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LONG EXPOSURE HORMONAL CONTRACEPTIVE HAS POTENTIAL RISK OF BREASTCANCER: A SYSTEMATIC REVIEW

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ABSTRACT:

Background: Every year there is a rise in the incidence of breast cancer (BC). Age before menopause, family history, obesity, and the use of hormonal products are the causes of breast cancer. One of the things that women require in order to manage birth is hormonal contraception (HC). This article wants to analyze the extent to which the use of hormonal contraceptives is a risk factor for breast cancer. Materials and Methods: Online databases Pubmed, ScienceDirect, Embase, and Crossref were searched for literature research for this investigation. Only open-access publications published between 2014 and 2024 are included in this systematic review.This study incorporates the original paper, which examined the impact of hormonal contraceptive methods on breast cancer in either long-term users or those with a history of usage. Result: PRISMA chart screening turned up 23 articles. These publications mostly demonstrate that using HC increases the risk of BC. A longer history of using hormonal contraceptives is usually linked to a higher risk of developing breast cancer. Conclusion: Hormonal imbalances caused by prolonged exposure to exogenous hormones, like those found in HC, can result in BC. To reduce the risk of BC and other dangers, it is recommended to employ a mix of contraceptive techniques, such as non-hormonal contraception in addition to HC alone.

Keywords: Hormonal Contraception, Breast Cancer

1. Introduction

One of the cancers that often occur in women is Breast Cancer (BC). BC is still a complex health problem in millions of people [1]. BC is known to experience an increase of 0.5% every year (2010-2019) [2]. The prevalence in 2014-2019 is known to increase from 30.4 to 50.6 per 10,000 population [3]. The increase in BC incidence in Central Asia is 54%, East Asia 89.5%, and South Asia 76.7%. Although the mortality rate decreased by 1.3% from 2011-2020, BC's morbidity and mortality are expected to increase by 2030 [4]. BC is still the leading cause of cancer deaths in the world in more than 400,000 individuals [5].

The significant increase in BC in the world could be due to prolonged life expectancy, lifestyle, and related risk factors [6]. The factors that cause BC are age before menopause, family history, alcohol consumption, smoking, obesity, and the use of hormonal products [7]. One of the hormonal products in question is hormonal contraction (HC). HC can be classified as progestin alone or a combination (progestin and estrogen) depending on its content [8]. Progesterone and synthetic estrogens in HC play a role by inhibiting the pituitary in secreting LH and FSH, resulting in anovulation occurring. In addition, HC can also suppress endogenous progesterone and estradiol, thereby inhibiting endometrial proliferation [9]. Although proven to be effective in preventing pregnancy, HC is often reported as one of the factors in the occurrence of BC [10].

Female hormones play an important role during the development of sexual characteristics in the mammary glands. During normal development, progesterone is required in alveologenesis and estrogen is required in duct elongation [11]. Excessive exposure to exogenous hormones, such as in HC, can result in hormonal imbalances that lead to BC [12]. HC acts as a mitogen capable of promoting the development of different types of cancer through various receptor-dependent signaling pathways [13]. Most women have been using HC for more than 30 years, which allows prolonged exposure to reproductive life to pose an early risk of BC [14]. Based on this description, this article wants to analyze the extent to which the use of hormonal contraceptives is a risk factor for breast cancer.

2. Materials and Methods

a. Search Strategy

The search for literature studies in this study was obtained from the following online databases Pubmed, ScienceDirect, Embase, and Crossref. Literature search with keywords hormonal contraception, Otho Tri-Cyclen, progestin-only, Lo Ovral, combined oral contraceptives, pills, and breast cancer. This systematic review only uses free-access articles with a publication range of 2014 to 2024.

b. Inclusion criteria

The inclusion in this study is the original article with an observation study. The review focused on breast cancer affected by interventions from hormonal contraceptives, either from long-term long-term users or from previous user histories.

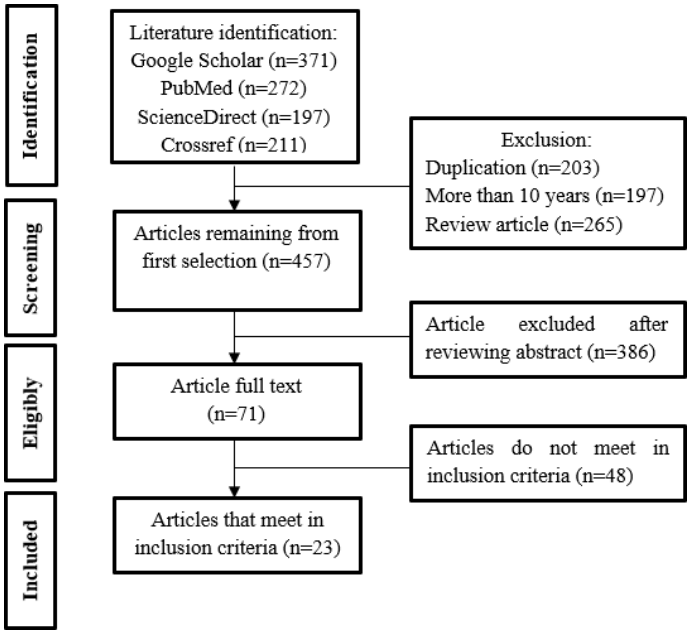

Figure 1. PRISMA chart

c. Study selection, quality assessment, and data extraction

The keywords mentioned in the literature search produce 1051 article. Then 665 articles were deleted because there were duplicates, >10 years, and were review articles. From the first screening, 457 articles were obtained, but they were excluded again because the abstract was not suitable and did not match the inclusion criteria.

3. Result

23 articles employing the HC technique in the forms of oral contraceptives (OC), ovral (LO), combination oral contraceptives (COC), otho tri-cyclen (OTC), progestin-only (POC), and levonogestrel -IUS passed the screening process using the PRISMA approach. The body of research indicates that using HC, particularly over an extended period of time, may increase the risk of BC. Table 1 presents the findings from the article analysis.

Table 1. Literature Table

Author	Ref	Method	result
Alipour et al, 2019	[15]	Case control study involving Golestan CS with control group and case	oral contraception use for more than10 years increases the risk of BC (OR: 3.17)
Wahidin et al,2018	[16]	A 2013 hospital-based case-control study involved 762 15-year-old women from five regions, including 381 with and without breast cancer diagnoses, examining factors like oral contraceptives	Breast cancer risk has been shown to rise in patients who use oral contraceptives. An increased risk of breast cancer is typically associated with longer oral contraceptive use.

Bardaweel et al, 2019	[17]	In a study with 450 Jordanian women between the ages of 18 and 65, the relationship between breast cancer risk and several factors was investigated using the Chi-square and Mann Whitney-U tests.	Regular use of OCs raises the risk of breast cancer, but not the duration of usage. Significant associations have also been observed with the age at puberty, menopause, previous pregnancies, menopausal status, and family history.
Solikhah et al,2022	[18]	Women using family planning for more than5 years in Indonesia (2014-2015)	HC use may lead to low-risk BC(OR: 0.10)
Dorchak et al,2018	[19]	case series retrospective study with users of Lo Ovral (LO), Combination oral contraceptives (COC), and Otho Tri-Cyclen (OTC)	OTC users relate to luminal A or benign, while ON relates to DCISand benign. LO user has no relationship with benign
Mørch et al, 2018	[20]	A prospective cohort study with women aged 15-49 years who did not have thromboembolism, cancer, and infertility treatment	BC risk in HC users over 5 years is 1.20, this includes progestin-only and COC users. after stopping taking HC, the risk of BC remains high. estimated 1 in 7690 HC users will experience BC
Niemeyer Hultstrand et al, 2022	[21]	study in Swedish women aged 15-34 years in 2005-2017 to assess the risk of BC with poisson regression	there was no increased risk of BC in COC users, but progestin-only users had a risk of 1.32. BC risk in HC users increases after more than 5 years (OR: 1.39). BC risk per 100,000 women was 29.8 in progestin-only users, 10.9 in COCusers, and 22.4 in non-HC users
Feriani et al, 2023	[22]	Cross sectional study on 125 cancer patients to investigate risk factors that cause BC	there is a relationship between the history of hormonal contraceptiveuse and BC (P<0.001)

Alsammarraie etal, 2020	[23]	200 people with cancer compared to 300 healthy women for a known risk of BC	49% of people with BC have a history of HC use. users of oral contraceptives had a BC risk of 1.73 with the highest risk of use before theage of 20 (OR: 6.62). ER and PR expression in BC was not affected byHC use.
Busund et al, 2018	[24]	to assess the effect of Progestin-only (POC) and COC use on the risk of breast cancer determined by hormone receptors in 74,862 premenopausal women	POC use ≥5 years was associatedwith ER+ (HR: 1.59) and cancer (HR: 1.63). The use of COCs was associated with ER− and ER−/PR− cancers, but did not increase the risk of ER+ and ER+/PR+ cancers.
Burchardt et al, 2022	[25]	The prospective cohort study involved 113,187 women using oral contraceptives from the age of 13 to early (1989) and updated theuse data up to 2009	oral contraceptives are at risk of developing BC (OR: 1.31), the risk increases to 1.56 with longer use (>5 years). Former users who have quit have the same risk as those who have never used (OR: 0.99). formulations in the form of levonogestrel have an OR risk: 2.83
Moradinazar et al, 2019	[26]	This case-control study used middle-aged periodical care forms from Iran's Ministry of Health and a healthy fertility program to assess 212 cases of breast cancer in people aged 25 to 49. A controlgroup consisted of people who had not received a diagnosis for	The use of hormones for contraception and hormone therapy greatly raises the risk of breast cancer, especially for women who have been receiving hormone therapyfor more than 120 months. The risk rises exponentially with the age of first menstruation and pregnancy, increases linearly with age, and becomes steeper beyond 20 years.
		up to two years.	
Motie et al, 2021	[27]	In this 2016–2018 case-control study, data from 460 women in academic hospitals in Mashhad were analyzed using logistic regression models, frequency tables, and SPSS software.	Breast cancer risk is significantly associated with BMI, menarche age, menopausal age, non-breast malignancy family history, and oral contraception pills, according to multivariate analysis.

Karlsson et al,2021	[28]	The UK Biobank is a large cohort study designed to improve disease prevention, diagnosis, and treatment. Between 2006 and 2010, it recruited 502,682 individuals, including 273,404 women, from 22 UK assessment centers. Participants shared data on lifestyle, medical history, exposures, and physical measures.	The study discovered age- and time-dependent relationships between the use of oral contraceptives and endometrial, breast, and ovarian cancers. Stopping use raised the riskof breast cancer. In personalized medicine, knowledge of the immediate and long-term impacts ofhormone exposure is essential for making well-informed decisions.
Heikkinen et al, 2016	[29]	data was obtained in2009 with 20,000 control populations and 7,000 BC cases	there was a positive association between BC risk and HR IUD users when compared to the group that had never used HC
Joukar et al, 2016	[30]	This case-control consisted of 225 women with BC and 225 healthy women	HC use over 16 years increases therisk of BC with OR: 2.3
Dianatinasab et al, 2017	[31]	this case-control has 526 BC cases and 526control cases	oral contraceptive use increases the risk of BC (OR: 1.46)
Jareid et al, 2018	[32]	case control study involving Norwegian women, information obtained by questionnaire	levonogestrel-IUS users increasedthe risk of BC by oR: 1.03
Brinton et al, 2018	[33]	The case control study involved 55-year-old	History of OC use is associated with BC risk (OR: 1.1)

		Atlanta women with 919 controls and 1031cases	
Chaveepojnkamjorn et al, 2017	[34]	case control study involving premenopausal women in Thailand (TPW) whouse Oral Contraception (OC) with a control group and a case	The TPW of OC users is at risk of BC by 3 times (OR: 3.39). An increase in the duration of OC use followed by an increase in BC risk (6years OR: 3.91 and 10 years OR: 4.23)
Hamdi-Cherif etal, 2020	[35]	This case study involved women with BC and a control groupduring 2012-2017	OC use is associated with BC risk(OR: 1.57)
Almasi-Hashianiet al, 2021	[36]	Case control study of Iranian women with confirmed BC group and control group (2005-2008)	increased risk of BC in OC userhistory (OR: 1.6)
El Sharif & Khatib, 2021	[37]	This control study on women in the West Bank of Palestine	women who use HC have a 2-fold higher risk of BC (OR: 2.2)

3. Discussion

Through family planning, people can use contraceptive techniques to limit the number of children and pregnancies they wish to have. For human rights and health, it is essential [38]. Maternal illness and pregnancy-related mortality decrease when unwanted pregnancies are avoided. One of family planning's major health benefits is that it can postpone pregnancies in young girls and older women, who are at higher risk of illness. Contraception methods vary in effectiveness, with some available over the counter, while others may require medical advice or surgical intervention [39]. Both contemporary and conventional methods of contraception are available. The IUD, injectables, female sterilization, the pill, and barrier techniques (condom, foam, jelly, and diaphragm) are examples of contemporary techniques. Conventional techniques include withdrawal, vaginal douching, and periodic abstinence (rhythm method) [40].

Hormonal contraceptives, primarily composed of synthetic progesterone or progestin and synthetic estrogen like ethinyl estradiol, can cause contraceptive effects when introduced individually [41]. To produce a contraceptive state, progesterone and estrogen work through several paths and processes. While estrogen suppresses LH release, progestin limits follicular sensitivity to FSH and reduces LH production. The fundamental dynamics of both progestin-only and combined hormonal contraceptive therapies are captures by two significant autocrine effects in the model [42]. The primary mechanism of progestin action is its suppresion of FSH's capacity to generate LH-sensitive follicular tissue, P4's suppresion of LH synthesis results in a reduction in follicular sensitivity to FSH in the early stages of the follicular phase [43]. Estrogen works similarly to progestin as a contraceptive by preventing the pituitary gland's secretion of LH and FSH. LH surges are prevented by insuficient gonadotropins, and progestindosage is decreased by adding estrogen [41]. Combination of estrogen and progestin enhances progesterone's effect but inhibits LH release. It upregulates progesterone receptor expression, increasing P4's effectiveness and potentially primes P4 receptors for the luteal

phase [43].

Combination hormonal preparations (CHC) are used for treating gynecological and endocrine disorders, including acne, menorrhagia, dysmeehea, perimenopause dysfunction, and polycystic ovary syndrome. They are effective in treating treatment-resistant acne, menopausal symptoms, bone mineral density decreases, and menstrual irregularities [44]. Long-term use of hormonal contraception (HC) increases the risk of venous thromboembolic illness, heart disease, cervical cancer, and breast cancer, among other health problems. Ischemic stroke and myocardial infarction are associated with current CHC usage, although VTE raises the risk. The risk of cervical cancer decreases after stopping use but slightly increases with prolonged use. The risk of breast cancer rises with usage frequency [45]. Breastcancer ranks second overall in frequency and is the most common cancer in women. It also accounts for the majority of women's cancer-related deaths [46]. As over half of women globally between the ages of 15 and 49 use hormonal contraception, a Danish study finds that these methods raise the risk of breast cancer [47].

Female hormones play a significant role during the development of sexual characteristics in the breast glands, acting as mitogens able to promote the progression of a wide range of cancers through a variety of receptor-dependent signaling pathways [48]. Breast cancer (BC) is caused by highly invasive and metastatic malignant tumors, which affect a large number of women and pose a threat to their health and quality of life [49]. One risk factor alone cannot be the only cause of breast cancer as the disease develops in response to a multitude of biological, psychological, and environmental variables, including the consumption of exogenous hormones [50].

Molecular pathways alter throughout time due to the mammary gland's varying sensitivity to specific hormones based on a woman's developmental stage [51]. Normal development requires progesterone (P) to act on mammary epithelial cells (MEC) to cause ductal side branching and alveologenesis, and requires estrogen (E) signaling for pubertal ductal elongation [52]. Milk production in the mammary gland and the proliferation of epithelial cells depend on prolactin (PRL). The cytokine receptor superfamily's membrane PRL receptors (PRLr), which are responsible for its biological activity, serve both autocrine and paracrine roles. By PRL synthesis and PRLr gene deletion, the PRL and PRLr pathways function as significant regulators of mammary gland development. For the purpose of producing and secreting milk, PRLr signaling promotes more mammary alveologenesis during pregnancy. Moreover, there is a continuum of overlapping and highly integrated signaling pathways that are essential for both genomic integrity and cancer susceptibility because E and P are expressed in distinct normal MEC populations and there is significant paracrine crosstalk between E and P signaling as well as between P and PRL signaling. Exogenous hormones may alter distinct signaling pathways and raise the risk of BC. Examples of such hormones include those includedin hormonal contraceptive medications [53].
Breast cancer, a prevalent health issue affecting many women, is caused by invasive, metastatic malignant tumors. The disease's development is influenced by biological, psychological, and environmental factors, including hormone intake, making the causal mechanism complex [54]. Female hormones function as mitogens, greatly influencing the sexual features of the breast gland and accelerating the development of cancer by way of receptor-dependent signaling pathways [55]. E and P are essential for the correct growth of mammary epithelial cells (MECs). P is required for alveologenesis and ductal side branching, but E is necessary for pubertal ductal elongation. The production of milk and the proliferation of epithelial cells depend on prolactin (PRL). Mammary gland development is

regulated by the PRL and PRLr pathways, which promote more mammary alveologenesis during pregnancy and milk production. Different MEC populations express E and P differently, which results in a highly integrated signaling network that is essential for maintaining genomic integrity and increasing the risk of cancer. These pathways can be impacted by exogenous hormones, such as those included in hormonal contraceptive medications [53].

Research on the mutagenesis processes reveals that E and P, which are abundant in the breast and other tissues, hydrolyze estrogens to form reactive oxygen species, or catechol reactive estrogens [56]. They also act on the P-450 1BI enzyme complex. Additional genome-sequencing analyses have revealed evidence of genome-wide DNA mutations associated with cytidine deamination by the APOBEC3 genes (A3A and A3B), a family of enzymes that convert cytidine to uridine and hence modify RNA or DNA [57]. This leads to breaks in DNA strands, which interfere with DNA repair systems and contribute to the genomic instability that fuels the growth of cancer, as demonstrated by mutations in BRCA1 and BRCA2 [58]

4. Conclusion

Family planning reduces unwanted pregnancies, which is crucial for both health and human rights. Among the numerous methods of contraception are injectables, tablets, barrier techniques, female sterilization, and IUDs. Hormonal contraceptives, which mostly consist of synthetic progesterone and estrogen, can have contraceptive effects when used on their own. Combining progesterone with estrogen and progesterone increases its effects while inhibiting the release of LH. Combination hormonal preparations are used in the treatment of gynecological and endocrine disorders such as acne, menorrhagia, dysmenorrhea, perimenopause dysfunction, and polycystic ovary syndrome. Long-term hormone therapy has been linked to adverse effects of hormones, including venous thromboembolic illness, arterial and cardiovascular disease, breast cancer, and cervical cancer. These effects are brought on by P and E hydrolyzing estrogens in breast tissues, which then acts on the P-450 1BI enzyme complex and forms reactive oxygen species. Genome sequencing research has identified DNA alterations linked to cytidine deamination caused by the APOBEC3 gene. These mutations cause breaks in DNA strands and genomic instability, both of which contribute to the onset of cancer. By using long-term hormonal contraceptives and noninvasive screening methods, high-risk patients might be detected early, and the safety of innovative hormonal treatments could be enhanced.

Conflict of Interest
No conflict of interest

Author Contribution
All author contributed to the process of preparing this sytematic review article

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