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# Prescribing Oral Contraceptives in Women With Breast Diseases: A Matter of Concern for the Gynecologist

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ABSTRACT

**Background:** The association of exogenous steroid hormones with breast malignancy has long been, and still is, a subject of investigation. This manuscript, as part of a series of articles about effects of exogenous sex hormones on breast conditions, reviews the adverse and beneficial effects of oral contraceptives in various entities separately: benign and malignant breast diseases, women with risk factors of breast cancer, and the general population.

**Methods:** We first reviewed international clinical guidelines about the subject. Then, a comprehensive search of the literature was carried out using appropriate keywords. Clinical trials, population-based or cohort studies, nested case-control studies, and narrative/systematic reviews were reviewed and relevant data were extracted.

**Results:** Oral contraceptives are contraindicated in women with current or previous breast cancer. Among women at high risk for breast cancer, those with preceding chest wall irradiation should not use pills, while these are allowed in cases with *BRCA* mutations or with a positive family history of breast cancer. Oral contraceptives may be beneficial for benign breast diseases. For low-risk woman, pills either pose no risk or may induce a very mild risk for breast cancer.

**Conclusion:** Oral contraceptives are generally safe regarding breast diseases except in breast cancer patients or high-risk women, especially those with a history of chest wall irradiation.

## Introduction

Effects of endogenous sex hormones on breast tissue development and the relationship of these hormones with breast disorders and breast cancer (BC) are well recognized. Furthermore, the association between malignancies of the breast and some exogenous hormones has been confirmed.[1-6]

Oral contraceptive pills (OCPs) are widely used exogenous sex steroids. Short and long-term benefits and side effects of these drugs have been investigated extensively. However, the effect of OCP on breast carcinogenesis, although widely explored, is still a matter of debate because of the problems of actual risk assessment. Long latency periods of cancers, varying types of marketed OCPs over time, individual variations in pattern and duration of OCP use, confounding factors such as reproductive history, and other features make this assessment problematic.[7]

The International Agency for Research on Cancer (IARC) of the World Health Organization classifies environmental factors, including food and drugs, according to their carcinogenic potential. As stated in the latest update in 2019 (https://monographs.iarc.fr/agents-classified-by-the-iarc), 120 agents are

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classified as carcinogenic to humans (Group 1), 82 probably carcinogenic to humans (Group 2A), and 311 possibly carcinogenic to humans (Group 2B). Oral contraceptives containing both estrogens and progesterone are classified as Group 1, with a notice that evidence also shows protective effects for endometrial and ovarian cancer, and those comprising only progesterone are classified as Group 2B.[8]

All these details lead to uncertainty and worry when prescribing hormonal medications. This article reviews the concerns physicians confront while prescribing OCPs to women undergoing BC treatment, BC survivors, groups at high risk for BC, women with benign breast disorders (BBDs), and healthy women.

## Methods

The objective of our search was to find the most valid scientific material as well as reviewing the latest findings, recommendations, and suggestions about the subject. First, we investigated international clinical guidelines and references, including the guidelines of the Society of Family Planning, WHO's Medical Eligibility Criteria for Contraceptive Use (MEC), the US Selected Practice Recommendations for Contraceptive Use, and the US Medical Eligibility Criteria for Contraceptive Use by the Centers for Disease Control and Prevention (CDC), the Canadian Contraception Consensus, the IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, the Clinical Management Guidelines for Obstetrician-Gynecologists by the American College of Obstetricians and Gynecologists (ACOG), UpToDate (from January 2019), and the Clinical Practice Guidelines in Oncology, 4th edition, by the National Comprehensive Cancer Network (NCCN). All the relevant topics and points were extracted from these references. Then, we performed a comprehensive search of the literature for all relevant publications using the following keywords: contracept*, breast cancer, breast neoplasia, risk factor, benign breast, fibroadenoma, breast fibrocystic, steroid hormone, family history, high risk, *BRCA*, chest wall radiation, and screening. Search phrases were synthesized using various combinations of 2, 3, or 4 of these keywords. We carried out our first screening by reading titles and abstracts to detect review articles, systematic reviews, clinical trials, population-based and cohort studies, and nested case-control works. Thereafter, we sorted out selected works based on journal impact factors and citations of papers and excluded the last quartile of the resulting list from the investigation. In our second screening, we studied methods, results, and conclusions of articles and selected papers that contained pertinent scientific material. Finally, eligible articles were carefully read to extract any point and fact that was related to our subject.

## Results and Discussion

*Types of Oral Contraceptive Pills*

OCPs have been used for many years now and have always been a very common and quite effective method of birth control. They have also been used for therapeutic purposes in disorders such as menstrual irregularities, premenstrual syndrome, endometriosis, uterine lesions, and even acne. OCPs are made of synthetic sex steroid hormones, namely, estrogens and progesterone compounds. The formulation of the drugs, specifically type and dosage of components, has been modified through time to increase safety. More than 30 types of OCP are in use today, which can be classified into two groups in terms of hormonal constituents: combined OCP (cOCP), which contain both estrogens and progestins and are used more frequently, and progesterone-only pills (POPs), which contain only progestins. Older forms of OCPs that were marketed before 1975 contained higher doses of estrogen, whereas newer preparations contain lower doses, mostly 20 or 30 μg of ethinyl estradiol per tablet.[9-11] Also, the progestin component of OCP varies widely across products. There are four generations of progestins in the market, with varying levels of androgenic activity; therefore, various kinds of OCP harbor diverse desired or adverse defects.[12-15] Some forms of OCPs increase progestin exposure up to fourfold normal serum level.[16]

One of the most common side effects of most kinds of OCP is breast tenderness,[9,10,17] which makes users worry about their breast health and seek medical care. However, OCP-induced breast tenderness can be viewed as a welcomed excuse for performing breast examination or BC screening and is not accompanied by breast disease. Like most adverse effects of OCPs, the symptom is usually mild and resolves with time or by consuming another kind of OCP.[9]

Emergency or postcoital contraception is used after unprotected intercourse and consists of several methods, taking POPs and cOCPs being one of them. While the latter is used less frequently nowadays,[18] the former is gaining popularity.[10]

*1. OCP in Newly Diagnosed BC*

Soon after a diagnosis of BC, therapeutic modalities with varying sequences are instituted. Cytotoxic drugs of chemotherapy may induce anovulation and temporary or permanent infertility. Failure of ovarian function occurs at a rate of 14% to 100% depending on age and the type of agent used. Also, hormone therapy may contribute to contraception to some degree.[19] However, ovulation might take place under any therapeutic regimen, and pregnancy can occur.[20,21] Therefore, to prevent potential harms to the fetus as well as interference

with medical plans, contraception adherence is imperative during all stages of treatment, including surgery, chemotherapy, radiotherapy, endocrine therapy, and targeted therapy. Patients should be instructed about the necessity of contraception and counseled on appropriate methods; nonetheless, these do not occur every so often. In a recent study, women of reproductive age who had undergone breast cancer treatment within the previous 5 years were interviewed about what they knew and how they had been informed about correct methods of contraception during their treatments. There was a serious lack of accurate knowledge on the topic. Moreover, because of deficient instructions from physicians, patients recognized their peers as a decent source of information.[22] Also, in a survey carried out among women diagnosed with BC before the age of 40, results showed that most of the patients had neither been notified about nor used contraception while under chemotherapy or endocrine therapy.[23] This malpractice may be due to the bulk of information that BC patients should receive in a short time, which makes medical staff overlook the subject. But unfamiliarity with the best applicable contraceptive approach during BC management also plays a significant role.

No study has been designed to investigate the use of OCP during BC treatment, because these drugs may significantly contribute to tumor progression. According to international guidelines, when a new breast mass is detected in a woman on OCP, she can remain on it till the diagnosis of breast cancer is made, and a substitute effective contraception is initiated. However, cOCP and POP are contraindicated in newly diagnosed breast cancer patients and those under treatment.[10,24-30] The best contraceptive methods in these patients are nonhormonal modes, which will be discussed in relevant parts of these series of articles.

The risk of using emergency OCP in patients under treatment for BC has not been studied. When postcoital contraception is needed, one-time use of emergency pills should not cause any harm, but effects of repeated consumption are questionable. Then again, a non-OCP method would be superior, which has been discussed elsewhere.[31]

*2. Oral Contraceptive Pills in Breast Cancer Survivors*

Studies assessing the safety of pregnancy following BC treatment and the safe time interval between diagnosis and conception have found that a minimum interval of 2 years, depending on the type and stage of BC, would yield favorable results.[32-39] Nonetheless, pregnancy should be prevented at any other time when the patient does not wish to have a baby. It has been shown that, as in patients under treatment, BC survivors of reproductive age underuse contraception in comparison with their control counterparts.[40]

A large portion of the literature about OCPs and BC risk is centered on women with average risk, and research about the consequences of OCP consumption in breast cancer survivors is heterogeneous and limited while prospective studies are lacking. Decisions and recommendations regarding the limitation of hormonal contraceptive methods in breast cancer survivors are actually an extrapolation of the data obtained from the former, and also reflects general fear of administering hormonal products in these high-risk women.[41]

For the time being, both cOCP and POP are contraindicated in BC survivors as well as those under treatment.[10,25,29,30,41] However, emergency hormonal contraception is allowed in these patients,[10] although the frequency of use should probably be limited. In these women, non-OCP emergency contraception is preferred.[42]

*3. Oral Contraceptive Pills in Groups at High Risk for Breast Cancer*

Because prospective trials are difficult to design about this challenging subject, there is insufficient consistent literature about the use of OCP in high-risk groups.[41] Still, numerous works have been carried out in order to answer the question of safety of OCPs in women with a positive family history or genetic predisposition to BC.

*3.1. Family History of Breast Cancer*

Women with a family history of BC, especially when several young first and second degree relatives are affected, are at greater risk for BC. Whether the risk increases further with consumption of OCP has been considered in a number of studies.

In an evaluation of nearly 3500 cases of BC and 4500 controls, simultaneous positive family history and OCP consumption had cumulative positive effects on BC risk,[43] and investigation of around 1500 cases and controls showed an increment in the risk of BC in women with a history of the disease in their first-degree relatives.[44] Likewise, in a cohort of more than 3 000 women in 426 family lineages of BC patients, significantly higher risk of BC was found in women who had used OCP and who also had a first-degree relative with BC. One important point is that this positive association was mainly related to high-dose estrogen pills which were used before 1975. Thus the question remained open for more inquiry about recent low-estrogen formulations.[45]

However, null results were more often obtained in earlier studies. In a case-control study enrolling about 1000 cases and 900 controls, women who used OCP and who had sisters with BC had only a nonsignificant additional risk.[46] Also, in the evaluation of nearly 1000 cases and 10000 controls from a cohort of nurses, OCP use caused no increase in BC risk in women with a BC family history

involving their mothers or sisters.[47] Assessment of about 1000 cases and controls with BC in close relatives in another work yielded similar findings.[48] Comparable results were obtained from a population-based case-control study of more than 1200 cases and controls with a first-degree family history of BC. This result did not change with longer duration of OCP consumption or with higher-dose estrogen formulations.[49] In another research carried out in around 2500 high-risk women attending a family cancer center, no increased risk of BC was detected with cOCP use in women with a positive family history of BC.[50] Also, in a very recent retrospective cohort study in more than 2 500 women with BC in their relatives, no association was discovered between BC and duration of OCP use or dose of estrogens.[51]

Unexpectedly, a differing result was reached in a large cohort study consisting of more than 27 000 women from the "Canadian National Breast Screening Study," where OCP consumption was found to decrease the risk of BC in women with a history of BC in first-degree relatives.[52]

On the other hand, studies that have reviewed and combined data of previous works have returned various results. The reanalysis of 52 studies with a total number of nearly 60000 cases of BC and 102000 controls, including about 7500 women with BC in their first-degree relatives in each group, showed an increased risk of BC with recent (in the preceding 10 years) OCP use in women younger than 50 years whose relative had been affected by the disease before the age of 50.[53] However, a systematic review of works published from 1966 to 2008 concluded that OCP did not increase the risk of BC in women with a positive family history of BC.[54] Another systematic review about OCP use and risk of BC in women with a positive family history (covering papers from 2000 to 2012) found no significant difference in risk of BC due to OCP intake between women with positive family history and the general population.55 Finally, a systematic review by Freund and colleagues concluded that OCP did not increase BC risk in patients with a positive family history.[56]

All the above works had considered either invasive BC or all types of BC. There is also one study on the risk of DCIS in relation to OCP consumption, which disclosed no added risk of BC for the combination of OCP use and positive family history.[57]

*3.2. BRCA Mutations*

Mutations in BRCA1 and BRCA2 are known risk factors for BC. Whether OCP use further increases this risk is a very important question because, on the one hand, these pills are used frequently and, on the other hand, OCP intake has been shown to decrease the risk of ovarian cancer, to which carriers of BRCA mutations are highly susceptible. Present publications have yielded contrasting results over this topic. Some studies have shown no additional increased BC risk for OCP use in women carrying defective BRCA genes, while others have shown a positive association.

A study of 83 BC patients with mutated BRCA1 or BRCA2 genes found no increased risk of BC for OCP users in comparison with controls.[58] In another research, involving nearly 1500 BC cases under the age of 50, of whom 94 carried mutated BRCA genes, and 450 healthy matched controls, OCP use had no effect on the risk of BC.[59] Also, in an assessment of more than 2 500 high-risk women attending a family cancer center, cOCP had no effect on the risk of BC in genetically-positive women.[50]

However, publications favoring some unfavorable effects of OCP consumption on risk of BC in BRCA carriers are not scarce. In a sample of 50 Ashkenazi Jewish women with BC, 14 of whom were positive for BRCA1 or BRCA2 mutations, consuming OCP for more than 4 years in advance of the first pregnancy was recognized as a probable risk factor for BC.[60] In partial agreement with this finding, a large case-control study encompassing 52 centers in 11 countries and comprising 1311 pairs of BRCA1 or BRCA2 mutation carriers found no association between OCP use and risk of BC in carriers of BRCA2 mutation, while women with mutated BRCA1 who consumed OCPs manufactured before 1975, who used OCPs for more than 5 years, or who had begun using them before age 30 were more likely to develop BC at an early age.[61] However, a study involving around 500 carriers of BRCA1 and 300 carriers of BRCA2 mutations found BC risk increments with long-term (> 5 years), but not with short-term (< 1 year), OCP use.[62] Also, in a retrospective cohort of more than 1500 women with mutations in BRCA1/2 (the International BRCA1/2 Carrier Cohort Study [IBCCS]), a positive association between risk of BC and OCP intake, intensified with consumption for more than 4 years before first full-term pregnancy, was detected. Age of the patient at the time of beginning OCPs or recent versus previous use did not affect the risk.[63] One more investigation among 888 Jewish Israeli women with mutated BRCA1 or BRCA2 genes revealed a positive association between OCP use and risk of BC, especially early-onset BC.[64] Additionally, a case-control study assessing around 2500 matched pairs of BRCA1-positive women showed an increased risk of early-onset BC with OCP use before age 20 or 25, enhanced with the length of consumption.[65] One study on 200 BRCA-positive women also showed that OCP users tended to develop BC at younger ages than non-users.[66]

The contrast seen in these various works is reflected in the results of review papers and meta-analyses investigating the subject, which also involved different inclusion criteria for entering studies in their evaluations. A work which analyzed

studies performed before December 2009 found heterogeneous and inconsistent results.[67] However, two independent works reviewing studies carried out till March 2010 and from 2000 to 2012 found null results.[55,68] Likewise, the meta-analysis of case-control studies performed before September 2013 could not find any relationship, while a positive association was detected from the combination of hazard ratios of cohorts carried out till that date, where the duration of use of the pills had no effect.[69] Finally, in a very recent work recruiting participants of several cohorts, past data and new information (via questionnaires) about OCP consumption and other issues were gathered from around 10000 BRCA1 or BRCA2 positive women and were analyzed both retrospectively and prospectively. Although a positive association between consumption of OCP and risk of BC was not proved, results were inconsistent, and authors conclude that safety of OCP for BRCA carriers is unclear in the long term and should only be used for contraceptive purposes, and that as the second-line option.[70]

### *3.3. History of Chest Wall Radiation*

Specific studies have not been performed, but considering the increased likelihood of BC in women who have received radiotherapy of the chest wall (mantle field radiation) in childhood, OCP is generally contraindicated in these cases.[10,42]

### *3.4. General Recommendations on High-Risk Women*

As inferred from above studies, and according to international societies and clinical guidelines, cOCP and POP can be used in women with a family history of BC and are not contraindicated in those with *BRCA* mutations, albeit as a second-line choice. Because of lack of sufficient consistent data, these should not be used in women with a history of chest wall radiation.[8,26,27,30,41,42,71]

## *4. Oral Contraceptive Pills in the General Population*

The question of possible carcinogenetic effects of OCPs in the breast has been considered since many years ago and is still an area of active investigation.

In 1977, the cohort study of the Royal College of General Practitioners, which enrolled around 50 000 women using OCP and followed them to age 44 years, revealed an increased risk of BC in current as well as recent users.[72] Several years later, the Collaborative Group on Hormonal Factors in Breast Cancer reviewed and analyzed nearly all epidemiological evidence of that time about hormones and breast cancer. Results showed an increased risk of BC with current or recent (within the preceding 10 years) use of OCP, especially in those who had started pill consumption before the age of 20, but not with earlier use. BCs in OCP users were less advanced, particularly with high-dose formulations. They discuss that these findings might be due to earlier detection of the disease because of tighter screening and should be investigated further.[73] Results of the Norwegian-Swedish Women's Lifestyle and Health Cohort Study, with more than 100000 participants, aiming at understanding any association between OCP and BC were published 6 years later. Long-term, higher-dose users, as well as current/recent users of OCP, were shown to be at a higher risk of BC.[74] In a recent case-control study involving 1031 cases of BC and 919 controls, all younger than 55 years, a relative risk of 1.1 was shown for ever use of OCP.[75] In a very recently published prospective cohort study, which raised many arguments and debates, a 20% to 30% increase in risk of BC was observed for current and recent users of OCP, and the risk was correlated with the duration of consumption.[76] These figures, although apparently high, mean only one extra case of BC in a year for every 7690 women consuming OCP.[77]

Opposite results, favoring the safety of OCP in relation to BC, have been reported in several works, including very large cohort studies with prolonged follow-up. In 1976, among 17000 women recruited for the Oxford Family Planning Association Contraceptive Study, a decreased hospital referral for BC was revealed in women who had used OCP.[78] The Nurses' Health Study, using data from about 3 400 BC patients with a follow-up of 1.6 million person-years, showed null results even for long-term intake of OCP.[79] Similar results came out of the interview of more than 9200 BC cases and controls, where even adjustments for estrogen dose or current versus past use did not alter the results.[49]

Findings were null also in an updated analysis of the data from the large cohort study of the Royal College Of General Practitioners, comprising around 740000 and 340000 woman-year of observation for never users and ever users of OCP, respectively.[80] Thereafter, the last update of the Oxford Family Planning Association Contraceptive Study was released, where the previous results (no association) were confirmed.[81] A very recent report of the NIH-AARP Diet and Health Study, which covered more than 100000 women with more than 11000 cases of BC, found no association of the disease with OCP use.[15]

The above large-scale studies had taken place in Western countries, but studies have also been conducted in other countries. A case-control study on 225 women with and without BC in Iran has demonstrated a rise in BC with OCP use for more than 16 years.[82] Also, a systematic review in Iran analyzed the data on 46260 patients from 26 studies carried out in the country between 2000 to 2015 and concluded that using OCP increased the risk of BC up to 1.52 times in Iranian women.[83]

In a case-control study in Thailand among 514

Thai premenopausal women, OCP use was found to increase the risk of breast cancer threefold, and the risk was higher in those with a longer duration of consumption.[84]

A recent study in Korea has shown that the consumption of OCP could lead to a rise of 3.4 cases of breast cancer per 10,000 women. The risk was not higher in women older than 45 years in comparison with younger women.[85]

Besides studies considering invasive cancers or all types of BC, a study investigated nearly 900 cases of DCIS and 1000 controls and found no association with OCP consumption, length of use, dose of estrogen, or timing of the last usage.[57]

Few studies have focused on the effects of POPs on BC risk. The association of POP (except for mini pills) use after the age of 40 and before menopause with BC was studied in women enrolled in the French E3N Cohort Study. No increased risk of BC with POP use was detected, except for long-term (> 4.5 years) current use.[86]

A systematic review published in 2016 concentrated on the relationship between BC and using progesterone compounds, including oral and injectable contraceptives as well as implantable forms or intrauterine devices, and revealed no association for progestin contraceptives. Of 6 studies included in the study, only 2 (both published in 2002) were about POPs.[87] One of these 2 studies involved more than 9000 cases and controls and included more than 7000 women who had ever used OCPs. Nonetheless, a very small fraction (32 and 39 cases and controls, respectively) had ever used POPs. In this small sample, no increased BC risk was detected.[49] The second was the Women's Lifestyle and Health Study, with more than 100000 participants. Although the risk of BC was shown to increase with cOCP use or consumption of both cOCP and POP, ever use of POP alone did not affect BC risk.[74]

Another study carried out shortly after the above review tried to investigate POP effects in near 5000 BC cases, 135 of whom consuming POPs. Although the sample size was too small to allow a definite conclusion, the group using POP had a lower breast cancer mortality.[88]

In contrast to previous publications, the Norwegian Women and Cancer Study (NOWAC) including near 75000 women with 1245 BC cases documented an increased risk of BC by consumption of POP.[89]

As pointed above, the subject is still being considered, but it can be deduced overall that OCP may cause only a very small, if any, increase in BC risk in women without predisposing factors.

### *4.1. Oral Contraceptive Pills and Risk of Breast Cancer by Hormone Receptor Status*

Because of the diversity of hormonal profile of breast malignancies and the dissimilar clinical behavior of subtypes, a number of researchers have investigated the effects of OCP on BC by estrogen receptor (ER), progesterone receptor (PR), and HER2 status.

Several studies suggest that OCP intake may contribute to ER-, PR-, and HER2-negative (triple-negative tumors) tumors. In one study, immunohistochemical assessment of near 900 tumors showed that OCP use for one or more years increased the risk of triple-negative BC 2.5-fold, especially with longer and more recent use. For women 40 years of age or younger, OCP intake for 1 or more years was associated with a 4.2-fold increased risk for triple-negative BC.

The risk for other subtypes was not affected by OCP use.[90] Also, in a cohort study conducted among African American women, the use of OCP was positively associated with hormone receptor–negative BC, and this relation was stronger with longer duration and more recent use.[91] Besides, in a study on more than 3 200 women, a 2.9-fold increase in triple-negative BC risk was detected among those between 45 to 64 years of age who had begun using OCP before the age of 18.[92]

But then again, some studies have reported contradictory findings. In the evaluation of more than 155,000 participants of the Women's Health Initiative, OCP use was not found to be associated with any subtype of BC.[93]

In addition, in a population-based case-control study of more than 1800 women under age 45, the difference in risk of ER-negative and triple-negative BC with OCP use was not significant between those using for ≥ 15 years and current users for 5 years.[94] A nested case-control study with 1105 BC survivors found a nonsignificant propensity for $ER^+$ tumors with consumption of high-estrogen OCPs.[95]

Two systematic reviews about the relationship between OCPs and BC subtypes revealed that OCP use had a possible negative association with luminal A subtype[96] and a significant positive[97] or possible[96] association with triple-negative BC.

Given the different effects for estrogen and progestin components of OCPs, the relationship between cOCP or POP and BC subtypes was investigated in the NOWAC study as well.

The researchers used data on 74862 pre-menopausal women and the 1245 BC events. They demonstrated an increase in risk of ER-positive BCs in women who had used POP for ≥ 5 years and an increase in risk of ER-negative BCs with cOCP consumption.[89]

### *4.2. Screening for Breast Cancer Before Initiating Oral Contraceptive Pills*

BC is not common in women of reproductive age. As a consequence, despite the contraindication for OCP use in current BC and survivors, the WHO's

Medical Eligibility Criteria for Contraceptive Use (MEC), the US Selected Practice Recommendations for Contraceptive Use, and the US Medical Eligibility Criteria for Contraceptive Use have mentioned that no screening for breast cancer is necessary before initiating OCPs in women who have no symptom of the disease.[24,26,27] According to WHO-MEC, even in those who have a mass in the breast that has not yet been assessed, OCP can be initiated while the assessment of the mass is being undertaken.[24]

*5. Oral Contraceptive Pills in Benign Breast Disorders*

BBDs are very common lesions with heterogeneous clinical and pathological pictures. Some conditions such as fibrocystic changes (FCC) impose no risk on the patient; certain lesions such as fibroadenomas (FA) may slightly increase the risk for BC; some particular disorders, including papillomas, might count as risk factors for BC; and others such as atypical ductal hyperplasia may even be a precancerous lesion. FCC is the most common BBD, and FA is the most frequent benign tumor of the breast. FAs respond to endogenous sex hormones, as normal breast tissue does. Normal breast tissue and FA have similar ER levels; however, FAs have higher protein levels of PR-A and PR-B, suggesting that sex hormones and PR may play a role in FA development.[98]

Most works inspecting the relationship of BBD and OCP have been performed in far past times, and, because large cohorts were involved, multiple reports have been released through time. Results encompass mainly favorable effects of OCP on BBD. Nevertheless, medical staff has not been acquainted with this subject, as a survey of patients and physicians showed that the latter believed OCP should not be used in BBD, and advised the former as such.[99]

In a comparison between women under age 40 harboring benign breast masses and controls who were hospitalized for non-breast lesions, use of OCP for more than 2 years was recognized as a protective factor against BBD and decreased the risk of undergoing a biopsy up to 4-fold.[100]

In another study involving 640 women with either pathologically confirmed BBD or normal breasts, there was no association between OCP use and BBD,[101] while another study performed in the same period showed that hospitalization for FCC and FA decreased with use of OCP for more than one year, and this negative association strengthened with longer duration of use.[102] Similarly, in the Oxford Family Planning Association Contraceptive Study, referral to hospital for BBDs was less frequent in OCP users.[78] In the large-scale, prospective Royal College of General Practitioners' Oral Contraception Study, OCPs containing higher doses of progestins had a higher impact on BBD risk reduction.[72] The subsequent report of the Oxford Family Planning Association Contraceptive Study, with a 5-year interval from the previous one, again announced that OCPs were negatively associated with FA and FCC. Current pill users, especially those with prolonged use, had the lowest risk, and progestin dose seemed to mediate the reduction in FCC risk.[103] In contrast with previous works, a study in women hospitalized for BBD showed an increased risk of FCC with OCP use in postmenopausal but not in premenopausal women.[104] However, the update of the Royal College of General Practitioners' Study and another large cohort, the Canadian National Breast Screening Study, again emphasized that OCP use had a protective effect on BBD.[105,106] Similar results were found for FA in a large cohort in China.[107] The succeeding report of the Oxford Family Planning Association Study confirmed a reduced rate of hospitalization for FA and FCC with longer consumption of cOCP, especially in recent users.[108] However, in a study comparing the effects of cOCP associated with estriol or placebo on FA, it was demonstrated that estriol hampered the effectiveness of cOCPs in decreasing FA size.[109] Also, in a study carried out on 50 cases of FA under the age of 45 and 100 controls, lower age at first OCP consumption was found to be a risk factor for the development of breast FA.[110]

Atypical lesions have also been considered in regard to OCP consumption. The Canadian National Breast Screening Study, enrolling about 55,000 women aged 40-59 years, of whom 2000 had BBDs, found that OCP consumption was inversely associated with BBD risk, especially with longer duration of use, but longer use of OCP (> 7 years) was associated with increased risk of atypical lesions.[106] A study investigating the possible role of exogenous estrogen and/or progesterone consumption in atypical hyperplasia of the breast also showed a positive association between them; however, type of hormone and whether OCP was investigated is not clear in that publication.[111]

According to the US Medical Eligibility Criteria for Contraceptive Use and the US Selected Practice Recommendations for Contraceptive Use, there is no limitation for consuming OCP in BBD.[26,27] All studies on the subject are old, and none (except one) has assessed the effect of OCP on FA size. It appears that OCP can be prescribed in patients with FA if the diagnosis is made according to the histologic review of biopsy specimens. When the diagnosis is based on typical clinical and imaging findings, prescription of OCP with close observation and short-time follow-up of the mass is probably safe. FCC was previously known as fibrocystic disease and was named with various terminologies. The recent term shows that this is not a disease and may even not be a disorder, but just a "change." Considering the present

**Table 1.** Recommendations regarding use of oral contraceptive pills in various breast conditions

| BBD | Normal | FH + | BRCA + | CWI | BC survivor | Current BC |
|---|---|---|---|---|---|---|
| Yes | Yes | Yes | Yes* | No | No | No* |

*Nonhormonal methods preferred
**Pay attention to proper counseling and careful contraception during and after BC treatment
BBD: benign breast disorders, BC: breast cancer, CWR: chest wall irradiation, FH: family history.

knowledge, OCP consumption need not be limited in FCC.

Table 1 summarizes OCP limitation in various conditions of the breast according to the current knowledge.

Despite the bulk of research, questions regarding the association of OCP with different breast conditions still exist and need to be answered by further investigations.

**Conflict of Interest**

The authors have none to declare.

**References**


1. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. The New England journal of medicine. 2006;354(3):270-82.
2. Hankinson SE, Willett WC, Manson JE, Colditz GA, Hunter DJ, Spiegelman D, et al. Plasma sex steroid hormone levels and risk of breast cancer in postmenopausal women. J Natl Cancer Inst. 1998;90(17):1292-9.
3. Wang K, Li F, Chen L, Lai YM, Zhang X, Li HY. Change in risk of breast cancer after receiving hormone replacement therapy by considering effect-modifiers: a systematic review and dose-response meta-analysis of prospective studies. Oncotarget. 2017;8(46):81109-24.
4. Pizot C, Boniol M, Mullie P, Koechlin A, Boniol M, Boyle P, et al. Physical activity, hormone replacement therapy and breast cancer risk: A meta-analysis of prospective studies. European Journal of Cancer. 2016;52:138-54.
5. Toniolo PG. Endogenous estrogens and breast cancer risk: the case for prospective cohort studies. Environmental health perspectives. 1997;105 Suppl 3:587-92.
6. Clemons M, Goss P. Estrogen and the risk of breast cancer. New England Journal of Medicine. 2001;344(4):276-85.
7. Gierisch JM, Coeytaux RR, Urrutia RP, Havrilesky LJ, Moorman PG, Lowery WJ, et al. Oral contraceptive use and risk of breast, cervical, colorectal, and endometrial cancers: a systematic review. Cancer Epidemiology and Prevention Biomarkers. 2013;22(11):1931-43.
8. Humans IWGotEoCRt, Cancer IAfRo, Organization WH. Hormonal contraception and post-menopausal hormonal therapy: World Health Organization; 1999.
9. Cooper DB, Adigun R. Oral Contraceptive Pills. StatPearls [Internet]: StatPearls Publishing; 2017.
10. Bucciero M, Parda-Chlebowicz M. Contraception: Overview. Ambulatory Gynecology: Springer 2018. 33-57.
11. Hall KS, Trussell J. Types of combined oral contraceptives used by US women. Contraception. 2012;86(6):659-65.
12. Goldstuck N. Progestin potency–Assessment and relevance to choice of oral contraceptives. Middle East Fertility Society Journal. 2011;16(4):248-53.
13. Apgar BS, Greenberg G. Using progestins in clinical practice. American family physician. 2000;62(8):1839-46, 49-50.
14. Davtyan C. Four generations of progestins in oral contraceptives. Proceedings of UCLA healthcare. 2012;16:1-3.
15. Michels KA, Pfeiffer RM, Brinton LA, Trabert B. Modification of the associations between duration of oral contraceptive use and ovarian, endometrial, breast, and colorectal cancers. JAMA oncology. 2018;4(4):516-21.
16. Lovett JL, Chima MA, Wexler JK, Arslanian KJ, Friedman AB, Yousif CB, et al. Oral contraceptives cause evolutionarily novel increases in hormone exposure: A risk factor for breast cancer. Evolution, medicine, and public health. 2017;2017(1):97-108.
17. Kurian A, Kaushik K, Subeesh V, Maheswari E, Kunnavil R. Safety Profile of Levonorgestrel: A Disproportionality Analysis of Food and Drug Administration Adverse Event Reporting System (Faers) Database. Journal of reproduction & infertility. 2018;19(3):152.
18. Obstetricians ACo, Gynecologists. Emergency Contraception. ACOG Practice Bulletin Number 69: Clinical Management Guidelines for Obstetrician-Gynecologists. Obstetrics & Gynecology. 2015;106(6).
19. Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM. Pharmacological interventions for fertility preservation during chemotherapy: a systematic review and meta-analysis. Breast cancer research and treatment. 2010;122(3):803-11.
20. Koren G, Carey N, Gagnon R, Maxwell C, Nulman I, Senikas V. Cancer chemotherapy and pregnancy. Journal of Obstetrics and Gynaecology Canada.

2013;35(3):263-78.
21. Howell S, Shalet S. Gonadal damage from chemotherapy and radiotherapy. Endocrinology and metabolism clinics of North America. 1998;27(4):927-43.
22. Mody SK, Panelli DM, Hulugalle A, Su HI, Gorman JR. Contraception concerns, utilization and counseling needs of women with a history of breast cancer: a qualitative study. International ; journal of women's health. 2017;9:507.
23. Castro-Sanchez A, Martinez-Cannon BA, Platas A, Mohar A, Fonseca A, Vega Y, et al. Suboptimal Use of Effective Contraceptive Methods in Young Mexican Women With Breast Cancer. Journal of global oncology. 2018(4):1-7.
24. Altshuler AL, Gaffield ME, Kiarie JN. The WHO's medical eligibility criteria for contraceptive use: 20 years of global guidance. Current opinion in obstetrics & gynecology. 2015;27(6):451.
25. Casey PM, Faubion SS, MacLaughlin KL, Long ME, Pruthi S. Caring for the breast cancer survivor's health and well-being. World journal of clinical oncology. 2014;5(4):693-704.
26. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. US medical eligibility criteria for contraceptive use, 2016.
27. Curtis KM, Jatlaoui TC, Tepper NK, Zapata LB, Horton LG, Jamieson DJ, et al. US selected practice recommendations for contraceptive use, 2016.
28. Evans G, Sutton EL. Oral contraception. The Medical clinics of North America. 2015;99(3): 479-503.
29. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. Canadian Contraception Consensus (Part 3 of 4): Chapter 8–Progestin-Only Contraception. Journal of Obstetrics and Gynaecology Canada. 2016;38(3):279-300.
30. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. No. 329-Canadian contraception consensus part 4 of 4 chapter 9: Combined hormonal contraception. Journal of Obstetrics and Gynaecology Canada. 2017; 39(4):229-68. e5.
31. Patel A, Schwarz EB. Cancer and contraception. Contraception. 2012;86(3):191-8.
32. Calhoun K, Hansen N. The effect of pregnancy on survival in women with a history of breast cancer. Breast disease. 2005;23:81-6.
33. Blakely LJ, Buzdar AU, Lozada JA, Shullaih SA, Hoy E, Smith TL, et al. Effects of pregnancy after treatment for breast carcinoma on survival and risk of recurrence. Cancer. 2004;100(3):465-9.
34. Kranick JA, Schaefer C, Rowell S, Desai M, Petrek JA, Hiatt RA, et al. Is pregnancy after breast cancer safe? The breast journal. 2010;16(4):404-11.
35. Lambertini M, Kroman N, Ameye L, Cordoba O, Pinto A, Benedetti G, et al. Long-term Safety of Pregnancy Following Breast Cancer According to Estrogen Receptor Status. J Natl Cancer Inst. 2018;110(4):426-9.
36. de Bree E, Makrigiannakis A, Askoxylakis J, Melissas J, Tsiftsis DD. Pregnancy after breast cancer. A comprehensive review. Journal of surgical oncology. 2010;101(6):534-42.
37. Pagani O, Partridge A, Korde L, Badve S, Bartlett J, Albain K, et al. Pregnancy after breast cancer: if you wish, ma'am. Breast cancer research and treatment. 2011;129(2):309-17.
38. Hartnett KP, Mertens AC, Kramer MR, Lash TL, Spencer JB, Ward KC, et al. Pregnancy after cancer: Does timing of conception affect infant health? Cancer. 2018;124(22):4401-7.
39. Kroman N, Jensen MB, Wohlfahrt J, Ejlertsen B. Pregnancy after treatment of breast cancer--a population-based study on behalf of Danish Breast Cancer Cooperative Group. Acta oncologica (Stockholm, Sweden). 2008;47(4): 545-9.
40. Dominick SA, McLean MR, Whitcomb BW, Gorman JR, Mersereau JE, Bouknight JM, et al. Contraceptive practices among female cancer survivors of reproductive age. Obstetrics and gynecology. 2015;126(3):498.
42. Patel A, Schwarz E. Society of Family Planning. Cancer and contraception. Release date May 2012. SFP Guideline# 20121. Contraception. 2012;86(3):191-8.
43. Rosenberg L, Palmer JR, Rao RS, Zauber AG, Strom BL, Warshauer ME, et al. Case-control study of oral contraceptive use and risk of breast cancer. American Journal of Epidemiology. 1996;143(1).
44. Ursin G, Ross RK, Sullivan-Halley J, Hanisch R, Henderson B, Bernstein L. Use of oral contraceptives and risk of breast cancer in young women. Breast cancer research and treatment. 1998;50(2):175-84.
45. Grabrick DM, Hartmann LC, Cerhan JR, Vierkant RA, Therneau TM, Vachon CM, et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. Jama. 2000;284(14):1791-8.
46. Brinton LA, Hoover R, Szklo M, FRAUMENI Jr JF. Oral contraceptives and breast cancer. International journal of epidemiology. 1982;11(4):316-22.
47. Hennekens CH, Speizer FE, Lipnick RJ, Rosner B, Bain C, Belanger C, et al. A case-control study of oral contraceptive use and breast cancer. JNCI: Journal of the National Cancer Institute. 1984;72(1):39-42.
48. Harris RE, Zang EA, Wynder EL. Oral contraceptives and breast cancer risk: a case-control study. International journal of

epidemiology. 1990;19(2):240-6.
49. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptives and the risk of breast cancer. New England journal of medicine. 2002;346(26): 2025-32.
50. Toss A, Grandi G, Cagnacci A, Marcheselli L, Pavesi S, De Matteis E, et al. The impact of reproductive life on breast cancer risk in women with family history or BRCA mutation. Oncotarget. 2017;8(6):9144.
51. Grandi G, Toss A, Cagnacci A, Marcheselli L, Pavesi S, Facchinetti F, et al. Combined hormonal contraceptive use and risk of breast cancer in a population of women with a family history. Clinical breast cancer. 2018;18(1):e15-e24.
52. Silvera SA, Miller AB, Rohan TE. Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study. Cancer causes & control. 2005;16(9):1059-63.
53. Cancer CGoHFiB. Familial breast cancer: collaborative reanalysis of individual data from data from 52 epidemiological studies including 58209 women with breast cancer and 101986 women without the disease. The Lancet. 2001; 358(9291):1389-99.
54. Gaffield ME, Culwell KR, Ravi A. Oral contraceptives and family history of breast cancer. Contraception. 2009;80(4):372-80.
55. Moorman PG, Havrilesky LJ, Gierisch JM, Coeytaux RR, Lowery WJ, Peragallo Urrutia R, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. Journal of Clinical Oncology. 2013;31(33): 4188-98.
56. Freund R, Kelsberg G, Safranek S. Do oral contraceptives put women with a family history of breast cancer at increased risk? *J Fam Pract.* 2014;63(9):540,549.
57. Claus EB, Stowe M, Carter D. Oral contraceptives and the risk of ductal breast carcinoma in situ. Breast cancer research and treatment. 2003;81(2):129-36.
58. Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, et al. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiology and Prevention Biomarkers. 2005;14(2):350-6.
59. Lee E, Ma H, McKean-Cowdin R, Van Den Berg D, Bernstein L, Henderson BE, et al. Effect of reproductive factors and oral contraceptives on breast cancer risk in BRCA1/2 mutation carriers and noncarriers: results from a population-based study. Cancer Epidemiology and Prevention Biomarkers. 2008;17(11):3170-8.
60. Ursin G, Henderson BE, Haile RW, Pike MC, Zhou N, Diep A, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? Cancer Research. 1997;57(17): 3678-81.
61. Narod SA, Dubé M-P, Klijn J, Lubinski J, Lynch HT, Ghadirian P, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Journal of the National Cancer Institute. 2002;94(23):1773-9.
62. Haile RW, Thomas DC, McGuire V, Felberg A, John EM, Milne R L, et al. BRCA1 and BRCA2 mutation carriers, oral contraceptive use, and breast cancer before age 50. Cancer Epidemiology and Prevention Biomarkers. 2006;15(10):1863-70.
63. Brohet RM, Goldgar DE, Easton DF, Antoniou AC, Andrieu N, Chang-Claude J, et al. Oral contraceptives and breast cancer risk in the international BRCA1/2 carrier cohort study: a report from EMBRACE, GENEPSO, GEO-HEBON, and the IBCCS Collaborating Group. Journal of clinical oncology. 2007;25(25):3831-6.
64. Bernholtz S, Laitman Y, Kaufman B, Shimon SP, Friedman E. Cancer risk in Jewish BRCA1 and BRCA2 mutation carriers: effects of oral contraceptive use and parental origin of mutation. Breast cancer research and treatment. 2011;129(2):557.
65. Kotsopoulos J, Lubinski J, Moller P, Lynch HT, Singer CF, Eng C, et al. Timing of oral contraceptive use and the risk of breast cancer in BRCA1 mutation carriers. Breast cancer research and treatment. 2014;143(3):579-86.
66. Rieder V, Salama M, Glöckner L, Muhr D, Berger A, Tea MK, et al. Effect of lifestyle and reproductive factors on the onset of breast cancer in female BRCA 1 and 2 mutation carriers. Molecular genetics & genomic medicine. 2016;4(2):172-7.
67. Cibula D, Zikan M, Dusek L, Majek O. Oral contraceptives and risk of ovarian and breast cancers in BRCA mutation carriers: a meta-analysis. Expert review of anticancer therapy. 2011;11(8):1197-207.
68. Iodice S, Barile M, Rotmensz N, Feroce I, Bonanni B, Radice P, et al. Oral contraceptive use and breast or ovarian cancer risk in BRCA1/2 carriers: a meta-analysis. European journal of cancer. 2010;46(12):2275-84.
69. Friebel TM, Domchek SM, Rebbeck TR. Modifiers of cancer risk in BRCA1 and BRCA2 mutation carriers: a systematic review and meta-analysis. Journal of the National Cancer Institute.

2014;106(6):dju091.
70. Schrijver LH, Olsson H, Phillips K-A, Terry MB, Goldgar DE, Kast K, et al. Oral Contraceptive Use and Breast Cancer Risk: Retrospective and Prospective Analyses From a BRCA1 and BRCA2 Mutation Carrier Cohort Study. JNCI Cancer Spectrum. 2018;2(2):pky023.
71. Cancer IAfRo. Hormonal contraceptives, progestogens only. IARC monographs on the evaluation of carcinogenic risks to humans. 1999;72:339-97.
72. Practitioners RCoG. Oral Contraception Study: Effect on hypertension and benign breast disease of progestogen component in combined oral contraceptives. Lancet. 1977;1(8012):624.
73. Calle E, Heath C, Miracle-McMahill H, Coates R, Liff J, Franceschi S, et al. Breast cancer and hormonal contraceptives: further results: Collaborative group on hormonal factors in breast cancer. Contraception. 1996;54(3):1-106.
74. Kumle M, Weiderpass E, Braaten T, Persson I, Adami H-O, Lund E. Use of oral contraceptives and breast cancer risk: The Norwegian-Swedish Women's Lifestyle and Health Cohort Study. Cancer Epidemiology and Prevention Biomarkers. 2002;11(11):1375-81.
75. Brinton LA, Brogan DR, Coates RJ, Swanson CA, Potischman N, Stanford JL. Breast cancer risk among women under 55 years of age by joint effects of usage of oral contraceptives and hormone replacement therapy. Menopause (New York, NY). 2018;25(11):1195-200.
76. Morch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard O. Contemporary Hormonal Contraception and the Risk of Breast Cancer. The New England journal of medicine. 2017;377(23):2228-39.
77. Machado RB. Hormonal Contraceptives and Risk of Breast Cancer: How to Explain it without Controversy. Revista Brasileira de Ginecologia e Obstetrícia. 2018;40(2):57-8.
78. Vessey M, Doll R, Peto R, Johnson B, Wiggins P. A long-term follow-up study of women using different methods of contraception—an interim report. Journal of biosocial science. 1976;8(4):373-427.
79. Hankinson SE, Colditz GA, Manson JE, Willett WC, Hunter DJ, Stampfer MJ, et al. A prospective study of oral contraceptive use and risk of breast cancer (Nurses' Health Study, United States). Cancer Causes & Control. 1997;8(1):65-72.
80. Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ (Clinical research ed). 2007;335(7621):651.
81. Vessey M, Yeates D. Oral contraceptive use and cancer: final report from the Oxford–Family Planning Association contraceptive study. Contraception. 2013;88(6):678-83.
82. Joukar F, Ahmadnia Z, Atrkar-Roushan Z, Hasavari F, Rahimi A. The Investigation of Risk Factors Impacting Breast Cancer in Guilan Province. Asian Pacific journal of cancer prevention: APJCP. 2016;17(10):4623.
83. Soroush A, Farshchian N, Komasi S, Izadi N, Amirifard N, Shahmohammadi A. The role of oral contraceptive pills on increased risk of breast cancer in Iranian populations: a meta-analysis. Journal of cancer prevention. 2016;21(4):294.
84. Chaveepojnkamjorn W, Pichainarong N, Thotong R, Sativipawee P, Pitikultang S. Relationship between breast cancer and oral contraceptive use among Thai premenopausal women: a case-control study. Asian Pacific journal of cancer prevention: APJCP. 2017;18(5):1429.
85. Cho MK. Use of Combined Oral Contraceptives in Perimenopausal Women. Chonnam medical journal. 2018;54(3):153-8.
86. Fabre A, Fournier A, Mesrine S, Desreux J, Gompel A, Boutron-Ruault M-C, et al. Oral progestagens before menopause and breast cancer risk. British journal of cancer. 2007;96(5):841.
87. Samson M, Porter N, Orekoya O, Hebert JR, Adams SA, Bennett CL, et al. Progestin and breast cancer risk: a systematic review. Breast cancer research and treatment. 2016;155(1):3-12.
88. Samson ME, Adams SA, Mulatya CM, Zhang J, Bennett CL, Hebert J, et al. Types of oral contraceptives and breast cancer survival among women enrolled in Medicaid: a competing-risk model. Maturitas. 2017;95:42-9.
89. Busund M, Bugge NS, Braaten T, Waaseth M, Rylander C, Lund E. Progestin-only and combined oral contraceptives and receptor-defined premenopausal breast cancer risk: The Norwegian Women and Cancer Study. International journal of cancer. 2018;142(11):2293-302.
90. Dolle JM, Daling JR, White E, Brinton LA, Doody DR, Porter PL, et al. Risk factors for triple-negative breast cancer in women under the age of 45 years. Cancer Epidemiology and Prevention Biomarkers. 2009;18(4):1157-66.
91. Rosenberg L, Boggs DA, Wise LA, Adams-Campbell LL, Palmer JR. Oral contraceptive use and estrogen/progesterone receptor–negative breast cancer among African American women.

Cancer Epidemiology and Prevention Biomarkers. 2010;19(8):2073-9.
92. Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, et al. Use of four biomarkers to evaluate the risk of breast cancer subtypes in the women's contraceptive and reproductive experiences study. Cancer research. 2010;70(2):575-87.
93. Phipps AI, Chlebowski RT, Prentice R, McTiernan A, Wactawski-Wende J, Kuller LH, et al. Reproductive history and oral contraceptive use in relation to risk of triple-negative breast cancer. Journal of the National Cancer Institute. 2011;103(6):470-7.
94. Beaber EF, Malone KE, Tang M-TC, Barlow WE, Porter PL, Daling JR, et al. Oral contraceptives and breast cancer risk overall and by molecular subtype among young women. Cancer Epidemiology and Prevention Biomarkers. 2014;23(5):755-64.
95. Beaber EF, Buist DS, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. Cancer research. 2014;74(15):4078-89.
96. Barnard ME, Boeke CE, Tamimi RM. Established breast cancer risk factors and risk of intrinsic tumor subtypes. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer. 2015;1856(1):73-85.
97. Li L, Zhong Y, Zhang H, Yu H, Huang Y, Li Z, et al. Association between oral contraceptive use as a risk factor and triple-negative breast cancer: A systematic review and meta-analysis. Molecular and clinical oncology. 2017;7(1):76-80.
98. Branchini G, Schneider L, Cericatto R, Capp E, Brum IS. Progesterone receptors A and B and estrogen receptor alpha expression in normal breast tissue and fibroadenomas. Endocrine. 2009;35(3):459-66.
99. Janerich DT, Glebatis DM, Dugan JM. Benign breast disease and oral contraceptive use. Jama. 1977;237(20):2199-201.
100. Vessey MP, Doll R, Sutton PM. Oral contraceptives and breast neoplasia: a retrospective study. Br Med J. 1972; 3(5829): 719-24.
101. Nomura A, Comstock GW. Benign breast tumor and estrogenic hormones: a population-based retrospective study. Am J Epidemiol. 1976; 103(5):439-44.
102. Ory H, Cole P, MacMahon B, Hoover R. Oral contraceptives and reduced risk of benign breast diseases. The New England journal of medicine. 1976;294(8):419-22.
103. Brinton LA, Vessey MP, Flavel R, Yeates D. Risk factors for benign breast disease. American journal of epidemiology. 1981;113(3):203-14.
104. Berkowitz GS, Kelsey JL, LiVolsi VA, Holford TR, Merino MJ, Ort S, et al. Oral contraceptive use and fibrocystic breast disease among pre-and postmenopausal women. American journal of epidemiology. 1984;120(1):87-96.
105. Vessey M. Oral contraception and health. The British Journal of General Practice. 1998;48(435):1639.
106. Rohan TE, Miller AB. A cohort study of oral contraceptive use and risk of benign breast disease. Int J Cancer. 1999;82(2):191-6.
107. Coriaty Nelson Z, Ray RM, Gao DL, Thomas DB. Risk factors for fibroadenoma in a cohort of female textile workers in Shanghai, China. Am J Epidemiol. 2002;156(7):599-605.
108. Vessey M, Yeates D. Oral contraceptives and benign breast disease: an update of findings in a large cohort study. Contraception. 2007;76(6):418-24.
109. Estevao RA, Nazario AC, Baracat EC. Effect of oral contraceptive with and without associated estriol on ultrasound measurements of breast fibroadenoma: randomized clinical trial. Sao Paulo medical journal = Revista paulista de medicina. 2007;125(5):275-80.
110. Bidgoli SA, Eftekhari T. Role of exogenous and endogenous sources of estrogen on the incidence of breast fibroadenoma: case-control study in Iran. Asian Pacific journal of cancer prevention : APJCP. 2011;12(5):1289-93.
111. Zera RT, Danielson D, Van Camp JM, Schmidt-Steinbrunn B, Hong J, McCoy M, et al. Atypical hyperplasia, proliferative fibrocystic change, and exogenous hormone use. Surgery. 2001;130(4):732-7.