Original Article

The Relationship between Hormonal Contraception and Breast Cancer

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Abstract

Background: Breast cancer is the most common cancer among women in the world and has become a growing important problem in low- and middle-income countries. Different patient variables have been reported for their association with breast cancer over time, including family background, age, sex, breast mass, monarchal age, contraception use, diet, physical inactivity, and obesity among others. Contraceptive pills are the most commonly prescribed method of birth control and account for 13% of the 140 million consumers worldwide. Data indicate that OC use for a long duration can increase breast cancer risk in women below 45 years of age. **Method:** This systematic review was carried out, including PubMed, Google Scholar, and EBSCO. Topics regarding the relationship between breast cancer and hormonal contraceptives and other articles were used in making the article. The found articles were screened by titles and reviewing the abstracts. **Results and Conclusion:** The review included 11 randomized studies that discussed the relationship between breast cancer and hormonal contraceptives. Although hormone is an efficient way of contraception, many studies have reported a potential risk of BC. The risk of breast cancer should be balanced against the benefits of using hormonal contraceptives. Awareness about breast cancer self-examination is very necessary and should be raised among hormonal contraceptive users, so women do it correctly.

Keywords: Relationship, Hormonal Contraception, Breast Cancer, women, Contraceptive pills, breast malignancy

Introduction

Breast cancer is the most common cancer among women in the world and has become a growing important problem in low-and middle-income countries [1-3]. Globally, it has been estimated that approximately 1.4 million new patients are identified annually with almost 10% of recently diagnosed cases affecting women under the age of 40 [4]. Over the years, though, the trend of oral contraceptive use has changed; currently, less than 0.5% of women aged 45-50 years used a pill before the age of 20 relative to 25% of women who are now 23 years of age [5]. Different patient variables have been reported for their association with breast cancer over time, including family background, age, sex, breast mass, monarchal age, contraception use, diet, physical inactivity, and obesity among others [6, 7].

Hormonal contraceptives are just an important and reversible form of birth control with side effects including headache, hypertension, venous thrombosis, and tumors [8]. There have been two identified general classes of hormonal contraception obtainable: combination contraceptives (estrogen and progestin) and progestin-only contraceptives. The mechanism of hormonal contraception is to prevent pregnancy by preventing ovulation by feedback inhibition of the hypothalamic-pituitary axis [9]. Contraceptive pills are the most commonly prescribed method of birth control and account for 13% of the 140 million consumers worldwide. Roughly 140 million females around the world use oral contraceptives; this proportion accounts for at least 13% of females aged 15-49 years of age [10]. OC usage is related to a major reduction in ovarian cancer, endometrial cancer, and colorectal cancer [11, 12].

Data indicate that OC use for a long duration can increase the risk of breast carcinoma in women below 45 years of age. The risk could be increased in women who use OCs after 40 years of age [13]. Increased risk of developing breast cancer was identified not only in consumers of hormonal birth control tablets, contraception patches, and vaginal rings but also in women who used progestin-only implants and injections and hormonal IUDs [14]. Actually, all oral

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How to cite this article: Mahjoub Musa Mohamed, A., Khalifah Ayed Alshammari, F., Fahad Saleh Alotayfi, R., Hameed Mamlooh Alenazi, Kh., Mofareh S Alruwaili, A. The Relationship between Hormonal Contraception and Breast Cancer. Arch Pharma Pract 2020;11(4):124-9.

contraceptives bear alerts and recommendations for a higher risk of breast malignancy. Several researches reported that using combined progestin and estrogen treatment is usually associated with the risk of developing breast tumors, which may depend on the form of estrogen and progestin [15]. Assessments of modern hormonal contraceptive preparations confirm observed data of an up to 20% rise in breast cancer incidence for women that use or have previously used contraceptive pills [15]. External estrogen and progestogen were classified as a group I cancer-causing agent because of the mitogenic action of estrogen and progestin and estrogen's carcinogenic metabolites by the International Agency for Research on Cancer (ISDA).

A previous analysis that included 54 studies and >150 000 cases worldwide assessed the relationship between malignancy of the breast and hormonal-based contraceptive use reported augmented risk of malignancy of the breast in existing or new users of contraceptive pills, which were no longer evident after the termination of hormonal therapy for 10 years [5].

Assessment of more than 10 retrospective trials and 60 case-control reports affecting more than 60,000 breast cancer women found a small but contradictory association of contraceptive pill consumers with elevated relative risk between existing and new users [16]. The 2013 meta-analysis calculated the cumulative actual risk rise for breast cancer that has ever been associated with OCs versus never used at approximately 0.89% [17]. According to the increasing number of women using hormonal birth control, it is important to study its associated risks and side effects especially its association with breast cancer.

Aim of the Study:

This study was conducted in order to discuss the results of previous studies investigating the relationship between breast cancer and hormonal contraceptives.

Methods and Materials

Sample & study groups

PubMed and EBSCO Information Services were chosen as the search databases for the publications used within the study, as they are high-quality sources. PubMed is one of the largest digital libraries on the internet established by the National Center for Biotechnology Information (NCBI), which is a part of the United States National Library of Medicine. Topics concerning the relationship between contraceptive hormones and breast malignancy or cancer in addition to other articles were used in making the article. The found articles were chosen by titles, and reviewing the abstracts. Inclusion criteria: the articles were chosen based on the relevance to the project which should include one of the following topics: 'breast cancer, OCP as a threat for malignancy of the breast, OCP and cancer risk' as showed in figure (1). Exclusion criteria: all other articles, which did not have one of these topics as their primary end, or repeated studies and review studies were excluded.

Statistical analysis

No software will be utilized to analyze the data. The data were extracted based on a specific form that contained (title of the publication, author's name, objective, summary, results, and outcomes). These data were reviewed by the group members to determine the initial findings and the modalities of performing the surgical procedure. Double revision of each member's outcomes were applied to ensure the validity and minimize the mistakes.

During article selection, studies and their results were doubled-reviewed to assure that we enrolled the studies related to the objective of our study, and to avoid or minimize errors in the results. We acknowledged some limitations we had in the making of this study. We tried to include articles that fit the outcome criteria for inclusion in our review. Certainly, bigger sample size provided more significant results.

Results:

A total of 117 studies were included for title screening, 74 of which were included for abstract screening, which led to the exclusion of 39 articles. The remaining 35 publications' full-texts were reviewed. The full-text revision led to the exclusion of 24 studies, and 11 were enrolled for final data extraction (Table 1).

The included studies had different study designs.

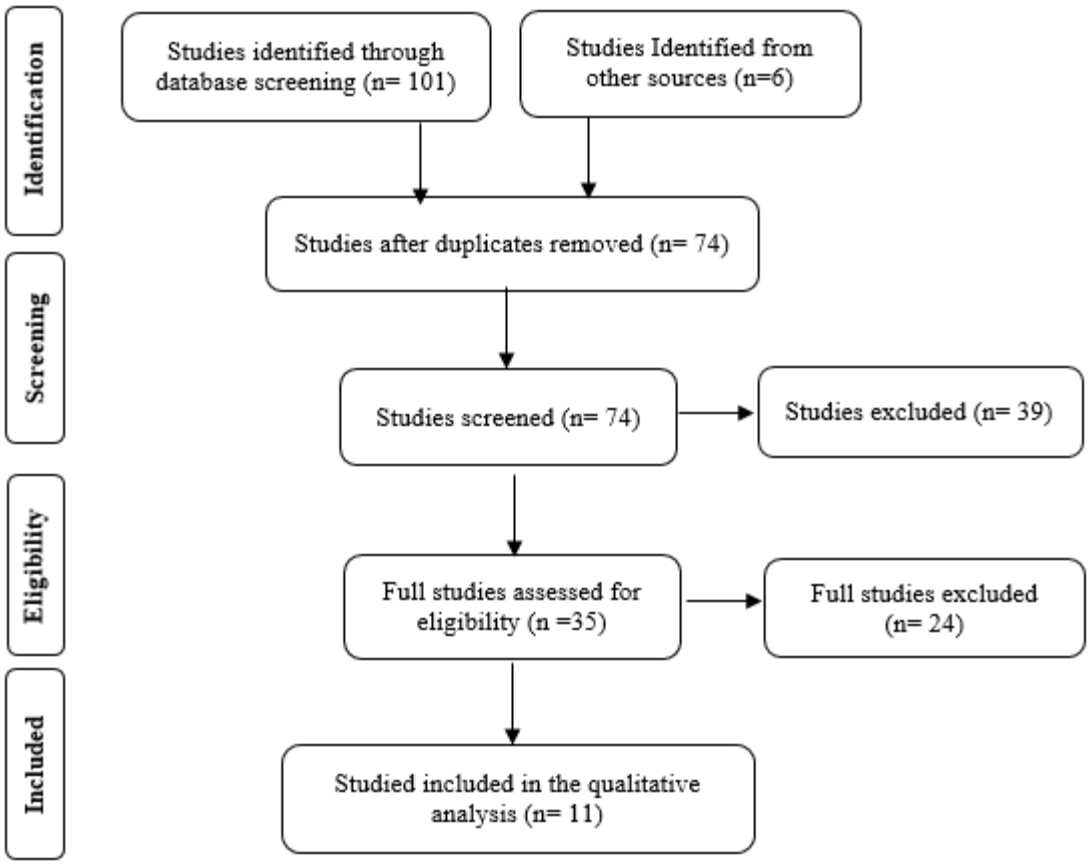

Figure 1: Flow chart illustrating the process of data extraction for the study

Table 1: Author, country, year of publication, methodology, and results:

Authors	Methodology and Objective	Results and Conclusion
Dorchak et al., 2018 [18]	A retrospective case series analysis, using data derived from questionnaires and histopathological diagnoses of 656 women participating in the Department of Defense (DoD) Clinical Breast Care Project (CBCP), examined correlations between breast cancer and hormonal birth control use pathology, even benign breast pathologies.	Risk factors related to patient as age, genetic history of breast cancer, body mass index (> 30), and extent of oral contraceptive use have been found to raise the risk of carcinoma of the breast and should be taken into consideration when determining which form of hormonal birth control to be used to reduce the likelihood of evolving of carcinoma of the breast.
Layde, et al. [19]	A multicenter case-control study, 4599 women aged between 20-55 years old were included in the analysis.	All contraceptives induce breast cancer that even may delay a woman's first pregnancy (and presumably reducing her overall pregnancy numbers) raises breast cancer risk. The relationship between the pill and breast cancer continues to be ambiguous and cannot be explained by relying solely on positive subsets.
Bardaweel, et al. 2019 [20]	A retrospective study included 450 cases in Jordon to discover any probable relation between the existence and period of OCs use in women of Jordan women and the hazard of breast malignant tumor.	Use of OCs could be related to a greater risk of breast malignant tumor ($p = 0.002$) along with other risk factors showed a substantial link with the elevated risk of malignant tumor of the breast as the age of menarche and menopause, number of pregnancies, state of menopause, and history of cancer in households.
Ji, et al. (2019) [21]	a systematic review and meta-analysis included 10 studies used summary relative risk (RR) and 95% confidence intervals (CIs) to assess potential linear and non-linear dose-response relationships.	A linear dose-response relationship was detected between the age at first OC use and BC risk.

Hunter, et al. (2010) [22]	The cohort study included 116,608 female nurses aged 25-42 years evaluated lifetime oral contraceptive use and the precise preparations they used using a follow-up questionnaire to get evidence on exposure grade and the incidence of breast malignant tumor and other main disorders.	Oral contraceptive use history has not been linked with risk of malignant tumor of the breast Current use of any oral contraceptive has been accompanied by a moderately considerable rise in risk.
No Author Listed [23]	A systematic review included 54 studies performed in 26 countries including 53,297 females with breast malignant tumor and 100,239 females with no breast cancer.	The study reported a minor rise in the risk of breast malignancy during the current use of usual oral contraceptive pills and cases stopped it 10 years ago but no longer. 41% of the cases with breast malignancy and 40% of the participants without breast malignancy had used contraceptive pills at some time.
Pragout, et al. [24]	A systematic review was undertaken to review cancer risks related to hormonal contraception.	The study reported no increase in incidence or mortality of all types of cancer in users of contraceptive hormones while the use of estrogestin is related to an augmented risk of breast malignancy during use, and a lower risk of endometriosis, ovaries, and lymph nodes and colorectal cancer.
Chaveepojnkamjorn, et al., 2017 [25]	A retrospective study of 257 patients and 257 controls in 2013-2014 to measure the relation between breast malignancy with contraceptive pills (OC) use between pre-menopausal Thai females	OC use increased the hazard of breast malignancy by influence of over three times.
Cibula, et al., 2010 [26]	A systematic review included all follow-up, cohort, and retrospective design up to December 2008.	A slightly increased hazard of OC was observed in present consumers of oral contraceptives, a consequence that fade after 5-10 years of discontinuing use.
Dumeaux, et al. [27]	An E3N cohort study on 68,670 women using regression analysis of information on postmenopausal women	No rise in the threat of breast malignancy was related to past use of OC in postmenopausal ladies, probably due to the initiation had secured.
Schneyer, & Lerma, (2018) [28]	A review article to review recent literature on the consequences concomitant with the use of hormonal contraception with a focus on breast cancer.	Several considerations surrounding the risk of breast malignancy associated with hormonal contraception use should be considered.

Results and Discussion:

Worldwide, about 140 million women use oral contraceptives; about 13% of females aged 15-49 years use oral contraceptives [10]. It was estimated that the incidence of breast malignancy in the world was 43.1 per 100,000 women with 12.9 per 100,000 deaths among them [29]. The reasons for breast malignancy were still unknown, but almost all its risk factors have a direct or indirect relationship with the accumulation of estrogen hormones in the human body and estrogen imbalance with progesterone [30]. Obesity, physical inactivity, alcohol consumption, and genetic mutations were all related to increased breast cancer risk, as well as long-term use of oral contraceptives is associated with a small elevation in the risk of breast cancer in young women [16, 31-33]. Studies of the risk of breast cancer in women who received hormonal contraceptives have shown inconsistent results from no elevations in the risk to a 20-30% increase in risk [34]. Most studies have evaluated women according to whether they had ever used oral contraceptives or whether they were past, recent, or current users of oral contraceptives [35]. This is a simple systematic review conducted to discuss the results of previous studies investigating relationship between breast cancer and hormonal contraceptives.

The Collaborative Group on Hormonal Factors in Breast Cancer concluded that women who were previous or current users of OCs had a significantly higher chance of developing breast cancer. However, ten years or so after they started taking OCs, their risk of getting breast cancer returned to the degree at which it would have been if they had never used them [5]. Our findings indicated that Chaveepojnkamjorn, et al. reported BC risk increased 3 folds among OC users [25], which was consistent with the previous studies [36-42]. Wingo et al. and Althuis et al. [43-46] found that the risk of breast cancer among premenopausal women associated with recent use of OCs decreased with increasing age. A large-scale observational study in Denmark concluded that there is an elevation in risk, yet small, (about 20%), but in contrast to ours, the risk was proportional with the duration of use [15]. Another study, with a smaller sample size, reported an elevation in the risk of BC (RR = 1.3; 95% CI, 1.0–1.7) associated with current OCs use, especially with the use of a triphasic OC [22]. Four meta-analyses showed that BC risk was higher for OC users compared to non-users [11, 45, 46]. Dolle et al. reported an elevated risk of BC in women who were younger than 40 years, with different effects in premenopausal and postmenopausal women [47]. A study reported that the use of OC was not associated with BC risk in women aged 50 to 79 years [48].

On the other hand, Dumeaux et al. [28] reported no BC risk among hormonal contraceptive users agreeing with results of other studies [49-54].

Conclusion:

Although hormonal provide an efficient way of contraception many studies have reported a potential risk of BC. The risk of breast cancer should be balanced against the benefits of using hormonal contraceptives. Awareness about breast cancer self-examination is very necessary and should be raised among hormonal contraceptive users, so women do it correctly. Studies suggest careful consideration of alternative methods of contraception such as non-hormonal, long-acting, or reversible contraceptives.

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