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Review Article

THE LINK BETWEEN HORMONAL CONTRACEPTIVES AND BREAST CANCER RISK: A SYSTEMATIC REVIEW

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Abstract:

Objectives: This systematic review aims to investigate the association between hormonal contraceptives (HC) and breast cancer (BC) risk. **Methods:** A comprehensive search of relevant databases was conducted to identify studies that met the inclusion criteria. PubMed, MEDLINE, and Embase were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process. **Results:** Our results included eight studies with a total of 14,336,867 women. The eight studies included women that used variable HC and four studies did not specify the types of HC. Six studies demonstrated that HC usage was a significant risk factor for the development of BC. Early use before the age of 20 is associated with the highest risk of BC and longer duration of HC use significantly increases the risk of BC. Interestingly, one study found that HC use is not linked to BC usage and another study found that the use of HC is a protective factor against the development of BC. **Conclusion:** Many studies have indicated a possible risk of BC, despite the fact that hormones offer an effective method of birth control. It is important to weigh the advantages of using HC against the dangers of BC. It is imperative that those using HC are made aware of the importance of BC self-examination and how to conduct it correctly. Research indicates that considering non-hormonal, long-acting, or reversible contraceptives should be carefully considered as alternate forms of birth control.

Keywords: Hormonal contraceptives; Breast cancer; Risk factors; Systematic review.

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INTRODUCTION:

BC is one of the most common forms of cancer in women, with millions of cases diagnosed each year worldwide. While the exact causes of BC are still not fully understood, research has shown that certain factors, such as genetics, lifestyle choices, and hormonal influences, can increase a woman's risk of developing the disease. One such hormonal influence that has been the subject of much debate and study is the use of HC [1].

HC, such as birth control pills, patches, injections, and intrauterine devices, works by altering a woman's hormone levels to prevent pregnancy. These contraceptives contain synthetic versions of the hormones estrogen and progesterin, which regulate the menstrual cycle and ovulation [2]. While HC is highly effective at preventing pregnancy, there has been ongoing concern about its potential link to an increased risk of BC [3].

Several studies have been conducted over the years to investigate the relationship between HC and BC risk. Some studies have suggested that women who use HC may have a slightly higher risk of developing BC compared to women who have never used them. This increased risk is thought to be due to the hormonal changes caused by these contraceptives, which can stimulate the growth of breast tissue and potentially lead to the development of cancerous cells [4].

However, it is important to note that the overall increase in BC risk associated with HC is relatively small. According to the American Cancer Society, the risk of developing BC from using HC is still considered to be low, especially when compared to other risk factors such as age, family history, and lifestyle choices [5]. Additionally, the risk of developing BC decreases once a woman stops using HC, and the risk returns to normal levels within a few years [6].

It is also worth mentioning that not all types of HC carry the same level of risk when it comes to BC. For example, some studies have suggested that contraceptives containing high doses of estrogen may pose a higher risk compared to those with lower estrogen levels. Additionally, the risk of BC may vary depending on the duration of contraceptive use, with long-term users potentially facing a slightly higher risk compared to short-term users [7].

Despite the potential link between HC and BC risk, it is important to remember that these contraceptives offer numerous benefits beyond preventing pregnancy [8]. HC is commonly used to regulate menstrual cycles, manage hormonal imbalances, and treat

conditions such as endometriosis and polycystic ovary syndrome. For many women, the benefits of using HC outweigh the potential risks, and it is ultimately a personal decision that should be made in consultation with a healthcare provider [9].

There is ongoing debate and uncertainty regarding the potential link between the use of HC and the risk of developing BC. While some studies suggest a possible association, others have found inconclusive results. Therefore, a systematic review is needed to comprehensively analyze the existing literature and provide a clearer understanding of the relationship between HC and BC risk. The aim of this systematic review is to investigate the link between the use of HC and the risk of developing BC, providing a comprehensive analysis of existing literature to clarify the association and inform healthcare practices and public health policies.

Study Significance

Public Health Impact: Understanding the relationship between HC and BC risk is crucial for public health policymakers in making informed decisions regarding contraceptive use recommendations.

Clinical Guidance: Findings from this systematic review can provide healthcare providers with evidence-based information to counsel patients on the potential risks associated with HC.

Future Research Directions: The results of this study can help identify gaps in the existing literature and guide future research efforts to further investigate the link between HC and BC risk.

Empowering Women: By clarifying the association between HC and BC risk, this study can empower women to make informed decisions about their contraceptive choices and overall health.

Study Objectives:

1. To systematically review and analyze published studies on the association between HC and BC risk.
2. To assess the overall risk of developing BC associated with the use of HC.
3. To examine potential differences in BC risk based on the type of HC used.
4. To investigate the impact of factors such as duration of HC use, age at initiation, and family history of BC on the relationship between HC and BC risk.
5. To identify specific subpopulations of women who may be at a higher risk of developing BC due to the use of HC.

6. To provide evidence-based recommendations for healthcare providers and policymakers regarding the use of HC and BC risk.
7. To highlight areas for future research to further elucidate the link between HC and BC risk and address any existing gaps in the literature.

Methods

This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. A thorough search of electronic databases such as PubMed, MEDLINE, and Embase was undertaken to identify pertinent studies published in English. The search strategy incorporated keywords pertaining to HC and BC risk. Two reviewers independently screened the search outcomes, chose relevant studies, extracted data, and evaluated the quality of selected studies using suitable assessment tools.

Eligibility Criteria

Inclusion Criteria:

1. Studies that investigate the association between HC and BC risk.
2. Studies published in English.
3. Studies involving human participants.
4. Studies that report quantitative data on the risk of BC associated with the use of HC.
5. Studies that provide information on the type of HC used (e.g., oral contraceptives, contraceptive patches, hormonal IUDs).
6. Studies that examine the impact of factors such as duration of HC use, age at initiation, or family history of BC on the relationship between HC and BC risk.

Exclusion Criteria:

1. Studies not related to the association between HC and BC risk.
2. Studies published in languages other than English.
3. Animal studies, reviews, case reports, and editorials.
4. Studies with insufficient data on the risk of BC associated with HC.
5. Studies that do not specify the type of HC used.
6. Studies that do not address the impact of duration of HC use, age at initiation, or family history of BC on the relationship between HC and BC risk.

Data Extraction

The search results were verified using Rayyan (QCRI) [11] to ensure accuracy. Inclusion and exclusion criteria were applied to the search results to assess the relevance of titles and abstracts. Selected papers meeting the inclusion criteria underwent detailed scrutiny by reviewers. Any conflicts were resolved through discussion. A pre-prepared data extraction form was utilized to input relevant study details, such as titles, authors, study year, location, participants, menopausal state, type of HC, percentage of HC usage, and key outcomes. A separate document was created for the assessment of bias risk.

Data Synthesis Strategy

Summary tables were generated based on information extracted from relevant studies to provide a qualitative evaluation of the research findings and components. Once data for the systematic review is collected, the most effective approach for utilizing the information from the included studies was determined.

Risk of Bias Assessment

The Joanna Briggs Institute (JBI) [12] critical assessment criteria for studies reporting prevalence data were employed to evaluate research quality. This tool comprises nine questions, with a score of 1 assigned to affirmative responses and 0 to negative, ambiguous, or not applicable responses. Overall quality ratings of < 4 , 5 to 7, and ≥ 8 will be considered as low, moderate, and excellent quality, respectively. Researchers independently assessed study quality, with any discrepancies resolved through discussion.

RESULTS:

Search results

The systematic search yielded 632 study articles in total, of which 202 duplicates were eliminated. 430 studies were eliminated after 366 studies had their titles and abstracts screened. Of the 64 reports that were requested to be retrieved, only 4 items were found. After screening 60 papers for full-text assessment, 38 were rejected due to incorrect study results, 12 were rejected due to incorrect population type, and 2 articles were editor's letters. This systematic review had eight study papers that met the eligibility criteria. **Figure 1** presents an overview of the process used to select the studies.

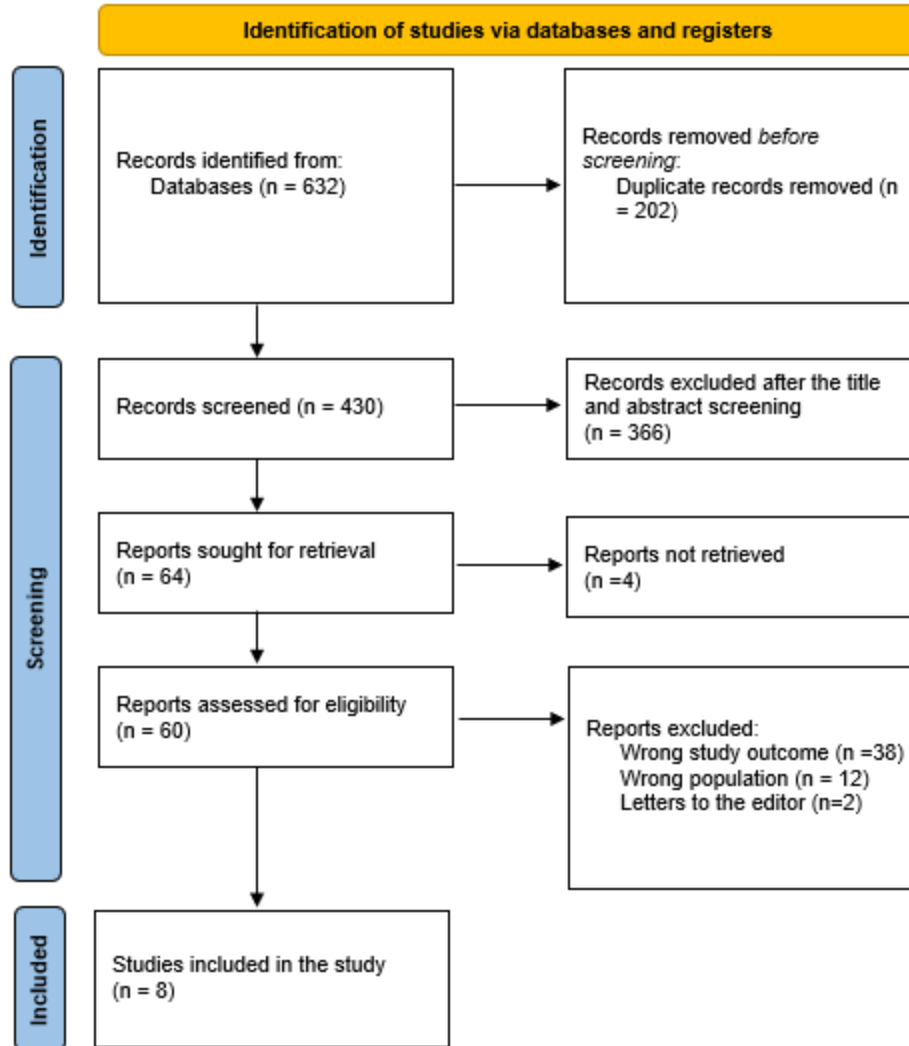


Figure (1): Study decision is summed up in a PRISMA diagram.

Characteristics of the included studies

The sociodemographic details of the research articles that are included are shown in **Table 1**. Our results included eight studies with a total of 14,336,867 women. Four studies were cross-sectional [16, 17, 19, 20], two were case-control [13, 18], one was retrospective in nature [14], and one was prospective in nature [15]. Four studies were conducted in Indonesia [16-18, 20], two in Iraq [13, 19], one in the USA [14], and one in Sweden [15].

The clinical features are displayed in **Table (2)**. The eight studies included women that used variable HC [13-15, 18] and four studies did not specify the types of HC [16, 17, 19, 20]. Only two studies mentioned the menopausal state [13, 15]. Six studies demonstrated that HC usage was a significant risk factor for the development of BC [13, 15, 16, 17, 19, 20]. Early use before the age of 20 is associated with the highest risk of BC [13] and longer duration of HC use significantly increases the risk of BC [17]. Interestingly, one study found that HC use is not linked to BC usage [14] and another study found that the use of HC is a protective factor against the development of BC [18].

Table (1): Sociodemographic characteristics of the included participants.

Study	Study design	Country	Participants	Mean age
Alsammarraie et al., 2020 [13]	Case-control	Iraq	200 BC cases and 300 controls	48.5
Ostroot et al., 2021 [14]	Retrospective cohort	USA	No HC used (N = 1273) and HC used (N = 97)	18-51
Hultstrand et al., 2022 [15]	Prospective cohort	Sweden	14,330,806	15-34
Solikhah et al., 2022 [16]	Cross-sectional	Indonesia	3,517	NM
Dwi Andayani et al., 2019 [17]	Cross-sectional	Indonesia	396	NM
Yermi et al., 2023 [18]	Case-control	Indonesia	70 cases and 70 controls	NM
Hisham Mohammed et al., 2022 [19]	Cross-sectional	Iraq	75 cases and 25 controls	25-65
Putri et al., 2021 [20]	Cross-sectional	Indonesia	38	<20 to >35

*NM=Not-mentioned

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Menopausal status (%)	Type of HC	Usage of HC	Main outcomes	JBI
Alsammarraie et al., 2020 [13]	202 (40.4%)	COCs	A notably greater percentage (49%) of BC patients reported a positive history of using combined oral contraceptives.	The odds ratio [OR] for those who have never used oral contraceptives is 1.73; 95% confidence interval = 1.2–2.5, p = 0.003. Early use before the age of 20 is associated with the highest risk (OR = 6.62, p = 0.02); longer use does not significantly increase the risk of BC.	Moderate
Ostroot et al., 2021 [14]	NM	OCP, patch, vaginal ring, medroxyprogesterone injection, etonogestrel implant, or levonorgestrel-releasing IUD	One type of HC was prescribed to ninety-seven women (7.08%).	The use of HC following a diagnosis and remission of BC is not linked to an increased risk of recurrence, according to the study.	Moderate
Hultstrand et al., 2022 [15]	Non-menopausal	CoCs and POPs	NM	When compared to women who have never used HC, women aged 15 to 34 who now use progestogen-only methods have a slightly higher relative risk of BC or BC in situ. In contrast, among current users of combined HC, they were unable to find any evidence of an overall increase in risk. But with progestogen-only and combination HC, the risk seems to peak in the first 10 and five years of use, respectively.	Moderate
Solikhah et al., 2022 [16]	NM	HC	NM	HC use was identified as one of the risk variables that increased the incidence of BC; however, long-term HC use did not significantly increase the risk of BC. According to our research, using HC may indicate a significant window for BC induction.	Moderate
Dwi Andayani et al., 2019 [17]	NM	HC	Out of the 125 individuals who used HC for more than five years, 60 (48.1%) had BC. However, none of the 239 responders (65.8%) who had been taking HC for less than five years had BC.	The chi-square value is p = 0.000 < 0.005, indicating a strong positive connection between the length of HC use and the incidence of BC. Using HC for longer than five years has been shown to raise the incidence of BC occurrences.	High
Yermi et al., 2023 [18]	NM	Oral and injectable HC	31/ 70 cases used HC	The use of HC is a protective factor against the development of BC and has no effect on it (large OR: 0.42).	Moderate
Hisham Mohammed et al., 2022 [19]	NM	OCPs	NM	According to this study, there is a greater risk of BC when using OCPs.	Low
Putri et al., 2021 [20]	NM	HC	NM	Although the relationship between using HC and an increased risk of BC was found, it was not statistically significant (OR= 1.37; 95% CI= 0.62 to 3.32; p = 0.428).	Moderate

*NM=Not mentioned

DISCUSSION:

Contraceptive techniques are recognized to provide significant non-contraceptive benefits to users [21, 22]. According to guidelines that are now available, most women, including those who are perimenopausal or have a family history of BC, can safely use HC [23, 24]. With the goal of enhancing the safety profile of contraceptives in terms of side effects and convenience of use, contemporary techniques come in a range of combinations and routes of administration (oral, injectable, transdermal, subdermal, intrauterine, and intravaginal). This in turn makes it possible for women with chronic illnesses to utilize HC, and also gives premenopausal women a way to manage the symptomatology linked to their aging reproductive system at the same time. In order to help providers and users balance the pros and cons of each procedure depending on a woman's preferences and medical conditions, these guidelines also include the essential contraindications. However, there is now controversy regarding whether the modern usage of HC affects the risk of BC in young, premenopausal women, given the rising incidence of BC in these populations. Nevertheless, as demonstrated by BRCA1 and BRCA2 mutations, the development of BC is not only attributed to the mitogenic activity of female hormones that can cause the genomic instability that propels the growth of cancer [25, 26]. Furthermore, there is conflicting data about this issue; although some reports indicate no association, others suggest that HC users may have a 40% higher risk of BC [27]. These factors led us to perform this systematic review of the literature utilizing HC on the risk of BC development.

Six out of the eight included studies demonstrated that HC usage was a significant risk factor for the development of BC [13, 15, 16, 17, 19, 20]. We also found that early use before the age of 20 is associated with the highest risk of BC [13] and longer duration of HC use significantly increases the risk of BC [17]. Similarly, **Mohammed et al.** reviewed eleven randomized trials that examined the connection between HC and BC were included in the study. Despite the fact that hormone is an effective method of birth control, numerous studies have noted a possible risk of BC. It is important to weigh the advantages of using HC against the dangers of BC [28]. **Utami et al.** used a meta-analysis approach to examine how the usage of HC, both injectable and tablet, affected the incidence of BC. BC risk is increased by HC that are injectable and tablets [29].

It is extremely challenging to assess the data on the strength of the association between HC usage and BC

due to the variety of study designs and risk factors taken into account [30], according to another narrative assessment of prospective and retrospective studies published between 1995 and 2022. The documented advantages for women's health and the efficacy of all forms of contraception in preventing pregnancy exceed the low quality of evidence on BC risk [31, 32]. Because of this, we recommend that contraceptive counseling adhere to national or WHO recommendations [34], which are based on selection criteria based on a woman's health conditions and her reproductive needs. We also recommend that each country apply its recommendations for the early detection of BC and that populations at risk of complications related to the chosen method be followed.

Finally, there is still no clear consensus on the function that sex steroid hormones play in the growth of female breasts and the origin of BC. As breast cells are most vulnerable to carcinogens before pregnancy until the first full-term pregnancy, Bonfiglio et al. concluded that the timing of the commencement of hormonal exposure across a woman's lifespan is probably the definitive risk factor for subsequent cancer development [35]. Furthermore, it is challenging to ascertain whether women at increased risk respond to exogenic hormones in a particular way, whether risk accumulates in any of its distinct histologic forms, or whether age at last exposure, age of onset of use, or length of exposure determine excess risk due to the complexity of BC genetics.

As is evident, the variability in study design, sample size, population investigated, and confounding factors among the studies make it challenging to interpret the evidence for HC's role in the development of BC. Moreover, studies typically did not distinguish between groups based on the method's timing of usage, formulation type, or administration route.

If new users intend to use a hormonal method for an extended period of time, they should consent to use it based on a clinical analysis of their risk factors for BC, the advantages of not getting pregnant, and the management of other gynecological conditions that impact their quality of life. This will help reduce the incidence of BC. In a similar vein, patients should not be told to stop using a method that they have been using without experiencing any negative effects. Instead, healthcare professionals can make use of follow-up appointments to ask patients about any changes they have noticed to their breasts. If at all possible, a medical examination should be done to detect breast lumps early on. Subsequent diagnostic testing should be ordered based on clinical findings as

well as individual clinical and genetic risk factors for BC. Adopting healthier habits has to be promoted as well.

CONCLUSION:

Many studies have indicated a possible risk of BC, despite the fact that hormones offer an effective method of birth control. It is important to weigh the advantages of using HC against the risk of BC. It is imperative that those using HC are made aware of the importance of BC self-examination and how to conduct it correctly. Research indicates that considering non-hormonal, long-acting, or reversible contraceptives should be carefully considered as alternate forms of birth control.

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