiet place away from the interference of others (including telephone calls, etc.). It is not necessary to give all the information to the patient at once. The physicians should allow the patient to react to this information, show their sympathy and try to make it possible for the patient to express her worries. Depending on the patient's psychological conditions, it is recommended that the physicians begin with general explanation and eventually inform her of the importance and type of the disease; It is highly recommended that the physician inform the patient of her disease with comprehensible words and avoid using medical terms.<sup>21</sup> Even better to avoid applying the word directly, however, it is not acceptable that the patient remain unaware of the process and outcome of her disease. To reduce patient's anxiety, more emphasis can be placed on the successful aspects of treatment and medical advances. Yet, the conditions should not be in a way that the patient feels she cannot live (even for a short period of time) without an aggressive treatment. The physicians should give the patient realistic hope and emphasize that the health care team will provide the best possible care and will support her throughout this process. In response to the patient's question of "how long will I survive?", she should be told the average and median of the survival of the patients in the similar stage of the disease with emphasizing its uncertainty and considering her mental and psychological conditions.

3) Who should tell the patient the diagnosis? The diagnosis of the patient may best be disclosed to her by the chief physician in charge of the patient, who is well informed of various aspects of her disease, including breast cancer treatment. However, in some references, breast care nurses and social worker, and oncologist have been considered to be the best persons to inform the patient.<sup>22</sup>

## Paying Attention to the Psychological and Social aspects of the Disease

The severity of the disease, the high cost of the treatment, the life-threatening nature, and the side effects of the treatment impose a huge challenge to

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all aspects of the life of the patient and her family, especially psychological and social dimensions.

1) Paying attention to the patient's mental condition: Like all patients with cancer, patients with breast cancer have a lot of questions along with having a high level of anxiety. This anxiety exists from the appearance of the first symptoms so the physicians should consider the anxiety and restlessness that sometimes aggravates the course of the disease. They feel they are at the risk of imminent death; consequently, the questions may be increasing in number and, in many cases, a question may be asked several times. It is imperative that the physician, besides giving enough attention to the patient and her questions, provide the most appropriate answers to all patient questions within the best possible time with allocating enough time. However, it is not always easy as spending abundant time for addressing all concerns of the patient might in conflict with the physician or health center income considering the high number of patients which needs to be visited in public hospitals or even some day care clinics.

2) Paying attention to patient's family relationships: Although the degree of bond between the patient and the family may differ in various cultures, some patients may receive psychosocial support from the other individuals. It goes without saying that the family can play an effective role in this regard.<sup>23</sup> Traditional Eastern and Asian culture is generally family-oriented; hence, interaction, communication, and support of family members in the process of treatment and recovery are very strong, and this should be considered in the management plan.

3) Providing essential information for family members and companions of the patient: The medical team should provide the patient's relatives with general information about the disease and early instructions about the issues that may affect the patient and her family. For example, the marital relationship of women undergoing chemotherapy can be completely different under the influence of these treatments, which last for at least 5 months; therefore, the patient's husband must be aware of this and should receive the necessary information on how to react. In the example of chemotherapy, the patients might have vaginal dryness or have less libido but sexual needs might be intact. So, the husband should be informed that sexual relation can continue as before continuing as before and this does not pose a risk to the patient and the partner. If this issue is not taken into account, there may be important problems in the patient's relationship with her husband, who expects "no-relationship" or "relationship as before". These cases, accompanied by simple instructions such as "the person who is under chemotherapy does not pose a risk to others", will make the patient live in a much better condition

within her family.

4) Informing the family members and relatives about the diagnosis of disease: In many cases, families try to convince the physician that they should be informed of the diagnosis and the patient should remain unaware. This request is often considered unethical since, in many cases, the disease is considered a medical secret and cannot be shared with others without the patient's permission. Yet, in societies with more traditional family relationships, and with family being the main pillar of psychosocial support for the patient, most patients go to the doctor with their family and spend the stages of diagnosis and treatment together. In such cases, where the patient is satisfied with this sharing of information, disclosing the diagnosis for family members would not be a problem, according to the patients' preference; however, the critical point is not to tell the patient about the diagnosis.

5) Exceptions for telling the truth to the patient: The only situation that the doctor can deny telling the truth to the patient is the situation that she is reluctant to know the diagnosis, herself. In such situations, firstly, a person should be replaced at the request of the patient in order to continue the process of decision making and, secondly, this issue must be documented in the patient's record.

6) The doctor's attention to the patient's socioeconomic level: One of the important points in interacting with the cancer patients is paying attention to their socioeconomic level. Diagnosis and treatment of breast cancer is costly. Especially in countries where all or part of this cost is paid by the patient, this becomes even more challenging. The physician is, ethically, obliged to consider this issue in his medical advice. In fact, the physician needs to consider the economic aspects of treatment for the feasibility of treatment by the patient and the community. It is clear that expensive treatment modalities will aggravate the situation when the patient has financial problems even for her primary care. In these circumstances, the physicians are recommended to be aware of the types of the treatments and the differences in success rates of affordable and more expensive modalities and simply explain them to the patient. Expressing the complicated concepts of medical economics can worry and confuse the patients; hence, the information should be provided to the patient in such a way that is understandable for her and makes it easy for her to make informed decisions. In these cases, the physician informs the patient of cost-effectiveness of all treatment modalities, regardless of the cost. Ultimately, it is desirable that the patient chooses an affordable option with an acceptable level of effectiveness, considering her economic circumstances.

## Job Excellence

Recent medical advances in the field of cancer have been remarkable in diagnostic, therapeutic, and

rehabilitative aspects. A medical specialist in the field of cancer is required to be informed of the latest developments and their level of evidence and to implement them according to the patients' needs and circumstances.

However, methods that their effectiveness is not proven should not be used in the routine treatment of patients (apart from research); simply because they are in the news. In brief, ethically, a physician cannot recommend less effective treatments with more side effects simply because s/he is not familiar with new technologies and medical advances.

#### Interaction with Other Medical Team Colleagues

The nature of breast cancer has led to a multidisciplinary approach in all major centers around the world. Studies have shown that this results in better decisions, lower costs and better therapeutic outcomes. A physician working on breast cancer is required to use this pattern in delivering the best care to the patients.<sup>24,26</sup>

In some cases, it might be even necessary to consult with other specialists in the same field. For instance, professional consult might be essential to decide whether or not to carry out breast-conserving surgery for a patient.

If the patient completes part of the treatment and visits another doctor for getting advice, the counselor should not confuse the patient. It is obvious that if there is a modifiable shortcoming in the treatment process, the patient should be carefully informed; however, in cases that the previous procedure is medically sound and can be accepted in the form of controversies, it is necessary to reassure the patient about the treatment process and avoid confusing the patient or making him distrust the previous physician.

#### Conflict of Interest

The most common definition for conflict of interest is Thompson's definition as "a situation in which a professional decision on a primary goal is influenced by a secondary gain".<sup>27</sup> In the clinical setting, commitment to the patient is of utmost importance; however, acquiring scientific information might come first in scientific research activities. Secondary benefits such as financial benefits, individual credibility, and reputation brought about by academic promotion might also exist.<sup>28</sup> Conflict of interest does not necessary mean that personal interest replaced the professional commitment toward the patient; but, the mere implication of a secondary benefit is sufficient for a person to be in a conflict of interest status. However, it is not unethical to be in a conflict of interest position; in fact, failure to declare and manage it would be considered immoral. In the same venue, awareness of the replacing position,<sup>29</sup> the disclosure,<sup>30</sup> announcement to the official authorities,<sup>31</sup> and

"prohibition "and "avoidance" are the ethical codes that can be considered as the proper ways of managing the conflict of interest.<sup>32</sup> Putting the patient's benefits in the first priority is the main pillar of medical professional commitments.

Undeniably, the expensive and diverse nature of anti-cancer therapies may have some benefits for pharmaceutical companies; sometimes, these benefits may be preferred to patient benefits, which may be in conflict with medical professional commitments. In this regard, there are two very important issues in the field of cancer in general, and breast cancer in particular:

1) Physician relationship with pharmaceutical and medical equipment companies: The pharmaceutical industry is introducing and marketing new products every day and in an increasing rate especially in the field of chemotherapeutic and recombinant therapies (targeted therapy). The volume of financial transactions in this area is amazingly huge. In many cases, these companies bring about attractive suggestions to physicians, as part of their marketing and business development strategies, in order to implement or prescribe their products. Physicians should be aware that this is one of the most important challenges facing them. Even if attending scientific conferences and scientific visits with the sponsorship of pharmaceutical and medical instrument companies lead to a physician's attitude toward prescribing of the products without sufficient evidence, it will be considered unprofessional and unethical, no matter this risk of the bias to use the product improperly would be real or potential.<sup>33, 34</sup> The only issue the physicians should consider in using these facilities or prescribing medications is to prescribe them in full accordance with the latest and the best medical evidence. In other words, a physician should prefer the benefits of a patient, in all aspects, to his/her own benefits and preferences, and avoid all the situations that can undermine this issue. Altogether, based on the similar cases, the relationship between the physician and the business corporations should be completely transparent and declarable.35,36

2) Receiving gifts from the patients: In different cultures, patients occasionally send gifts to their physicians to show their gratitude before, during or after the course of treatment. Although, in most cases, these gifts are not costly, the physician must always be aware that they should not influence his medical decisions. In some cases, the patients expect their doctors to decrease the waiting time for a visit or surgery, to write longer than required sick-leave letters for absence from work, etc. As stated previously, this interaction must be transparent and declarable and the rights to other patients or society must not be neglected. The value of gifts should also be at the level of the performed tasks. Rejection of

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these gifts in some cultures may also disappoint the patients. Therefore, it is necessary to take into account the customary and cultural issues in each region. The general points about gifts including the priority of patient benefits, lack of significant financial value, and transparency (to be able to declare the subject in public) should always be kept in mind by physicians.

#### Medical Education in the Field of Breast Cancer

The physician should ensure that the best care is provided to the patient in educational settings. Disclosure of the patient's diagnosis and treatment to the learners is always a major challenge in hospitals and academic centers. Devolving some health care to the learners is required, if, according to standard protocols, there is a complete assurance that the patient is not harmed. The patient should be able to choose her physician, especially in the educational settings. This means that diagnostic and therapeutic tasks can be performed by the learners only with the attendance and supervision of the physicians and of course, after the consent of the patient.<sup>37</sup>

## Medical Ethics and Breast Cancer Research

All principles and codes of medical ethics that are generally introduced for medical research are necessary in the field of breast diseases, especially breast cancer.<sup>38</sup> A major challenge in this area is to carry out drug research and therapeutic interventions without observing the ethical standards of research. No medical test or intervention, without the informed consent, can be performed on patients, even if some of them are in the final stages of the disease and there is little hope for their recovery. Obviously, informed consent of the patients in all research activities should be taken into consideration. On the other hand, the cost of all actions undertaken in these studies must necessarily be provided by the sponsor organization or pharmaceutical company, and the patient should not pay all or a part of these costs. While collecting the patient data, it should be taken into consideration that all data should be confidential and used just only in the scientific research projects.

Moreover, the direct and indirect interference of medical and pharmaceutical companies on how to report and publish research outcomes needs to be given special consideration. In some basic and clinical studies, there is a conflict of interest in funding research, which needs to be considered and declared by the physicians in their interactions and decisions.

#### Medical Ethics in Prevention of Breast Cancer

Prevention has become one of critical issues in breast cancer science. Thanks to the progress made in identifying high-risk individuals through genetic tests and performing preventive measures, many apparently healthy people who are at a high risk of cancer can prevent the onset of their disease. But, in some cases, this causes a lot of worries and harms to the quality of life of the client and their families.<sup>39</sup> For instance, a person whose genetic test result is positive may be recommended to perform prophylactic mastectomy and oophorectomy. This usually puts the patient in a serious dilemma, whether to lose two feminine organs or to continue living with the anxiety caused by knowing the high risk of a life-threatening disease.

In fact, from the perspective of medical ethics, the physician should consider autonomy of the patient and share all possible means before taking any actions. The physician is required to provide the patient with full explanation of the test (including the costs). In the next steps and if the test results are positive, the physician should spend enough time with the client to figure out whether she is prepared for aggressive interventions like prophylactic mastectomy or not.<sup>40</sup> Many patients do not have psychological preparedness to perform preventive measures; and if the physicians, without sharing all the possible ways, apply for the test and confront the patient with positive results, the patient may become extremely horrified and anxious, having a dilemma whether to lose her organ or her life.

#### References

- Gabel S. Ethics and values in clinical practice: whom do they help? Mayo Clin Proc. 2011;86(5):421-4.
- 2. Key TJ, Verkasalo PK, Banks E. Epidemiology of breast cancer. Lancet Oncol. 2001;2(3):133-40.
- 3. Neishaboury M, Davoodzadeh K, Karbakhsh M. Does embarrassment contribute to delay in seeking medical care for breast cancer? A review. Archives of Breast Cancer. 2015;2(3):75-8.
- 4. Wolinsky H. Bioethics for the world. EMBO Rep. 2006;7(4):354-8.
- 5. McCarthy RL. Ethics and patient privacy. J Am Pharm Assoc. 2008;48(6):e144-52; quiz e53-4.
- 6. Jenkins G, Merz JF, Sankar P. A qualitative study of women's views on medical confidentiality. J Med Ethics. 2005;31(9):499-504.
- Sankar P, Mora S, Merz JF, Jones NL. Patient perspectives of medical confidentiality: a review of the literature. J Gen Intern Med. 2003;18(8):659-69.
- 8. Kiser K. Protecting Patient Privacy. Minn Med. 2015;98(6):8-10.
- Karbani G, Lim JN, Hewison J, Atkin K, Horgan K, Lansdown M, *et al.* Culture, attitude and knowledge about breast cancer and preventive measures: a qualitative study of South Asian breast cancer patients in the UK. Asian Pac J Cancer Prev. 2011;12(6):1619-26.
- 10. Wai D, Katsaris M, Singhal R. Chaperones: are we protecting patients? Br J Gen Pract.



2008;58(546):54-7; discussion 6-7.

- 11. Sinha S, De A, Jones N, Jones M, Williams RJ, Vaughan-Williams E. Patients' attitude towards the use of a chaperone in breast examination. Ann R Coll Surg Engl. 2009;91(1):46-9.
- 12. Lindau ST, Abramsohn EM, Baron SR, Florendo J, Haefner HK, Jhingran A, *et al.* Physical examination of the female cancer patient with sexual concerns: What oncologists and patients should expect from consultation with a specialist. CA Cancer J Clin. 2016;66(3):241-63.
- 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.
- 14. Zahedi F, Larijani B. Truth telling across cultures: Islamic perspectives. Iranian Journal of Medical Ethics and History of Medicine. 2010;3:1-11.
- 15. Asghari F, Mirzazadeh A, Fotouhi A. Patients' preferences for receiving clinical information and participating in decision-making in Iran. J Med Ethics. 2008;34(5):348-52.
- Mobasher M, Nakhaee N, Tahmasebi M, Zahedi F, Larijani B. Ethical issues in the end of life care for cancer patients in iran. Iran J Public Health. 2013;42(2):188-96.
- 17. 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. Iran J Cancer Prev. 2011;4(3):130-4.
- 18. Truth telling in clinical practice. Lan et. 2011;378(9798):1197.
- Parsa M, Bagheri A, Larijani B. Telling bad news and its various aspects. Iranian Journal of Medical Ethics and History of Medicine. 2011;4(6):1-14.
- Ibn Ahmadi A, Heydari N. Is there a proper method of truth telling? Iranian Journal of Medical Ethics and History of Medicine. 2010;3(2):16-28.
- 21. Shakeriniya I. Telling bad news: the necessity of its training. Iranian Journal of Medical Ethics and History of Medicine. 2010;3:29-38.
- 22. KavianiA, Mehrdad N, Yunesian M, Shakiba B, Ebrahimi M, Majidzadeh K, *et al.* Psychosocial Care for Breast Cancer: Physicians' Perspective. Iranian Journal of Cancer Prevention. 2012;3(1):23-7.
- Muhamad M, Afshari M, Kazilan F. Family support in cancer survivorship. Asian Pac J Cancer Prev. 2011;12(6):1389-97.
- 24. Shachar SS, Gallagher K, McGuire K, Zagar TM, Faso A, Muss HB, *et al.* Multidisciplinary Management of Breast Cancer During Pregnancy. Oncologist. 2017;22(3):324-34.
- 25. Pruthi S, Brandt KR, Degnim AC, Goetz MP,

Perez EA, Reynolds CA, *et al.* A multidisciplinary approach to the management of breast cancer, part 1: prevention and diagnosis. Mayo Clin Proc. 2007;82(8):999-1012.

- 26. Taylor C, Shewbridge A, Harris J, Green JS. Benefits of multidisciplinary teamwork in the management of breast cancer. Breast Cancer (Dove Med Press). 2013;5:79-85.
- 27. Thompson DF. Understanding financial conflicts of interest. New England Journal of Medicine. 1993;329:573-.
- Parsa M, Aramesh K, Larijani B. A comparison between conflict of interest in Western and Islamic literatures in the realm of medicine. Journal of medical ethics and history of medicine. 2014;7.
- 29. Palmer N, Braunack-Mayer A, Rogers W, Provis C, Cullity G. Conflicts of interest in divisions of general practice. Journal of medical ethics. 2006;32(12):715-7.
- Norris SL, Holmer HK, Ogden LA, Burda BU. Conflict of interest in clinical practice guideline development: a systematic review. PLoS One. 2011;6(10):e25153.
- Lemmens T, Singer PA. Bioethics for clinicians: 17. Conflict of interest in research, education and patient care. CMAJ. 1998;159(8):960-5.
- 32. Dickens BM, Cook RJ. Conflict of interest: legal and ethical aspects. Int J Gynaecol Obstet. 2006;92(2):192-7.
- 33. Chimonas S, Brennan TA, Rothman DJ. Physicians and drug representatives: exploring the dynamics of the relationship. J Gen Intern Med. 2007;22(2):184-90.
- 34. Field MJ, Lo B, editors. Conflict of Interest in Medical Research, Education, and Practice. The National Academies Collection: Reports funded by National Institutes of Health. Washington (DC) 2009.
- 35. DeAngelis CD. Conflicts of interest in medical practice and their costs to the nation's health and health care system. Milbank Q. 2014;92(2):195-8.
- 36. Gibbons RV, Landry FJ, Blouch DL, Jones DL, Williams FK, Lucey CR, *et al.* A comparison of physicians' and patients' attitudes toward pharmaceutical industry gifts. J Gen Intern Med. 1998;13(3):151-4.
- 37. larijani b, mobasher m. Do you accept patients' gifts? Iranian Journal of Medical Ethics and History of Medicine. 2010;3(2):64-8.
- 38. Ghanei M, Saadat SH, Parsapour A, Bamdadi F, Robati AM, Keramati A. Executive management of bioethics in medical researches: The results of a workshop. Journal of Medical Ethics and History of Medicine. 2008;1(1):3.
- 39. Ustun C, Ceber E. Ethical issues for cancer screening. Asian Pac J Cancer Prev. 2003;4(4):3736.
- 40. Plutynski A. Ethical issues in cancer screening and prevention. J Med Philos. 2012;37(3):310-23.





## DOI: 10.19187/abc.20174381-83 Ethical Analysis of Husband's Consent to His Wife's Treatment

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The concept of informed consent has its roots in respect for patient's autonomy.<sup>1</sup> Autonomy means selfgovernance of a person without others interferences. Respect for autonomy is to acknowledge a person's right to make choices and act based on his/her own values and believes.<sup>2</sup> Everyone has equal right to individual freedom and should be free from others' interference in his/her personal affairs. Every mature and grown-up person has a right to make decision in her best interest and no one is allowed to interfere in her personal affairs, particularly intervention on her body. Respect for patient's autonomy is a part of respect for her human dignity.<sup>3,4</sup> The professional duty of the physician in this regard is to inform and empower the patients to choose the treatment approach and to obtain consent for any diagnostic or therapeutic intervention on their bodies. Serious attention has been paid to respect for autonomy in the recent century. Before that, physicians had a paternalistic approach toward medical decisions and were less exposed to requests for information by patients. Nowadays, the patients prefer to receive information about their disease, even if it has a poor prognosis, and participate in choosing a treatment method.<sup>5</sup> The protective role of the families in the treatment process of the patients, especially patients with cancer, is undeniable, but the right to autonomy and the fiduciary duty of the physicians require that the patient's information not be shared with other people without the patient's permission.

In traditional male-dominant societies, some men wish to receive information on their wives' disease, and this request is accepted by some physicians.<sup>6,7</sup> On the other hand, some women, willingly, leave decision-making to their husbands.<sup>8,9</sup>In Iran, many

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physicians require the husband's consent to gynecologic operations, especially surgery on the reproductive organs.

The physicians do not face any ethical challenges when the wife consents to share information with her husband and the husband agrees to and supports the necessary treatment. However, there may be a problem when a female patient seeks treatment in the absence of her husband or without his company or when the husband disagrees to the treatment.

Unfortunately, the approach of such physicians challenges the receipt delivery of medical care by women. No serious attempts have been made to modify this wrong attitude among physicians.

The present research provides an analysis of this attitude with regard to ethical, legal, and religious considerations.

#### Magnitude of the Problem

Taking the husband's consent to his wife's treatment has scarcely been discussed in the western ethics and patient rights literature, because it is obvious that a woman, as a mature independent wise person, is free to decide about treatment on her body, and her freedom and rationality should be respected. However, in male-dominant societies, it is necessary to obtain the husband's consent to his wife's treatment for cultural reasons.6 Although obtaining the husband's consent to the treatment of his wife is rarely mentioned in national law,<sup>10</sup> it is common as an unwritten rule in many Middle Eastern countries, such as Iran and physicians respect this tradition. Reports of this approach can be observed in countries like Mexico, Pakistan, Nigeria, and Saudi Arabia.<sup>7-9, 11-13</sup> In Malaysia, the Ministry of Health mandates a husband's consent to the wife's treatment, if the wife is dependent on her spouse.<sup>10</sup> The Iranian law does not require a husband's consent to his wife's treatment. This discriminatory process is an unwritten praxis that is sometimes recommended to clinicians and passed down to the next generations by physicians. Jarayedi et al. evaluated the knowledge and performance of the residents of surgery, gynecology, urology, and

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orthopedic surgery regarding a person from whom consent should be obtained according to the law. The highest and lowest prevalence of the believes in sufficiency of the female patient's consent was observed in orthopedic surgery (87.8%) and urology residents (60%), respectively. In practice, 84.4% of general surgery residents obtained a husband's consent to surgery. The rate was the lowest for orthopedic surgery residents (56.1%).<sup>14</sup>

## *Physicians' Professional Commitment and Moral Duty*

This issue can be discussed from three ethical standpoints: autonomy, confidentiality, and commitment to improve access to healthcare.

Autonomy: similar to men, women are entitled to independence and human dignity, and medical procedures should only be subjected to their own consent. There is no difference between men and women in terms of human rights and ethical theories. Justice requires that if a certain right is considered for a person in a special situation, it should also be considered for other similar people in the same situation. The right of control over own body is a part of the right to autonomy to which every man and women is entitled. Therefore, a woman's informed consent could be enough for performing medical or surgical procedures on her body.

Confidentiality: it is one of the physicians' professional duties.<sup>15</sup> Any information obtained from the patient during the process of diagnosis or care should be considered confidential and can only be shared with others contingent upon the patient's consent. Physicians should not ignore the female patients' right to confidentiality when their spouses ask for their information, and should find out the patients' wishes in this regard.

Improving Access to Healthcare:<sup>16</sup> some groups of the society do not have an appropriate access to healthcare services due to cultural reasons or social stigmata. From the professional commitment point of view, physicians should try to improve the access of these groups to health services. The physicians and the healthcare system not only should accentuate social stigmata and traditions which result in limiting the access of some people to healthcare services, but also they should try to pave the way for their better access through protecting their health rights.

## Religion and Law

Article 158 of the Islamic Penal Code of Iran states that legitimate surgical or medical operations are not considered crime if they are done by the consent of the patient or his/her parents or natural or legal guardians, or legal representatives.<sup>17</sup> Consent should be obtained from the patient's legal guardian when the patient lacks decision-making capacity. In competency and guardianship chapter of Iran's civil

law, these cases are defined as 1) children, 2) mentally incompetent people, and 3) cognitive impaired people.<sup>18</sup> According to the law, women are not considered incompetent and, except for some very limited cases, when the husband's consent is required women are considered independent decision makers (According to Iran's civil law, women need their husband's consent for leaving the country and according to the Islamic jurisprudence, they need their husband's consent for leaving the house and working out of the house). There is no article in law requiring the husband's consent for medical procedures (whether or not affecting fertility).

Since men tend to press charges against physicians more than women, some physician may require the husband's consent to avoid charges. The right to complain is not exclusive to the patient, and the patient family members can press charges against the physician; however, it cannot be concluded that the patient's information should be available to any person who claims to have a right and treatment cannot be contingent upon their approval. It is important that if informed consent be obtained from the patient, the patient's family cannot press charges against the physician regarding medical intervention without their consent; on the other hand, if a medical error has occurred, obtaining consent from the patient does not deprive the patient of her right to make a formal complaint.

There are different opinions in this regard in Islam. The dominate idea of Sunni scholars, including scholars of 4 schools of Sunni jurisprudence, is that the husband is not obliged to pay for the treatment of his wife.<sup>19</sup> In an article, Alhusseini explained the normal procedure in Saudi Arabia necessitates obtaining informed consent from the husband; the author claimed that obtaining the husband's consent is required for operations on sexual organs (including C-section) according to Islam, and if the wife's and the husband's opinions differ, the husband's opinion is preferred.<sup>11</sup> This opinion does not exist in the fatāwā of Shia scholars. In his article, Parsapour has presented the opinions of Shia Maraji in this regard.<sup>20</sup> Ayatollah Sistani, Ayatollah Shahroudi, Ayatollah Saanei, Ayatollah Golpaygani, and Ayatollah Makarem have stated, in their fatāwā, that there is no necessity for the husband's consent for medical interventions, even if the interventions affect fertility.<sup>20,21</sup>

#### Dialogue in the Family and Social Support

A wife and husband have moral duties toward each other. They are both entitled to receive support from each other and are morally obliged to share the information affecting the family. In family-centered societies like Iran, the family members share information and consult with other members of the family before making a decision. However, the ,



husband may not be available when the patient needs receiving care, or the patient may not be willing to share information, regarding her physical problems with her husband due to weak martial relationships. In these circumstances, it is not the physician's duty to share the patient's information with her husband without her permission, or suspend treatment based on the husband's decision. The physician is morally required to persuade the patient to let her family members help her receive proper and integrated care. This issue is even more important in serious diseases like cancer. Nonetheless, it is the patient who determines from whom she seeks help and with whom she wishes to share information. As was mentioned earlier, the physician needs asking the patient with whom she prefers to share the information of her illness, to what extent she is willing to share information, and how she wishes to share informaton; whether by herself or by the physician.

The tradition of obtaining husband's consent is neither ethical nor legal and based on Islamic jurisprudence. This gender discrimination deprives a group of female patients of their right to access medical care. Unfortunately, many physicians recommend this praxis to their colleague as a rule, and it is, now, a common wrong belief among people. It is the duty of the physicians to modify this misconception in order to uphold medical ethics, support the patients' right to necessary care, pass correct information, and train their assistants and students. Moreover, necessary corrections should be made in hospital policies and procedures to remove this challenge. The health system, as a policy making venue, should clearly state this policy and support the physicians who undertake the process of informed consent correctly.

## References

- 1. Irabor D. Informed consent for surgery: a historical review. West African journal of medicine. 2006;25(4):301-4.
- Beauchamp TL, Childress JF. Principles of biomedical ethics: Oxford University Press, USA; 2001.
- 3. Brännmark J. Respect for Persons in Bioethics: Towards a Human Rights-Based Account. Human Rights Review. 2017;18(2):171-87.
- 4. Dillon R, Respect Zalta E. The Stanford encyclopedia of philosophy. Spring; 2014.
- 5. Asghari F, Mirzazadeh A, Fotouhi A. Patients' preferences for receiving clinical information and participating in decision-making in Iran. Journal of medical ethics. 2008;34(5):348-52.
- 6. McKennis AT. Caring for the Islamic patient. AORN journal. 1999;69(6):1185-96.
- 7. Ashraf B, Tasnim N, Saaiq M. An audit of the knowledge and attitudes of doctors towards

Surgical Informed Consent (SIC). International journal of health policy and management. 2014;3(6):315.

- 8. Ezeome ER, Marshall PA. Informed consent practices in Nigeria. Developing World Bioethics. 2009;9(3):138-48.
- 9. Pieters J. How do traditional values affect a woman's likelihood to utilize prevention screening techniques? : Arizona State University 2006[Available from:https://www.asu.edu/cou rses/css335/jppage3.html.]
- Chin C. A consent form may not be binding for medical treatment. : The Star Online. ; 2013[Available from:http://www.thestar.com. my/news/nation/2013/11/24/a-consent-formmay-not-be-binding/.]
- 11. Al Husseini DI. The Implications of Religious Beliefs on Medical and Patient Care. 2011.
- 12. Jafarey A. Informed consent: views from Karachi. 2006.
- 13. Marshall PA, Adebamowo CA, Adeyemo AA, Ogundiran TO, Vekich M, Strenski T, *et al.* Voluntary participation and informed consent to international genetic research. American journal of public health. 2006;96(11):1989-95.
- 14. Jarayedi Z. Knowledge and performance of surgical residents regarding the person from whom informed consent should be taken for surgery and from whom the consent is taken in practice. [MD thesis]. Tehran: Tehran University of Medical Sciences; 2014.
- 15. WMA International Code of Medical Ethics. Amended by the 57th WMA General Assembly, Pilanesberg, South Africa. October 2006 [Available from:http://www.wma.net/en/30publications/10pol millennium: a physicians' charter. The Lancet. icies/c8/index.html.]
- 16. Project MP. Medical professionalism in the new 2002;359(9305):520-2.
- 17. Islamic Reprimantive law of Islamic republic of Iran. 2013. 2nd revision: [Available from: http://rc.majlis.ir/fa/news/show/845002.
- 18. Civil law of Islamic republic of Iran. 1928.
- 19. Obligation to payfor medical treatment of his wife. Islamweb.2007. [Available from: http://www.islamweb.net/emainpage/index.php?p age=showfatwa&Option=FatwaId&Id=101312.]
- 20. Parsapoor A. One point and one hundred ambiguity. Sepid 2011.
- 21. Sanei Y. Medical Fatawa. Qom: Meysam Tamar; 2004.





## DOI: 10.19187/abc.20174384-86 Breast Cancer Susceptibility Genetic Testing; Where Should Medical Professionals Stand Between Providers and Customers?

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Cancer had become the second leading cause of death in the United States in 1970 when National Cancer Act of 1971 was signed by President Nixon. Over the past few decades "War on Cancer" has urged the medical fraternity to try to decode this entity and strike the molecularly defined targets that are presumed to drive the cancer. Identification of breast cancer susceptibility genes BRCA1/2 therefore has been overwhelmingly hypothesized to be a keystone in this regard.<sup>1</sup> It is worth reminding that together, BRCA1 /BRCA2 mutations account for about 20 to 25 percent of hereditary breast cancers.<sup>3</sup>

Pathogenic (disease causing) mutations of BRCA1/2 have said to be hereditary and have high penetrance but the penetration is incomplete meaning that some carriers do "not" develop cancer in their lifetime.<sup>4</sup> Also, incidentally discovered carriers often do not report family history.<sup>5</sup>

National Comprehensive Cancer Network (NCCN) criteria for further genetic evaluation in hereditary Breast and Ovarian Cancer requires a detailed family history that even in specialized centers is dependent on patient's reporting accuracy. Therefore, identification of high-risk patients is not easy and flawless.

Myriad Genetics Inc. was the sole provider of commercial full sequence BRCA1/2 test for some time but with new developing techniques and competitors trying to hold tight and not lose the game, new test panels as well as direct to customer testing are emerged. This has resulted in significant disparity in variant classification within and among

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Breast cancer susceptibility genetic tests are performed in two settings: 1) Diagnostic genetic testing which is offered to the affected person (i.e. patient who already has pathological evidence of breast cancer) in a family with an unknown BRCA 1/2 mutation. 2) Predictive genetic testing which is offered to at risk but not affected biological kin once the disease-causing mutation has been identified within the family.

It means that in both settings the first person tested need to be the breast cancer patient. For any DNA testing the individual's autonomy should be respected. For that, person authorizing DNA testing should be under no pressure from family, society or third parties to agree. Till now, besides a few research trials that have reported PARP inhibitor therapeutic effect in some BRCA-mutated breast cancers, there is no clear evidence that the outcome of the disease will change for a patient diagnosed with BRCA-mutated breast cancer after finding out about BRCA status. That said, the most important incentive for a breast cancer patient "freely" authorizing genetic test would be providing information for not herself but other at risk relatives. This will have harmful effects on patient's emotion and social relationships as well as financial burden. As mentioned above, more than 70% of hereditary

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breast cancers have nothing to do with BRCA1/2 mutations and about 90% of all breast cancers are not BRCA1/2 mutation related meaning that counseling need to be an integral part of this procedure. This highlights how socially and scientifically irresponsible it is to promote direct to customer genetic tests.

Although precision medicine approach has worked in some hematological malignancies with clonal proliferation, breast cancer is among solid cancers in which carcinogenesis happens as a result of multistep complex biological mechanisms and epithelial stromal interactions are more relevant than clonal proliferation.<sup>8</sup> That is why interpretation of estimates of the cumulative risk of cancer (to age 70 years) for BRCA1 /2 mutations that vary substantially between studies should be carried out with much caution. Reported estimates for breast cancer (range from 40 to 87% for BRCA1 mutation carriers and from 27 to 84% for BRCA2 mutation carriers) are mostly based on retrospective studies that can not necessarily be implemented in real world practice.<sup>5</sup> It is noted that BRCA1/2 mutation spectrum differs between the patients with breast cancer in the Cancer Genome Atlas (TCGA) and the carriers of the BRCA1/2 mutation in the general population. Several genetic and life-style cancerrisk modifying factors are identified that are not considered in the risk model predictors applied in those trials.<sup>4</sup> A prospective cohort study was reported recently in which 3886 (out of 9856 recruited BRCA1/2 carrier women in 1997-2011) were eligible for breast cancer analysis.<sup>9</sup> The results show that the breast cancer incidences per decade of age was between 23.5 to 28.3 per 1000 persons-years of age for age 31 to 70 years for BRCA1 carriers and between 21.9 to 30.6 per 100 person-years across 41-80 years for BRCA2 carriers. The cumulative risk estimate for breast cancer by age of 80 was in line with previous retrospective studies. Breast cancer risk varied based on mutation location. The results of this study suggest that a precise family history and mutation position should be well assessed in individualized counseling. These highlight the caution to be taken before suggesting direct to customer tests.

D'Andrea *et al* have recently published a review article where they conclude that there is no evidence of cost-effectiveness for BRCA screening of all newly diagnosed cases of breast/ovarian cancers followed by cascade testing of relatives.<sup>10</sup> It seems that more surveys are necessary to be conducted before BRCA testing can be implemented in daily basis practice. As an Austrian study has shown, unfortunately younger and more educated females are seeking genetic counseling for hereditary breast and ovarian cancer due to Angelina Jolie Effect since 2013.<sup>11</sup> Cultures differ widely in their traditions of gender roles, marriage and family life. In many communities, the genetic information will surely affect the decision about prospective marriage and deteriorate quality of life of young women and their families. Although in guidelines such as NCCN and European Society of Medical Oncology (ESMO) for clinical practice, referral for BRCA testing is recommended after genetic counseling, trained medical genetics specialists are not always accessible in some healthcare systems and in the case of direct to customer tests, genetic specialists are more or less employed by the provider which may pose a conflict of interest. That is why the burden of providing genetic testing and counseling to patients might fall on oncology medical practitioners. Medical professionals might not be able to police the unsupervised information on media and internet about the hype, but what they can and must be obliged to is 2500 years old Hippocratic oath and Primum non nocere. Medical practitioners should be very careful not to fall into defensive medicine practice for fear of liability. Using irrelevant terms such as "genetic screening test" for breast cancer and overstating benefits and downplaying harms of interventions available at present for possible BRCA1/2 mutation carriers are morally and ethically unacceptable. It is essential to remember that genetic risk is only a part of a person's overall risk and theoretical benefits that have not been confirmed in clinical practice should not be mistaken for facts. Information transparency and high literacy are among the crucial elements to adhere to ethical principles in this era of emerging genetic testing for breast cancer.

#### References

- 1. Graffeo R, Livraghi L, Pagani O, Goldhirsch A, Partridge AH, Garber JE. Time to incorporate germline multigene panel testing into breast and ovarian cancer patient care. Breast cancer research and treatment.2016;160(3):393-410.
- 2. Easton DF. How many more breast cancer predisposition genes are there? Breast Cancer Research. 1999;1(1):14.
- 3. Campeau PM, Foulkes WD, Tischkowitz MD. Hereditary breast cancer: new genetic developments, new therapeutic avenues. Human genetics. 2008;124(1):31-42.
- 4. Movassagh M, Mudvari P, Horvath A. Co-Occurrence of COMT and BRCA1/2 Variants in a Population. N Engl J Med. 2017;376(21):2090-1.
- 5. Milne RL, Antoniou AC. Modifiers of breast and ovarian cancer risks for BRCA1 and BRCA2 mutation carriers. Endocr Relat Cancer. 2016;23(10):T69-84.
- 6. Vail PJ, Morris B, van Kan A, Burdett BC, Moyes K, Theisen A, *et al.* Comparison of locus-specific databases for BRCA1 and BRCA2 variants reveals disparity in variant classification within and among databases. Journal of community genetics. 2015;6(4):351-9.



- Dizdar O, Arslan C, Altundag K. Advances in PARP inhibitors for the treatment of breast cancer. Expert Opin Pharmacother. 2015;16(18):2751-8.
- 8. Lazebnik Y. What are the hallmarks of cancer? Nature reviews Cancer. 2010;10(4):232.
- 9. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, *et al.* Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402-16.
- D'Andrea E, Marzuillo C, De Vito C, Di Marco M, Pitini E, Vacchio MR, *et al.* Which BRCA genetic testing programs are ready for implementation in health care? A systematic review of economic evaluations. Genetics in Medicine. 2016;18(12):1171.
- 11. Staudigl C, Pfeiler G, Hrauda K, Renz R, Berger A, Lichtenschopf R, *et al.* Changes of Sociodemographic data of clients seeking genetic counseling for hereditary breast and ovarian cancer due to the "Angelina Jolie Effect". BMC cancer. 2016;16(1):436.

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## Cancer Disclosure in Iran: Attitude of Patients and Their Families

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#### ABSTRACT

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Key words: Disclosure, patients with cancer, truth telling, families, attitude

#### Introduction

Cancer is the third underlying cause of death worldwide, accounting for about 12% of all recorded deaths.<sup>1</sup> The prognosis of patients with cancer is generally poor if left untreated, and surgery or other invasive interventions have a considerable influence on survival and quality of life of the patients.<sup>2</sup>

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**Background:** The present study aims at determining the proportion of clinical information known by the patients with cancer and their families about diagnosis of their disease as well as investigating the different attitudes of patients and their families towards informing the patients of the malignant nature of the disease.

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**Methods:** We designed a structured questionnaire which was completed by patients with cancer who were under follow up in Cancer Institute of Tehran University of Medical Sciences, and one member of their families who accompanied them while being treated. Patients, physicians, and patients' family members were interviewed separately.

**Results:** A total of 250 cancer outpatients and 250 patients' family members were interviewed. Overall, 227 patients (90.8%) desired to be informed of their diagnosis, and 98 patients (38.8%) declared that physicians informed them completely. One hundred fifty-three family members (61.2%) believed that patients are entitled to know the truth. Stepwise multiple logistic regression analysis indicated that patients' educational grade (odds ratio: 6.08; 95% CI, 1.27 to 29.07) and patients' age (odds ratio: 7.97; 95% CI, 1.25 to 50.59) were predictable factors for requesting to know the truth.

**Conclusions:** Findings of the present research indicated that most patients and family members wanted to be informed of the diagnosis; The present study suggests that physicians respect the patients' rights to know the truth and inform them accordingly. This can help them adapt themselves to new condition and manage their own life.

Therefore, several studies showed that cancer diagnosis is not routinely disclosed in many cultures, and clinicians prefer to tell the truth about cancer diagnosis to the relatives before the patients.<sup>4-7</sup> However, the majority of physicians and patients have accepted that patients are entitled to know the diagnosis and other necessary information of their disease.<sup>4, 8, 9</sup> It has been shown that awareness of the patients with cancer about their disease may lead to a more appropriate care via better communication and cooperation between patients and their physicians. In addition, disclosure of the necessary information about cancer diagnosis and prognosis help the patients manage their non-medical issues including personal, familial, and occupational issues, appropriately.<sup>10-12</sup>



Some studies have shown a strong wish for the disclosure of cancer diagnosis among the patients<sup>13-15</sup>; however, the attitude of relatives of the patients was different and the patients were more eager to know the truth than their family members.<sup>2, 16</sup> Patients and their families may differ in their attitude towards such a disclosure. Relatives of the patients with cancer generally prefer not to disclose the detailed clinical information and not to tell patients the truth in order to protect them from psychological and emotional distress.<sup>17-20</sup>

In this study, we investigated the attitude of the patients with cancer and their family members towards the disclosure of clinical information about the diagnosis, treatment, and prognosis. Moreover, we investigated factors affecting the attitude of patients and their family members towards truthtelling and their satisfaction with the disclosure of clinical information.

## Methods

The present cross-sectional study was conducted in Cancer Institute of Tehran University of Medical Sciences. We interviewed 250 patients and their companions including parents, siblings, spouses, and other relatives or friends who had a close relationship with patients who were treated at the cancer institute under the routine follow-up.

We interviewed only patients who had at least 18 years old and could communicate with the interviewers. The interviewers were physicians and nurses specifically trained for this study.

We used 2 types of questionnaire to collect the data for this the study. The questionnaires were designed based on previous studies, were revised based on the expert opinions of the research team, and were finalized based on a pilot study among a few research subjects.

The questionnaires included demographic information (age, gender, socioeconomic status, habitual history, and relationship between patients and their companions), clinical information (i.e. diagnosis, breast cancer diagnosis and the time duration between the diagnosis and the interview, treatment methods, and complications), attitudes about truth-telling, satisfaction with information provided by the physician, and the patient's desire to participate in truth telling for the other patients with the same diagnosis.<sup>3</sup> Face to face interviews were performed with patients and their companions, separately. Ethics Committee of Tehran University of Medical Sciences approved the present study.

Statistical Analyses

The questionnaires with incomplete data were excluded from analysis. We performed descriptive analyses to describe the distribution of the studied variables. We used Chi-square and t tests to determine the association between variables. Considering the positive attitude of truth-telling as a dependent variable, we performed stepwise multiple logistic regression analyses to determine the contributing factors affecting it. SPSS statistic software (Version 11.5) was used for data analysis.

## Results

Five hundred participants including 250 patients with cancer and one of their family members were accrued in this study. Characteristics of the participants are presented in Table 1. Among the patients group, 96 (38.8%) were male and 153 (61.2%) were female and the overall average age was 48 years ( $\pm 15.13$ ).

## Attitude of the patients

While 17 (6.8%) patients disagreed with the diagnosis disclosure, 233 (93.2%) patients wanted to be informed of the diagnosis. A total of 228 (91.2%) patients preferred full disclosure, 1 (0.4%) partial disclosure, and 21 (8.4%) no disclosure. One hundred fifty-three (61.2%) patients preferred the disclosure of diagnosis, treatment methods, and their effectiveness which as shown in Table 2.

High educated patients were more likely than others believed in full disclosure of the truth (p<0.001). Patients preferred to be informed of their real disease first by their physicians (58.5%). Other preferable ways were: patients in the same situation (20%), press and literature (15%), media (10%), relatives and friends (4%), internet (1.6%), and other patients introduced more than one source for getting informed (17.6%).

The relationship between level of education and using other ways of getting information showed that the way of getting information about the diagnosis is different among different levels of education

Table 1. Characteristics of patients and family members

Variables	Patient N(%)	Family
		members N(%)
Age± SD	48± 15.19	40±11.63
Gender		
Men	94(37.6%)	124(49.6%)
Women	153(61.2%)	124(49.6%)
Education*		
Low educated	234(93.6%)	205(82%)
High educated	16(6.4%)	44(17.6%)
Economic status**		
Good	16(6.4%)	
Intermediate	158(63.2%)	
Poor	64(25.6%)	
Relationship to Patients		
Spouse		69(27.6%)
Offspring		90(36%)
Sibling		45(18%)
Parents		19(7.6%)
Others		27(8.1%)
*Education: Low edu	cated: Finished high sch	nool and below

\*Education: Low educated: Finished high school and below (first 12 years of education), High educated: University education \*\* Monthly income: Good >25,000,000 IRR, Intermediate: 10,000,000-25,000,000 IRR, Poor <10,000,000 IRR

#### (p=0.001).

Patients with high education level used at least one more root to get information and the most common way for these patients was media.

One hundred fifteen patients (46.5%) from 250 participants were satisfied with information that physicians give them about the diagnosis of their real disease. There was also statistical differences between economic status and satisfaction with being informed of the diagnosis and prognosis; patients with good economic status were more satisfied with

being informed of the diagnosis (p=0.01).

There was no significant difference between the proportions of socio-demographic factors in patients who wished to know the truth.

#### Attitude of the family members

Among the family members, 25 (10%) accepted partial disclosure and 72 (28.8%) did not desire any disclosure. Attitude of the relatives on the necessity of truth-telling and physicians' authority over disclosure are presented in Table 3 and Table 4.

<b>Tuble M</b> , I allents preference about the discrossive of diagnosis, deathent methods, and then enced veness	Table 2. Patients preference about the disclosure of diagnosis, treatment methods, and their	r effectiveness
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Patient questions	Yes	General Information	No
Do you know the diagnosis of your disease?	160(64%)		90(36%)
Do you want to know about the diagnosis of your disease?	233(93.2%)		17(6.8%)
Are you informed of all the details of your disease?	97(38.8%)	91(36.4%)	62(24.8%)
Do you wish to be informed of the details of your disease?	228(91.2%)	1(0.4%)	21(8.4%)
Are you informed of treatment methods?	163(65.2%)	48(19.2%)	39(15.6%)
Do you wish to be informed of treatment methods?	234(93.6%)	8(3.2%)	8(3.2%)
Are you informed of the effectiveness of treatment methods?	71(28.4%)	37(14.8%)	142(56.8%)
Do you wish to be informed of the effectiveness of treatment methods?	242(96.8%)	4(1.6%)	4(1.6%)

One hundred forty-one healthy family members (92.8 % from 153 family members), who thought patients are not entitled to know the truth, would not desire to be informed of the diagnosis if they are affected by cancer in future, while 47 (68.1%) of whom with the same point of view wished to know the truth. One hundred eight (52.7%) family members from low educated group thought that the physicians had to give relatives consent to inform patients and 97 (32.5%) thought that physicians should not follow families request about telling patients the truth (p = 0.001). A total of 108 relatives (57.7%), who believed their patient consent is necessary to inform the family, thought that if they are affected by cancer in future, physicians should not get patients permission to inform the family.

One hundred forty-six family members (58.4%) believed that informing patients of their real disease may lead to desirable outcome in treatment, 88

(35.2%) thought that the disclosure could reduce the treatment efficacy, and 13 (5.2%) thought the disclosure could not influence the treatment process.

However, 84 (49.7%) low educated family members believed that informing patients of their real disease could hamper treatment, while just 6 (13.33%) from high educated group had the same viewpoint (p=0.001).

## Multiple Stepwise Logistic Regression Analyses of Influential Factors on Truth-telling

Four stepwise logistic regression analyses of factors influencing the patients' attitude towards truth-telling were identified by 2 models:

1. The necessity of disclosure from patients' point of view

2. Informing the patients by physicians and 2 other models

3. Patients agreement to physicians' truth-telling

Table 3. Attitude of patients' relatives about the necessity of truth-telling

Relatives questions	Yes	General Information	No
Do you believe that the patients are entitled to know their diagnosis with the details?	153(61.2%)	25(10%)	72(28.8%)
Should the physicians inform the relatives with the details?	222(88.8%)	20(8%)	8(3.2%)
Table 4. Attitude of patients' relatives about physicians' au	thority over disclosu	re	
Relatives questions	Yes	Sometimes	No
Should the physicians inform the patients according to your consent?	116(46.4%)	41(16.4%)	93(37.2%)
Is the patient consent necessary to inform you?	28(11.2%)	35(14%)	187(74.8%)



4. Relatives being informed by the physicians

Unlike gender, economic status, and place of living, the first two models indicated that patients' level of education was likely to influence the attitudes towards truth-telling (Table 5). Other two models showed the influence of patient educational level on physicians' informing relatives and the influence of relatives' state of living on patients' agreement to physicians' truth-telling (Table 6).

 Table 5. Odds ratio and 95% CIs from Logistic Regression Analysis of factors influencing patient's attitude towards truth-telling

Variables	Should there be disclosure? (Yes) Did the physi		Did the physicians	icians inform you? (Yes)	
	Odds Ratio	95% CI	Odds Ratio	95% CI	
Gender					
Female	0.70	0.25 to 1.98	0.91	0.43-1.91	
Male	1		1		
Education***					
Without formal education	1		1		
Primary school	1.92	0.47- 7.77	1.71	0.62-4.70	
Secondary school	3.65	0.77- 17.35	1.10	0.39- 3.05	
High school	6.08*	1.27-29.07	6.19**	1.93-19.77	
Higher educated	4.39	0.36- 52.32	15.04	1.57-144.01	
Place of Living					
Village	2.40	0.38- 14.87	1.43	0.48-4.21	
City	1		1		
Economic status****					
Good	1		1		
Intermediate	0	0	1.35	0.25-7.26	
Poor	0	0	0.74	0.11- 4.65	
Relatives' attitudes towards truth-telling	2				
(Should there be disclosure?)					
Yes	2.22	0.82-6.02	1.51	0.73-3.14	
No	1		1		

\*P<0.05

\*\*P<0.01

\*\*\* Primary school: First 5 years of education, Secondary school: Second 3 years, High school: Third 4 years, Higher educated: University education \*\*\*\* Monthly income: Good >25,000,000 IRR, Intermediate: 10,000,000-25,000,000 IRR, Poor <10,000,000 IRR

Table 6.	Odds ratio	and 95%	CIs from	Logistic	Regression.	Analysis	predicting	attitudes	towards	truth-telling
				0	0	2	1 6			0

Variables	Patients' agreement	to informing relatives	Physicians informed relatives		
	Odds Ratio	95% CI	Odds Ratio	95% CI	
Gender					
Female	0.82	0.21- 3.22	1.14	0.55-2.34	
Male	1		1		
Place of Living					
Village	2.68	0.28-25.72	0.47	0.15-1.49	
City	1		1		
Education**					
Without formal education	1		1		
Primary school	0.52	0.09- 2.80	1.71	0.62-4.70	
Secondary school	1.33	0.16-11.13	4.08*	0.39- 3.05	
High school	6.24	0.42-91.22	2.54	1.93-19.77	
Higher educated	1.03	0.05-21.57	11.27*	1.03-122.98	
Relative's Place of Living					
Village	0.04*	0.004- 0.52	1.41	0.33- 5.95	
City	1		1		
Relative's Education**					
Without formal education	1		1		
Primary school	0.36	0.02- 6.34	0.55	0.14-2.11	
Secondary school	0.08	0.005- 1.49	0.79	0.21-3.00	
High school	0.30	0.01- 6.63	1.14	0.30- 4.28	
Higher educated	0.02	0.007- 6.20	5.25	0.75-36.40	

<sup>\*</sup> P<0.05

\*\* Primary school: First 5 years of education, Secondary school: Second 3 years, High school: last 4 years of the school, Higher educated: University education

## Discussion

Receiving a diagnosis of cancer is often emotionally traumatic for the patients. Patients who feel they are not being told enough, often suffer from a feeling of insecurity due to a lack of information about what is going to happen in the immediate future.<sup>18</sup>

Recent studies clearly indicate that physicians must be educated to routinely ask the patients about their wishes for knowing the truth, because telling patients the truth may lead to more appropriate care and many physicians believe that disclosure have many advantages; for instance, it enables patients to cooperate with physicians better, to settle the incomplete business, to manage their life better, and to be treated according to their own values and preferences.<sup>10-12,18</sup>

Truth-telling benefits, reported in other studies, are accompanied by less pain, anxiety, and depression as well as less interference in daily lives and higher levels of satisfaction with pain management.<sup>21,22</sup> Higher levels of anxiety, tension, irritability, and suicidal tendency in the patients who did not know their diagnosis were reported in similar studies.<sup>16</sup> Not telling the truth can harm the patients in many ways; patients who remain uninformed of their condition may fail to obtain medical attention when necessary. They may also make decisions affecting their lives that they would not make, if they were aware of their condition.<sup>23</sup>

The attitudes of patients with cancer and their families towards telling the truth about cancer diagnosis and prognosis differs across cultures.<sup>18-20</sup> An international survey reported the different percentage of patients with cancer who were given the truth.<sup>4</sup>

The rate of disclosure may influence the physician and family attitude as well as the hospital policy.<sup>18</sup>

The main finding of the present study was that 90% of patients desired to be informed of their real disease. This finding is in line (83%-96%) with the previous studies.<sup>24,25</sup> However, a study conducted in China reported that 69.3% of patients preferred disclosure, which is significantly less than other studies. The authors found relationship between a number of factors such as type of cancer, etc.<sup>26</sup> Traumatic influences of receiving the diagnosis of cancer as an incurable disease can be the main reason for rejecting disclosure by some patients.

Another important finding of the present study was that patients and family members differed in attitudes towards the disclosure of real diagnosis to patients with cancer. Patients were more interested to be informed about the diagnosis and prognosis than their families. Similar results were observed by previous studies.<sup>24,27,28</sup>

The majority of patients wanted to be informed of their real disease; this is significantly different from

the corresponding proportion in the family member group, meaning that we found a great difference in attitudes of patients and family members toward the truth being disclosed to them. Most of the patients were satisfied with the information which they received from their physicians about their disease and treatment protocol; nevertheless, less than 40% of patients were informed of the outcome and complications of treatment. The majority of family members knew the real disease, potential complications, and outcomes. The reason for this difference may be that families believed disclosure could make patient feel hopeless and make her suffer from psychological disorders such as anxiety, appetite loss, and insomnia that can hamper her life quality. Another reason for this difference may be explained by the difference between educational level of patient and families and cancer disclosure. Low educated family members believed that informing patients of their real disease may prohibit treatment improvement, while just a minority of the high educated group had the same idea; more than 80% of family members were low educated.

In some countries, physicians prefer to follow the families' wish on disclosure, so they comply with the request of not telling the truth to the patient; however, they believe that informing the patients of their real illness is beneficial in establishing satisfactory relationship among the physicians, patients, and the family.<sup>18</sup> The family surrounds the patient during difficult time of the disease and, in many societies, the family is still the strongest supporting entity. Families often believe that it is their duty to protect the patient from harm. In Middle East countries, such as Egypt and Saudi Arabia or Eastern Asia, and in Spain and Italy, the physician prefers to tell the truth about the cancer diagnosis to the relatives before the patient. They argue that there are many valid reasons justifying this; they have enough experience about the likely reactions of the patient than the health-care professionals, and at the same time, they usually deliver the necessary support and physical care.<sup>29-35</sup> The present study, like other studies, shows that patients' relatives play an important role in cancer disclosure.

A large proportion of patients (83.6%) wanted family members to know about their disease, but some patients did not agree with informing families without their consent (6%) because, for instance, they did not want their relationships change, miss their jobs, social position, and experience some other.<sup>36</sup> The assessment of these different attitudes indicated the necessity of patients' preferences. Families who resist on the disclosure of truth should be recommended about the importance of truth-telling, much as they might be counseled about the appropriate management of any medical problem; however, it is important to bear in mind that substantial variability exists within cultures and that



cultural values can change.<sup>23</sup>

In the present study, the attitude towards the disclosure was not shown to be related with the patients' socio-demographic factors such as gender, educational degree, and economical status, but in some other studies, unlike the present study, some characteristics influenced the patients' desire to know the truth;<sup>24, 25, 36</sup> however, patients' lack of education and poor economic status have been related to lower rates of truth-telling and the present research showed that the education level of the patients was a significant factor influencing the patients' awareness of the malignant nature of their disease. Some other studies have shown that elderly patients are less likely to be told their diagnosis.<sup>16, 21</sup> Moreover, low level of education and low socioeconomic status were reported as effective factors in concealment of the truth.<sup>21</sup>

In the present study, physician was introduced as an appropriate person to disclose the diagnosis; patients and their relatives had the same idea in other studies.<sup>25, 36, 37</sup> Investigating the relatives attitude towards informing patients showed that a large number of family members (82%) would desire to be informed if they happen to have cancer, in the future; similar results were observed by Gongal *et al.*<sup>38</sup> where 70% of family members who thought patients were not entitled to know the truth, would desire to know the truth, in case that they would have a malignancy, themselves.

Based on the findings of the present study, a large proportion of family members (58.4%) believed that informing patients of their real disease would lead to desirable results of treatment; some other studies from other countries have reported benefits of cancer disclosure.<sup>16,21,22</sup>

To sum up, the present study showed that a large number of patients favored full disclosure of the real diagnosis. Physicians and family members should respect the patients' viewpoint, because patients are entitled to know about their own condition and all information should, first, be told to the patient by the physician.

Although there is no legal obligation for cancer disclosure to patients and family members in Iran, it must be defined as a professional policy with enforceable guidelines for physicians and medical staff; they have to be trained specially to get adequate communication skills for effective communication with patients and relatives to prepare the setting for telling patients the truth with the intention of minimizing stress and avoiding sustained harmful loss.

## **Conflict of Interest**

We have no financial relationship with the organization that sponsored the present research. We have full control of all primary data and we agree to allow the journal to review the data, if requested.

Ethics Committee of Tehran University of Medical Sciences approved the study.

## References

- 1. World Health Organization. Report of the Director General: The world health report 1998. Geneva: WHO. 1998.
- 2. Miyata H, Tachimori H, Takahashi M, Saito T, Kai I. Disclosure of cancer diagnosis and prognosis: a survey of the general public's attitudes toward doctors and family holding discretionary powers. BMC Med Ethics. 2004;5:E7.
- Miyata H, Takahashi M, Saito T, Tachimori H, Kai I. Disclosure preferences regarding cancer diagnosis and prognosis: to tell or not to tell? Journal of Medical Ethics. 2005;31(8):447-51.
- 4. Holland JC, Holland JC, Geary N, Marchini A, Tross S. Psychosocial Issues: an international survey of physician attitudes and practice in regard to revealing the diagnosis of cancer. Cancer Investigation. 1987;5(2):151-4.
- 5. Surbone A. Truth telling to the patient. JAMA. 1992;268(13):1661-2.
- 6. Harrison A, Al-Saadi A, Al-Kaabi A, Al-Kaabi M, Al-Bedwawi S, Al-Kaabi S, *et al.* Should doctors inform terminally ill patients? The opinions of nationals and doctors in the United Arab Emirates. Journal of Medical Ethics. 1997;23(2):101-7.
- Hamadeh GN, Adib SM. Cancer truth disclosure by Lebanese doctors. Social Science & Medicine. 1998;47(9):1289-94.
- 8. Bertakis KD, Roter D, Putnam SM. The relationship of physician medical interview style to patient satisfaction. J Fam Pract. 1991;32(2):175-81.
- Field D. Special not different: general practitioners' accounts of their care of dying people. Social Science & Medicine. 1998;46(9):1111-20.
- 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.
- Emanuel LL, Barry MJ, Stoeckle JD, Ettelson LM, Emanuel EJ. Advance directives for medical care—a case for greater use. New England Journal of Medicine. 1991;324(13): 889-95.
- 12. Wolf SM, Boyle P, Callahan D, Fins JJ, Jennings B, Nelson JL, *et al.* Sources of concern about the patient self-determination act. New England Journal of Medicine. 1991;325(23):1666-71.
- Ajaj A, Singh M, Abdulla A. Should elderly patients be told they have cancer? Questionnaire survey of older people. BMJ. 2001;323(7322): 1160.

- 14. Jenkins V, Fallowfield L, Saul J. Information needs of patients with cancer: results from a large study in UK cancer centres. British Journal of Cancer. 2001;84(1):48.
- Parker PA, Baile WF, de Moor C, Lenzi R, Kudelka AP, Cohen L. Breaking bad news about cancer: patients' preferences for communication. Journal of clinical oncology. 2001;19(7):2049-56.
- 16. Horikawa N, Yamazaki T, Sagawa M, Nagata T. Changes in disclosure of information to cancer patients in a general hospital in Japan. General Hospital Psychiatry. 2000;22(1):37-42.
- Mystakidou K, Tsilika E, Parpa E, Katsouda E, Vlahos L. Patterns and barriers in information disclosure between health care professionals and relatives with cancer patients in Greek society. European Journal of Cancer Care. 2005;14(2): 175-81.
- Mystakidou K, Parpa E, Tsilika E, Katsouda E, Vlahos L. Cancer information disclosure in different cultural contexts. Supportive Care in Cancer. 2004;12(3):147-54.
- 19. Elwyn TS, Fetters MD, Sasaki H, Tsuda T. Responsibility and cancer disclosure in Japan. Social Science & Medicine. 2002;54(2):281-93.
- 20. Yeung CW. The ethics of collusion and nondisclosure in cancer care: A perspective from professional psychology. Professional Psychology: Research and Practice. 2017; 48(1):46.
- Lin C-C. Disclosure of the cancer diagnosis as it relates to the quality of pain management among patients with cancer pain in Taiwan. Journal of Pain and Symptom Management. 1999;18(5): 331-7.
- 22. Last B, Van Veldhuizen A. Information about diagnosis and prognosis related to anxiety and depression in children with cancer aged 8–16 years. European Journal of Cancer. 1996;32(2):290-4.
- 23. Hébert PC, Hoffmaster B, Glass KC, Singer PA. Bioethics for clinicians: 7. Truth telling. Canadian Medical Association Journal. 1997;156(2):225-8.
- 24. Yun YH, Lee CG, Kim S-y, Lee S-w, Heo DS, Kim JS, *et al.* The attitudes of cancer patients and their families toward the disclosure of terminal illness. Journal of Clinical Oncology. 2004;22(2):307-14.
- 25. Seo M, Tamura K, Shijo H, Morioka E, Ikegame C, Hirasako K. Telling the diagnosis to cancer patients in Japan: attitude and perception of patients, physicians and nurses. Palliative Medicine. 2000;14(2):105-10.
- 26. Jie B, Feng ZZ, Qiu Y, Zhang YQ. Association between socio-demographic factors, coping style, illness perceptions and preference for disclosure/nondisclosure of diagnosis in Chinese patients with hepatocellular carcinoma. J Health

Psychol. 2017:1359105317707258.

- 27. Noone I, Crowe M, Pillay I, O'Keeffe S. Telling the truth about cancer: views of elderly patients and their relatives. Irish medical journal. 2000;93(4):104-5.
- 28. Abebe E, Abebe H. Types of cancers diagnosed and the preference of families of adult patients with cancer about disclosing diagnosis to the patients. Ethiopian Journal of Health Sciences. 2017;27(3):255-62.
- 29. Al-Ahwal M. Cancer patients' awareness of their disease and prognosis. Annals of Saudi medicine. 1998;18:187-9.
- 30. El-Ghazali S. Is it wise to tell the truth, the whole truth, and nothing but the truth to a cancer patient? Annals of the New York Academy of Sciences. 1997;809(1):97-108.
- 31. Pronzato P, Bertelli G, Losardo P, Landucci M. What do advanced cancer patients know of their disease? Supportive Care in Cancer. 1994;2(4):242-4.
- 32. Olarte JMN, Guillén DG. Cultural issues and ethical dilemmas in palliative and end-of-life care in Spain. Cancer control. 2001;8(1):46-54.
- 33. Li S, CHOU JL. Communication with the cancer patient in China. Annals of the New York Academy of Sciences. 1997;809(1):243-8.
- 34. Mystakidou K, Parpa E, Tsilika E, Kalaidopoulou O, Vlahos L. The families evaluation on management, care and disclosure for terminal stage cancer patients. BMC Palliative Care. 2002;1(1):3.
- 35. Uchitomi Y, Yamawaki S. Truth-telling Practice in Cancer Care in Japan. Annals of the New York Academy of Sciences. 1997;809(1):290-9.
- 36. Phungrassami T, Sriplung H, Roka A, Mintrasak E-n, Peerawong T, Aegem U. Disclosure of a cancer diagnosis in Thai patients treated with radiotherapy. Social Science & Medicine. 2003;57(9):1675-82.
- 37. Jiang Y, Liu C, Li JY, Huang MJ, Yao WX, Zhang R, *et al.* Different attitudes of Chinese patients and their families toward truth telling of different stages of cancer. Psycho-Oncology. 2007; 16(10):928-36.
- 38. Gongal R, Vaidya P, Jha R, Rajbhandary O, Watson M. Informing patients about cancer in Nepal: what do people prefer? Palliative Medicine. 2006;20(4):471-6.



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## Conflict of Interest: The Attitude of Iranian Physicians Involved in Breast Cancer Management

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#### ABSTRACT

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## Introduction

Preservation of trust between physicians and patients is the cornerstone of many healthcare policies, as the efficacy of clinical interventions depends on it.

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**Background:** Evidence on physicians' attitude toward conflict of interest is scant on a global scale and almost non-existent in a regional/national scale. This investigation is a pioneer to evaluate this issue in the Middle East and Iran.

**Methods:** We invited physicians of different (sub)specialties/educational levels who were engaged in breast cancer management to take an online 13question survey regarding their attitude toward different statements on conflict of interest. The responses were then collected and analyzed.

**Results:** The questionnaire was returned by 91 out of 157 recipients (response rate = 57.9%). Based on the answers, advertisement by pharmaceutical sales representatives in academia was considered inappropriate (63.8%) and influential on clinical practice (80.2%). It was the belief of 59.4% of participants that local practice norms defined whether or not to accept travel grants. According to these norms, they might have accepted paid travels (53.9%), but not financial offers (72.2%). It was acceptable to deliver (74.8%) or attend (68.9%) a speech when a financial/scientific relationship with industrial companies existed and 93.4% believed that the disclosure and transparency rules should be respected in such situations. Physician-industry financial contracts were generally unfavorable (60.5%), especially when it came to prescribing a drug among other equally effective choices (71.1%). The majority of respondents (92.3%) stated that they would choose the best approach for the patients regardless of possible prejudgments on conflict of interest.

**Conclusions:** The observed variation in physicians' standpoints highlights the necessity for more comprehensive training and implementation of rigorous protocols regarding conflict of interest.

Conflict of interest (COI), as a major source of potential threat to achieving this goal, has become the concern of healthcare policymakers in recent decades. By definition, COI is a conflict between a professional responsibility and financial or professional interest.<sup>1</sup> Although not every financial relationship or professional interest constitutes a COI, there is always a possibility. Since inappropriate policies can easily turn this potential threat into an actual ethical problem, many academic medical centers have established new


Although personal advantage can be discussed in different aspects, in majority of cases the most concerning COI is the financial one.<sup>5, 6</sup> Evidence suggests that financial connections between pharmaceutical industry and oncology have grown over time.<sup>7</sup> Despite being common, this relationship can eventually increase the influence of industry on oncology research and practice. In the United States, this issue has become even more concerning as a result of a shift in prominent clinical trials from being government-funded in the past to industry-funded in recent years.<sup>7</sup>

In the literature, little evidence exists regarding the physicians' awareness of and attitude towards COI on a global scale, and the evidence is almost non-existent in a regional or national scale. Hence, this study was conducted to present an overview of the current state of Iranian physicians' mindset on this issue.

#### Methods

A self-administered online questionnaire was designed in two parts. The first part (Table 1) included questions on age, gender, highest level of education, training in the medical ethics, and oncology practice background. The second part contained 13 questions to assess the attitude of physicians towards COI. Respondents were asked to answer each question by selecting one of the five options: strongly agree, agree, undecided/neutral, disagree, and strongly disagree.

Table1. Questonnaire

First Part: Demographic information

1. Age (years): .....

2. Gender: Male 🗌 Female 🗌

3. Level of Education:

Resident 🗌 Board-certified specialist 🗌 Fellowship student 🗌 Fellowship graduate 🗌

4. Specialty: ..... / Fellowship sub-specialty: .....

5. Professional experience in oncology (years): .....

6. Average number of patients you visit in a week: .....

- 7. Have you ever attended workshops/courses on "medical ethics and professionalism": Yes 🗌 No 🗌
- 8. Have you ever attended workshops/courses on "Conflict of Interest": Yes 🗌 No 🗌

Second Part: Survey on Physicians' Attitude

Q1. I consider it inappropriate if pharmaceutical sales representatives attend an academic environment.

Q2. The presence and advertisement of pharmaceutical sales representatives subconsciously affects the clinical and therapeutic decisions.

Q3. It is acceptable if I travel abroad for which a pharmaceutical company will pay the costs (not accompanied by my family).

Q4. Local practice norms determine whether or not to accept any gifts or travel grants.

Q5. In case of any financial relationship with healthcare industries, I will adhere to the disclosure and transparency rules in national meetings/seminars should I give presentations on pertinent issues.

Q6. In my opinion, neither scientific cooperation nor financial relationships with medical centers interfere with giving lectures in relevant seminars.

Q7. Knowing that a lecturer has received grants from a corporation on the associated topic, I cannot attend as an audience.

Q8. Financial contracts with medical centers (e.g. laboratory or imaging centers) is acceptable if no further cost is imposed on the patients.

Q9. Financial contracts with medical centers are justifiable if the gain is devoted to development of medical services or charity purposes.

Q10. In case two drugs are similar and equally effective, selecting the one for which there is a contract between a physician and a company in not right.

Q11. According to my country's practice norms, it is not unethical to accept offers from pharmaceutical / medical instrument corporations.

Q12. Suggesting options of referral laboratory / imaging centers to patients, while respecting their choices , is suspicious and damages the patient-physician trust.

Q13. I consider what is best for my patient and prejudgements and doubtful situations, with regard to possible conflict of interest, do not influence my approach.



The questionnaire was developed by the authors using a discussion method over several meetings. It was then finalized through consultation with a panel of ethics experts.

We asked 157 physicians engaged in the field of breast cancer to participate in this survey via an email containing a link to the pre-designed online questionnaire. All participants were also sent a cover letter requesting them to complete the questionnaire. The answers were collected anonymously, without linking it to the participant's email address or any other personally identifiable information.

Data analysis was performed with SPSS software (version 19.0; IBM Corp., Armonk, NY). All frequencies are expressed as percentage.

#### Results

Ninety-one out of 157 physicians participated in the survey (response rate: 53.5%), of whom 36.3% were surgeons, 28.6% were oncologists, and 35.1% were of other specialties, including radiotherapy, radiology, and pathology. The participants were 60.4% male and 39.6% female with the mean age of 44 years (SD: 8.76, Range: 26–68 y). Of the total participants, 31.9% were board-certified MDs, 57.1% were fellowship students/graduates, and 11% were residents. All respondents were physicians working in the field of breast cancer, with a mean experience of 9.99 years (SD: 9.01, Range: 1-40 y). At least one course of medical ethics training was attended by 51.6% of participants, of whom 29.8% (15.4% of total participants) had also received training in COI. Table 2 shows a summary of demographic information.

Variables (N=91)	N (%)	Mean (±SD)
Age± SD Gender		44 (±8.769)
Male	55 (60.4%)	
Female	36 (39.6%)	
Specialty		
Surgeon	33 (36.3%)	
Oncologist	26 (28.6%)	
Radiotherapist	13 (14.2%)	
Radiologist	6 (6.6%)	
Pathologist	4 (4.4%)	
Other	7 (7.7%)	
Missing	2 (2.2%)	
Education*		
Resident	10 (11.0%)	
Board certified	29 (31.9%)	
Fellowship student	15 (16.5%)	
Fellowship graduate	37 (40.6%)	
Ethics training		
Yes	47 (51.6%)	
No	44 (48.4%)	
COI training	14 (15.4%)	
Yes	77 (84.6%)	
No		
Average breast cancer patie	ents (N)	16.82 (±26.52)
Oncology experience (Y)		9.99 (±9.01)

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The majority of respondents believed that the presence of pharmaceutical sales representatives in academia is not appropriate (Q1, 63.8% "agree" or "strongly agree") and may unintentionally influence the practice of physicians (Q2, 80.2% "agree" or "strongly agree").

More than half of the respondents (53.9%) considered it acceptable for pharmaceutical companies to pay for the costs of their travel or other personal expenses, if their family members were not included (Q3). Decision on the acceptance of travel grants or other gifts was assumed to be dependent on the local practice norms by 59.4% of the respondents (Q4).

A large number of participants (93.4%) valued the disclosure and transparency rules in national presentations, while four (4.4%) stated that they would not abide by it (Q5), and two (2.2%) were neutral/undecided. The majority (74.8%) believed that financial or scientific relations with industrial companies had no conflicts with giving speech in medical seminars (Q6). Also, participating as an audience member when the speaker has such relations was acceptable (Q7, 68.9%).

Financial contracts between physicians and medical institutions or companies to administer specific products were not generally acceptable (38.5% "strongly disagree", 22% "disagree", 3.3% "undecided/neutral"), even without imposing any extra costs on patients (Q8). However, it became more justifiable (38.5% "strongly agree", 17.6% "agree") when the resultant profit was to be spent on developing medical services or for charity purposes (Q9). Also, it was commonly (71.1%) stated that a financial contract between a physician and a pharmaceutical company to prescribe a drug developed by that company would be unethical if other equally effective drugs were available (Q10).

Accepting financial offers from companies did not enjoy a good reputation among participants (Q11, 72.2% "disagree" or "strongly disagree"). The participants did not believe that giving extra information to patients to help them choose from available choices could damage their trust due to suspicion on probable existing interests when referring them to other medical centers (Q12, 60% "disagree" or "strongly disagree"). Also, a solid majority (92.3%) stated that they would consider the best approach for their patients, without being affected by prejudgments and doubts on possible COI (Q13).

#### Discussion

We performed this investigation to assess Iranian clinicians' awareness of and attitude toward COI. To the best of our knowledge, the few previous studies were primarily focused on authors' disclosure of conflict of interest in medical articles,<sup>8</sup> and our study is among the first in Iran to document the attitude to COI in medical practice.

We found that physicians are generally against the presence of pharmaceutical sales representatives in academic environments and believe that this may unintentionally affect their practice. This common perception was in accordance with the recent systematic review by Fickweiler et al.9 In a comprehensive search of literature from 1992 to 2016, in PubMed, EMBASE, Cochrane Library, and Google Scholar, they found that pharmaceutical industry and sales representatives influence "physicians' attitudes and their prescribing behavior."<sup>9</sup> Another study on 379 Polish physicians by Makowska showed that 35% of participants would usually meet with pharmaceutical sales representatives in their offices during working hours, despite its illegality in Poland.<sup>10</sup> Also, 72.3% of them trusted the information provided by the representatives, which could influence their knowledge and practice.<sup>10</sup>

In a survey of 1386 clinicians in Germany (response rate = 11.5%), Lieb and Scheurich demonstrated that acceptance of gifts, participation in sponsored continuing medical education, and the perception of receiving adequate information from sales representatives were associated with biased prescription.<sup>11</sup> In a different study, Chressanthis, a former employee of global sales and marketing consulting firm "ZS Associates", and his colleagues analyzed clinical decisions of up to 72,114 physicians using AccessMonitor<sup>™</sup> database created by ZS Associates.<sup>12</sup> In contrast to others, they highlighted the importance of having access to pharmaceutical representatives and reported that limiting this access may reduce proper reactions to negative information on a drug as well as positive information on an innovative product.<sup>12</sup> Overall, the optimal level of restriction for pharmaceutical sales representatives still remains controversial, especially considering the fact that most representatives may not meet the standards of medical knowledge.<sup>13</sup> Also, there is an undeniable body of evidence describing the adverse effects of pharmaceutical representatives on medical prescription.9-11,14-18

More than half of our respondents were willing to accept the gifts or payments from the pharmaceutical companies for the costs of travel or personal expenses. According to the American Medical Association (AMA), a gift from industry can be accepted only if it "will directly benefit patients, including patient education" and "is of minimal value."<sup>19</sup> Furthermore, physicians are expected to reject cash gifts from an entity when it directly benefits from their prescriptions or when the reciprocity is implied.<sup>19</sup> In addition to general rules, there are many regional and internal policies that ban the medical personnel from accepting any gifts or payments from industry. For example, internal guidelines of Harvard Medical School prohibits

faculty members from accepting "any personal gifts, meals, or fees for professional meeting registration and/or related travel" from industrial companies.<sup>20</sup> Despite all these policies, many physicians continue to receive royalties and payments. In 2016, Iyer et al. analyzed the Open Payments Database, which details payments from industry to physicians and teaching hospitals.<sup>21</sup> They found that from 2,697,015 recorded payments to physicians, the majority (56.1%) were royalties.<sup>21</sup> Another study by Patel et al. in 2016 identified the financial relationship between industry and faculty surgeons within colon and rectal fellowship programs as a potential source of COI.<sup>22</sup> They found that a total of 65 companies had made payments to surgeons, with 80.1% of the funding categorized as general payments, 16.2% as investments, and only 3.7% as research payments.<sup>22</sup>

Although financial contracts between physicians and medical institutions or companies were not generally accepted according to our study, 36.2% of participants were still in favor of such contracts. Based on the AMA guidelines, "direct or indirect influence of financial interests on prescribing decisions" is a clear case of COI.<sup>19</sup> Accordingly, receiving any payments from pharmaceutical/ medical instruments corporations to prescribe their products and referring patients to a "pharmacy that the physician owns or operates" are not ethical.<sup>19</sup>

In the last decade, there has been a worldwide demand to reduce financial COI. In the most recent attempt, in 2013, the United States enacted a federal legislation named Physician Payments Sunshine Act (PPSA) to increase transparency regarding payments from pharmaceutical and medical device industries to physicians and teaching hospitals for travel, meals, gifts, speaking, etc.<sup>23</sup> This piece of legislation and the related free-access Open Payments Database drew attentions to the importance of physician-industry relations. The total value of such payments were \$8.18 billion in 2016.<sup>24</sup>

In Iran and many developing countries, there is no such clear policies regarding COI; nor does there exist any thorough inspection mechanism nor penalty protocols. Even the number of studies focusing on this topic are scarce. Although complete elimination of the COI in the health-care system seems practically impossible and the effectiveness of transparency rules in the outcome of COI is in question, they are not excuses to avoid, neglect or postpone the implementation of robust preventive policies in our country. This study was an attempt to fill this knowledge gap; however, there were some limitations. The validity and reliability of our questionnaire were not evaluated, even though it was discussed and approved by an expert panel. Also, the number of participants was limited. Conducting further investigations is crucial to expose the root of the pertinent challenges and problems that physicians are facing on this matter.



#### References

- 1. Lockhart AC, Brose MS, Kim ES, Johnson DH, Peppercorn JM, Michels DL, *et al.* Physician and stakeholder perceptions of conflict of interest policies in oncology. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(13): 1677-82.
- 2. Andresen NS, Olson TS, Krasowski MD. Medical student and medical school teaching faculty perceptions of conflict of interest. BMC research notes. 2017;10(1):272.
- 3. HamsM, Wilkinson WG. A new survey to evaluate conflict of interest policies at academic medical centers. 2017;12(3):e0172472.
- Shnier A, Lexchin J, Mintzes B, Jutel A, Holloway K. Too few, too weak: conflict of interest policies at Canadian medical schools. PloS one. 2013;8(7):e68633.
- 5. Swift S, Rizk D, Lose G. Conflict of interest: what is it, and how do journals manage it in the publication process? International urogynecology journal. 2017;28(7):969-70.
- 6. Rothenberg ML, Johnson DH. Conflict of interest, conflicting interests, and effective collaboration between academia and industry on preclinical and clinical cancer research. JAMA oncology. 2017;3(12):1621-2.
- 7. Moy B, Jagsi R, Gaynor RB, Ratain MJ. The impact of industry on oncology research and practice. American Society of Clinical Oncology educational book American Society of Clinical Oncology Meeting. 2015:130-7.
- 8. Heidari A, Adeli SH, Mehravaran S, Asghari F. Addressing ethical considerations and authors' conflict of interest disclosure in medical journals in Iran. Journal of bioethical inquiry. 2012;9(4):457-62.
- 9. Fickweiler F, Fickweiler W, Urbach E. Interactions between physicians and the pharmaceutical industry generally and sales representatives specifically and their association with physicians' attitudes and prescribing habits: a systematic review. BMJ open. 2017;7(9): e016408.
- 10. Makowska M. Polish physicians' cooperation with the pharmaceutical industry and its potential impact on public health. PloS one. 2017;12(9):e0184862.
- 11. Lieb K, Scheurich A. Contact between doctors and the pharmaceutical industry, their perceptions, and the effects on prescribing habits. PloS one. 2014;9(10):e110130.
- 12. Chressanthis GA, Khedkar P, Jain N, Poddar P, Seiders MG. Can access limits on sales representatives to physicians affect clinical prescription decisions? A study of recent events with diabetes and lipid drugs. Journal of clinical hypertension (Greenwich, Conn). 2012;14(7):

435-46.

- 13. Lassen CL, Fragemann K, Klier T, Meyer N, Graf BM, Wiese CH. Knowledge levels of pharmaceutical sales representatives in pain therapy: a descriptive questionnaire-based study. European journal of clinical pharmacology. 2012;68(2):161-70.
- 14. Lexchin J. Interactions between physicians and the pharmaceutical industry: what does the literature say? CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 1993;149(10):1401-7.
- 15. Workneh BD, Gebrehiwot MG, Bayo TA, Gidey MT, Belay YB, Tesfaye DM, *et al.* Influence of medical representatives on prescribing practicesin Mekelle, northern Ethiopia. PloS one. 2016;11(6):e0156795.
- 16. Habibi R, Lexchin JM, B., Holbrook A. Unwarranted claims of drug efficacy in pharmaceutical sales visits: are drugs approved on the basis of surrogate outcomes promoted appropriately? British journal of clinical pharmacology. 2017;83(11):2549-56.
- 17. HajjarR, Bassatne A, Cheaito MA, Naser El Dine R, Traboulsy S, Haddadin F, *et al.* Characterizing the interaction between physicians, pharmacists and pharmaceutical representatives in a middleincome country: A qualitative study. 2017;12(9): e0184662.
- Lieb K, Brandtonies S. A survey of german physicians in private practice about contacts with pharmaceutical sales representatives. Deutsches Arzteblatt international. 2010; 107(22):392-8.
- 19. AMA Council on Ethical and Judicial Affairs. Chapter 9: Opinions on professional selfregulation. AMA Code of Medical Ethics: American Medical Association 2016. 560 p.
- 20. Harvard University Faculty of Medicine. Policy on conflicts of interest and commitment. May 2016 [Available from: https://ari.hms. harvard.edu/book/section-i-faculty-medicinepolicy-conflicts-interest-and-commitment.]
- 21. Iyer S, Derman P, Sandhu HS. Orthopaedics and the Physician Payments Sunshine Act: an examination of payments to U.S. orthopaedic surgeons in the Open Payments Database. The Journal of bone and joint surgery American volume. 2016;98(5):e18.
- 22. Patel SV, Klingel M, Sonoda T. An assessment of the industry-faculty surgeon relationship within colon and rectum surgical training programs. Journal of surgical education. 2016;73(4):595-9.
- 23. Krimsky S. If the "Physician Payments Sunshine Act" is a solution, what is the problem? The American journal of bioethics : AJOB. 2017;17(6):29-30.
- 24. Open Payments Database [Available from: https://openpaymentsdata.cms.gov].





DOI: 10.19187/abc.20174399-103 Factors Affecting the Physician's Disclosure of Truth to Cancer Patients in Iran

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#### ABSTRACT

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#### Introduction

Telling the truth about diagnosis and prognosis of the disease to patients is an essential issue for administrators, physicians and nurses.<sup>1</sup> General physicians believe that truth-telling and disclosing the information may present an ethical issue.<sup>2</sup> Practitioners working in vital health sections, such as

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**Background:** One of the essential issues in doctor-patient relationship is the matter of telling the truth of cancer diagnosis to patients. This is not only important from an ethical standpoint, but also can have legal implications. Thus, truth-telling and its associated factors are of great importance especially in cancer patients. The aim of this study was to evaluate factors effective in doctors' telling the truth to their patients.

**Methods:** The statistical population included specialists and subspecialists working in the field of cancer treatment in Tehran. Overall, 161 questionnaires, designed for our study, were gathered and evaluated.

**Results:** According to our study, 87.6% of the responders would tell the truth to their patients, while 12.4% wouldn't do so. They believed that the best person to tell the truth to the patient is the physician or the psychiatrist specialized in this field. Ninety-two percent of physicians felt the need for developing a guideline on educating patients. There was a significant difference between oncologists and non-oncologists in terms of tendency to tell the truth, with non-oncologists showing more tendency. Most of the doctors preferred to tell the truth to their middle-aged (51–70 years) patients rather than to their younger or older patients.

**Conclusions:** Only 25.5% of physicians in our study had the policy to tell the truth to majority of their patients, and almost all of them felt the need for having a formal guideline regarding informing and educating cancer patients. This highlights the significance of cultural-religious context of our country and the importance of having a practical guideline to educate our physicians.

cancer medical care and psychological health, hold the view that truth-telling has become an ethical issue.<sup>3-5</sup> There are multiple studies evaluating physicians' attitude towards patients ideas and preferences about truth-telling.<sup>6</sup> In the early 1950's, patients were asked about their views on cancer diagnosis and being told the truth about it. Studies of Kelly and Friesen, Brown<sup>7</sup>, and Aitken-Swan and Easson<sup>8</sup> demonstrated that patients would prefer to know the truth about their disease. Also, there are numerous studies investigating the physicians' view as one of the groups involved in this process. In Fitts and Radvin's survey<sup>9</sup>, when physicians were asked whether they would tell the truth to their patients, Only 3% stated that they always tell, and only 28% stated that they usually tell the truth. Approximately 70% either never tell or usually do not tell.<sup>7:9</sup> Recent research on physicians' attitude towards telling the truth about cancer diagnosis demonstrated that multiple factors are influential in this setting, the most important of them being the society's culture.<sup>10-12</sup>

In fact, there are different viewpoints regarding truth-telling.<sup>13</sup> The goal of this study was to evaluate the standpoints of specialists in Tehran regarding truth disclosure to cancer patients and its association with the type of specialty and where they worked. Also, we wanted to determine the physicians attitude towards the best way of telling the truth to patients.

#### Methods

The statistical population of our survey included specialists and subspecialists working in the field of cancer treatment in Tehran. We distributed the questionnaires to physicians in academic centers or oncology meetings, and encouraged them to participate in the survey. Overall, 161 questionnaires were returned and evaluated. The questionnaire consisted of several sections. The first section was about the individual's personal and professional information. The second section inquired about the point of view, preference, and behavior of responders with regard to telling the truth to patients, which was designed according to Ajzen's planned behavior theory.<sup>14</sup> The planned behavior model is one of the most reliable models for predicting behavior and, since it has structures considering important aspects of behavior, can be utilized for evaluating opinions, values and attitudes behind the process of truthtelling. It is a cognitive social theory that is designed to discern and predict the possibility of showing or not showing a behavior and is a developed form of logical action theory. Accordingly, our evaluation consisted of 11 questions for attitude, 3 questions for preference, and 2 questions for behavior. The questions of this section were designed as a 5-poin scale ranging from 1 (totally disagree) to 5 (totally agree). For the final analysis of the questionnaire, Cronbach's alpha coefficient was calculated. Alpha coefficients for attitude, desire, and behavior were 0.76, 0.67 and 0.51, respectively. As for data analysis, descriptive statistics and inferential statistics including t test and analysis of variance were used.

#### Results

#### Descriptive statistics

The population in our study consisted of physicians in different specialties. The frequency distribution of responders according to age, sex, level of graduation, work place, work experience, and number of new cancer patients visit per year are presented in table 1.

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Variables	Patient N(%)	Family members N(%)
Age (Mean $\pm$ SD)		$43.4\pm11.2$
Sex	Male Female	59% 41%
Age distribution		
	< 35 years 35-50 years > 50 years	27.4% 56.6% 16%
Specialty	s of years	/
Works	Specialist Subspecialist	112 44
work place	Private services Public services	19.5% 46.5%
	Both	34%
Work experience		
	< 10 years 10–20 years >20 years	50% 36.2% 13.8%
Number of new		
patient visits per year	< 50 patients per year 51-100 patients per year 101-150 patients per year > 150 patients per year	43% 26% 13.6% 17.4%
Specialty	> 150 patients per year	17.470
	Oncology Surgery OB & GVN	21.9% 17.9% 9.9%
	Internal medicine Other	25.2% 23.1%

Then we requested the physicians to characterize their general method of facing cancer diagnosis; 87.6% would tell the truth to their patients and 12.4% would not do so. Regarding the tendency to change their general attitude towards cancer diagnosis, the results showed that 66% of the physicians had little, 27% had medium, and 7% had high interest in changing it.

According to different patient age groups, 34% of the physicians preferred to tell the truth to patients younger than 50 years old; 52% to patients between 50 and 70 years old; and 14%, to patients older than 70 years old.

Responders believed that the best person to tell the truth to the patient is his physician or the psychiatrist specialized in the field. Family and patient support system were in the second place. In terms of the priorities of physicians in telling the steps of the disease management, results demonstrated that the first priority was the treatment method (62.2%), the second one was complications of the treatment (39.3%), and the third and fourth ones were prognosis and diagnosis, respectively.

#### Physicians' attitude by gender

We evaluated the difference in attitude between male and female physicians using the t test. The results showed no significant difference in attitude towards truth-telling for male and female physicians.

#### *Physicians' attitude by specialty*

We also evaluated the difference in physicians' attitude according to their specialty. The following hypothesis we tested:

There was a difference in attitude towards telling the truth between physicians in different specialties and subspecialties.

A t test was performed, and the results showed that there was no significant difference in attitude towards truth-telling between physicians with specialties or subspecialties.

## Comparison of tendency for truth-telling between oncologists and non-oncologists

To compare the tendency of oncologists and nononcologists for truth-telling, we tested the following hypothesis:

There is a significant difference in the tendency for truth-telling between oncologists and nononcologists.

Results of the t test revealed a significant difference between oncologists  $(10.9 \pm 1.82)$  and non-oncologists  $(11.8 \pm 2.1)$  in terms of tendency to telling the truth, with non-oncologists showing more tendency for telling the truth (t=2.08, P=0.041).

#### *Attitude and behavior of physicians towards truth-telling according to their service location*

To evaluate the difference in physicians' truthtelling behavior according to their service location (private, public, or both), we tested the following hypothesis:

There is a significant difference in physicians' truth-telling behavior according to their service location.

A one-way analysis of variance (ANOVA) was performed, and the results showed that there is a significant difference among physicians working in these three sectors; therefore, the null hypothesis was rejected. Post-hoc analysis using the Dunken test demonstrated that there was a difference in behavior between private sector physicians (mean = 8.87) and public-private sector physicians (mean = 8.62).

Also, to evaluate the difference in physicians' attitude based on service location (public, private, or both), we examined the following hypothesis:

There is a significant difference in physicians' attitude towards truth-telling according to their service location.

The results of ANOVA test showed that there was a significant difference between physicians working in the three sectors; therefore, the null hypothesis was rejected. The results of Duncan's post-hoc test revealed a significant difference in attitude between doctors working in public-private sectors (mean = 44.14) and those working in public (mean = 41.57) and private (mean = 39.92) sectors.

#### Discussion

There are numerous of individual, cultural and ethical issues related to telling the truth to cancer patients. These factors have been evaluated in several studies.

Results of a study by Zamani and colleagues in Iran showed that, with regard to telling the truth, 88% of patients and 90% of physicians agreed on telling the truth about early stage cancer, and 78% of patients and 72% of physicians agreed on telling the truth to patients with advanced cancer. Most of the patients and physicians agreed that talking about the diagnosis should be explicit; the economic status of the patient should not affect the truth-telling; disclosing the truth should happen immediately after the diagnosis; and the best person to tell the cancer diagnosis is the physician. Results of this study showed that in our society's culture (Iran), apart from different opinions about methods of truth-telling, most of the patients and physicians had a positive view regarding the necessity of telling the reality to a patient with cancer.<sup>14</sup> Another study evaluated the views of family doctors about telling the truth to cancer patients in Croatia. They studied 134 physicians, of whom 71.6% stated that they sometimes told the truth to their patients, and 51.5% said they would tell the truth to the patients' families without their permission. The majority of responders (70.3%) though that the family doctor was in the best position to tell the truth of the diagnosis, although 32.1% expressed difficulties in communicating with terminal patients.15

Grassi et al. studied physicians' view regarding truth-telling and its problems in Italy. About 45% believed that patients should be aware of their diagnosis, but only 25% would tell the truth to patients. Young surgeons stated that surgeons working at public hospitals were more likely to tell the truth about the diagnosis to their patients. About one-third of the physicians thought that patients should never know about their real diagnosis. Nearly all physicians confirmed that the presence of other family members while talking about patients' diagnosis is of great help, although they stated that patients' families prefer not to be involve their patients with reality. Ninety-five percent of the physicians believed that the general practitioner should be involved in the process of diagnosis and communicating with the patient, and 48% stated that physicians should be the one to break the news to the patient. Also, 86% of physicians considered having an informative handbook essential.<sup>16</sup>

In a study by Seo *et al.* in 2000 in Japan, 53% of the physicians believed that the truth must be told to patients; however, 46% of Japanese people still believed that the patient's family should be the first to know about the diagnosis, and most of Japanese physicians confer with patient.<sup>17</sup> Fielding *et al.* studied

the ways of telling the truth to Chinese patients with cancer. This study focused on methods of physicians in delivering the information. Among the doctors interviewed, 46% used a sudden approach to disclose the truth of diagnosis, and 19% used a slow and gradual method. Among the others who did tell the truth, more than half of them conducted it with the help of family members. Although some believe the negative reaction of patients to be the major reason for withholding the truth, the responders were that 25% of patients get depressed upon hearing the news, while the remaining 75% keep calm.<sup>18</sup> In a study of truth disclosure to cancer patients from the standpoint of specialists, patients, and their families in Iran, Beirughi and colleagues demonstrated that most of the doctors and nurses considered revealing the truth about the diagnosis as a mistake. Patients' families thought that information should be given gradually depending on the patients' psychological status. However, most of the patients believed that telling the whole truth was the best way. All of the doctors, most of the nurses, and all of the patients believed that the physician was the best person to disclose the truth. All of the patients wanted their physician to take the control of their treatment decision-making process.<sup>19</sup>

Tieying *et al.* analyzed the views of 634 specialists working in Chinese hospitals about telling the truth to cancer patients. They concluded that in order to raise the knowledge of cancer patients, specialists should receive more information about how to inform their patients, and it is essential to use special guidelines and methods.<sup>20</sup>

The results of our study showed that 34.8% of the responders would tell the truth to less than 25% of the patients, while 25.5% would tell the truth to more than 76% of their patients. Consistent with this finding, results of a study showed that the physicians informed only 25% of their patients about the true diagnosis.<sup>16</sup> Therefore, taking into account the underlying factors affecting the process of informing cancer patients in any society, the limitations of this issue in our country becomes more prominent.

Patients' age had a clear effect on doctors' tendency to tell the truth: most of our doctors preferred to tell the truth to their middle-aged (51–70 years) patients rather than their younger or older patients. Regarding the physicians' general attitude towards cancer patients, 87.6% stated that they would tell the truth to their patients, whereas 12.4% would not do so. With respect to changing their general attitude towards cancer patients, the results showed that the desire to do so was low in 66% of physicians, average in 27% and high in 7% of them.

Our responders believed that the most appropriate persons to tell the truth to the patient are the physician and the psychiatrist specialized in this field. This is in favor of the findings of Beyraghi *et al.*<sup>19</sup> that all of the physicians, most of the nurses, and all of the patients believed that the physician was the best person to tell the truth. It is also consistent with Zamani *et al.*,<sup>14</sup> which showed that the best person to tell the cancer diagnosis was the physician. The best place to do so was the physician's office, in patients' opinion; and somewhere quiet and without disturbance, in physicians' opinion. Grassi showed that 95% of the physicians believed that the general physician should be included in the process of diagnosis and communication with the patient, and 48% stated that the physician should tell the truth to patients about the diagnosis.<sup>16</sup>

With respect to physicians' opinion on steps of informing patients about disease management, the results showed that the first priority was the treatment method (62.2%), the second priority was treatment complications with (39.3%), and the third and fourth ones were prognosis and diagnosis, respectively.

One of the solutions that can be helpful nowadays is having a guideline in that field of specialty. In our study, 92% felt the need for having a guideline on educating patients. This is consistent with the finding of Tieying *et al.*<sup>20</sup> (in large hospitals of China) that in order to improve the knowledge of the cancer patients, the specialists needed to be well-informed about how to inform patients and that having special methods and guidelines were necessary. Also, Grassi showed that 86% of physicians considered having an informative booklet necessary.<sup>16</sup>

All in all, only 25.5% of our physicians had the policy to tell the truth to majority of their patients. Overall, only 34% of our respondents were interested in changing their general attitude towards truth-telling. According to our findings, non-oncologists were significantly more willing to tell the truth compared with oncologists, and we found no significant differences between other groups evaluated. Finally, almost all our physicians felt the need for having a formal guideline regarding informing and educating cancer patients.

In conclusion, truth-telling is an essential issue for the physicians involved with cancer patients. The majority of physicians would tell the truth to their patients, and they like to change their general attitude. Physicians prefer to tell the truth to younger patients, and the treatment method is the most important issue they would like to talk about with patients. Our study showed that 92% of physicians felt the need for having a guideline on educating patients. This highlights the significance of cultural-religious context of our country and the importance of having a practical guideline to educate our physicians.

#### References

- McNeill PM, Walters JD, Webster IW. Ethical issues in Australian hospitals. Med J Aust. 1994;160(2):63-5.
- 2. Tomlinson T, Brody H. Ethics and communication in do-not-resuscitate orders. N

Engl J Med. 1988;318(1):43-6.

- 3. Jones T, FitzGerald M. Withdrawal of lifesupport treatment: the experience of critical care nurses. Aust Crit Care. 1998;11(4):117-21.
- 4. Taylor EJ, Ferrell BR, Grant M, Cheyney L. Managing cancer pain at home: the decisions and ethical conflicts of patients, family caregivers, and homecare nurses. Oncol Nurs Forum. 1993;20(6):919-27.
- 5. Tuckett A. Bending the truth: professionals narratives about lying and deception in nursing practice. International journal of nursing studies. 1998;35(5):292-302.
- 6. Drickamer MA, Lachs MS. Should patients with Alzheimer's disease be told their diagnosis? N Engl J Med. 1992;326(14):947-51.
- 7. Kelly WD, Friesen SR. Do cancer patients want to be told?. Surgery. 1950 Jun 1;27(6):822-6.
- Aitken-Swan J, Easson EC. Reactions of cancer patients on being told their diagnosis. BMJ. 1959 Mar 21;1(5124):779.
- Fitts WT, Ravdin IS. What Philadelphia physicians tell patients with cancer. Journal of the American Medical Association. 1953;153(10):901-4
- SurboneA, Zwitter M. Learning from the world. The editors' perspective. Ann N Y Acad Sci. 1997;809:1-6.
- 11. LevyL. Communication with the cancer patient in Zimbabwe. Annals of the New York Academy of Sciences. 1997;809(1):133-41.
- 12. Field HL. Communication With the Cancer Patient: Information and Truth. Psychosomatics. 2001;42(6):534.
- 13. Ajzen I, Fishbein M. Understanding attitudes and predicting social behaviour. 1980.
- 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):1-9.
- 15.Blazekovic-Milakovic S, Matijasevic I, Stojanovic-Spehar S, Supe S. Family physicians' views on disclosure of a diagnosis of cancer and care of terminally ill patients in Croatia. Psychiatr Danub. 2006;18(1-2):19-29.
- Grassi L, Giraldi T, Messina EG, Magnani K, Valle E, Cartei G. Physicians' attitudes to and problems with truth-telling to cancer patients. Support Care Cancer. 2000;8(1):40-5.
- 17. Seo M, Tamura K, Shijo H, Morioka E, Ikegame C, Hirasako K. Telling the diagnosis to cancer patients in Japan: attitude and perception of patients, physicians and nurses. Palliat Med. 2000;14(2):105-10.
- 18. Fielding R, Wong L, Ko L. Strategies of information disclosure to Chinese cancer patients in an Asian community. Psychooncology. 1998;7(3):240-51.
- 19. 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):130-4.

- 20. Tieying Z, Haishan H, Meizhen Z, Yan L, Pengqian F. Health professionals' attitude towards information disclosure to cancer patients in China. Nursing ethics. 2011;18(3):356-63.
- 21. Elwyn TS, Fetters MD, Gorenflo DW, Tsuda T. Cancer disclosure in Japan: historical comparisons, current practices. Social science & medicine. 1998;46(9):1151-63.
- 22. Vahdaninia M, Montazeri A. True-telling to cancer patient: a cross-sectional study. Payesh. 2003;1(5):259-68.





### DOI: 10.19187/abc.201743104-107 Balance Between Confidentiality and Duty to Warn: A Case Commentary on Breast Cancer

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#### **Case Presentation**

A 22-year-old woman was referred to the breast clinic with the complaint of palpation of a large mass in her right breast. In the medical investigations, the diagnosis of breast cancer was made based on the core needle biopsy. The standard treatment plan, lumpectomy and chemotherapy, was offered. She was informed of the diagnosis, but she insisted that the diagnosis remain confidential and nothing be told to her fiancé, who planned to be her husband in the near future. In response, the surgeon explained that, in her treatment, the side effects of the procedures could not be concealed and recommended that it would be better share the information with her fiancé, but she to refused. This case raised the question whether, in this case, confidentiality is absolute or priority should be given to duty to warn?

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#### ABSTRACT

**Background:** Most people consider health information to be highly personal, therefore confidentiality is the main issue in physician-patient relationship. However, there are some situations that the physician may feel that another person's health or well-being is in danger and there may be a duty to warn him. Making balance between these two professional obligations is not easy in all cases.

**Case Presentation:** This case commentary is discussing about the issue of confidentiality in cancer patients, especially when the medical situation of the patient and the treatment plan could not be concealed from others. By reviewing the physician's duty of confidentiality, its importance and exceptions, the pros and cons of the issue are discussed in this paper. Controversial aspects such as the duty to warn the third party and the value of mutual arguments are also discussed.

**Conclusions:** In cases such as breast cancer, when a patient is competent and wishing not to tell any information to her family, it is the physician's obligation to acknowledge patient's preferences. However, by shaping a good therapeutic relationship and conducting effective counseling the physician may persuade patient to share her health problem by relatives.

#### Introduction

"Whatever I see or hear, professionally or privately, which ought not to be divulged, I will keep it secret and tell no one."<sup>1</sup>

#### Confidentiality and its importance in medicine

The above-mentioned statement is one of the pledges in Hippocratic Oath, which exists in almost all different versions of medical profession's code of conduct all over the world. Respect for confidentiality is a solid tradition in medicine. However, what is confidentiality in medicine? Generally, if a person gives some information to another in a confidence relationship, it is the person's obligation, the receiver of information, not to disclose it. This obligation can be expressed explicitly or may be implicit based on the nature of relationship.

The term confidentiality should be distinguished from privacy. Patient's interest to control their information, access to their bodies, and freedom to make decisions about health care refer to privacy concerns.<sup>2, 3</sup> Based on privacy concerns, patients may choose some information to disclose to their physicians or may consider some to be too intimate or sensitive to disclose. On the other hand, confidentiality refers to further disclosure of patient's information. For example, a patient may decide some of her information should not be disclosed to her family, insurance company, or public health officials; therefore, the confidentiality is about what the physician may tell the third party, rather than what the patient prefers and chooses to tell the physician. When patients reveal their sensitive personal information to physicians, the presumption is that the physician should and would keep this information confidential, unless the patient consents to disclose them; thus, the duty of confidentiality provides the foundation for trust in the therapeutic relationship.<sup>4</sup>

Why is confidentiality important in medical interactions? There are some ethical foundations for confidentiality obligation in health care. First of all, keeping the medical information confidential shows respect for patients,<sup>5</sup> who expect the physicians to maintain confidentiality; this means that maintaining confidentiality in a therapeutic relationship is the clinician's duty to respect patient's autonomy. Likewise, it has some beneficial impacts for patients and physician-patient relationship. Keeping the patient's information confidential encourages people to seek medical care and disclose sensitive information, voluntarily. Furthermore, keeping confidentiality prevents patients from harmful consequences, such as discrimination and stigmatization.<sup>6</sup> Another moral justification for the importance of confidentiality in physician-patient relationship is based on the nature of the clinical encounter and duties, which are presupposed for this kind of relationship.<sup>7</sup>

Although confidentiality is an important part of the ethical code of conduct for health care providers, there are some concerns about its absoluteness. In this regard, there are counter-arguments, supporting breaching confidentiality in some situations. While the ethical principle of respecting autonomy supports the rule of confidentiality, the nonmaleficence principle requires both patients and physicians to avoid harming other people and to prevent harming others. In this regard, even the principle of autonomy is not absolute, and personal autonomy may, legitimately, be constrained when the exercise of such freedom puts others at risk of harm;<sup>8</sup> in medical information confidentiality context, this means that a patient's right for not sharing her information may be overridden by an obligation in order not to harm others. Some epidemic situations, such as HIV and controversies on genetic information have shaped debates over the issue and proposed the duty to warn for keeping other people's health and life safe. Duty to warn was a fundamental issue addressed by California Supreme Court in the case of *Tarasoff* in 1976.<sup>9</sup> Although,

it was the first time that this duty was mentioned and considered in many other legislations but since then, many therapists have argued that this requirement goes too far.<sup>10</sup>

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Hence, in order to provide important benefits to patients or to prevent serious harm to third parties, overriding confidentiality might be justified. These exceptions require careful justification, because not every beneficial outcome warrant the disclosure omedical information without the patient's permission.

#### Reasons justifying exemption from confidentiality

Reasons justifying exemption from confidentiality could be categorized as: protecting third parties, including reporting to public officials, in case of infectious disease or injuries caused by weapons, crimes, or violence by psychiatric patients. Protecting patients; for instance in case of child or elderly abuse. Partner notification by public health officials and warning by physicians to person at risk could be some other concerns in this regard.<sup>11</sup>

The balance between preventing harm to third parties and protecting patient's confidentiality needs considering some conditions. In general, all following conditions should be met, while breaching confidentiality is attempted: a) the potential harm to identifiable third party should be serious, b) the harm should be highly probable, c) there should be no less invasive and alternative way for warning or protecting the person at risk, d) breaching confidentiality could allow the third person to protect himself or take steps to prevent harm, and e) the harm of breaching confidentiality for the patient should be minimized and acceptable. In these circumstances, the general judgment is that the overall harm to another person is greater than the harm to patient resulting from overriding confidentiality."

However, there are concerns about situations, in which the harm of the patient's disease for another person is not definite or the probable worry is emotional or in situations, such as the abovementioned case, in which the patient's disease may affect her and her partner life.

Furthermore, while disclosing the patient's information to family members, there may be some ethical issues. Relatives and friends often ask about the patient's health condition, such as the diagnosis, therapeutic plan, or the severity of the medical condition and its outcome. Generally, patients want their relatives to be involved in their disease process; they also ask the physician to talk to their family and, in some societies, physicians may do it even without the patient's permission. In some cases, however, the patient may reject this and refuse the information to be shared with others. In this regard, some countries have different regulations. For example, based on the Health Insurance Portability and Accountability Act (HIPAA), the United States federal government issued health privacy regulations. The HIPAA privacy regulations in injuries, such as car accident, mention that the health care providers should notify the patients that their relative would better be informed, unless the patient refuses the request;<sup>12</sup> it means that the physician can presume that the patients would desire their family members to be notified, unless advised otherwise.

In addition to the general desire of patients to inform their families, there are some ethically justified reasons in this regard; the relatives may provide valuable information about the patient previous health condition, they may know the patient's best interest, and they may assist the patient in decision making or treatment planning.

However, these presumptions can be different case by case. If the patient is oriented and the physician knows about the patients' preferences and the patient requests not to disclose the information, the physician should regard the patient's family members as estranged and not give them the information of the patient, even if the physician believes that such communication may be required to help better monitoring of the patient's condition or arrange follow-up care.

#### **Commentary on the case**

With respect to confidentiality, the abovementioned case illustrated some moral issues. The physician knew that the patient's condition, breast cancer, would not allow her to conceal the issue from her fiancé. Moreover, due to the nature of the disease, therapeutic plan, and its prospect outcome, she would need emotional support in her life and fiancé can help her to overcome the situation. Therefore, the principle of beneficence could be the foundation of the physician's argument in sharing the information to the patient's fiancé. However, the principle of autonomy and respecting the patient's desire in not disclosing the information will oblige the physician to keep confidentiality as his duty to the patient as well as the professional code of conduct.

Yet, it is evident that the patient's fiancé will encounter some emotional suffering and financial cost. The patient's condition may influence her future life, and the situation may lead them to end their emotional relationship. The question would be: is there any "duty to warn" for the physician to divulge the situation to the patient's fiancé? Looking back at the conditional criteria for breaching confidentiality, it seems that none of the criteria is at hand in this case. Neither there is serious health harm for the patient's fiancé nor does breaching confidentiality have a health benefit for him. Therefore, the duty to warn could not be a justifying argument for disclosing patient's information. Furthermore, the patient was competent and orientated and sharing her information against her desire would disrespect her autonomy.

However, the physician should advise her patient that her spouse need to be aware of her condition. It is important to explain the reasons why it is better to share information in this situation, as she may require ongoing treatment and need emotional support. Spending time discussing the physician's concerns about disclosing and offering support to deal with these concerns may bring about a change of mind on the patient's part. The physician should counsel the patient, regarding the importance of trust and veracity in an intimate relationship like marriage. In jurisdictions, where not telling such issues to spouse may be envisioned as deceiving, further persuasion may be needed for the patient to consent to share the information.

However, the clinicians should be aware of the local, legal, and professional standards, concerning how they should act in such situations, and appropriate psychological support should be provided for both parties.

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#### **Conflict of Interest**

No conflict of Interest.

#### References

- 1. Baker RB, McCullough LB. The Cambridge World History of Medical Ethics. 1993.
- 2. Stanford encyclopedia of philosophy: Privacy and Medicine. 2009. [Available from: http://plato.stanford.edu/entries/privacymedicine/.]
- 3. Afshar L. Privacy in Health Care Provider and Patients Relationship, in Applied Ethics in Iran and Islam. Iranian Social and Cultural Studies. 2009.
- 4. Razzaghi MR, Afshar L. A conceptual model of physician-patient relationships: a qualitative study. Journal of medical ethics and history of medicine. 2016;9(1):
- 5. Beauchamp TL, Childress JF. Principles of Biomedical Ethics. 6th ed. New York: oxford University Press; 2009.
- 6. Singer PA, Viens AM. The Cambridge textbook of bioethics: Cambridge University Press; 2008.
- 7. Pellegrino ED. Humanism and the Physician. 1979.
- 8. Mill JS. Utilitarianism, On Liberty, Essay on Bentham edited by Mary Warnock. Great Britain: William Collins. 1962.
- Tarasoff V. Regents of University of California. California Supreme Court (17 California Reports, 3rd series, 425, Decided July, 1, 1976). 1976.



- 10. Munson R. Intervention and reflection: basic issues in bioethics: Cengage Learning; 2013.
- 11. Lo B. Resolving ethical dilemmas: a guide for clinicians: Lippincott Williams & Wilkins; 2012.
- 12. Office for Civil Rights H. Standards for privacy of individually identifiable health information. Final rule. Federal Register. 2002;67(157): 53181.





### DOI: 10.19187/abc.201744108-109 Automated Breast Ultrasonography as a Supplementary Screening Method in High Risk Populations

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Mammography has been the main modality of breast cancer screening programs for many years and is still the only proved diagnostic method to decrease breast cancer related deaths.<sup>1</sup> However in some specific subpopulations like women with dense breasts, mammography could give the false negative result, in about 50% of cancerous cases.<sup>2</sup> About 43% of American women aged between 40-75 years and nearly half of younger women have heterogeneously or extremely dense breasts tissue<sup>3,4,</sup> which can highly decrease the accuracy of mammography.<sup>5, 6</sup> Moreover dense breast is an independent risk factor for developing cancer.<sup>7,8</sup>

Recent studies have suggested using new supplementary methods.<sup>9</sup> There are some techniques to improve radiologic detection of breast cancer in women with dense and heterogeneous breasts such as 3-Dimensional digital breast tomosynthesis (DBT), ultrasonography (US), contrast enhanced breast imaging and magnetic resonance imaging (MRI).<sup>9,10</sup>

Most studies have agreed that adding US as an excellent supplementary method could significantly improve detection of mammographically subtle breast cancers.<sup>10</sup> In fact, supplementary US helps to detect additional 6.8 cancer cases per 1000 screening exams in asymptomatic women<sup>6</sup> and about 4.2 per 1000 cases among women with elevated risk and/or dense breast tissue.<sup>11</sup> The latter incremental rate equals 55% improvement in cancer screening efficacy.<sup>3, 10</sup> The other remarkable point is that the majority of occult tumors identified by supplementary

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Address: Honor Health Breast and Research Center 19646 N 27th Ave Suite 205, Phoenix, AZ 85027 Tel: +1 623 434 2777 Email: Hedieh.Saghari@honorhealth.com US were proved to be less than 1cm in size, more likely to be invasive (83-100%) and node negative (89-97%).<sup>12</sup>

There are two different available ultrasonography methods, conventional hand-held US (HHUS) and automated breast US (ABUS); ABUS can be done with a linear-array transducer which covers the entire breast and automates the ultrasound scanning process. It serves as a standardization technique and decreases the problems of operator dependency and variations. This screening technique improves not only the detection of breast cancer but also the efficiency of workflow.<sup>3, 10</sup> Additionally it allows the transverse images to be reconstructed into 3D images and be interpreted in coronal planes, which has been proved to improve readers' cancer detection.3, 13 ABUS is approved by Food and Drug Administration (FDA) in 2012 for screening use in women who have dense breast tissue and negative mammography result.<sup>3</sup>

Although ABUS has many other advantages over HHUS like it requires less time to perform (approximately 10 minutes versus 20 minutes) and it is more reproducible. However, according to a study by Shin et al, in cases of suspicious findings, HHUS would be often necessary to confirm the lesion detected by ABUS as well as ultrasound-guided biopsy.<sup>3</sup> A comprehensive systematic review in 2016 discussing the evidence on comparison of these two methods, showed that despite the excellent negative predictive value (NPV=98%) of both techniques, they have more false positive results and consequently lower positive predictive value (PPV) than mammography alone (3.2-7.5% for HHUS and 4.1% for ABUS).<sup>3, 14</sup> Researchers found a sensitivity of 80-83% and specificity of 86-94% for HHUS and sensitivity and specificity of 67-85% and 74-91% for ABUS, respectively.14,15

In another recent study, radiologists' performance in breast cancer detection were compared using mammography alone and mammography combined with ABUS. The area under ROC curve (AUC) was 0.72 for mammography and 0.82 for combination method; it means that ABUS yielded 14% relative increment. Overall specificity was 78.1% for mammography alone and 76.1% for combination method.<sup>16</sup>

In conclusion, we suggest combining mammography with ABUS, compared with mammography alone, provides significantly higher accuracy in detection of breast cancer especially in women with dense breasts. Also, this combination can be more helpful to distinguish benign from the malignant breast lesions. Although ABUS could be greatly helpful as the supplementary tool in the screening program of high-risk populations, further evaluation is needed to clarify whether these groups of population have a significantly better outcome or not. Moreover, making the decision between HHUS and ABUS with mammography as a screening method in high-risk patients with dense breast is still questionable.

#### **Conflict of Interest**

Authors declare no conflict of interests.

#### References

- 1. Myers ER, Moorman P, Gierisch JM, Havrilesky LJ, Grimm LJ, Ghate S, *et al.* Benefits and Harms of Breast Cancer Screening: A Systematic Review. JAMA. 2015;314(15): 1615-34.
- 2. Mandelson MT, Oestreicher N, Porter PL, White D, Finder CA, Taplin SH, *et al.* Breast density as a predictor of mammographic detection: comparison of interval- and screen-detected cancers. J Natl Cancer Inst. 2000;92(13):1081-7.
- 3. Shin HJ, Kim HH, Cha JH. Current status of automated breast ultrasonography. Ultrasonography. 2015;34(3):165-72.
- 4. Sprague BL, Gangnon RE, Burt V, Trentham-Dietz A, Hampton JM, Wellman RD, *et al.* Prevalence of mammographically dense breasts in the United States. J Natl Cancer Inst. 2014;106(10).
- 5. Kolb TM, Lichy J, Newhouse JH. Comparison of the performance of screening mammography, physical examination, and breast US and evaluation of factors that influence them: an analysis of 27,825 patient evaluations. Radiology. 2002;225(1):165-75.
- 6. Moon HJ, Kim EK. Characteristics of breast cancer detected by supplementary screening ultrasonography. Ultrasonography. 2015;34(3): 153-6.
- Boyd NF, Guo H, Martin LJ, Sun L, Stone J, Fishell E, *et al.* Mammographic density and the risk and detection of breast cancer. N Engl J Med. 2007;356(3):227-36.
- 8. Harvey JA, Bovbjerg VE. Quantitative assessment of mammographic breast density:

relationship with breast cancer risk. Radiology. 2004;230(1):29-41.

- Kim MJ. Medical auditing of whole-breast screening ultrasonography. Ultrasonography. 2017;36(3):198-203.
- Faguy K. Breast Sonography and Mammography: Complementarity and Correlation. Radiol Technol. 2017;89(1):45M-64M.
- 11. Berg WA, Blume JD, Cormack JB, Mendelson EB, Lehrer D, Bohm-Velez M, *et al.* Combined screening with ultrasound and mammography vs mammography alone in women at elevated risk of breast cancer. JAMA. 2008;299(18):2151-63.
- 12. Kim SY, Kim MJ, Moon HJ, Yoon JH, Kim EK. Application of the downgrade criteria to supplemental screening ultrasound for women with negative mammography but dense breasts. Medicine (Baltimore). 2016;95(44):e5279.
- 13. Hooley RJ, Scoutt LM, Philpotts LE. Breast ultrasonography: state of the art. Radiology. 2013;268(3):642-59.
- 14. Golatta M, Baggs C, Schweitzer-Martin M, Domschke C, Schott S, Harcos A, *et al.* Evaluation of an automated breast 3Dultrasound system by comparing it with handheld ultrasound (HHUS) and mammography. Arch Gynecol Obstet. 2015;291(4):889-95.
- 15. Melnikow J, Fenton JJ, Whitlock EP, Miglioretti DL, Weyrich MS, Thompson JH, et al. Supplemental Screening for Breast Cancer in Women With Dense Breasts: A Systematic Review for the U.S. Preventive Services Task Force. Ann Intern Med. 2016;164(4):268-78.
- 16. Giger ML, Inciardi MF, Edwards A, Papaioannou J, Drukker K, Jiang Y, *et al.* Automated Breast Ultrasound in Breast Cancer Screening of Women With Dense Breasts: Reader Study of Mammography-Negative and Mammography-Positive Cancers. AJR Am J Roentgenol. 2016;206(6):1341-50.



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## Breast Cancer Prognostication by Pathologic Node Staging (pN-staging) System Versus Lymph Node Ratio (LNR): A Critical Review of Conflicts With Number of Nodes, Z-0011 Trial, Staging Cut-points, Neo-adjuvant Therapy, and Survival Estimation

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Key words: Breast cancer, prognostication, pathologic node staging, lymph node ratio, Z-0011 trial, neo-adjuvant chemotherapy ABSTRACT

**Background:** The AJCC pN-staging system is the current risk stratification strategy for axillary nodal staging in most cancer centers. Recently, another staging system named "Lymph Node Ratio" or LNR has been developed and also postulated to have prognostic value. Precise prognostication of breast cancer by these two systems has multiple methodological dilemmas which are overlooked in the literature and still remain matters of debate.

**Methods:** These two issues are categorized into seven queries, including: the number of nodes considered adequate for proper axillary staging; attitude toward Z-0011 trial; impacts of neo-adjuvant therapies; the origin and evolution of stratification cutoffs; the position where patients without axillary involvement should be placed; role of diverse endpoints in survival definition, outcome analyses and prognosis prediction; and ultimately the current opinion regarding the superiority of the 2 systems. This review sought to explore these topics through analysis of 58 recently published articles found by MEDLINE search.

**Results:** The analysis revealed that precise prognostication by pN-staging system requires at least 10 excised-nodes, but LNR system minimally depends on the quantity of excised-nodes. Adhering to Z-0011 trial findings obstructs the provision of sufficient nodes for pN-staging. Neo-adjuvant chemotherapy alters the axillary nodal climate and therefore disrupts proper axillary staging. Cutoffs of LNR system have a more clear history of formation than the pN-staging's. Breast cancer-specific survival is the type of survival better portraying cancer-related events.

**Conclusions:** LNR system seems at least as accurate as pN-staging in prognostication of breast cancer patients.

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#### Introduction

In a heterogeneous patient population and distinctive subtypes of breast cancer (BC), "staging" is assumed to detect cancer spread and assign optimal therapy, while "prognostication" has to determine the exact course of the disease, estimate treatment success, and predict patients' survival. In

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fact, staging is the classification of patients into categories based on the extent and severity of the disease at presentation and explains how the patients are at diagnosis, whereas prognostication is the outcome estimation based on the pre-experienced analysis of stage outcomes and explains how the patients will end up. As a standard global approach to cancer classification, the TNM-staging system was developed in 1987 by merging 2 former staging systems from the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). Today, this is known as the "AJCC cancer staging system", and the 8<sup>th</sup> edition has recently been published.<sup>1</sup> The TNM-staging

system comprises 3 elements: the T-stage represents the primary tumor size and level of invasion, the Nstage defines the level of lymph node (LN) involvement, and the M-stage describes the extent of metastases.

In BC prognostication, patients with advanced Tstages or positive metastases at presentation are considered to have an already poor prognosis; the Nstage in such patients does not provide much prognostic information. The majority of BC-patients are currently diagnosed at early stages thanks to refined screening and diagnostic modalities by modern medicine, and that is when the tumor has not yet invaded to surrounding structures or distantly

Table 1.	Ineligible	patients for	or node-based	prognostication
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Category of ineligibility	Details
Advanced disease	patients with distant metastases <sup>9, 19, 25, 27, 30, 33, 40, 41, 51, 59, 66, 78</sup> tumor sizes more than 5cm <sup>23</sup> T3-T4/clinical N2-N3 (metastases in ipsilateral internal mammary or supra-clavicular LNs) <sup>27</sup> bilateral BC <sup>24, 41, 58</sup> with secondary malignancy (except for non-melanoma skin cancer or in situ cervical cancer) <sup>10, 27, 40</sup> inflammatory breast disease <sup>21, 24, 60, 79</sup> those surviving less than one month <sup>23</sup>
Very early-stage	in-situ BC 9, 23, 30, 33, 59, 66
Residual disease	involved surgical margins <sup>27</sup> recurrence of breast cancer <sup>60</sup> incomplete adjuvant therapy <sup>27</sup> undergoing palliative therapy <sup>25</sup>
Neo-adjuvant therapy (controversial, see the discussions)	patients undergoing neo-adjuvant chemotherapy <sup>2, 3, 6, 10, 19, 24, 25, 27, 28, 30, 33, 40, 58-60</sup>
Missing data on axillary status	no evidence of LN metastasis <sup>2, 5, 23, 27, 33, 40, 41, 51, 66</sup> nodal involvement not confirmed by pathologic examinations <sup>5, 9, 27, 33, 59</sup> those undergoing sentinel LN biopsy (SLNB) alone (unclear status of non-sentinel nodes) <sup>2, 6</sup> LNs excised less than the adequate <sup>5, 19, 30, 58</sup> (see the discussions)
Miscellaneous	Male breast cancer <sup>24,60</sup>

metastasized.

The dominant TNM-scheme in those with less advanced disease looks like " $T_{1,2} N_{any} M_{0,x}$ ", in which the T- and M-stages do not necessarily deliver much useful prognostic information. Consequently, with the current progressed diagnostic conditions, the only evidence remaining is the N-stage to convey the severity of the disease, characterize the tumor behavior, and determine its potential for further and future progression. The capability of the N-stage in prognostication has frequently been addressed in recent literature and now, it makes the cornerstone of prognostication for early stage BCs without metastasis. Conversely, some patient populations having breast cancer are not good candidates for node-based prognostication. These cases are outlined in table 1.

The pathologic N-stage by the AJCC system (to

wit the pN-stage) is based on the absolute number of involved axillary LNs dissected. If none of the excised nodes are involved by the cancer, the stage is pN0, if 1 to 3 nodes are involved the stage is pN1, 4 to 9 is pN2, and  $\geq 10$  is pN3. A more advanced stage in this system indicates a more advanced disease, and thus, a worse prognosis might be expected. But recently, the prognostic value of pNstaging system has been put into question by a novel system named "Lymph Node Ratio" (LNR). The advent of LNR has added a new entry in the oncologic lexicon as it has been widely postulated to have prognostic value for many types of cancers.<sup>2-4</sup> LNR, rather than depending on the absolute number of involved nodes, is in the form of a mathematical fraction, showing the decimal proportion of axillary nodal involvement. In this fraction, the absolute number of involved nodes is the numerator,



and the total number of dissected nodes is the denominator. It can be envisioned that the LNR concept arose in response to the need for adaptation to the unintentional variability of excised LNs for cancer staging, as it regards the excised LNs and their rate of involvement as a sample from the axilla, representing the whole axillary nodal climate. The most common classification scheme by the LNR system places the patients into 3 categories. The grouping is based on 2 cut-points in the LNR quantity, which are 0.20 and 0.65. Accordingly, the patients having 0<LNR $\leq$ 0.20 are categorized to be of low-risk, those with 0.20<LNR $\leq$ 0.65 as intermediate-risk, and those with LNR>0.65 as high-risk.<sup>5</sup>

Both the AJCC and LNR conceptual frameworks have established capacities for prognostication. The hierarchical approach to node-based staging and prognostication virtually comprise 3 steps: the axillary surgery and nodal excision, the staging strategies based on the number of nodes retrieved, and the prognostication process. Multiple dilemmas are encountered while utilizing the 2 systems, which require careful attention since these areas, may effectively alter the precision of prognostication. In the first step (i.e. axillary workup), the most challenging issue is the number of LNs needed for an appropriate staging of the axilla; this refers to the extent of axillary dissection. But, before the nodal excision, there is the neo-adjuvant chemotherapy having the potential to change both the total number and positivity of axillary LNs; this also might invoke staging conflicts. Meanwhile, the findings of Z-0011 trial obligate to minimize axillary manipulations to merely excision of the sentinels; by adhering to these findings, no axillary staging is practically permitted. In the second step, there is the diversity of systems' strategies in patient stratification into risk categories that makes comparatively heterogeneous groups; a system providing a more holistic approach towards the inclusion of various subsets of patients logically would be favored in comparison. The third step is the prognostication process, which is an outcome estimation based on pre-experienced analyses. For survival analyses, we have various start- and endpoints (events), defining different types of survival; each of these points in time describe the disease outcomes in their point of view that are not necessarily the same. Added to many other questions, these topics concern with how these a systems measure the stage and prognosis, and if they do the same task, why their outcomes of analysis sometimes widely conflict? There is a necessity for discussion on the strengths and weaknesses of the 2 systems and the obstacles in the precision of their prognostication, which may determine the superior system. We have tried to address these topics in this narrative review (Figure 1).

#### Methods

#### Search strategy and selection criteria

Multiple procedural approaches, methodological metrics, and therapeutic modalities may impact precise prognostications based on axillary nodal staging, and these are often overlooked in the literature. We had 7 queries in mind, knowing the answers of which could elucidate unknown aspects of node-based prognostications and provide greater accuracy in predicting patients' survival. The queries were:

1. The number of excised-LNs considered adequate for appropriate axillary staging;

2. Attitude against Z-0011 trial findings regarding the extent of axillary dissection;

3. Complexities in staging made by neoadjuvant chemotherapy;

4. The origin and evolution of stratification cutoffs by the 2 systems;

5. The LNR risk group corresponding to pN0 in pN-staging system;

6. Start- and end-points best evaluating patients with breast cancer survival;

7. And finally, benefits, limitations, and comparative value of both staging systems in prognostication.

To address these issues, we searched MEDLINE for English-language sources, using the following keywords: breast cancer, lymph node ratio or LNR, pN-staging, pathological node staging, overall survival or OS, disease-free survival or DFS, survival, and prognosis. To get the most recent data, sources published in 2000 or later (until early March 2017) were selected. Among the retrieved articles, we searched bibliographies for relevant papers, evaluating either of the 2 systems individually or comparing the 2 staging systems in the areas of interest of the queries. We had a finally 58 papers that met our criteria for covering the 7 issues described above. Opinions expressed under each topic may also reflect our personal viewpoints.

#### **Results and Discussion**

*How many LNs should be excised for accurate staging of the axilla?* 

Both the LNR and pN-staging systems inherently depend on the quantity of excised axillary LNs, and therefore, some degrees of axillary LN dissection (ALND) are required. The question raised here is that how extensive the ALND must be performed and how many LNs should it minimally provide for a proper axillary staging? The literature, unfortunately, fails to define a precise minimum level or adequacy goal for nodal excision that suffices the staging requirements, while there are a variety of recommendations for this, such as 3, 4, 6, 11, 12, 13, 14, 15, and 16.<sup>3,5-19</sup> Even full clearance of the axilla has been suggested.<sup>8,20</sup> With these, it is quite apparent that there is no consensus about the target

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**Figure 1.** Hierarchical steps of node-based staging and prognostication and areas where dilemmas appear: this process has 3 steps, including axillary surgery, node-based staging, and prognostication. In step 1, with or without NAC, patients undergo axillary sampling; but, in those undergoing NAC, the number and positivity of axillary nodes might be altered. In patients indicated for SLNB, no further axillary workup would be performed if the results are negative, but if positive, ALND is the standard approach, while findings of Z-0011 trial prohibits ALND and subsequently the staging (for those having up to 2 positive sentinels). In those undergoing ALND (directly or after SLNB), the extent of dissection is a matter of query. Step 2 is based on the pathologic results of axillary sample; the dilemmas of categorization schemes by the 2 systems are reflected here. Step 3 describes how different end-points make different survival results.

SLNB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection; LNR: Lymph Node Ratio; pN-stage: Pathologic Node Stage.

number of nodes needed to be excised for axillary staging.

Prior to discussing the adequacy level for ALND, a distinction must be made between the "total number of nodes excised" and the "number of involved nodes excised"; because the first one is the crude product of ALND and contains a mixture of involved and uninvolved LNs, while the second is the basis for pN-staging system with thresholds described in the introduction. For a proper pNstaging, the minimal extent of ALND must logically provide as much LNs that fulfill the requirements of the highest pN-stage. Consider this example: a patient with 9 examined nodes that all are involved by the cancer (the whole specimen contents) would be staged as pN2, while we have no clue about the involvement of the 10<sup>th</sup> node if it was excised. If the 10<sup>th</sup> excised node was involved, the patient would be staged as pN3, and with 9 of 9 involvement rate, the probability of 10<sup>th</sup> node involvement seems quite high. The uncertainty about the 10<sup>th</sup> node may raise the doubt that we might have understaged the axilla (pN2 vs. pN3). As a matter of fact, to report the highest pN-stage for a patient (i.e., pN3), the examined axillary specimen must include at least 10 involved nodes, meaning that the total number of nodes excised should exceed the quantity of 10. The minimum of 10 is the minimum logical quantity for excision and pathologic examination so that if all were involved, the patient, then, would be staged as pN3. This fact also applies to the lower pN-stages as you may never stage a patient as pN2 unless you have excised  $\geq 4$  nodes. On the other hand, as a more extensive ALND significantly increases the chance to find more involved nodes<sup>3, 21, 22</sup> and we have no maximum level defined for the extent of ALND, the ALND may theoretically be continued until 10 involved nodes are found, since any number beyond 10 will still be regarded as pN3. However, this idea is not approved by many surgeons due to possible morbidities. The minimum of 10 is the threshold approved by many studies.<sup>3,6,7,11,15,23-35</sup> The NSABP B-04 study acknowledges that this minimum increases the reliability of reported axillary LN status;<sup>11, 36, 37</sup> also, the precision of prognostication has been found by Axelsson et al. to significantly improve when at least 10 axillary LNs are dissected.<sup>38</sup>

Irrespective of the goal to excise a specific number of nodes, it is not always feasible for the surgeons to resect the precise number of nodes, as the nodes might be non-palpable or indistinguishable from the surrounding adipose tissue. What a surgeon does through ALND is the excision of axillary fatpad, while the exact number of nodes is later revealed by the pathologic examination of the specimen. Variables influencing the final number of examined nodes include the extent of ALND, the method of analysis used by the pathologist, and the actual physiologic number of nodes individually existing from the patient.<sup>39, 40</sup> These conditions practically diminish the surgeons' capacity to predetermine the number of nodes needed to be excised. On the other hand, surgeons' clinical concept and personal intent also may contrast regarding the extent of ALND; as some have doubts and fears about adverse aftermaths following an extensive ALND like lymphedema and injuries to local neurovasculature<sup>7,8</sup> or do not believe that an extensive ALND might improve patients' survival.<sup>2</sup> Conversely, some others deem an extensive ALND not only clears involved LNs, but also removes potential routes of metastasis by the excision of uninvolved LNs, and thereby may improve survival.<sup>41</sup> Testifying to that, Krag et al. demonstrated that even when all regional LNs are pathologically negative, the number of nodes removed is associated with survival.<sup>42</sup> Vinh-hung et al. similarly reported that removal of uninvolved nodes increases the 5-year survival.<sup>43</sup>

Three issues worth emphasizing here about the pN-staging system: firstly, achieving a minimum of 10 nodes is not actually under the full control of the surgeon as s/he only resects the axillary fat-pad. Secondly, after 10 involved nodes are identified, any number of involved nodes beyond that is still regarded as stage pN3. And thirdly, the extent of ALND is associated with morbidities. These 3 issues may have had active roles in the conceptualization of the LNR system. The LNR as a fraction is not confined by the number of excised LNs as it works with proportions and still can be calculated with as few LNs provided through sentinel LN biopsy (SLNB).<sup>7,44-47</sup> The LNR system also makes difference between the patients with over 10 involved nodes based on the proportion made with the total number of excised LNs. Moreover, the less extensive ALND needed for LNR staging may lower the risk of morbidities. With these, the LNR system seems theoretically so versatile and capable to overcome these obstacles, and this makes it more clinically appealing than the pN-staging system.

## Attitude against the Z-0011 trial: the debate on the extent of axillary surgery

Adhering to the standards, surgeons often perform ALND if axillary involvement is revealed by SLNB.<sup>21</sup> In 2010, 2011, and newly in 2016, the American College of Surgeons Oncology Group (ACOSOG) published the results of Z-0011 trial, which has prospectively assessed the patients with sentinel node metastasis.<sup>48-50</sup> These patients were randomized to undergo ALND after SLNB vs. SLNB alone without specific axillary treatment, and then, they were evaluated for loco-regional recurrence. The results of this study surprisingly showed that after a median follow-up of 9.25 years, the 2 groups were not significantly different regarding loco-regional recurrence and prognosis.<sup>48</sup> Despite the confirmed repetition of the results through the

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follow-up reports, the idea seems to have multiple flaws that may conflict with the current staging systems:

1. Generalizability: as defined by the trial, eligible patients for exemption from ALND must be over 18 years, have clinical T1 T2 N0 disease (be clinically node-negative), and in whom the involvement of up to 2 sentinels is detected by hematoxylin and eosin staining (not by immunohistochemistry). A positive sentinel was regarded to LNs including any of the 3 pathologic forms of macro-metastasis (pN1, 2 or 3), micrometastasis ( $pN1_{(mi)}$ ), or isolated tumor cells ( $pN0_{(i+)}$ ), and no distinction was made between them since at the time that trial was initiated, the 5th edition of AJCC cancer staging manual was in effect which considered all the 3 forms as positive nodes.<sup>50</sup> They also must have undergone "whole" breast irradiation after "partial" mastectomy (breast conserving therapy) with adjuvant systemic chemotherapy by choice.<sup>11, 21, 35, 39</sup> These specifications point out that the Z-0011 trial cannot be extended to the patients undergoing mastectomy or lumpectomy without radiotherapy, those not receiving whole-breast tangential field radiotherapy or undergoing accelerated partial breast irradiation or taking third field (nodal) irradiation, those with more than 2 sentinel nodes involved, patients with multi-centric disease, patients receiving neo-adjuvant therapy, or having matted nodes, and those the involvement of sentinels is detected by immunohistochemistry.<sup>11,35,51</sup>

2. Prohibiting the axillary staging: by limiting the axillary workup to mere excision of the sentinels, no axillary staging is actually permitted by the Z-0011 trial. As mentioned before, the AJCC pN-staging requires at least 10 nodes to be excised for a proper axillary staging, but according to Z-0011 trial, whether or not the sentinel is involved, no further axillary dissection must be performed (note that if more than 2 sentinels were involved, the ALND must be performed). The omission of ALND obstructs the realistic prospection of the axillary disease burden. Even Z-0011 trial itself acknowledges that 27.3% of non-sentinel nodes in the ALND-group harbored metastases;<sup>21,50</sup> this is in a group of patients who have been clinically negative for axillary involvement, and as clear it is, the clinical presentation may widely differ from the factual dimensions of axillary involvement.

3. Loco-regional control: without clearing the axilla from cancer, the chance remains for the residual axillary disease to spread, while the findings of the Z-0011 trial do not necessitate loco-regional control. It should be noted that ALND not only provides prognostic information, but also optimizes regional control and remains a strongly recommended surgical procedure for clinically node-positive patients or for patients with bulky disease.<sup>3, 19</sup> As a rule, any study population is a sample, and as the trial

included macro-metastases too, the results of the Z-0011 trial on 891 cases may not be repeated by other studies (contrary to IBCSG 23-01study that only included micro-metastases as limited sentinel LN involvement-see below).

4. Limiting the LNR value: The information provided by the LNR can identify the subpopulations of patients requiring adjuvant radiotherapy or prognosticate the patients without altering the current treatment guidelines or undergoing extensive ALND.<sup>2, 11, 21, 35</sup> These are useful applications of LNR that we may lose if ALND is not performed. LNR calculation requires the quantification of both positive and total numbers of excised LNs, which is provided through ALND, and the ALND again is not permitted following Z-0011 trial findings. However, the LNR can be calculated, using few LNs provided by SLNB (sentinels LNR or SLNR), and this has been reported to independently predict the involvement of non-sentinels.<sup>7, 11</sup> But theoretically, the involvement probability of the sentinels is surely beyond the non-sentinels, which lifts the numerator of the SLNR fraction and does not necessarily indicate the factual balance of involved and uninvolved nodes. Having this in mind, the "up to 2 positive sentinels" among the unpredictable few numbers of dyed LNs may decline the precision of calculated SLNR.

The former rationale for axillary clearance was that it could eliminate micro-metastases and isolated tumor cells harbored in axillary LNs, and therefore, it could provide therapeutic benefits.<sup>2, 3, 52</sup> The Z-0011 trial itself contradicts the concept that ALND gives better loco-regional control or improves survival. Congruently, the recent International Breast Cancer Study Group (IBCSG) 23-01 study on patients with micro-metastases in sentinels showed no statistical difference in disease-free survival of patients, who underwent ALND versus those who did not.<sup>5</sup> Additionally, the data from NSABP B-04 trial also indicate that axillary dissection in the framework of radical surgery does not improve survival (however, it was not powered to detect differences of 5% or less).<sup>37</sup> By now, it can be regarded as evidential that survival and prognosis would not necessarily be altered by the excision of involved sentinels instead of extensive ALND, and therefore, we had better preserve the advantages of ALND for the many patients, who do not meet the Z-0011 trial application criteria.

#### *Challenging complexities of staging after neoadjuvant chemotherapy*

Added to the many therapeutic benefits of neoadjuvant chemotherapy (NAC), it has been mainly used to downsize large tumors for the ease of resection, and this has decreased the rate of mastectomies as breast conservation becomes feasible for more patients. <sup>32, 54</sup> NAC may influence staging in several areas:

1. Concerning the primary tumor (pT-stage), pathologic examination of patients receiving NAC has revealed multiple foci of scattered residual tumor cells interspersed with fibrotic cells. In these patients, a precise pT-staging necessitates the removal of larger margins or a wider local excision. <sup>55,56</sup>

2. The NAC has the potential to decline the "total number of axillary Lns," and the post-NAC ALND may provide fewer numbers of excised LNs. If this number declines to quantities fewer than 10, the axillary pN-staging might not be reliable.<sup>24,32,57</sup>

3. The administration of NAC also has the potential to change the axillary histological environment by decreasing the "number of involved nodes." The axilla subsequently might be understaged; a phenomenon referred to as "stage migration".<sup>2,3,6,10,19,24,25,27,28,30,33,40,58-60</sup>

4. Based on the new post-NAC stage, the adequacy of the treatments delivered to these patients is a matter of query.<sup>2,4,24,32,39,41,57,60,61</sup>

5. By fluctuating numbers of total and involved nodes, the LNR might hypothetically transit towards either of the two extremes, since it is not predictable to what degrees the numerator and the denominator of LNR may change, thus, the resultant LNR might not be that reliable.

No doubt that NAC may widely disrupt both the LNR and pN-staging systems, therefore, most of the authors prefer to stage the axilla prior to the commencement of any treatments, and consider the NAC an exclusion criterion for node-based staging.<sup>2</sup> 3,6,10,19,24,25,27,28,30,33,40,58-60 But, contrary to this, emerging trends strongly suggest that NAC can be administered prior to axillary workups. In support of this, Pilewskie et al. recently postulated that if 3 or more post-NAC sentinels are excised, the results of SLNB remain accurate, and thereby, nodal positivity is reliable.<sup>62</sup> Studies analyzing LNR value after NAC or comparing prognostic value of LNR vs. pNstaging systems in post-NAC patients are so few; some concluded that the LNR system takes precedence over the pN-staging system by its added adaptive staging compatibilities,<sup>32, 57, 63</sup> while Saxena et al. believe both LNR and pN-staging systems remain significant prognostic factors in post-NAC patients.<sup>3</sup>

#### Cutoff points: origins and evolution

In spite of its widespread acceptance, clues are so scarce regarding how pN-staging cutoffs have been developed. It seems that they were rather empirically discovered than being mathematically calculated. LNR with its growing interest, on the other hand, has an apparent history of formation. LNR, as a continuous variable, inherently lacks any categories within it; therefore, group stratification based on patients' LNR requires some thresholds to be defined in the quantity of LNR. While no clear consensus has yet been reached for the optimal LNR cutoffs,<sup>7,11,22,58</sup> many authors have categorized the patients based on a two-group strategy, using a single cutoff point. This cutoff has approximately been proposed to lie somewhere between 0.10 and 0.40 and, more precisely, found to be 0.20 or 0.25.<sup>7, 22, 26, 35, 58, 61, 64, 65</sup> Stratifications to more than 2 groups (normally 3 groups by 2 cutoffs) have more frequently been suggested, where the lower threshold in these studies is congruent with the cutoff defined by two-group classification scheme. The thresholds more commonly used here are 0.10 and  $0.30^{22}$ , 0.10 and  $0.50^{16,17,40,61}$ , 0.18 and  $0.64^{30}$ , 0.20 and  $0.60^{66}$ , 0.20 and  $0.65^{2,4,5,9,11,12,14,19,21,29,32,34,51,59,60,67,68}$ , 0.25 and  $0.50^{61}$ , 0.30 and 0.8040 and 0.40 and 0.80.25 Knowing the processes by which these cutoffs have been established, may help better comprehend the LNR stratification rationale. These cutoffs are based on:

1. The median LNR; the patients above and below the median were put into separate groups;<sup>15</sup> 2. Similarity of patient numbers in each group;<sup>17,</sup><sup>22</sup>

3. Equal percentile segmentation; such as quartile grouping (e.g. <25%, 25-49%, 50-74%, 75-100%);<sup>24,28</sup>

4. Unequal percentile segmentation with no clear causality (e.g. 0.1 and 0.5 or 0.2 and 0.6)<sup>27</sup> or addressed to previously published analyses;<sup>11,16,67</sup>

5. The magnitude of log-rank test  $\chi^2$  for pair-wise comparisons; <sup>4,22</sup> the log-rank test is used to evaluate survival groups defined by Kaplan-Meier curves. While significant, a higher  $\chi^2$  means a better discrimination of subdivided groups.

6. Receiver operating characteristic (ROC) curves; <sup>26, 69</sup> the ROC curve is a graphical plot, showing the performance of a binary classifier system by varying discrimination thresholds. A threshold best discriminating the patients regarding prognosis is selected as a cutoff point.

7. Bootstrapping procedure; <sup>5, 27</sup> in simple terms, this procedure is literally "stratification by trial", in which cutoff points are proposed from a very close point to the beginning of LNR (i.e., 0.00) to the highest level of LNR (i.e., 1.00) at very short intervals (e.g., 0.05). At any iteration of the procedure (sampling with replacement), the resulting groups are evaluated for their difference in prognosis by submission to Cox regression analysis. Accordingly, LNR levels, which make groups with the strongest significant difference in their prognosis, are used as cutoff points.

The bootstrapping procedure employed by Vinh-Hung *et al.* in 2009 defining 2 thresholds (0.20 and 0.65) has most been referenced and used as cutoff points<sup>5</sup> because it uses a reasonable mathematical method, which - compared with the other methods - is more stable, reliable, and capable in discriminating the patients in terms of prognosis. In the work of Vinh-Hung *et al.*, three risk groups were defined based on 2 thresholds in the LNR: the low-risk

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on 2 thresholds in the LNR: the low-risk group (LNR $\leq 0.20$ ), the intermediate-risk group (0.20<LNR $\leq 0.65$ ), and the high-risk group (LNR>0.65).<sup>5</sup> Although the method of Vinh-hung *et al.* is the most credited in the literature, a metaanalysis by Lui *et al.* in 2013 showed that a variety of available proposed thresholds in the literature could be used (except for 0.80).<sup>39</sup>

#### The dilemma of LNR0: should this be included?

The pN-staging system uses absolute integers for classification of node-positive patients, but it gives distinctive credits to the positivity versus negativity of the LNs; therefore, this system allocates a distinct "pN0" group for the inclusion of node-negative cases. But, for LNR, the story is different. Curiously, the majority of studies utilizing LNR staging system have included only node-positive cases<sup>2,5,9,11,12,14,17,19,29,</sup> 31, 34, 51, 59-61, 67, 68 and the quantity of LNR by them is regarded as a positive decimal value ( $0 \le LNR \le 1$ ). In this system, there is no room for node-negatives, despite the fact that mathematically the numerator of a fraction is allowed to take the value of zero, and then, the overall value of the fraction would be equal to zero. So, theoretically the LNR system must include an "LNR0" group, since it is clinically quite probable for patients undergoing ALND that none of their excised nodes turn out to be positive. Why the LNR0 group is widely overlooked may be because of the lack of its role clarity, or the wrong assumption considering the node-negative cases who had undergone ALND are equal to those not even getting the indication of ALND. This point conversely has been clearly noted by the pN-staging system. However, among the studied papers for this review, only few have accredited the inclusion of an LNR0 group in the LNR system to place node-negatives in.<sup>4, 11, 15, 21, 32</sup> The LNR0 is a separate risk category standing lower than the "low-risk group" in the common LNR scheme. In systems with a lower cutoff point not excluding node-negative cases (e.g. LNR<0.2 as the lower cutoff), LNR0 patients may erroneously be placed in the low-risk group that creates confusion while performing subgroup analysis. Integrating the LNR0 group into the LNR system makes it utterly comprehensive and provides a holistic approach when confronting patient populations with different N-stages, and ultimately makes it more comparable with the pN-staging system.

Statistically, comparisons need a baseline so that the groups of patient population can be compared with. As in "case-control studies," patients are compared with the control group regarding the "characteristic of interest". It seems reasonable that patient groups having the characteristic of axillary involvement be compared with patients without that characteristic. In "Cox-regression analysis", patients are stratified based on "hazard ratios", which describes the proportionality of hazards of (at least) 2 groups, of which one is considered as baseline. In this type of analysis, the group containing more cases within it, is referred to as the baseline group to increase the statistical power and more accurate discrimination of group differences. Likewise, for this type of analysis, the selection of pN0 or LNR0 as baseline groups may better demonstrate the probable stepwise increase in hazard ratios of the ordinal risk groups (i.e. pN1, 2, 3 and LNR low, intermediate and high). In "Kaplan-Meier survival estimates," groups are evaluated based on their survival functions, where a significant log-rank test conveys a statistical difference between at least 2 of the subgroups. In Kaplan-Meier analysis, the overall P values representing the significance of log-rank test do not necessarily mean that all the subgroups are significantly distinct regarding survival or prognosis (with only 2 groups being statistically different, the P value of the log-rank test will be significant). Thus, if node-positive subgroups of LNR or pN-staging systems did not statistically differ regarding the prognosis by Kaplan-Meier analysis, by the inclusion of pN0 or LNR0, the significance of logrank test might be expected (this significant difference may occur between the pN0 -or LNR0group and any of other higher stages). For the purpose of both statistical needs and comprehensiveness of LNR, it seems rational to include node-negative cases as the LNR0 group in LNR risk stratification system.

# What end-points are most appropriate for breast cancer survival analyses?

In survival analyses (like Kaplan-Meier and Coxregression), 2 points in time should be defined that are the start-point and the end-point; the survival is the time interval between these 2 points. In any way, the patients are stratified into subgroups (pN-staging or LNR systems), these points should clearly be defined. There are no major conflicts among the authors about the start-point, as the date of diagnosis<sup>2,4,6,11,16,24,27,67,70</sup>, the date of surgery or tumorexcision,<sup>10, 27, 40</sup> or the date of randomization into treatment groups<sup>35</sup> are typically used.

However, authors use different definitions of survival based on the "end-points." This can cause multiple different survivals (Figure 1). Whenever the end-points are met, they are marked as "events" in data sheets, and when there is no event for a patient, she will be "censored" at the last registered followup she is known to be alive. Consistent utilization of possible definitions for survival is important, while a special attention must be paid to the "cause of death". Three types of survival are often studied:

1. Overall Survival (OS): in this type of survival, "death from any cause" is considered as the endpoint.<sup>3,4,11,24,32,33,70</sup> No matter what happens between the start- and end-points, the interval is considered the

patient's survival.

2. Disease Free Survival (DFS): in which "disease-related events" or again "death from any cause" make the end-points.<sup>2, 6, 10, 11, 27, 40</sup> A variety of survivals derive from DFS, such as event-free survival,<sup>70</sup> recurrence-free survival,<sup>22, 35</sup> local recurrence-free survival,<sup>71</sup> metastasis-free survival,<sup>15</sup> or distant metastasis-free survival.<sup>65</sup> Some of the exact end-points defined for DFS are any recurrence (local, regional, or distant), contra-lateral invasive breast cancer or ductal carcinoma in situ, or a second primary cancer.<sup>6,22,40</sup>

3. Cancer-specific Survival (CSS)<sup>41</sup> or breast cancer-specific survival (BCSS):<sup>16,67</sup> survivals of this type also define the end-points as cancer-related events, such as recurrence and metastasis, but place an emphasis on"deaths from breast cancer".<sup>70</sup>

The information which is crucial for patients with breast cancer is the accurate prediction of recurrence and mortality of "breast cancer",<sup>22</sup> not "deaths from any cause" or "disease non-specific deaths". Accordingly, the OS and DFS derived survivals necessarily cannot determine the patient's survival solely based on her breast cancer, since multiple factors other than breast cancer itself may alter the outcomes. Analysis results may widely differ based on the end-points selected, and each presents a unique portrayal of survival functions in their own viewpoints. Although not explicitly stated in the literature, but it is a logical implication that BCSS best suits for BC survival analyses. However, there are limitations using BCSS since the data on cause of death or recurrence are not always at reach, and if it was, it could improve the precision. On the other hand, the current knowledge on the prognostic value of LNR and pN-staging systems has mostly come from analyses using OS- and DFS-derived endpoints.<sup>32,33</sup>

# LNR or pN-staging: which is superior in prognostication?

An optimal analogy between the LNR and pNstaging systems is when their prognosticative performances are assessed on a single patient population. Two of the most credited methods for survival analysis are Kaplan-Meier (KM) survival estimates (curves) and Cox proportional hazard ratios. The KM analysis evaluates the survival functions of the subgroups (of pN-staging or LNR systems), and its results contain a log-rank test  $\chi^2$ value, a P value, a survival table, and a graphical plot by choice. The log-rank test calculates the  $\chi^2$ , which shows survival differentiation between the subgroups, and P value represents the significance of the difference.<sup>72</sup> In the graph, the survival functions of the subgroups are plotted as curves on 2 perpendicular axes, while the X-axis of the plot shows serial times and the Y-axis defines the probability of surviving at a given time on the curve.

When KM results of the 2 systems are statistically compared, the superiority of a system might be revealed by a significant P value, or if both P values were significant, the superiority of a system might be revealed by the magnitude of  $\chi^2$  value. When the graphs are compared, the system more efficiently stratifying the patients would ideally have distinct curves with no crosses and a balanced distance between the curves (distances are approximately equal); a wider distance between the curves indicates better subgroup discrimination by that classifier system, while a narrower distance means those subgroups have similar survivals. Overlaps of the curves mean those curves have the same survival function at that interval, while crosses are points in time where survival functions of one or both of the curves change discordantly in regard of the other (the steepness of the curves change directions). Among the references of this review, better survival differentiation and much better balance between the curves have been reported by the LNR system (Figure 2, Graphs A, B, and C).  $^{2,5,9,11,19,21}$ 

The Cox-regression method also follows similar principles; however, it uses proportional hazard ratios instead of survival functions and provides visually similar curves to the KM method, but somehow upside-down (at time 0, the survival rate is 1, while the hazard ratio is 0). The curves of this analysis show the increased rate of having an event proportionate to the baseline group (usually the one with the lowest risk) (Figure 2, Graph D). The curves of Cox proportionate hazard ratios normally do not cross, and if so, the proportionality of the hazards might be questioned. The added advantage of this method is the feasibility of inclusion of several predictor covariates into the regression so that to see if one can independently predict the event occurrence. In Cox analysis, when the LNR and pNstaging systems were included in the regression as covariates, the pN-staging system has repeatedly been reported to lose its significance as an independent predictor of survival. 5,6,9,11,19,21,28,35,57,61,65,66,

Comparisons have been made concerning the prognosticative efficacy of the 2 systems among certain subgroups of patients, like women in younger ages and those undergoing breast conservation, certain subtypes of tumors like her2/neu-enriched,60 triple-negative,<sup>2</sup> and luminal-A tumors;<sup>6</sup> again, the LNR system was proved by them to be a better survival predictor than the pN-staging system (despite the need to incorporate these biologic factors has been recognized by the 8<sup>th</sup> edition of AJCC cancer staging manual).<sup>1</sup> More interestingly, the LNR system has been capable of stratifying separate risk groups with different survivals within the pN-staging system subgroups.9, 27 This means even if the LNR system does not get the chance to surrogate the pN-staging system, by its integration

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Figure 2. Visual and graphical differences of survival and hazard curves by Kaplan-Meier and Cox-regression analyses; Graph A represents an optimal discrimination of patient-groups by a classifier system, including 4 categories (e.g. the LNR system). The curves are well-balanced as the distances between the curves are approximately the same. There are no crosses or overlaps in this graph and the group with lowest risk stays at top of the others until the endpoint, while the survival functions of higher risk groups respectively start to step down earlier in the time. Graph B shows the same information as graph A, but the curves are not balanced since the distances between the curves are not equal and change through the time. Graph C indicates the presentation of a flawed classifier system. The curves not only are not balanced, but also the blue curve crosses both the green and red curves and hits to the bottom somewhere around the 60 point; this means the last patient of this group has experienced an event at that time. The higher steepness of the blue curve shows more trends to experience events across the time; perhaps this curve must be defined as the highest risk-group in that classifier system not the second. The overlap by the green and violet curves means their group members had the same survivals at that time interval. Graph D depicts hazard ratios of four-group classifier system. Despite the distances are not equal, they follow a stepwise increase; this represents stepwise increase of hazards compared to the baseline group. Groups with better survivals (lower hazards) stay lower in this graph. The curves from survival functions start from the highest point on cumulative survival axis, while the hazard curves start from the 0 point on the cumulative hazard axis since at time 0, the survival rate is 1, while the hazard ratio is 0.

into the pN-staging system, it may improve the staging and prognostication.<sup>21</sup> Moreover, by its more accurate determination of the extent of axillary LN involvement without extensive axillary dissection, LNR can identify patients requiring adjuvant radiotherapy.<sup>2, 35, 73</sup> When the number of excised LNs is so few that the pN-staging system cannot go further than the pN1-stage (excision limited to the sentinels), the LNR system, thereupon, can predict the involvement of non-sentinels.<sup>2,21</sup>

Ultimately, among the reference papers comparing the 2 staging systems, only few have concluded that pN-staging system may more accurately prognosticate BC patients than the LNR system, or support that the 2 systems have equal prognostication values,<sup>3,6,16,19,27,33,66</sup> while the majority of authors acknowledge that LNR system outperforms the pN-staging systems in many investigated domains<sup>2-7,10,16,19,22,24,26-28,30-34,39-41,58,59,61,65,66,68,</sup> <sup>71, 74-77</sup> and provides a tailored approach to address the diversity of patient populations.

The precise and realistic prognostication by pNstaging system requires at least 10 LNs in the pathologic specimen, while LNR system minimally depends on the quantity of LNs and maintains its prognostic value with various numbers of excised LNs. Adhering to the findings of Z-0011 trial obstructs the provision of sufficient LNs for a proper pN-staging, but with those few LNs, LNR can still be calculated. Neo-adjuvant therapies may reduce both the total and positive axillary LNs to inadequate levels of pN-staging; however, the accuracy of staging by LNR system in post-neo-adjuvant patients has been supported by some articles. There is ambiguity in the literature about how the pNstaging cutoffs have evolved, whereas common LNR cutoffs have been calculated through a reasonable mathematical method. Among different types of survival, BCSS better portrays cancer-related event. The integration of LNR0 into the LNR system makes it comprehensive and comparable to the pN-staging system. With the evidence compiled in this review, LNR is potentially competent to surrogate the pNstaging system and become the standard of classification for early-stage breast cancer.

#### Authors' contribution

AS conceived the project, raised the queries, provided topic scenarios as well as categorization schemes, drew the diagrams, and wrote the drafts and the final manuscript. SZ and NM did the initial literature search; the results were reviewed by SZ, AE, NM, and AS. AK organized and managed the team, supervised the work, and did the scientific edits. DNK edited and critically revised the content and approved the final work. All authors have approved the final article.

#### **Conflict of interest**

The authors declare that they have no conflicts of interest.

#### References

- 1. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, *et al.* Breast Cancer-Major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(4):290-303.
- 2. Ahn SH, Kim HJ, Lee JW, Gong GY, Noh DY, Yang JH, *et al.* Lymph node ratio and pN staging in patients with node-positive breast cancer: a report from the Korean breast cancer society. Breast Cancer Res Treat. 2011;130(2):507-15.
- 3. Dings PJ, Elferink MA, Strobbe LJ, de Wilt JH. The prognostic value of lymph node ratio in node-positive breast cancer: a Dutch nationwide population-based study. Ann Surg Oncol. 2013;20(8):2607-14.
- Zhu C, Wu XZ. Proposal of new classification for stage III breast cancer on the number and ratio of metastatic lymph nodes. J Surg Oncol. 2012;106(6):696-702.
- 5. Vinh-Hung V, Verkooijen HM, Fioretta G, Neyroud-Caspar I, Rapiti E, Vlastos G, *et al.* Lymph node ratio as an alternative to pN staging in node-positive breast cancer. J Clin Oncol. 2009;27(7):1062-8.
- 6. Wang F, He W, Qiu H, Wang X, Guo G, Chen X, *et al.* Lymph node ratio and pN staging show different superiority as prognostic predictors depending on the number of lymph nodes dissected in Chinese patients with luminal A breast cancer. Clin Breast Cancer. 2012;12(6): 404-11.
- 7. Kim JY, Ryu MR, Choi BO, Park WC, Oh SJ, Won JM, *et al.* The prognostic significance of the lymph node ratio in axillary lymph node positive

breast cancer. J Breast Cancer. 2011;14(3):204-12.

- 8. 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.
- 9. Danko ME, Bennett KM, Zhai J, Marks JR, Olson JA, Jr. Improved staging in node-positive breast cancer patients using lymph node ratio: results in 1,788 patients with long-term follow-up. J Am Coll Surg. 2010;210(5):797-805.
- Inal A, Akman T, Yaman S, Ozturk SC, Geredeli C, Bilici M, *et al.* Is lymph node ratio prognostic factor for survival in elderly patients with node positive breast cancer? The Anatolian Society of Medical Oncology. Ann Ital Chir. 2013;84(2):143-8.
- 11. Schiffman SC, McMasters KM, Scoggins CR, Martin RC, Chagpar AB. Lymph node ratio: a proposed refinement of current axillary staging in breast cancer patients. J Am Coll Surg. 2011;213(1):45-52.
- 12. Wiznia LE, Lannin DR, Evans SB, Hofstatter EW, Horowitz NR, Killelea BK, *et al.* The number of lymph nodes dissected in breast cancer patients influences the accuracy of prognosis. Ann Surg Oncol. 2014;21(2):389-94.
- Liao GS, Chou YC, Golshan M, Hsu HM, Hong ZJ, Yu JC, *et al.* Prognostic value of the lymph node ratio in breast cancer subtypes. Am J Surg. 2015;210(4):749-54.
- 14. Wu SG, Sun JY, Zhou J, Li FY, Zhou H, Lin Q, et al. Number of negative lymph nodes can predict survival of breast cancer patients with four or more positive lymph nodes after postmastectomy radiotherapy. Radiat Oncol. 2014;9:284.
- 15. van der Wal BC, Butzelaar RM, van der Meij S, Boermeester MA. Axillary lymph node ratio and total number of removed lymph nodes: predictors of survival in stage I and II breast cancer. Eur J Surg Oncol. 2002;28(5):481-9.
- 16. Truong PT, Vinh-Hung V, Cserni G, Woodward WA, Tai P, Vlastos G. The number of positive nodes and the ratio of positive to excised nodes are significant predictors of survival in women with micrometastatic node-positive breast cancer. Eur J Cancer. 2008;44(12):1670-7.
- 17. Voordeckers M, Vinh-Hung V, Van de Steene J, Lamote J, Storme G. The lymph node ratio as prognostic factor in node-positive breast cancer. Radiother Oncol. 2004;70(3):225-30.
- Gangadaran S. Axillary Nodal Examination in Breast Cancer: How Much Is Enough? Evidence for a New Minimum. Archives of Breast Cancer. 2016;3(4):126-9.
- 19. Ataseven B, Kummel S, Weikel W, Heitz F, Holtschmidt J, Lorenz-Salehi F, *et al.* Additional prognostic value of lymph node ratio over pN staging in different breast cancer subtypes based

on the results of 1,656 patients. Arch Gynecol Obstet. 2015;291(5):1153-66.

- 20.Peparini N, Chirletti P. Lymph node ratio, number of excised nodes and sentinel-node concepts in breast cancer. Breast Cancer Res Treat. 2011;126(3):829-33.
- Chagpar AB, Camp RL, Rimm DL. Lymph node ratio should be considered for incorporation into staging for breast cancer. Ann Surg Oncol. 2011;18(11):3143-8.
- 22. Yang C, Liu F, Li S, Li W, Zhai L, Ren M, *et al.* Lymph node ratio: a new feature for defining risk category of node-positive breast cancer patients. Int J Surg Pathol. 2012;20(6):546-54.
- 23. Chang YJ, Chung KP, Chen LJ. Recursive partitioning analysis of lymph node ratio in breast cancer patients. Medicine (Baltimore). 2015;94(1):e208.
- 24. Chen S, Liu Y, Huang L, Chen CM, Wu J, Shao ZM. Lymph node counts and ratio in axillary dissections following neoadjuvant chemotherapy for breast cancer: a better alternative to traditional pN staging. Ann Surg Oncol. 2014;21(1):42-50.
- 25. Chen YL, Wang CY, Wu CC, Lee MS, Hung SK, Chen WC, *et al.* Prognostic influences of lymph node ratio in major cancers of Taiwan: a longitudinal study from a single cancer center. J Cancer Res Clin Oncol. 2015;141(2):333-43.
- Demircioglu F, Demirci U, Kilic D, Ozkan S, Karahacioglu E. Clinical significance of lymph node ratio in locally advanced breast cancer molecular subtypes. Onkologie. 2013; 36(11):637-40.
- 27. Duraker N, Bati B, Caynak ZC, Demir D. Lymph node ratio may be supplementary to TNM nodal classification in node-positive breast carcinoma based on the results of 2,151 patients. World J Surg. 2013;37(6):1241-8.
- 28. Hatoum HA, Jamali FR, El-Saghir NS, Musallam KM, Seoud M, Dimassi H, *et al.* Ratio between positive lymph nodes and total excised axillary lymph nodes as an independent prognostic factor for overall survival in patients with nonmetastatic lymph node-positive breast cancer. Indian J Surg Oncol. 2010;1(4):305-12.
- 29. Jayasinghe UW, Pathmanathan N, Elder E, Boyages J. Prognostic value of the lymph node ratio for lymph-node-positive breast cancer- is it just a denominator problem? Springerplus. 2015;4:121.
- 30. Kim SI, Cho SH, Lee JS, Moon HG, Noh WC, Youn HJ, et al. Clinical relevance of lymph node ratio in breast cancer patients with one to three positive lymph nodes. Br J Cancer. 2013;109(5):1165-71.
- 31. Li Y, Holmes E, Shah K, Albuquerque K, Szpaderska A, Ersahin C. The prognostic value of lymph node cross-sectional cancer area in

node-positive breast cancer: a comparison with N stage and lymph node ratio. Patholog Res Int. 2012;2012:161964.

 $(\cdot)$ 

- 32. Saxena N, Hartman M, Aziz R, Rapiti E, Bhoo Pathy N, Lim SE, *et al.* Prognostic value of axillary lymph node status after neoadjuvant chemotherapy. Results from a multicentre study. Eur J Cancer. 2011;47(8):1186-92.
- 33. Saxena N, Hartman M, Yip CH, Bhoo-Pathy N, Khin LW, Taib NA, *et al.* Does the axillary lymph node ratio have any added prognostic value over pN staging for South East Asian breast cancer patients? PLoS One. 2012;7(9):e45809.
- 34. Solak M, Turkoz FP, Keskin O, Aksoy S, Babacan T, Sarici F, *et al.* The lymph node ratio as an independent prognostic factor for nonmetastatic node-positive breast cancer recurrence and mortality. J BUON. 2015; 20(3):737-45.
- 35. Tausch C, Taucher S, Dubsky P, Seifert M, Reitsamer R, Kwasny W, *et al.* Prognostic value of number of removed lymph nodes, number of involved lymph nodes, and lymph node ratio in 7502 breast cancer patients enrolled onto trials of the Austrian Breast and Colorectal Cancer Study Group (ABCSG). Ann Surg Oncol. 2012;19(6):1808-17.
- 36. Axillary dissection. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Canadian Association of Radiation Oncologists. CMAJ. 1998;158 Suppl 3:S22-6.
- 37. Fisher B, Jeong JH, Anderson S, Bryant J, Fisher ER, Wolmark N. Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. N Engl J Med. 2002;347(8):567-75.
- 38. Axelsson CK, Mouridsen HT, Zedeler K. Axillary dissection of level I and II lymph nodes is important in breast cancer classification. The Danish Breast Cancer Cooperative Group (DBCG). Eur J Cancer. 1992;28A(8-9):1415-8.
- 39. Liu D, Chen Y, Deng M, Xie G, Wang J, Zhang L, *et al.* Lymph node ratio and breast cancer prognosis: a meta-analysis. Breast Cancer. 2014;21(1):1-9.
- 40. Xiao XS, Tang HL, Xie XH, Li LS, Kong YN, Wu MQ, *et al.* Metastatic axillary lymph node ratio (LNR) is prognostically superior to pN staging in patients with breast cancer--results for 804 Chinese patients from a single institution. Asian Pac J Cancer Prev. 2013;14(9):5219-23.
- 41. Vinh-Hung V, Joseph SA, Coutty N, Ly BH, Vlastos G, Nguyen NP. Age and axillary lymph node ratio in postmenopausal women with T1-T2 node positive breast cancer. Oncologist. 2010;15(10):1050-62.
- 42. Krag DN, Single RM. Breast cancer survival



according to number of nodes removed. Ann Surg Oncol. 2003;10(10):1152-9.

- 43. Vinh-Hung V, Cserni G, Burzykowski T, van de Steene J, Voordeckers M, Storme G. Effect of the number of uninvolved nodes on survival in early breast cancer. Oncol Rep. 2003;10(2):363-8.
- 44. Banerjee SM, El-Sheikh S, Keshtgar MRS. Intraoperative Assessment of Sentinel Lymph Nodes in Breast Cancer. Archives of Breast Cancer. 2014;1(2):44-52.
- 45. Barranger E, Coutant C, Flahault A, Delpech Y, Darai E, Uzan S. An axilla scoring system to predict non-sentinel lymph node status in breast cancer patients with sentinel lymph node involvement. Breast Cancer Res Treat. 2005;91(2):113-9.
- 46. Farshid G, Pradhan M, Kollias J, Gill PG. A decision aid for predicting non-sentinel node involvement in women with breast cancer and at least one positive sentinel node. Breast. 2004;13(6):494-501.
- 47. Parsaei R, Omranipour R, Elyasinia F, Ahmadi F, Jamei K, Sabri F, *et al.* Sentinel Node Ratio as a Predictor of Non-sentinel Lymph Node Involvement. Archives of Breast Cancer. 2014;1(3):81-5.
- 48. Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, *et al.* Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. Ann Surg. 2016;264(3):413-20.
- 49. 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.
- 50. Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, *et al.* Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg. 2010;252(3):426-32; discussion 32-3.
- 51. Hong R, Dai Z, Zhu W, Xu B. Association between Lymph Node Ratio and Disease Specific Survival in Breast Cancer Patients with One or Two Positive Lymph Nodes Stratified by Different Local Treatment Modalities. PLoS One. 2015;10(10):e0138908.
- 52. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival--a Bayesian meta-analysis. Ann Surg Oncol. 1999;6(1):109-16.
- 53. Galimberti V, Cole BF, Zurrida S, Viale G, Luini

A, Veronesi P, *et al.* Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297-305.

- 54. Scholl SM, Asselain B, Palangie T, Dorval T, Jouve M, Garcia Giralt E, *et al.* Neoadjuvant chemotherapy in operable breast cancer. Eur J Cancer. 1991;27(12):1668-71.
- 55. Bonadonna G, Veronesi U, Brambilla C, Ferrari L, Luini A, Greco M, *et al.* Primary chemotherapy to avoid mastectomy in tumors with diameters of three centimeters or more. J Natl Cancer Inst. 1990;82(19):1539-45.
- 56. Calitchi E, Otmezguine Y, Feuilhade F, Piedbois P, Pavlovitch JM, Brun B, *et al.* External irradiation prior to conservative surgery for breast cancer treatment. Int J Radiat Oncol Biol Phys. 1991;21(2):325-9.
- 57. Wu SG, Li Q, Zhou J, Sun JY, Li FY, Lin Q, *et al.* Using the Lymph Node Ratio to Evaluate the Prognosis of Stage II/III Breast Cancer Patients Who Received Neoadjuvant Chemotherapy and Mastectomy. Cancer Res Treat. 2015;47(4):757-64.
- 58. Bai LS, Chen C, Gong YP, Wei W, Tu Y, Yao F, et al. Lymph node ratio is more predictive than traditional lymph node stratification in lymph node positive invasive breast cancer. Asian Pac J Cancer Prev. 2013;14(2):753-7.
- 59. Ibrahim EM, Elkhodary TR, Zekri JM, Bahadur Y, El-Sayed ME, Al-Gahmi AM, *et al.* Prognostic value of lymph node ratio in poor prognosis node-positive breast cancer patients in Saudi Arabia. Asia Pac J Clin Oncol. 2010;6(2):130-7.
- 60. Kim SH, Jung KH, Kim TY, Im SA, Choi IS, Chae YS, *et al.* Prognostic Value of Axillary Nodal Ratio after Neoadjuvant Chemotherapy of Doxorubicin/Cyclophosphamide Followed by Docetaxel in Breast Cancer: A Multicenter Retrospective Cohort Study. Cancer Res Treat. 2016;48(4):1373-81.
- 61. Oven Ustaalioglu BB, Bilici A, Kefeli U, Seker M, Yildirim E, Salepci T, *et al.* Does the metastatic lymph node ratio influence the disease-free survival of patients with breast cancer: single-center experiences. Oncology. 2010;79(1-2):105-11.
- 62.Pilewskie M, Morrow M. Axillary Nodal Management Following Neoadjuvant Chemotherapy: A Review. JAMA Oncol. 2017;3(4):549-55.
- 63. Tsai J, Bertoni D, Hernandez-Boussard T, Telli ML, Wapnir IL. Lymph Node Ratio Analysis After Neoadjuvant Chemotherapy is Prognostic in Hormone Receptor-Positive and Triple-Negative Breast Cancer. Ann Surg Oncol. 2016;23(10):3310-6.
- 64. Lawn AM, Frampton AE, Krell J, Waheed S,

Stacey-Clear A. Lymph node ratio can further stratify prognosis in subpopulations of breast cancer patients with axillary nodal metastases. Future Oncol. 2013;9(10):1425-31.

- 65. Wu SG, He ZY, Li Q, Sun JY, Li FY, Lin Q, *et al.* Prognostic value of metastatic axillary lymph node ratio for Chinese breast cancer patients. PLoS One. 2013;8(4):e61410.
- 66.Martinez-Ramos D, Escrig-Sos J, Alcalde-Sanchez M, Torrella-Ramos A, Salvador-Sanchis JL. Disease-free survival and prognostic significance of metastatic lymph node ratio in T1-T2 N positive breast cancer patients. A population registry-based study in a European country. World J Surg. 2009;33(8):1659-64.
- 67. Truong PT, Lesperance M, Li KH, MacFarlane R, Speers CH, Chia S. Micrometastatic node-positive breast cancer: long-term outcomes and identification of high-risk subsets in a large population-based series. Ann Surg Oncol. 2010;17(8):2138-46.
- 68. Van Belle V, Van Calster B, Wildiers H, Van Huffel S, Neven P. Lymph node ratio better predicts disease-free survival in node-positive breast cancer than the number of positive lymph nodes. J Clin Oncol. 2009;27(30):e150-1; author reply e2.
- 69. Kim SW, Choi DH, Huh SJ, Park W, Nam SJ, Lee JE, *et al.* Lymph Node Ratio as a Risk Factor for Locoregional Recurrence in Breast Cancer Patients with 10 or More Axillary Nodes. J Breast Cancer. 2016;19(2):169-75.
- 70. Bolwell B, Andresen S, Pohlman B, Sobecks R, Goormastic M, Rybicki L, *et al.* Prognostic importance of the axillary lymph node ratio in autologous transplantation for high-risk stage II/III breast cancer. Bone Marrow Transplant. 2001;27(8):843-6.
- 71. Wu SG, Chen Y, Sun JY, Li FY, Lin Q, Lin HX, et al. Using the lymph nodal ratio to predict the risk of locoregional recurrence in lymph nodepositive breast cancer patients treated with mastectomy without radiation therapy. Radiat Oncol. 2013;8:119.
- 72. Rich JT, Neely JG, Paniello RC, Voelker CC, Nussenbaum B, Wang EW. A practical guide to understanding Kaplan-Meier curves. Otolaryngol Head Neck Surg. 2010;143(3):331-6.
- 73. Sindoni A, Iati G, Pontoriero A, Santacaterina A, Pergolizzi S. Comments on "Lymph Node Ratio as a Risk Factor for Locoregional Recurrence in Breast Cancer Patients". J Breast Cancer. 2016;19(3):334-5.
- Demircioglu F, Demirci U, Akmansu M. Lymph node ratio assessment of brain metastasis in early breast cancer cases. Asian Pac J Cancer Prev. 2013;14(3):1665-7.
- 75. Elkhodary TR, Ebrahim MA, Hatata EE, Niazy NA. Prognostic value of lymph node ratio in

node-positive breast cancer in Egyptian patients. J Egypt Natl Canc Inst. 2014;26(1):31-5.

 $(\cdot)$ 

- 76. Wang QX, Cai YF, Chen YY, Zhang W, Jin WX, Chen ED, et al. Additional Prognostic Value of Lymph Node Ratio (LNR) and Number of Negative Lymph Nodes (NLNs) in Chinese Patients with Triple Negative Breast Cancer. Ann Clin Lab Sci. 2017;47(1):68-75.
- 77. Wen J, Yang Y, Liu P, Ye F, Tang H, Huang X, et al. Development and validation of a nomogram for predicting survival on the base of modified lymph node ratio in breast cancer patients. Breast. 2017;33:14-22.
- 78. Jia XQ, Hong Q, Cheng JY, Li JW, Wang YJ, Mo M, *et al.* Nodal ratio of positive to excised nodes, but not number of positive lymph nodes is better to predict group to avoid chemotherapy among postmenopausal ER-positive, lymph nodepositive T1-T2 breast cancer patients. J Cancer Res Ther. 2015;11(4):740-5.
- 79. Chen LJ, Chung KP, Chang YJ. Ratio and log odds of positive lymph nodes in breast cancer patients with mastectomy. Surg Oncol. 2015;24(3):239-47.



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## Androgen Receptor Expression in Locally Advanced Breast Cancer Predicts Lack of Pathological Complete Response After Neoadjuvant Treatment

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#### ABSTRACT

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Key words: Androgen receptor, breast cancer, chemotherapy, neoadjuvant treatment **Background:** Data regarding the prognostic value of androgen receptor (AR) expression in locally advanced breast cancer (LABC) is limited. We aimed to determine the pathological complete response, defined as ypT0/is and ypN0, in a group of patients with AR-positive breast cancer after preoperative treatment.

**Methods:** We evaluated immunohistochemical AR expression in 40 patients treated in our referral center. Univariate and multivariate models were used to assess the association between AR expression and pathological complete response (pCR).

**Results:** AR expression varied from 75% in estrogen receptor-positive tumors to 11.7% in triple-negative tumors (P < 0.001). Three patients with AR-positive tumors achieved pCR. In the univariate model, AR expression was significantly associated with the absence of pCR (OR = 0.18; 95% CI, 0.04–0.75; P = 0.023). After adjusting for intrinsic breast cancer subtypes, AR-positive tumors had less probability of achieving a pCR compared with AR-negative ones (OR = 12.33; P=0.046).

**Conclusions:** AR expression was negatively correlated with pCR in our subset of patients with LABC who underwent neoadjuvant chemotherapy.

#### Introduction

Breast cancer is the leading cause of cancer death in women worldwide. In developing countries, high breast cancer mortality can be attributable to the large proportion of patients with locally advanced breast cancer (LABC) at diagnosis.<sup>1</sup> In Costa Rica, a middle-income country, LABC comprises around one-third of newly diagnosed cases.<sup>2</sup>

For patients with LABC, preoperative chemotherapy provides a reasonable mean for decreasing the tumor burden, assessing in vivo chemosensitivity,

Address for correspondence: Allan Ramos-Esquivel, M.D. Address: Departamento de Farmacología, Escuela de Medicina, Universidad de Costa Rica, Sede Rodrigo Facio, San José, Costa Rica, P.O. Box: 2082 San José Tel: (+506) 88448187 Fax: (+506) 22373930 E-mail address: allan.ramos@ucr.ac.cr and evaluating the possibility of breast- conservation surgery. Furthermore, if these patients achieve a pathological complete response (pCR) after neoadjuvant chemotherapy (defined as ypT0/is ypN0),<sup>3</sup> their long-term outcomes can improve. Pathological complete response has been associated with longer event-free survival and overall survival (OS), especially in triple-negative tumors and HER2-positive breast cancers.<sup>3-5</sup>

Previous studies have demonstrated the prognostic role of androgen receptor (AR) expression in breast cancer patients. Overall, AR-positive tumors are associated with better outcomes and longer OS compared with AR-negative tumors.<sup>6</sup>, <sup>7</sup> However, few studies have evaluated the predictive value of AR expression regarding pCR in the neoadjuvant setting, and they have yielded conflicting results.<sup>8,9</sup>

In this exploratory study, we aimed to determine

the association between AR expression and pCR in a subset of patients treated with preoperative chemotherapy for LABC.

#### Methods

The study protocol was approved by the institutional ethics committee and conducted according to the Helsinki declaration and its modifications.

We prospectively reviewed the clinical records of a sample of 40 patients who underwent neoadjuvant chemotherapy for LABC and who were treated in our referral center (Hospital México, San José, Costa Rica). The Breast Tumor Board decided to offer preoperative systemic treatment to patients with clinical stage IIIA or more (not for stage IV), and to patients in whom the relationship between tumor size and breast size could imply an up-front mastectomy instead of breast-conservation surgery. We excluded the patients who did not complete the preoperative systemic treatment schedule and those who refused surgical treatment. AR expression, as well as the presence or absence of estrogen receptors (ER), progesterone receptors (PR), or human epidermal growth factor receptor 2 (HER2), was determined in formalin-fixed, paraffin-embedded tissues by immunohistochemistry before preoperative treatment (DACO diagnostic Glostrup, Denmark; clone AR441; clone ERSP1; clone PgR636 and polyclonal HER2). Tumors with  $\geq 1\%$ nuclear-stained cells were considered positive for AR, ER, and PR. Immunohistochemical staining for HER2 was scored from 0 to 3+ according to the guidelines for HercepTest<sup>™</sup> (DACO, Denmark).<sup>10</sup> HER2 was considered positive when strong (3+)membranous staining was observed, whereas cases with 0 or 1+ were considered negative. In the case of samples scored 2+, a FISH assay was carried out using the PathVysion HER2 DNA Probe Kit (Abbott, Illinois, USA) according to the manufacturer's protocol. Breast tumor intrinsic subtypes were defined according to previous recommendations.<sup>11</sup> Tumor stage was defined according to the criteria set by the Seventh American Joint Committee on Cancer. Histologic grading followed the World Health Organization classification. The pathologist

in charge performed the aforementioned histological determinations before preoperative treatment and after surgery. The same pathologist also determined the criteria of pCR in case of absence of invasive tumor in the primary site and absence of metastases in the harvested lymph nodes (ypT0/is ypN0).

Preoperative chemotherapeutic scheme for each patient included one of the following combinations: 5-fluorouracil 500 mg/m<sup>2</sup>, epirubicin 100 mg/m<sup>2</sup>, and cyclophosphamide 500 mg/m<sup>2</sup> every 21 days for 4 cycles, followed by weekly paclitaxel 80 mg/m<sup>2</sup> for 12 weeks (FE<sub>100</sub>C +  $_{\rm w}$ T); the same regimen with trastuzumab 6 mg/kg loading dose followed by 4 mg/kg weekly for one year in the case of HER2positive tumors (FE<sub>100</sub>C +  $_{w}T+Tz$ ); epirubicin 100 mg/m<sup>2</sup> and cyclophosphamide 600 mg/m<sup>2</sup> every 15 days for 4 cycles ( $EC_{dd}$ ); or weekly paclitaxel 80  $mg/m^2$  for 12 weeks with trastuzumab 6 mg/kg loading dose followed by 4 mg/kg per week for one year (<sub>w</sub>T+Tz). The surgery was performed by the oncologist surgeon in charge 4 or 10 weeks after the last dose of chemotherapy.

#### Statistical Analysis

Categorical variables are presented as percentages, and the chi-square test or the Fisher exact test were applied to compare them. The chi-square test for trend was applied to compare AR expression among breast cancer subtypes. A logistic regression was carried out to assess the relationship between AR expression and the probability of achieving a pCR, using breast tumor intrinsic subtypes as covariates. A P value of less than 0.05 was considered statistically significant. Data were analyzed using SPSS for Mac 20.0 (Chicago, IL).

#### Results

General characteristics of the studied population are presented in Table 1. Overall, 19 patients exhibited AR positivity (47.5%). The AR expression was associated with HER2, ER, and PR coexpression. AR expression varied from 75% in ERpositive tumors to 11.7% in triple-negative tumors (Trend test: P < 0.001). Figure 1 shows positive and negative samples for AR immunohistochemistry.



Figure 1. Androgen receptor–positive (A) and receptor–negative (B) breast cancers according to immunohistochemical analysis



Variable		All patients (N = 40)	AR negative $(N = 21)$	AR positive (N = 19)	P-value
Age (years, SD) Stage		53.3 ± 10.3	$48.22\pm8.2$	54.6 ± 12.3	0.44
T					0.72
	T1c T2 T3 T4a T4d	2 (5) 9 (22.5) 24 (60) 3 (7.5) 2 (5)	$ \begin{array}{c} 0\\ 4(19.1)\\ 13(61.9)\\ 2(9.5)\\ 2(9.5)\\ \end{array} $	2 (10.5) 5 (26.3) 11 (57.9) 1 (5.3) 0	
Ν	1.0	- (1)	- (***)		0.66
	N0 N1 N2 N3	13 (32.5) 18 (45) 7 (17.5) 2 (5)	4 (19.1) 8 (38.1) 7 (33.3) 2 (9.5)	9 10 0 0	
Grade					0.9
	1 2 3	2 (5) 19 (47.5) 19 (47.5)	0 7 (33.3) 14 (66.7)	2 (10.5) 12 (63.2) 5 (26.3)	
Intrinsic subtype					< 0.001
	Luminal A Luminal B HER2-enriched Triple-negative	3 (7.5) 9 (22.5) 11 (27.5) 17 (42.5)	1 (4.7) 2 (9.5) 3 (14.3) 15 (71.5)	2 (10.5) 7 (36.8) 8 (42.2) 2 (10.5)	

Table 1. General characteris	ics of the studied population
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\* Statistically significant at P < 0.05

After preoperative chemotherapy, a breastconservation surgery was possible in 22 patients (55%), and the rest of them underwent for 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 are demonstrated 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%) After adjusting for each intrinsic breast cancer subtype (Table 2), the absence of AR was independently associated with the probability of achieving a pCR (OR = 0.08; P = 0.046), meaning that the chance of achieving pCR was 92% higher in AR-negative tumors than in AR-positive breast cancer. The Cox-Snell R2 for this model was 0.21, meaning that only 21% of the pCR rate could be explained by this regression model. Figure 2 shows one tumor with pCR and another sample with residual disease.

 Table 2. Odds of pathological complete response according to the immunohistochemical expression of breast cancer receptors

Receptor	pCR	Univariate	P-value	Adjusted	P-value
		odds ratio (95% CI)		odds ratio** (95% CI	)
AR+ (%)	3 (15.8)	0.18 (0.04-0.75)	0.023	0.08 (0.01-0.97)	0.046
ER+ (%)	2 (13.3)	0.25 (0.05-1.35)	0.09	0.41 (0.17-1.44)	0.44
HER2+ (%)	6 (35.3)	1.17 (0.31-4.44)	0.82	1.33 (0.63-3.77)	0.12
ER-/PR-/HER2- (%)	7 (41.2)	1.87 (0.50-7.19)	0.28	1.83 (0.41-6.72)	0.32

*AR*: androgen receptor; *ER*: estrogen receptor; *HER2*: human epidermal growth factor type 2; pCR: pathological complete response; *PR*: progesterone receptor. \* Statistically significant at P < 0.05 \*\* Adjusted for breast cancer intrinsic subtype



Figure 2. Complete pathological response (A) and residual disease (B) in two breast cancer samples after neoadjuvant chemotherapy

 $(\cdot)$ 

#### Discussion

Pathological complete response after preoperative chemotherapy is a valuable clinical endpoint because it has been associated with favorable longterm outcomes in patients with LABC,<sup>3</sup> especially for those with HER2 tumors and TNBC. Although some predictive markers have been developed to assess the probability of achieving this endpoint, there is still limited data on the relationship between AR expression and pCR. This possible relationship can be beneficial for improving the understanding and treatment of this particular subset of breast cancer patients.

In this short report, AR expression was positive in 47.5% of the patients, while previous studies have demonstrated a higher AR expression (70–80%). One reason for this inconsistency could be the cancer type, which in our study included mainly HER2-positive and triple-negative tumors. It has been well established that AR expression varies according to the breast cancer intrinsic subtype.<sup>12-14</sup> For example, Collins and colleagues reported the positivity of AR expression in 88% of ER-positive tumors, while only 32% of TNBC were AR-positive tumors was low, our data was in accordance with such distribution because the majority of ER-positive tumors also exhibited AR expression.

Our findings demonstrated an inverse association between AR expression and the probability of achieving a pCR. Similar results have been reported by Loibl and colleagues, who showed that AR negativity predicts the odds of achieving pCR. Specifically, these authors reported a pCR rate of 12.8% in AR-positive tumors, while patients with AR-negative breast cancer had a pCR rate of 25.4% (P < 0.0001).<sup>9</sup> On the contrary, Masuda and colleagues did not find any significant association between AR expression (determined by immunohistochemistry) and pCR in a cohort of 33 patients with triple-negative breast cancer (TNBC) who underwent preoperative chemotherapy.<sup>15</sup> These divergent results can be attributable to a lower statistical power due to small sample size, as well as the spectrum of patients as Masuda et al., only included TNBC patients in their study.<sup>15</sup> It has been demonstrated that patients with triple-negative breast cancer and AR expression have a very low pCR rate in comparison with other TNBC subtypes.<sup>16</sup> Our results are in accordance with this finding as the majority of patients with TNBC who achieved a pCR did not express AR on immunohistochemical analyses.

Having a small sample size and a unicenter design limit generalizability of our findings. Furthermore, information bias might have occurred if patients were misclassified by immunohistochemistry, although we tried to eliminate this bias by choosing only one experienced pathologist to report all samples.

In summary, our findings showed the predictive value of AR expression in patients with LABC undergoing neoadjuvant chemotherapy. However, we must notice that pCR rate can vary according to the presence of some other clinical variables, such as ER and HER2 expression. Further research is warranted to establish the role of androgens in breast cancer patients.

#### **Conflict of interest**

The authors declare no conflicts of interest.

#### References

- Anderson BO, Cazap E, El Saghir NS, Yip CH, Khaled HM, Otero IV, *et al.* Optimisation of breast cancer management in low-resource and middle-resource countries: executive summary of the Breast Health Global Initiative consensus, 2010. Lancet Oncol. 2011;12(4):387-98.
- 2. Srur-Rivero N, Cartin-Brenes M. Breast cancer characteristics and survival in a Hispanic population of costa rica. Breast Cancer (Auckl). 2014;8:103-8.
- 3. 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.
- Esserman LJ, Berry DA, DeMichele A, Carey L, Davis SE, Buxton M, et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL--CALGB 150007/150012, ACRIN 6657. J Clin Oncol. 2012;30(26):3242-9.
- 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.
- 6. Park S, Koo JS, Kim MS, Park HS, Lee JS, Lee JS, *et al.* Androgen receptor expression is significantly associated with better outcomes in estrogen receptor-positive breast cancers. Ann Oncol. 2011;22(8):1755-62.
- Shah PD, Gucalp A, Traina TA. The role of the androgen receptor in triple-negative breast cancer. Womens Health (Lond). 2013;9(4):351-60.
- 8. Chintamani, Kulshreshtha P, Chakraborty A, Singh L, Mishra AK, Bhatnagar D, *et al.* Androgen receptor status predicts response to chemotherapy, not risk of breast cancer in Indian women. World J Surg Oncol. 2010;8:64.
- 9. Loibl S, Muller BM, von Minckwitz G, Schwabe M, Roller M, Darb-Esfahani S, *et al.* Androgen receptor expression in primary breast cancer and its predictive and prognostic value in patients



treated with neoadjuvant chemotherapy. Breast Cancer Res Treat. 2011;130(2):477-87.

- Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med. 2014;138(2):241-56.
- 11. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thurlimann B, *et al.* Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol. 2013;24(9):2206-23.
- Park S, Koo J, Park HS, Kim JH, Choi SY, Lee JH, *et al.* Expression of androgen receptors in primary breast cancer. Ann Oncol. 2010;21(3):488-92.
- Agrawal A, Ziolkowski P, Grzebieniak Z, Jelen M, Bobinski P, Agrawal S. Expression of androgen receptor in estrogen receptor-positive breast cancer. Appl Immunohistochem Mol Morphol. 2016;24(8):550-5.
- 14. Collins LC, Cole KS, Marotti JD, Hu R, Schnitt SJ, Tamimi RM. Androgen receptor expression in breast cancer in relation to molecular phenotype: results from the Nurses' Health Study. Mod Pathol. 2011;24(7):924-31.
- 15. Masuda H, Masuda N, Kodama Y, Ogawa M, Karita M, Yamamura J, *et al.* Predictive factors for the effectiveness of neoadjuvant chemotherapy and prognosis in triple-negative breast cancer patients. Cancer Chemother Pharmacol. 2011;67(4):911-7.
- 16. Masuda H, Baggerly KA, Wang Y, Zhang Y, Gonzalez-Angulo AM, Meric-Bernstam F, et al. Differential response to neoadjuvant chemotherapy among 7 triple-negative breast cancer molecular subtypes. Clin Cancer Res. 2013;19(19):5533-40.



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## Effect of the Surgery Type, Mastectomy vs. Breast Conserving Surgery, on Outcomes of Patients With Locally Advanced Breast Cancer Receiving Neoadjuvant Therapy

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#### ABSTRACT

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**Background:** Breast cancer is the most prevalent site-specific cancer and one of the most frequent causes of cancer death in women worldwide. Neoadjuvant chemotherapy, along with surgical treatment—breast conserving surgery (BCS) or mastectomy—is an important part of treatment for locally advanced breast cancer. As BCS is preferred to mastectomy in terms of cosmetic, quality-of-life, and functional outcomes, it would be the preferred treatment for locally advanced breast cancer (LABC), if its oncological safety is confirmed.

Methods: In this study, we retrospectively compared the oncologic outcomes of post-neoadjuvant chemotherapy BCS with mastectomy in 202 patients with LABC.

**Results:** There were no significant differences between BCS and mastectomy regarding overall survival, local recurrence, contralateral breast cancer, and distant metastasis.

Conclusions: Our study showed that post-neoadjuvant chemotherapy BCS is an oncologically safe surgical treatment in LABC and that BCS can be considered as an acceptable treatment in selected patients with LABC.

#### Introduction

neoadjuvant chemotherapy,

breast-conserving surgery,

Key words:

mastectomy,

outcome, survival

Breast cancer,

Breast cancer is the most prevalent site-specific cancer among women. It is the first cause of cancer death among women in less developed regions (324,000 deaths, 14.3% of total), and the second in more developed regions (198,000 deaths, 15.4%).<sup>1</sup> Breast cancer is the leading type of cancer in Iranian females, accounting for 24.6% of all cancer cases, with average annual crude incidence rate of 22.6 per 100,000 (95% CI, 22.1-23.1)<sup>2</sup> It is reported to be the fifth cause of cancer death in Iranian females.<sup>3</sup>

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Stage of the disease is the most important prognostic factor in breast cancer. Patients at earlier stages of cancer have better survival than those at later stages.<sup>4</sup> Nowadays, in most parts of the world, breast cancer is frequently diagnosed at early stages,<sup>1,2</sup> although in some less developed countries diagnosis at later stages is common, probably due to poor access to medical care. The majority of breast cancer cases in Iran are diagnosed at early stages, and the prevalence of stage III (locally advanced breast cancer (LABC)) and metastatic breast cancers are reported to be 17% and 1.6%, respectively.<sup>3</sup>

Surgical treatment for breast cancer has changed over time from traditional Halsted radical mastectomy to less aggressive procedures like breast-conserving surgery (BCS). With the advent of different adjuvant modalities like chemotherapy and radiation therapy, limited surgical procedures with excellent local and distant control have become possible.

Nowadays, the standard treatment for LABC is mastectomy or BCS, followed by adjuvant/ neoadjuvant chemotherapy and adjuvant radiation. Neoadjuvant chemotherapy (NAC) is an important part of LABC treatment; NAC not only makes more tumors operable in LABC, but also makes more patients eligible for BCS—patients who otherwise would not be BCS candidates according to their initial tumor size.

As BCS is preferred to mastectomy in terms of cosmetic, quality-of-life, and functional outcomes, it would be the preferred treatment for LABC, if its oncological safety is confirmed. Many studies have shown that, in terms of local recurrence rate, disease-free survival, and overall survival, BCS produces outcomes comparable to or even better than mastectomy in patients with LABC.<sup>5-9</sup> However, as some reports have shown unfavorable results, such as more local recurrence after BCS, there is still some controversy about its safety.<sup>10, 11</sup> Therefor, more investigation is required.

In this study, we compared the outcomes of post-NAC BCS with post-NAC mastectomy to assess the safety of less aggressive procedures in patients with LABC.

#### Methods

Data on all patients (n = 322) with LABC (stage III breast cancer according to the American Joint

Committee on Cancer, 7<sup>th</sup> edition. 2010) who were admitted to Kaviani Breast Disease Institute (KBDI) in an 8-year period were evaluated retrospectively. Of them, 202 female patients who had undergone standard treatment for LABC, namely, neoadjuvant chemotherapy and surgery (mastectomy or BCS) followed by adjuvant radiotherapy (and adjuvant chemotherapy and hormone therapy as needed according to standard guidelines), were included in the study.

Data included age at diagnosis, number of neoadjuvant chemotherapy courses, histologic type (according to WHO classification), initial clinical tumor size, date of surgery, type of surgery (mastectomy vs BCS), pathologic tumor size after NAC, number of excised lymph nodes, number of involved lymph nodes, ratio of involved lymph nodes to total excised lymph nodes (LNR), hormone receptor status (ER, PR, and HER2, according to WHO classification), overall survival, disease-free survival, local recurrence, contralateral breast cancer, distant metastasis, and all-cause mortality.

Data were analyzed using R statistical software (version 3.3.3). Qualitative variables were analyzed using the chi-square test and the Fisher exact text, when appropriate. Survival analysis was preformed using the Kaplan-Meier method and log-rank test. The Cox proportional hazard test was used for multivariate analysis, as needed. P value was considered significant when it was less than 0.05.

 Table 1. Summary of patients' demographics

		Mastectomy	BCS	P-value
N		161	41	
Age, mean (SD), y		50.53 (11.96)	43.52 (10.51)	0.004
No. of neoadjuvant chemotherapy, median []	IOR]	6 (4–7)	6 (6–8)	0.164
Histological type				0.234
	IDC	136 (95.8)	31 (91.2)	
	ILC	4 (2.8)	3 (8.8)	
	other	2 (1.4)	0 (0.0)	
Tumor size after NAC, median [IQR]		25 (15-40)	20 (15-30)	0.066
No. of LN excised, median [IQR]		9 (6-12)	8.00 (5.25–11)	0.291
No. of LN involved, median [IOR]		2 (0-6)	1 (0-2.75)	0.013
ER (%)		~ /		0.394
	Positive	99 (69.7)	25 (78.1)	
	Negative	43 (30.3)	7 (21.9)	
PR (%)	6			0.326
	Positive	85 (59.9)	24 (70.6)	
	Negative	57 (40.1)	10 (29.4)	
HER2 (%)	6			0.839
(**)	Positive	47 (33.3)	10 (29.4)	
	Negative	94 (66.7)	24 (70.6)	
Triple-negative (%)		21 (15.1)	2 (6.2)	0.255
Involved/excised LNR (%)		()	= ()	0.587
	< 0.25	31 (34.1)	8 (44.4)	
	0.25-0.65	29 (31.9)	6 (33.3)	
	> 0.65	31(341)	4(22.2)	
Status	0.00		. ()	0.253
Suitus	Alive	98 (73 1)	30 (85 7)	0.200
	Deceased	5 (37)	2(57)	
	Local recurrence	3(22)	1(2.9)	
	Contralateral recurrence	3(22)	0(00)	
	Distant metastasis	25 (18.7)	2 (5.7)	
### Results

Data on 208 patients with LABC were evaluated. After excluding cases with missing data, 202 patients were analyzed, of whom 161 had undergone mastectomy, and 41 had undergone BCS after NAC.

The mean age at diagnosis was 50.53 and 43.52 years for the mastectomy and the BCS group, respectively (P = 0.004). The median number of chemotherapy courses for both groups was 6 cycles. The most prevalent histologic type in both groups was invasive ductal carcinoma (95.8% and 91.2% in the mastectomy and the BCS group, respectively). The median pathologic tumor size after NAC was 25 mm in the mastectomy group and 20 mm in the BCS group (P = 0.066). The median number of excised lymph nodes (LNs) were 9 and 8 in the mastectomy and the BCS group respectively (P = 0.291), and the median number of involved LNs were 2 and 1 in the mastectomy and the BCS group, respectively (P = 0.013).

The difference in LNR was not significant between the two treatment groups. Although more patients in the BCS group were hormone receptor-positive and HER2-negative than in the mastectomy group, no statistically significant difference was observed.

After a median follow-up of 556 days (range, 22–2622 days), there were 5 deaths, 3 local recurrences, 3 contralateral breast cancers, and 25 distant metastases in the mastectomy group; and in the BCS group there were 2 deaths, 1 local recurrence, no contralateral breast cancer, and 2 distant metastases. However, the difference between the two treatment groups on these events was not significant (P=0.253) (Table 1).

The two groups did not differ significantly on both overall 1-year survival (P = 0.38) and 5-year survival (P = 0.99) (Tables 2 and 3). Five-year disease-free survival rate was 98% for the mastectomy group and 96.1% for the BCS group (P = 0.39) (Table 4).

Also, no significant difference was observed between the two groups in terms of recurrence (either local or contralateral) (P=0.57) (Figures 1, 2, and 3). Mean and median survival times are presented in Tables 5 and 6.

 Table 2. Breast cancer survival probability by type of surgery by Log-Rank test

Survival	Mastectomy	BCS	P-value
1-year	98.2%	100%	0.38
5-year	85.6%	96.6%	0.99

Table 3. Restricted	mean survival	time of breast	cancer by type	e of surgerv
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Group	Ν	event	Restricted Mean Survival time (Days)	SE
Mastectomy	128	5	2028	58.5
BCS	30	1	1699	0

Table 4. One-year and five-year disease-free survival rates for the two groups

Disease-free survival	Mastectomy	BCS	P-value
1-year	100%	100%	NA
5-year	98%	96.1%	0.39

### Table 5. Mean and median survival time (in days) for all patients

Mean <sup>a</sup>					Medi	an	
95% Confidence Interval				95% Confiden	ice Interval		
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Lower Bound
1701.587	133.615	1439.701	1963.473	1729.000	183.291	1369.749	1369.749

a. Estimation is limited to the largest survival time if it is censored.

### Table 6. Mean and median disease-free survival time (in days) for all patients

Mean <sup>a</sup>					Medi	an	
95% Confidence Interval				95% Confider	nce Interval		
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Lower Bound
2217.446	110.616	2000.638	2434.254		•		

a. Estimation is limited to the largest survival time if it is censored.



Figure 1. Probability of breast cancer overall survival by type of surgery



Figure 2. Probability of breast cancer disease-free survival by type of surgery



Figure 3. Cumulative hazard of breast cancer recurrence by type of surgery

No significant difference was observed in overall survival between patients with ER+ and ER- tumors (P = 0.35), but the difference in survival between PR+ and PR- patients was significant (P = 0.012), with PR+ patients having better survival (Figure 4). There was also no significant difference in overall

survival between HER2- and HER2+ patients (P = 0.17). The difference in overall survival after adjusting for histologic types was also not significant (P = 0.89). The survival in patients with LNR > 0.65 was significantly lower than in patients with LNR < 0.65 (P = 0.045) (Figure 5).

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Figure 4. Probability of breast cancer survival by PR receptor status



Figure 5. Probability of breast cancer survival by LNR

### Discussion

This study showed that, in patients with LABC who had received NAC, there is no significant difference between BCS and mastectomy in terms of overall survival, local recurrence (one of the main concerns when substituting BCS for mastectomy), contralateral breast cancer, and distant metastasis.

These findings have been confirmed by other reports. In two studies on 284 and 147 patients, 10 years of follow-up did not reveal any significant difference in local recurrence and overall survival between those undergoing BCS and mastectomy after NAC.<sup>5,6</sup> In another study by Barranger *et al.* on 119 patients who initially were mastectomy

candidates, 5-year overall survival after BCS or mastectomy was 77%, and 5-year disease-free survival rates after BCS and mastectomy were 74% and 59%, respectively (not statistically significant). They concluded that, in patients with chemosensitive breast tumor, NAC results in a significant "mastectomy to BCS" conversion rate and that the type of surgery does not appear to affect the patient's overall and disease-free survival rates.<sup>7</sup> Chen and colleagues studied the patterns of local-regional recurrence (LRR) and ipsilateral breast tumor recurrence (IBTR) among 340 breast cancer cases treated with breast conservation therapy following neoadjuvant chemotherapy. After a median followup of 60 months, 5-year LRR-free and IBTR-free survival rates were calculated to be 91% and 95%, respectively.

They concluded that breast-conserving therapy following neoadjuvant chemotherapy would lead to reduced rates of LRR and IBTR in appropriately selected patients, even those with T3 or T4 disease.<sup>8</sup> Finally, Zhou and associates reviewed 8 trials with a total number of 3215 patients, and reported a 9.2% prevalence of local recurrence in the BCS group versus 8.3% in the mastectomy group (P = 0.66). They also found a non-significantly lower rate of 5-year local recurrence–free survival (LRFS) in the mastectomy group versus the BCS group (P = 0.74). They concluded that BCS after NCT is safe in terms of local recurrence and LRFS in LABC.<sup>9</sup>

Although most reports confirm excellent overall survival in patients with LABC treated with NAC and BCS, some studies mention higher rates of local recurrence after BCS. This poses a real concern as it has been proposed that local recurrence can have a detrimental effect on overall survival. In the study by Mauriac et al. on 134 women with T2 (> 3 cm) or T3N0–1M0 breast tumors, the majority of patients had undergone BCS at the end of neoadjuvant chemotherapy, with no significant difference in survival when compared with the mastectomy group. They considered post-NAC BCS as the new goldstandard treatment for patients with tumors too large to be treated immediately by conserving surgery. However, they deemed it necessary to inform the patient of the risk of local recurrence in breastconserving therapy.<sup>10</sup> In another study by Rouzier *et* al., the incidence and the prognostic value of IBTR were evaluated in 257 patients treated with primary chemotherapy and BCS and radiotherapy. At a median follow-up of 93 months, they reported relatively high rates of local recurrence: 16% (± 2.4%) at 5 years and 21.5% ( $\pm$  3.2%) at 10 years.<sup>1</sup> However, the higher rates of local recurrences in these studies may be explained by the use of different chemotherapeutic agents (epirubicin, vincristine, MTX, etc.) or adoption of non-precise criteria to make decision for a conserving surgical treatment (BCS was performed if the residual tumor, taking into account the breast size, could be removed with clear margins).<sup>10,11</sup>

This study suffers from some shortcomings. It was non-randomized and retrospective, making it difficult to draw a definite conclusion about post-NAC BCS outcomes. The relatively small number of patients, especially in the BCS group, is another weakness of this study. Relatively short follow-up of patients is another drawback of our study, as a remarkable number of recurrences in BCS patients occur after 2 years of treatment; therefor, longer follow-ups would be better. Although our results about the oncologic safety of post-NAC BCS are in concordance with most previous studies, prospective randomized trials with larger sample sizes and longterm follow-up will help draw a definitive conclusion.

According to the results of our study, post-NAC BCS is an oncologically safe surgical treatment for eligible patients with LABC. This kind of surgical management has potentially more favorable functional and cosmetic outcomes, which is especially important to younger patients. BCS can be considered an acceptable treatment in selected patients with LABC, and having an initially advanced stage of cancer in itself should not prevent the patient or the surgeon from pursuing BCS.

### **Conflict of Interest**

There is no conflict of interests in this study.

### References

- 1. 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. Int J Cancer. 2015;136(5):E359-86.
- 2. Jazayeri SB, Saadat S, Ramezani R, Kaviani A. Incidence of primary breast cancer in Iran: Tenyear national cancer registry data report. Cancer Epidemiol. 2015;39(4):519-27.
- 3. Akbari ME, Mozaffar M, Heidari A, Zirakzadeh H, Akbari A, Akbari M, *et al.* Recurrence and survival effect in breast conserving surgery: what are the predictive and/or prognostic factors? Iranian Journal of Cancer Prevention. 2011;4(2):49-54.
- 4. Surgeons. NcdoACo. 2016 [Available from: https://www.facs.org/~/media/files/quality%20 programs/cancer/ncdb/ncdb\_2016\_booklet\_v11 .ashx.
- 5. Levy A, Borget I, Bahri M, Arnedos M, Rivin E, Vielh P, *et al.* Loco-regional control after neo-adjuvant chemotherapy and conservative treatment for locally advanced breast cancer patients. The Breast Journal. 2014;20(4):381-7.
- Touboul E, Lefranc J-P, Blondon J, Buffat L, Deniaud E, Belkacémi Y, *et al.* Primary chemotherapy and preoperative irradiation for patients with stage II larger than 3 cm or locally advanced non-inflammatory breast cancer. Radiotherapy and Oncology. 1997;42(3):219-29.
- Barranger E, Antomarchi J, Chamorey E, Cavrot C, Flipo B, Follana P, *et al*. Effect of neoadjuvant chemotherapy on the surgical treatment of patients with locally advanced breast cancer requiring initial mastectomy. Clinical Breast Cancer. 2015;15(5):e231-e5.
- Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, *et al.* Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. Journal of Clinical Oncology. 2004;22(12): 2303-12.

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- 9. Zhou X, Li Y. Local recurrence after breastconserving surgery and mstectomy following neoadjuvant chemotherapy for locally advanced breast cancer-a meta-analysis. Breast Care. 2016;11(5):345-51.
- Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M, *et al.* Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. Annals of Oncology. 1999;10(1):47-52.
- 11. Rouzier R, Extra J-M, Carton M, Falcou M-C, Vincent-Salomon A, Fourquet A, *et al.* Primary chemotherapy for operable breast cancer: incidence and prognostic significance of ipsilateral breast tumor recurrence after breastconserving surgery. Journal of Clinical Oncology. 2001;19(18):3828-35.





### DOI: 10.19187/abc.201744136-140 Prediction of Hope of Life Based on Spiritual Well-being and Psychological Hardiness in Women With Breast Cancer

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### ABSTRACT

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Key words: Hope, spiritual well-being, psychological hardiness, breast cancer

### Introduction

Common cancers in women are cancers of breast, skin, colon, rectum, stomach, esophagus, the hematopoietic system, thyroid, ovary, and uterus.<sup>1</sup> Breast cancer is the most common cancer in women,

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**Background:** Psychological factors such as hope of life can slow cancer progression by improving immune function, which results in better protection against illness and may help the body to fight cancer. It is of high importance in cancer patients, especially in women with breast cancer who may experience more stress. The present study investigated the predictability of hope of life based on spiritual well-being and psychological hardiness in women with breast cancer.

**Methods:** The population of this study included all women with breast cancer who were referred to Cancer Institute of Iran for follow-up in the fall of 2016. Onehundred four patients were recruited based on purposive sampling. They completed the validated questionnaires for hope, spiritual well-being, and psychological hardiness (consisting of commitment, control, and challenge subscales). Data were analyzed by using Pearson's correlation coefficient and hierarchical multiple regression.

**Results:** Finding indicated a significant positive relationship between hope of life and spiritual well-being as well as psychological hardiness (commitment, control, and challenge) in women with breast cancer (P < 0.01). Spiritual well-being explained 39.5% of the variance in hope of life (P < 0.01). Psychological hardiness explained 16.7% of the variance in hope of life (P < 0.01), and only the commitment subscale predicted hope of life (P < 0.01) in women with breast cancer.

**Conclusions:** According to this study, patients with higher spiritual well-being and higher commitment (a subscale of psychological hardiness) had greater hope of life. Psychological interventions for strengthening these factors in women with breast cancer are suggested.

accounting for 24.4% of all malignancies.<sup>2</sup>

Cancer creates stress, which can significantly affect every aspect of a person's life.<sup>3</sup> Cancer has the greatest impact on hope in comparison with other chronic diseases and is one of the main hopeshattering factors in these patients.<sup>4,5</sup> Hope has been identified as an important resource for cancer patients that has an immense impact on their quality of life.<sup>6</sup> Cancer and its treatments cause fear and anxiety and often decrease hope in these patients.<sup>7</sup> Although cancer does not mean certain death, it evokes images of deformity, pain, financial and social problems, dependency, family rupture, and death, causing deep emotional problems in patients and their families.8

Breast cancer is intolerable to most women. These patients have a fear of the reaction of their spouses, if married, or worry about marriage, if unmarried. They are also concerned of being sterilized due to treatments and losing charm.<sup>9</sup> Ouality of life is seriously affected in patients with breast cancer.<sup>11</sup> The prevalence of depression in women with breast cancer has been reported to be 29.6%.<sup>12</sup> Long-term stress reduces the body's immune function and leads to faster progress of cancer cells as well as a slowed treatment process. Anything that can reduce mental problems in these patients will be effective in the recovery process and will increase their quality of life.<sup>13</sup> Psychotherapy can help reduce the psychological effects of cancer treatments in many ways.<sup>14</sup>

Hope is defined as "a cognitive set compromising" agency (belief in one's capacity to initiate and sustain actions) and pathways (belief in one's capacity to generate routes) to reach goals."<sup>15</sup> Hopeful people can tolerate the sickness crisis more easily.<sup>16</sup> On the other hand, research shows that religious/spiritual coping is an important strategy among cancer patients.<sup>17</sup> For those patients in the last stages of their illness, spirituality and religious peace may be even more important than physical and mental health. There is a significant positive relationship between hope of life and spiritual well-being in cancer patients,15 and individuals with high degrees of hardiness are presumed to be better able to cope with negative effects of life stressors like cancer.<sup>18</sup> Research has shown a significant positive correlation between hardiness and hope of life.<sup>3</sup>

Given the psychological, emotional, and behavioral problems in women with breast cancer, the aim of this study was to assess the association of hope of life with spiritual well-being and psychological hardiness and to predict hope based on spiritual well-being and psychological hardiness in women with breast cancer.

### Methods

The population of the study included all women with breast cancer who were referred to Cancer Institute of Iran for follow-up in the fall of 2016. One hundred four patients were recruited through purposive sampling. After providing necessary explanations about the study to participants and obtaining their informed consent, the researchers completed the questionnaires for them through structured interviews.

Inclusion criteria:

1. Age: 25–70 years old;

- 2. Ability to read and write and to comprehend the sentences of the questionnaire;
- 3. Having stage I, II or III breast cancer;
- 4. At least two months since disease diagnosis;

- 5. Having non-metastatic cancer;
- 6. Lack of a concomitant disease;
- 7. Not use of psychiatric drugs.

### Research Tools

Demographic questionnaire

Demographic data included age, education, job, and duration of disease.

### Hope scale

Snyder developed this scale in 1991, which consists of 12 items. Four items measure pathways (planning to meet goal), 4 items measure agency thinking, and 4 items are fillers. It is a 5-point Likert-type scale and the score can range from 8 to 40. Kermani *et al.* estimated the Cronbach's alpha at 0.86 and reliability at 0.81 through test-retest method for this scale.<sup>19</sup> In this study, Cronbach's alpha was 0.75, which indicates good internal consistency.

### Spiritual Well-Being Scale

This scale, which consists of 20 items, was developed by Paloutzain and Ellison in 1982. Ten items measure religious well-being and 10 items measure existential well-being. It is a 6-point Likerttype scale and scores can range from 20 to 120. Seyed-fatemi and colleagues estimated the Cronbach's alpha at 0.82 for this scale.<sup>20</sup> In this study, Cronbach's alpha was 0.88, indicating good internal correlation.

### Short form of hardiness scale

Kobasa *et al.* developed this shortened scale with 20 items in 1982, which consists of three subscales: commitment (9 items), control (7 items), and challenge (4 items). It is a 4-point Likert-type scale with scores ranging from 9–36 for commitment, 7–28 for control, and 4–16 for challenge. Cronbach's alpha for this scale was 0.67.<sup>21</sup> In this study, Cronbach's alpha was 0.79 for commitment, 0.78 for control, and 0.88 for challenge subscale, which indicated good internal correlation.

### Statistical analysis

Data were analyzed by using Pearson's correlation coefficient and hierarchical multiple regression. This model was used to examine the relationship between the two independent variables and the dependent variable to isolate predictors (spiritual well-being and psychological hardiness, which have a significant influence on hope of life). SPSS software (version 21) was used for data analysis.

### Results

The mean ( $\pm$  SD) age of patients was  $45.48 \pm 8.6$  years. Demographic data, consisting of age, education, job, and the duration of disease, are demonstrated in Table 1.



The mean ( $\pm$  SD) of variables for all participants and the correlation coefficients for the variables of study are presented in Table 2. Results showed a significant positive relationship between the subscales of psychological hardiness and hope of life (commitment: r = 0.673, P < 0.01; control: r = 0.511, P < 0.01; and challenge: r = 0.392, P < 0.01). Also, there was a significant positive relationship between spiritual well-being and hope of life in women with breast cancer (r = 0.593, P < 0.01).

After examining the assumptions of multiple regression analysis (i.e. normality, collinearity, and independence of errors), we conducted the regression analysis. The results of multiple regression for the prediction of hope of life based on spiritual well-being and psychological hardiness (commitment, control and challenge) are presented in Table 3.

**Table 1.** Demographic information of participants

	F F
Variables ( $N = 104$ )	N (%)
Age (year)	
$\leq 40$	31 (29.8)
41-45	23 (22.11)
45-50	23 (22.11)
$\geq$ 50	27 (26)
Education	
High school graduate	78 (75)
BS	19 (18.3)
MS and PhD	7 (6.7)
Job	
Housewife	79 (76)
Employed	11 (10.5)
Retired	14 (13.5)
Disease duration (year)	
<1	46 (44.2)
1–5	39 (37.6)
5-10	17 (16.3)
> 10	2 (1.9)

**Table 2.** Correlation matrix of descriptive analysis for all variables

Variables	Mean	SD	1	2	3	4	5
1. spiritual well-being	99.68	13.22	-				
2. hardiness (commitment)	22.97	6.51	0.521**	-			
3. hardiness (control)	17.89	4.98	0.482**	0.593**	-		
4. hardiness (challenge)	9.54	4.38	0.284**	0.478**	0.367**	-	
5. hope of life	30.87	5.52	0.593**	0.673**	0.511**	0.392**	-

\*P < 0.05; \*\*P < 0.01

As demonstrated in Table 3, in the first step, spiritual well-being was entered in the equation and predicted hope of life (F = 66.516, P < 0.01) and explained 39.5% of the variance in hope of life (R<sup>2</sup>= 0.395). The regression coefficient was positive and significant ( $\beta$  = 0.356, P < 0.01). In the second step, the subscales of psychological hardiness were entered in the equation, which increased the explanation of the variance in hope of life to 56.2% (R<sup>2</sup>= 0.562,  $\Delta$ R<sup>2</sup>= 0.167). It means that by entering the components of psychological hardiness (commitment, control and challenge) in equation and controlling for the effect of spiritual well-being, the explanation of the variance in hope of life was increased by 16.7% ( $\Delta$ F = 12.590, P<0.001).

The regression coefficient for the commitment subscale was positive and significant ( $\beta = 0.415$ , P < 0.01). The results demonstrated that spiritual wellbeing as well as the commitment subscale of psychological hardiness predicted hope of life in women with breast cancer.

### Discussion

The aim of this study was to investigate the role of spiritual well-being and psychological hardiness in prediction of hope of life in patients with breast cancer. Hope is increasingly considered as important for coping with a disease such as cancer, and it enables people to cope with difficult and stressful situations and suffering,<sup>22</sup> Therefore, it is important

**Table 3.** Hierarchical multiple regression for the prediction of hope of life based on spiritual well-being and psychological hardiness in women with breast cancer

	b	SE	β	t	P value
Step 1 (spiritual well-being) Spiritual well-being	0.149	0.034	0.356	4.391	0.001
	F(1, 10	2) = 66. 516, P -	< 0.01 R2 =	0.395	
Step 2 (psychological hardiness) Commitment Control Challenge	0.352 0.078 0.072	$\begin{array}{c} 0.079 \\ 0.098 \\ 0.096 \end{array}$	$\begin{array}{c} 0.415\\ 0.070\\ 0.058\\ 0.001 \qquad \mathbb{R}^2 = 0 \end{array}$	4.481 0.820 0.735	0.001 0.414 0.453
	Γ(4, 9) ΔF	= 12.59, P < 0.0	$\Delta R^2 = 0.16$	57 57	

to study the predictors of hope of life in patients with cancer. The present study indicated that there was a significant positive relationship between spiritual well-being and hope of life, and spiritual well-being had a major contribution to predicting hope of life (39.5%) in women with breast cancer. This finding is consistent with the results of other studies. Rostamizadeh showed a significant positive relationship between spiritual well-being and hope in people with metastatic cancer, people with treatable cancer, and healthy persons.<sup>23</sup> The findings of the study by Shohani et al. showed the role of religious beliefs in hope, and religious beliefs could predict 12% of the variance in hope in cancer patients.<sup>4</sup> Yeganeh reported a significant positive correlation between religious orientation and hope in women with breast cancer.<sup>24</sup> Fallah et al. showed that spiritual therapy significantly increased the level of hope and mental health in women with breast cancer.<sup>25</sup> Baljani et al. demonstrated the important role of religious and spiritual well-being in hope in cancer patients.<sup>16</sup> Considering the result of the present study that spiritual well-being predicted hope of life and explained 39.5% of the variance in hope of life, the importance of spiritual well-being (consisting of religious well-being and existential well-being) in prediction of hope in patients with breast cancer is further emphasized.

The results of the current study also showed a significant positive relationship between psychological hardiness (commitment, control, and challenge) and hope of life, and hardiness explained 16.7% of the variance in hope of life. However, the regression coefficients showed that only commitment subscale predicted hope of life in patients with breast cancer. These findings are consistent with some previous studies. The study by Sanei *et al.* showed a significant positive correlation between hardiness and hope in women with breast cancer.<sup>26</sup> Ghasempour *et al.* and Naderi *et al.* also demonstrated a significant positive correlation between hardiness and hope of life.<sup>27, 28</sup> Pollock and Duffy showed that hardiness is the main predictor of psychological and physiological compatibility.<sup>29</sup> Craft showed that hardiness had a positive impact on coping with cancer and increased patient's tolerance against disease.<sup>30</sup> Temoshok and Fox found that people with higher scores on hardiness scale show more resistance to the disease and survive longer than other patients.<sup>31</sup> The results of our study showed the role of psychological hardiness in prediction of hope in breast cancer patients.

According to the results of this study, hope of life is greater in patients with breast cancer who have higher spiritual well-being and psychological hardiness (commitment). Therefore, psychological interventions for improving spiritual well-being and psychological hardiness are suggested in order to increase hope of life and quality of life in women with breast cancer. Given the importance of quality of life and addressing the psychological, emotional, social, spiritual, and functional aspects of cancer, further research is essential in the field of psychoncology to explore the psychological, social, behavioral, clinical and ethical aspects of breast cancer for helping cancer patients and their families better adapt to cancer.

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### References

- 1. Almasi Z, Mohammadian-Hafshejani A, Salehiniya H. Incidence, mortality, and epidemiological aspects of cancers in Iran; differences with the world data. Journal of BU ON: official journal of the Balkan Union of Oncology. 2016;21(4):994-1004.
- 2. Sharifian A, Pourhoseingholi MA, Emadedin M, Nejad MR, Ashtari S, Hajizadeh N, *et al.* Burden of breast cancer in Iranian women is increasing. Asian Pac J Cancer Prev. 2015;16(12):5049-52.
- 3. Jafari E, Sorabi F, Jomehri F, Najafi M. The relation ship between type C personality, locus of control and hardiness in patients suffering from cancer and normal subjects. Journal of clinical psychology. 2009;1(1):47-66.
- 4. Shoohani F, Asghari E, Sheikholeslami F, Alitaleshi M. The relationship between religious beliefs and hope in cancer patients. depiction of health. 2015;5(4):1-5.
- Pourghaznein T, Hoshmand P, Talasaz Firouzi E, Esmailli H. The sources of inspiration and the level of hope among cancer patients. Iranian Journal of Psychiatry and Clinical Psychology. 2003;8(4):82-7.
- 6. Esbensen BA, Thomsen T. Quality of life and hope in elderly people with cancer. Open Journal of Nursing. 2011;1(02):26.
- Kamian S, Taghdisi MH, Azam K, Estebsari F, Ranjbaran S, Geravand A. Evaluating effectiveness of spiritual health education on increasing hope among breast cancer patients. Iranian Journal of Health Education and Health Promotion. 2014;2(3):208-14.
- 8. Malekian A, Alizadeh A, Ahmadzadeh GH. Anxiety and depression in cancer patients. J Res Behav Sci 2007;5(2):115-7.
- Fekri K, Shafiabady A, Sanaei Zaker B, Harirchi I. The efficacy of individual guided imagery method on the amount of anxiety and hope for life in women suffering from breast cancer. J Sci & Res Psychol. 2006;9(31):1-16.
- 10. Bolhari J, Naziri G, Zamanian S. Effectiveness of spiritual group therapy in reducing depression,



anxiety, and stress of women with breast cancer. Women Sociol 2012;3(9):87-117.

- 11. Zou Z, Hu J, McCoy TP. Quality of life among women with breast cancer living in Wuhan, China. International Journal of Nursing Sciences. 2014;1(1):79-88.
- Fonseca S, Lencastre L, Guerra M. Life Satisfaction in Women With Breast Cancer1. Paidéia (Ribeirão Preto). 2014;24(59):295-303.
- 13. Abolghasami S, Saeadi S, Morri NN. The effect of guided imagery and logo therapy on depression, anxiety and hopefulness in women with cancer in Ahwaz. 2010.
- 14. Newell SA, Sanson-Fisher RW, Savolainen NJ. Systematic review of psychological therapies for cancer patients: overview and recommendations for future research. Journal of the National Cancer Institute. 2002;94(8):558-84.
- 15. Snyder CR, Sympson SC, Ybasco FC, Borders TF, Babyak MA, Higgins RL. Development and validation of the State Hope Scale. Journal of personality and social psychology. 1996;70(2):321.
- 16. Baljani E, Khashabi J, Amanpour E, Azimi N. Relationship between spiritual well-being, religion, and hope among patients with cancer. Journal of hayat. 2011;17(3):27-37.
- 17. Mesquita AC, Chaves Éd CL, Avelino CCV, Nogueira DA, Panzini RG, Carvalho ECd. The use of religious/spiritual coping among patients with cancer undergoing chemotherapy treatment. Revista latino-americana de enfermagem. 2013;21(2):539-45.
- 18. Aflakseir A, Nowroozi S, Mollazadeh J, Goodarzi MA. The role of psychological hardiness and marital satisfaction in predicting posttraumatic growth in a sample of women with breast cancer in Isfahan. Iranian journal of cancer prevention. 2016;9(4).
- 19. Kermani Z, Khodapanahi M, Haidari M. Psychometric specifications of Snyder hope scale. J Applied Psychol 2011;5(3).
- Seyed Fatemi N, Rezaei M, Givari A, Hoseini F. The effect of prayer on spiritual well-being in patients with cancer. Payesh. 2005;5(4):295-304.
- 21. O'neal MR. Measuring resilience. Symposium at the annual meeting of the Mid-South1999.
- 22. RustøenT. Hope and quality of life, two central issues for cancer patients: a theoretical analysis. Cancer nursing. 1995;18(5):355-61.
- 23. Rostamizadeh E. Relationship between spiritual well-being, hope to life and death anxiety in patients with cancer (metastatic & treatable) and healthy people. Gilan; 2016.
- 24. Yeganeh T. Role of religious orientations in determination of hope and psychological wellbeing in female patients with breast cancer.Iranian J Breast Dis 2013;6(3):47-56.
- 25. Fallah R, Golzari M, Dastani M, Zahireddin A,

Mousavi M, Akbari ME. Effectiveness of spiritual group intervention on increasing hope and mental health in women with breast cancer. Thought & Behavior in Clinical Psychology. 2011;5(19):69-80.

- 26. Sanei M, Hezri Mogaddam N, Zainoddini Maimand Z. Relationship between religious attitude and hopefulness in women with breast cance. International Congress of Psychology and culture of life: Mobein 2015.
- 27. Naderi F, Hosseini S. Relationship between hope to life and psychological hardiness in students of Azad University of Gachsaran. Woman & Soci. 2010;2(1):140.
- 28. Ghasempour A, Hasanzade S. The role of forgiveness and psychological hardiness in prediction of hope. JSR. 2011;12(45):12-9.
- 29. Pollock SE, Duffy ME. The Health-Related Hardiness Scale: development and psychometric analysis. Nursing research. 1990;39(4):218-22.
- 30. Craft CA. A conceptual model of feminine hardiness. Holistic Nursing Practice. 1999;13(3):25-34.
- 31. Temoshok L, Fox BH. Coping styles and other psychosocial factors related to medical status and to prognosis in patients with cutaneous malignant melanoma. Impact of psychoendocrine systems in cancer and immunity. (Edited by Fox B. H. and Newberry B. H.). C. J.Hogrefe, New York, 1984:258-87.





### DOI: 10.19187/abc.201744141-145 The Bench of Primary Breast Lymphoma Treatment: A Review of the Literature and a Case Report

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### ARTICLE INFO

### ABSTRACT

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Key words: Breast lymphoma, primary breast lymphoma (PBL), diffuse large B-cell lymphoma (DLBCL)

### Introduction

Breast lymphoma is a rare type of extra-nodal lymphoma that could be categorized to primary breast lymphoma (PBL) and secondary breast lymphoma (SBL).<sup>1</sup> The criteria for the diagnosis of PBL were first defined by Wiseman and Liao in 1972, including (a) close anatomic association with mammary and lymphomatous tissue, (b) absence of a previous diagnosis of an extra-mammary lymphoma, (c) lack of any disseminated disease (except involvement of the ipsilateral axillary lymph node), and (d) adequate quality of the histopathological specimen. SBL is considered to be

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**Background:** Primary non-Hodgkin breast lymphoma is a rare pathology, representing 0.5 percent of malignant breast tumors.

**Case Presentation:** Here, we report a 54-year-old female presenting a mass in the left breast diagnosed by needle biopsy and IHC as a diffuse large B-cell lymphoma (DLBCL). Radiation therapy with conventional fields was applied for whole breast irradiation after the patient received 6 courses of R-CHOP (Rituximab plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) chemotherapy. At the follow-up period 11 months after radiation therapy, no morbidities occurred and the patient is surviving with no evidence of disease.

**Conclusions:** The common treatments for breast lymphomas are surgery, radiation therapy, and chemotherapy. Although no agreement has been reached on the best therapy for primary breast lymphomas, these methods are commonly applied alone or in combination. It seems that R-CHOP combined with radiation therapy regimen could be an important treatment modality in avoiding unnecessary surgery.

a presentation of lymphoma in the organs and lymph node regions other than the breast and regional lymph nodes.<sup>1</sup>

B-cell lymphomas are considered to be more common than T-cell lymphomas of the breast.<sup>2</sup> There are 2 stages of PBL, defined as stage IE, which is limited to the breast only, and stage IIE, which involves the breast and ipsilateral axillary lymph nodes.<sup>1, 3</sup> The treatments for breast lymphomas include surgery, radiation therapy (RT), and chemotherapy. These methods have been used alone and in combination.<sup>4</sup> The most common symptom of breast lymphoma is a painless mass in the breast, which is similar to breast carcinoma; thus, the initial treatment is considered to be surgery.<sup>4</sup> However, studies have shown that mastectomy is not the first choice for treatment of PBL, as both disease-specific survival and overall survival (OS) are significantly decreased after this procedure.<sup>4</sup> Extensive radical surgery could be damaging and surgery should be limited to lumpectomy.5 Previous prospective studies have demonstrated that chemotherapy



improves progression-free survival and OS in PBL and, thus, chemotherapy is the first choice for treatment.  $^{6,7}$ 

RT for PBL is deemed efficient to prevent ipsilateral relapse.<sup>4</sup> RT has been applied with conventional fields or three-dimensional conformal RT for whole breast irradiation.<sup>5</sup> Recently, a prospective study confirmed that combined treatment with RT and chemotherapy was more effective compared to single treatment, as it significantly improves overall and event-free survival.<sup>6</sup> In this case, we combined chemotherapy and RT as a treatment regimen. The outcome of this case report may help to establish more effective treatment guidelines for PBL.

### **Case Presentation**

### Clinical summary-History of patient

A 54-year-old female was referred to our center. She complained of swelling in her left breast. During a physical examination, palpation revealed a mass measuring 4cm in its maximum dimension which was tender, mobile, and firm to hard in consistency located in the upper outer periareolar region of the left breast, and a palpable lymph node of 1.5cm in diameter was found in the ipsilateral axillary tail. The overlying breast skin, areola, and nipple were unremarkable. Clinically, there was a suspicion of the breast lump.

Primary staging procedures comprised the following options: blood chemistry, complete blood

ultrasonography, bone marrow aspiration, MRI and computed tomography of the thorax, abdomen, and pelvis. Needle biopsy of the breast mass and the axillary lymph node were applied by the standard procedure. The results demonstrated that the patient had Stage IIE T-cell lymphomas of the breast.

### Clinico-radiologic examination findings

No other abnormalities in any organs and no evidence of lymph node involvement (except for the palpable ipsilateral axillary node) were detected on breast imaging. No abnormality was observed in computerized tomography (CT) of the thorax and abdomen, and only some edematous changes and skin thickening of the left breast were detected. Magnetic resonance (MR) with and without Gd studies revealed that there was a  $39 \times 31$ mm mass with a heterogeneous increased signal on STIR images at the upper outer periareolar region of the left breast. This mass showed inhomogeneous enhancement on post-Gd images with nonenhancing component and marginal irregularity with type 3 TICs (rapid washout) (suspicious morphology and suspicious kinetic). Enlarged lymph nodes were present at the left axillary region, with the largest one measuring about  $21 \times 12$ mm. Some of the lymph nodes also showed cortical hypertrophy and eccentric hilum. However, no speculated enhancing mass or architectural distortion was present in the right breast (Figure 1). Furthermore, PET scan was not performed.



**Figure 1.** Magnetic resonance imaging (MRI) showing: A, abnormal mass at the upper outer periareolar region of the left breast in axial section (solid white arrow); B, Enlarged lymph nodes present at the left axillary region (solid white arrow).

# Hematologic, Histologic, and Immunohistologic findings

Hematological findings were within normal limits. Left breast mass core needle biopsy was performed. Macroscopically, there were 5 creamy to yellow colored string shape tissue fragments that measured  $2 \times 0.4 \times 0.2$  cm. The sections revealed the breast tissue involved by a hypercellular malignant tumor composed of the diffuse proliferation of round and count, breast cuboidal tumor cells with

hyperchromic nuclei and a high N/C ratio. Tumor cells grew among adipose tissue without differentiation. Mixed inflammatory cells, necrosis, and multinucleated histiocytes were also seen. Special staining was negative for fibrosis and mucin production.

Immunohistochemistry (IHC) showed that these fragments of tissues, including parts of neoplasm composed of atypical lymphoid series, have somewhat larger vesicular nuclei. They were mixed with a smaller form having more hyperchromic nuclei. They were positive for CD20, but negative for CD3 expression. Histopathological findings in the tumor mass and lymph nodes verified the diagnosis of high grade diffuse large B-cell type primary breast lymphoma (DLBCL).

The bone marrow histopathology revealed all hematopoietic lineages with the different stages of maturation. Megakaryocytes exhibited normal morphology and blasts accounted for less than 3% of the population. No increase was seen in lymphocytes. The diagnosis was lymphoma.

### Treatment

The patient was treated with 6 cycles of the R-CHOP (Rituximab 375mg/m2 i.v. on day 1; Cyclophosphamide 750mg/m2 i.v. on day 1; Doxorubicin 50mg/m2 i.v. on day 1; Vincristine 2mg i.v. on day 1; Prednisone 100mg p.o. daily, days 1–5) regimen every 3 weeks. No abnormal involvement was observed in the contralateral breast tissue in imaging, so as with the cases of non-lymphoid breast cancer; the breast tangent technique was applied for RT to avoid radiation exposure to the adjacent organs, such as the lung and contralateral breast tissue.

RT was performed, using a linear accelerator high energy device with a dose of 50 Gy/25 F regimen with 2 tangential fields for treatment of the left breast and 2 supraclavicular and posterior axillary fields for the subclavian and axillary lymph node treatment (Figure 2).



**Figure 2.** Radiation Therapy fields for treatment of the left breast.

### Post-treatment outcomes and patient follow-up

After 6 cycles, no peripheral lymphadenopathy was seen. No pleural fluid was found, but pathological changes were observed in the spleen (splenomegaly).

Follow-up was performed 6 and 11 months later. The results of axillary breast ultrasound and thorax, abdomen, and pelvis CT scan and a whole-body bone scan were normal. Laboratory tests were within normal ranges, too. However, the patient complained of pain in her upper limb during its movements while dressing.

### Discussion

The breast is a rare site of malignant lymphomas that can be divided to primary breast lymphoma (PBL) and secondary breast lymphoma (SBL).<sup>1,8</sup> The median age of incidence of PBL varied between 60 and 65 years, and its mean age of onset has been reported to be approximately 58 years. The most common presentation of PBL is a painless mass (almost 61% of cases). Other symptoms included local inflammation (11%), local pain (12%), and palpable lymph nodes (25%).<sup>9</sup>

In our report, a 54- year-old patient was presented with swelling in her left breast. In physical examination, a mass that was tender, mobile, and firm to hard in consistency was palpated in the upper outer periareolar region of the left breast. Additionally, a palpable lymph node of 1.5cm in diameter was found in the ipsilateral axillary tail. Clinicopathological features indicated primary breast lymphoma. Needle biopsy of the breast mass and the axillary lymph node demonstrated that the patient had stage IIE disease, which was limited to the breast and ipsilateral axillary lymph nodes.<sup>1,3</sup> Primary breast lymphoma is a rare non-Hodgkin lymphoma (NHL) of the breast, and diffuse large Bcell lymphoma (DLBCL) is the most common subtype.10 Breast DLBCL accounts for 2% of all , 0.04% to 0.5% of all breast malignancies, NHL<sup>10</sup> and 0.85% and 2.2% of all extra-nodal malignant lymphomas.<sup>12</sup>

The clinicopathology of these cases has been discussed in prior studies.<sup>4,6,11</sup> Based on World Health Organization (WHO) classification system for breast tumors, the malignant lymphomas of the breast are divided to diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, extra-nodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT), and Burkitt's lymphoma.<sup>8</sup> In our case, histopathological findings in the tumor mass and lymph nodes confirmed the diagnosis of high grade diffuse large B-cell type primary breast lymphoma (DLBCL).

The immunophenotype of DLBCL can be approved by histochemistry or flow cytometry. Tumor cells in DLBCL express pan B-cell antigens (CD19, CD20, CD22, CD79a) as well as CD45. Expression of CD30 is present in approximately 25% of cases.<sup>13</sup>

The Immunohistochemistry (IHC) showed that the neoplasm was composed of atypical lymphoid series with large vesicular nuclei. They were mixed with smaller forms having more hyperchromic nuclei, which were positive for CD20, but negative regarding CD3 expression.

There are some special scenarios (e.g., gonadal lymphoma, central nervous system involvement), where additional therapy is required (e.g., intrathecal chemotherapy).<sup>14</sup>

Treatment options for breast lymphomas include



surgery, radiotherapy (RT), and chemotherapy.<sup>4</sup> Although no agreement has been reached for the best treatment for PBL, these methods can be applied alone or in combination.<sup>4</sup> Surgical interventions consist of biopsy, lumpectomy with or without axillary lymph node (ALN) dissection, and mastectomy with or without ALN dissection procedures.<sup>5</sup> The largest retrospective analysis demonstrated that mastectomy provides no survival benefit compared to lumpectomy or biopsy in PBL;<sup>4</sup> however, surgery does not have any role in the treatment of DLBCL. The standard care in diffuse large B-cell lymphoma (DLBCL) treatment is Rituximab, Vincristine, Doxorubicin, Cyclophosphamide, and Prednisone (R-CHOP). Rituximab is considered as a chimeric monoclonal antibody against the CD20 B-cell antigen and has more therapeutic role in diffuse large B-cell lymphoma.<sup>15,16</sup>

In this case, the patient was treated with combination therapy. We chose this regimen to rely on the reports of Lokesh *et al.*, which explained primary breast DLBCL is a rare entity; so, combination therapy involving chemotherapy and radiation could lead to a longer overall survival and avoidance of the morbidity of mastectomy.<sup>17</sup> Moreover, recently such regimens (R-CHOP and RT) are applied in limited stage diffuse large B-cell lymphoma of other sites.<sup>18</sup>

RT with three-dimensional conformal was applied for whole breast and axillary lymph nodes irradiation after chemotherapy with R-CHOP. The radiation doses vary greatly, in previous reports, fluctuating between 30 to 60 Gy. Thus, the optimal radiation dose of breast cancer is unknown, and the median dose in most reports is 40 Gy.<sup>4,19,20</sup> In our case, the mass was irradiated to a total of 50 Gy after a complete response to R-CHOP chemotherapy. After chemotherapy, the mass size was decreased remarkably. Previously doses up to 40 Gy applied for limited cases of breast lymphoma, small masses, and extensive surgery have been reported in various papers, but our choice of treatment for this patient was 50 Gy, 40 Gy for the whole breast and 10 Gy as a boost.<sup>6,21</sup>

Other studies confirmed that combined treatment with RT and chemotherapy was the best treatment compared to the single modality because it improves overall and event-free survival significantly.<sup>6</sup> The retrospective research study carried out by the International Extra-nodal Lymphoma Study Group confirmed that after combined radiation therapy and chemotherapy, the 5-year OS was 63%, which was significantly greater than either radiation therapy or chemotherapy alone.<sup>4</sup>

The management of PBL is not currently standardized. However, similar to other lymphomas, a diagnostic biopsy or limited surgery followed by chemotherapy accompanied by radiotherapy is suggested. A recent study emphasized the importance of combined therapy, which is important for avoiding an unnecessary mastectomy in PBL patients.<sup>22</sup> Although there was a clinical suspicion of PBL, an appropriate pre-therapeutic clinical workup with a core needle biopsy and IHC was helpful and avoided an unnecessary mastectomy in our patient. Due to the small number of such patients, the implementation of a single center randomized trial is impossible, so in the event of common multi-trials and using different therapies and prospective studies, it will be possible to evaluate the effects of each treatment separately as well as better staging methods that have not been well established in the case of PBL.

### **Conflict of Interests**

There is no conflict of interest.

### References

- 1. Wiseman C, Liao KT. Primary lymphoma of the breast. Cancer. 1972;29(6):1705-12.
- 2. Feder JM, de Paredes ES, Hogge JP, Wilken JJ. Unusual breast lesions: radiologic-pathologic correlation. Radiographics : a review publication of the Radiological Society of North America, Inc. 1999;19 Spec No:S11-26; quiz S260.
- 3. Talwalkar SS, Miranda RN, Valbuena JR, Routbort MJ, Martin AW, Medeiros LJ. Lymphomas involving the breast: a study of 106 cases comparing localized and disseminated neoplasms. The American journal of surgical pathology. 2008;32(9):1299-309.
- 4. Ryan G, Martinelli G, Kuper-Hommel M, Tsang R, Pruneri G, Yuen K, *et al.* Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2008;19(2):233-41.
- 5. SunY, Joks M, Xu LM, Chen XL, Qian D, You JQ, *et al*. Diffuse large B-cell lymphoma of the breast: prognostic factors and treatment outcomes. OncoTargets and therapy. 2016;9:2069-80.
- Aviles A, Delgado S, Nambo MJ, Neri N, Murillo E, Cleto S. Primary breast lymphoma: results of a controlled clinical trial. Oncology. 2005;69(3): 256-60.
- Aviles A, Castaneda C, Neri N, Cleto S, Nambo MJ. Rituximab and dose dense chemotherapy in primary breast lymphoma. Haematologica. 2007;92(8):1147-8.
- Sabate JM, Gomez A, Torrubia S, Camins A, Roson N, De Las Heras P, *et al*. Lymphoma of the breast: clinical and radiologic features with pathologic correlation in 28 patients. The breast journal. 2002;8(5):294-304.
- 9. Joks M, Mysliwiec K, Lewandowski K. Primary breast lymphoma a review of the literature and

report of three cases. Archives of medical science : AMS. 2011;7(1):27-33.

- Aviv A, Tadmor T, Polliack A. Primary diffuse large B-cell lymphoma of the breast: looking at pathogenesis, clinical issues and therapeutic options. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2013;24(9):2236-44.
- 11. Domchek SM, Hecht JL, Fleming MD, Pinkus GS, Canellos GP. Lymphomas of the breast: primary and secondary involvement. Cancer. 2002;94(1):6-13.
- 12. Surov A, Holzhausen HJ, Wienke A, Schmidt J, Thomssen C, Arnold D, *et al.* Primary and secondary breast lymphoma: prevalence, clinical signs and radiological features. The British journal of radiology. 2012;85(1014): e195-205.
- 13. Ottensmeier CH, Stevenson FK. Isotype switch variants reveal clonally related subpopulations in diffuse large B-cell lymphoma. Blood. 2000;96(7):2550-6.
- Freedman AS, Friedberg JW. Initial treatment of limited stage diffuse large B cell lymphoma 2017. [Available from:https://www.uptodate.com/ contents/initial-treatment-of-limited-stagediffuse-large-b-cell-lymphoma?source=see\_link]
- 15. CoiffierB, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, *et al.* CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. The New England journal of medicine. 2002;346(4):235-42.
- 16. Pedersen MO, Gang AO, Brown P, Pedersen M, Knudsen H, Nielsen SL, *et al.* Real world data on young patients with high-risk diffuse large B-cell lymphoma treated with R-CHOP or R-CHOEP -MYC, BCL2 and BCL6 as prognostic biomarkers. PloS one. 2017;12(10):e0186983.
- Lokesh KN, Sathyanarayanan V, Lakshmaiah KC, Suresh TM, Babu KG, Lokanatha D. Primary breast diffuse large B cell lymphoma report of 6 cases from South India with review of literature. Indian journal of surgical oncology. 2013;4(4):368-73.
- Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, Bouabdallah K, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. Blood. Oct 2017 [inpress].
- 19. Hosein PJ, Maragulia JC, Salzberg MP, Press OW, Habermann TM, Vose JM, *et al.* A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. British journal of haematology. 2014;165(3):358-63.
- 20. Jeanneret-Sozzi W, Taghian A, Epelbaum R, Poortmans P, Zwahlen D, Amsler B, et al.

Primary breast lymphoma: patient profile, outcome and prognostic factors. A multicentre Rare Cancer Network study. BMC cancer. 2008;8(1):86.

- 21. MillerTP, Dahlberg S, Cassady JR, Adelstein DJ, Spier CM, Grogan TM, *et al.* Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. The New England journal of medicine. 1998;339(1):21-6.
- 22. Topalovski M, Crisan D, Mattson JC. Lymphoma of the breast. A clinicopathologic study of primary and secondary cases. Archives of pathology & laboratory medicine. 1999;123(12):1208-18.



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2. Fitoussi AD, Berry MG, Fama F, Falcou MC, Curnier A, Couturaud B, *et al.* Oncoplastic breast surgery for cancer: analysis of 540 consecutive cases [outcomes article]. Plast Reconstr Surg 2010; 125(2): 454-62.

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