

Systematic Review on: Breast Cancer and its Relationship with Prolonged Use of Combined Oral Contraceptives

Revisión sistemática sobre: Cáncer de mama y su relación con el consumo prolongado de anticonceptivos orales combinados

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ABSTRACT

Introduction: Breast cancer is a neoplasm in breast tissues, diagnosed in 1 in 8 women, making it one of the most common cancers in the female population. **Objective:** To analyze the relationship between the constant use of oral contraceptives and the risk of developing breast cancer. **Methodology:** A systematic review was conducted using the Prisma method, utilizing PubMed and SCOPUS, selecting 14 relevant articles. **Results:** The reviewed studies showed variable results. Some studies with small samples found some association, while studies with larger populations did not confirm this relationship. Prolonged use of oral contraceptives was associated with a higher risk in young women. Factors such as advanced age at first childbirth and smoking also increased the risk. Most studies highlighted prolonged use (5 to 10 years) as a potential risk, along with modifiable factors like smoking and obesity. **Discussion:** Although some studies suggest a possible association between oral contraceptives and breast cancer, the results are inconclusive. Additional factors complicate interpretation. **Conclusion:** More research with large populations is needed to better understand the relationship between oral contraceptives and breast cancer.

Keywords: Oral contraceptives, breast cancer, reproductive autonomy.

Palabras claves:

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RESUMEN

Introducción: El cáncer de mama es una neoplasia en los tejidos mamarios, diagnosticada en 1 de cada 8 mujeres, siendo uno de los cánceres más comunes en la población femenina. **Objetivo:** Analizar la relación entre el uso constante de anticonceptivos orales y el riesgo de desarrollar cáncer de mama. **Metodología:** Se realizó una revisión sistemática con el método Prisma, usando PubMed y SCOPUS, seleccionando 14 artículos relevantes. **Resultados:** Los estudios revisados mostraron resultados variables. Algunos estudios con pequeñas muestras encontraron cierta asociación, mientras que estudios con poblaciones mayores no confirmaron esta relación. El uso prolongado de anticonceptivos orales se asoció con un mayor riesgo en mujeres jóvenes. Factores como la edad avanzada en el primer parto y el tabaquismo también aumentaron el riesgo. La mayoría de los estudios destacaron el uso prolongado (5 a 10 años) como un riesgo potencial, junto con factores modificables como el tabaquismo y la obesidad. **Discusión:** Aunque algunos estudios sugieren una posible asociación entre anticonceptivos orales y cáncer de mama, los resultados no son concluyentes. Factores adicionales complican la interpretación. **Conclusión:** Se necesitan más investigaciones con poblaciones amplias para comprender mejor la relación entre anticonceptivos orales y el cáncer de mama.

Palabras clave: anticonceptivos orales combinados, cáncer de mama, autonomía reproductiva

INTRODUCTION

Breast cancer is one of the most common types of cancer in the female population. This type of neoplasia forms in the breast tissues and ducts or tubules (1). Over the past 50 years, its incidence has increased significantly, with 1 in every 8 women being diagnosed with this pathology. According to the WHO, there were over 2.2 million cases worldwide, and 685,000 women died from it. In Ecuador, according to Solca's epidemiological bulletin, 32 out of every 100 women developed this cancer (2).

On the other hand, contraceptive pills have been used as a method of family planning and treatment for polycystic ovary syndrome, among other uses. Despite these advantages, several types of cancer have been related as a long-term side effect, and the relationship between contraceptives and breast cancer is being studied (3).

There are various risk factors that increase the likelihood of developing this neoplasia. Non-modifiable risk factors include genetics, while modifiable factors include those referred to in this systematic review for the confirmation or rectification of this hypothesis.

General Objective

To analyze the relationship between the constant use of hormonal contraceptives and the risk of developing breast cancer through a systematic review.

METHODOLOGY

A search strategy was employed for a systematic review, which involved the following steps: The research question was delimited, establishing its key components, such as the population of interest, the intervention or exposure of interest, comparators, outcomes, and context. Additionally, keywords were identified, listing the key terms related to each component of the research question. Synonyms and spelling variations were included to broaden the search coverage.

Subsequently, appropriate databases were selected to search for relevant literature. For this systematic review, the databases selected were PubMed, Scopus, and Scielo. Inclusion criteria defined the languages as English and Spanish, publications within the last 10 years, and studies with free full texts. The study population included human female studies (women) and the use of contraceptives.

The search strategy was executed in each selected database, obtaining results. The results were recorded in a spreadsheet, including information such as title, author, publication year, conclusions, number of participants, limitations, and a link to the article. Consequently, data were collected, and a relevant analysis of the included studies was performed to answer the research question.

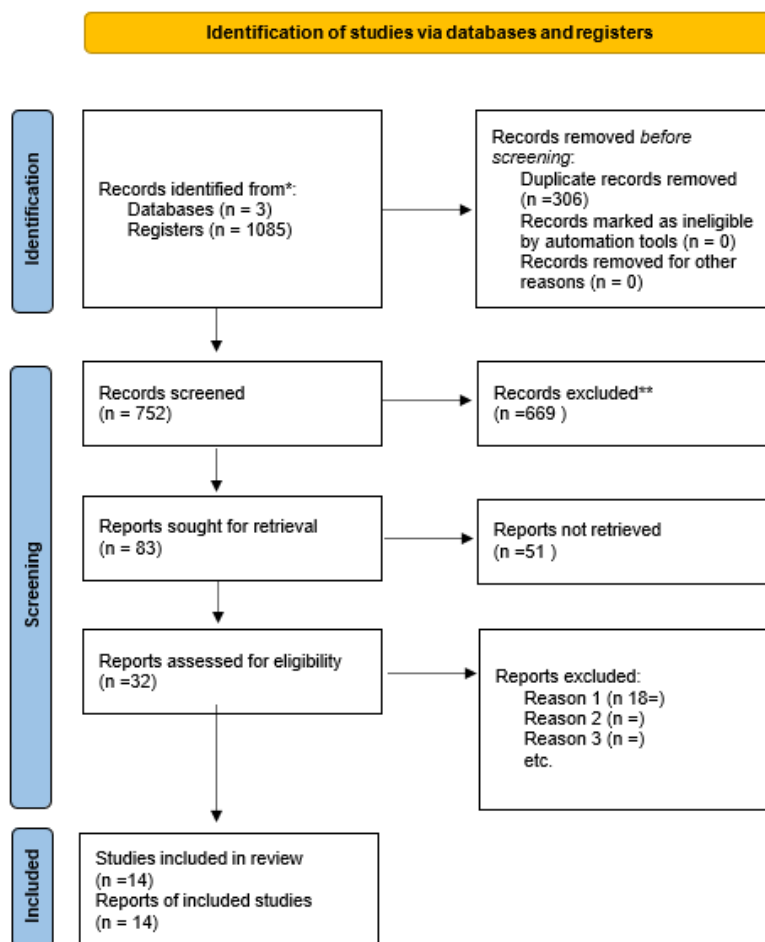
For this systematic review, a search was conducted in scientific search engines such as PubMed, Scielo, and SCOPUS, using the following keyword combinations: “Relationship” and “Neoplasms” and “Oral Contraceptives,” resulting in 7 articles in PubMed, 0 in Scielo, and 11 in SCOPUS; “Risk” and “neoplasms” and “Oral Contraceptives,” resulting in 56 articles in PubMed, 0 in Scielo, and 615 in SCOPUS; “Neoplasia” and “risk” and “anticonceptivos hormonales orales” resulting in no articles in the aforementioned databases; and “Risk” and “breast cancer” and “oral contraceptives,” resulting in 29 articles in PubMed, 0 in Scielo, and 367 in SCOPUS.

The inclusion criteria used for the search were: articles published in the last 10 years; availability of free full texts; studies in human females; texts in English or Spanish. By 2023, between May 11 and May 15, a total of 92 articles were found in PubMed, 0 in Scielo, and 993 in SCOPUS, totaling 1085 articles. After filtering out duplicate documents, 752 articles remained. Between May 18 and May 22, a selection was made by reading the titles, resulting in 83 documents. Subsequently, a filter was applied by reading the abstracts, selecting a total of 32 articles. Finally, during the week of May 25, after reading the 32 complete articles, 14 articles were filtered and included in the review.

The biases presented in this article include language bias, as it is limited to English and Spanish, and another potential bias is the limitation to free articles. Moreover, biases found in each review article include: not adjusting for mediators such as parity, susceptibility to survival biases since follow-up begins in 1976 after the use of Oral Contraceptives (OC), leading to an inability to observe acute effects, homogeneous population regarding race and generation, various risk factors that could increase the risk of breast cancer such as age of menarche, alcohol consumption, physical activity, and another bias is the BMI (Body Mass Index) information being only available for

women with children, OC use associated only with women carrying the BRCA1 and BRCA2 genes, and in one article, no association between the duration of OC use and age.

Figure 1.
Methodology for Study Identification.



Source: Own elaboration (2023)

RESULTS

Regarding the reviewed studies, it was found that the results vary concerning the relationship between hormonal risk factors and the incidence of breast cancer. Some studies with a smaller number of participants showed that 92 cases indicated a certain association, while other larger studies with at least 100,000 participants did not confirm this association. Some authors, such as (4) and (5), did not find any association between the use of oral contraceptives and the development of breast cancer.

On the other hand, (6) states that long-term use of oral contraceptives (OCs) and usage duration ≥ 5 years in a population of 985 cases were associated with an increased risk of breast cancer among women aged 20 to 44 years. Advanced age at first childbirth and



the use of oral contraceptives were associated with a higher risk of breast cancer. The reviewed studies indicate that recent use of oral contraceptives is associated with an increased risk of breast cancer. This was associated with certain causes of death, including higher breast cancer mortality rates.

Authors like (7) express that larger population-based studies are needed to confirm this finding. The data suggest that the use of OCs, particularly recent long-term use, is associated with a higher risk of breast cancer. From this, it can be inferred that the most relevant findings of the systematic review indicate that oral contraceptives do not seem to increase the risk of breast cancer among women who take these preparations. However, the use of OCs for more than 5 years may modify the development of breast cancer. Additionally, the reviewed studies mention risk factors that increase the likelihood, such as BMI, history of breast cancer, and smoking, among the most relevant (4), (8), (9), (10).

With the different systematic reviews ending with 16 articles, they mention that 12 of the 14 articles find an increased relationship between breast cancer and prolonged use of oral contraceptives, 1 article mentions a relationship with hormonal contraceptive methods in carriers of the BRCA1 and BRCA2 mutations, and 3 articles mention null associations between contraceptive use and breast cancer. Moreover, the conclusions of each article detail the prolonged use between 5 to 10 years of these preparations. In the articles that refer to a null association, they emphasize that in women who smoke and drink, the use of contraceptive methods increased the risk of the mentioned type of neoplasia.

Figure 2
Relationship between OCs and Breast Cancer



Table 1.
Related Studies

Studies (Authors)	Index	Age	Participants	Analysis
Santiesteban et al. (4)	483	20-44	985 cases and 882 controls	Current use for ≥ 5 years was associated with an increased risk of breast cancer among women aged 20 to 44 years.
Guarin et al. (11)	203	NA	17,035	Significant associations between reproductive factors and breast cancer; the use of oral contraceptives



Mira et al. (12)	483	20-49	1,102	increased the risk of breast cancer AR. Results suggest that recent use of contemporary oral contraceptives is associated with an increased risk of breast cancer.
Montes et al. (13)	95	NA	121,577	Longer duration of use was more strongly associated with certain causes of death, including premature mortality due to breast cancer.
Gómez et al. (14)	87	30-65	192 (92 cases and 100 controls)	Prolonged use of oral contraceptives (more than 10 years) may be associated with an increased risk of breast cancer in Saudi women.
Vega et al. (15)	33	NA	1,848	Results suggest that the use of oral contraceptives, particularly recent long-term use, is associated with an increased risk of breast cancer.
Lago et al. (8)	1130	NA	1.8 million	Associations between hormonal contraception use and the risk of invasive breast cancer.
Schrijver et al. (16)	25	18-80	2,276	No trends were found with duration, age at initiation, or recent use of oral contraceptives, limited to BRCA1 and BRCA2 mutation carriers.
Michell (9)	154	50-71	100,000	Associations between the use of oral contraceptives and breast and colorectal cancers were predominantly null.
Nicole Lorona (17)	0	21-49	1,701	Among current users and those within 5 years prior to diagnosis, increased duration of use was associated with lower odds of H2E breast cancer. No statistically significant association between oral contraceptive use and TN or luminal B breast cancer was found.
Ula Nur (10)	149	NA	49,259	Among 2,120 women with breast cancer, 1,268 (84%) reported ever using oral contraceptives, and 254 died within 10 years post-diagnosis.
Sanaa K. Bardaweel (18)	149	18-65	450	Our results indicated that regular use of oral contraceptives was associated with an increased risk of breast cancer (OR = 2.25, 95% CI: 1.34–2.79; p = 0.002).
Carrasco et al. (19)	111	NA	110,580	An increased risk of breast cancer was reported among women using oral contraceptives in 23 out of 42 trials, with a statistically significant increase in 14 trials.
Wieslaw Kanadys (20)	111	NA	198,680	The use of oral contraceptives by nulliparous women did not affect the risk of breast cancer (cOR, 1.02; 95% CI, 0.82–1.26; p = 0.85), although the use of pills before a first full-term pregnancy had a significant effect on increasing the risk of breast cancer.

Table 2
Studies Related to Oral Contraceptives

Years of Oral Contraceptive Use	Age	Risk Factors	Analysis
≥ 15 years	20 to 44 years	Family history of breast cancer, higher body mass index	Lifetime use of OCs for 15 years or more was associated with a 50% increase in breast cancer risk among all women. Current use for ≥5 years was associated with a 1.6-fold increased risk of breast cancer (4).
Average: years	12.8 NA	Anthropometry, reproductive history,	Advanced age at first childbirth and use of oral contraceptives were associated with an

		and exogenous hormone use	increased risk of AR-breast cancer (11).
>1 year	20 to 49 years	Parity, history of oophorectomy, family history of breast and/or ovarian cancer, and BMI	Recent use of oral contraceptives was associated with a 50% elevated risk of breast cancer compared to never or former use (12).
Followed prospectively for 36 years	18 to 44.1 years	Average BMI at 18 years (kg/m ²)	Longer duration of use was more strongly associated with certain causes of death, including premature mortality due to breast cancer, and reduced mortality rates from ovarian cancer (13).
More than 10 years	30 to 65 years	Family history of breast cancer or those harboring BRCA mutations	Prolonged use of OCs (more than 10 years) may be associated with an increased risk of breast cancer. Larger population-based studies are needed to confirm this finding in this population (14).
5 years	<40 years, 40 to 49 years, ≥50 years	Overweight or obesity, recent use of contraceptives	A combined analysis of 54 studies observed a 24% increase in breast cancer risk with current use of OCs and a 16% increase in risk within <5 years since stopping OC use (15).
10.9 years	15 to 49 years	Postmenopausal women, smoking	The relative risk of breast cancer among all current and recent users of hormonal contraceptives was 1.20. This risk increased to 1.09 with less than 1 year of use and 1.38 with more than 10 years of use. After discontinuation, the breast cancer risk remained higher among women who had used hormonal contraceptives for ≥5 years (8).
>6 months	40-50 years	BRCA1 and BRCA2 mutation carriers	Prospective analyses did not show that past OCP use was associated with an increased risk of breast cancer for BRCA1 mutation carriers in young to middle-aged women (16).
<1 year, 1-4, 5-9 or ≥10 years	50 to 71 years	Smokers, obese BMI	Null associations were suggested between OC use and breast cancer in most strata of our modifiers, but the magnitudes of most associations were in the direction of a slight increase in risk (typically 0 to 8%). However, long-term OC users who were current smokers had a higher risk of breast cancer (9).
5 years	21 to 49 years	NA	OC use may be more strongly associated with the risks of luminal A and TN breast cancer than with the risk of H2E tumors (17).
10 years	Average 55 years	Weight and smoking	Ever users of OCs had a higher risk of breast cancer-specific mortality compared to never users (10).
NA	18 to 65 years	Age at puberty, age at menopause, previous pregnancies, menopausal status, family history of cancer	Our results indicated that regular OC use showed an association with increased breast cancer risk, while the duration of OC use was not associated with higher breast cancer risk (18).



DISCUSSION

This systematic review analyzes the relationship between OCs and breast cancer. Various risk factors mentioned in each article and variations in age range were considered. The following section aims to compare the findings with external sources. In article (4), a relationship is mentioned with the use of oral contraceptives for over 15 years, along with the risk factor of a family history of breast cancer and a high body mass index.

However, in Girad's article (21), no such relationship is found between OCs and this neoplasia, even with prolonged use, indicating that the primary factors contributing to breast cancer are familial and environmental. Several articles, such as (4), (12), (14), (18), mention age as a risk factor for the relationship between OCs and breast cancer. However, in Grabrick DM's article (22), a lack of evidence is reported between the use of OCs and breast cancer in women with a mean age of 43 years. All the articles selected for this systematic review also related the duration of OC use to the analysis of its relationship.

The usage duration ranged from over 6 months to over 15 years. Each article found a relationship with this neoplasia. However, in the article by Mendieta and Rojas (23), there is no clarity on the relationship of the mentioned factors with a 5-year consumption period. Conversely, a decrease is observed after 10 years of discontinuing OCs. In 2010, research on the association between breast cancer mortality and contraceptive use (24) was conducted. In this article, Hannaford PC mentions no difference in mortality rates between OC users and those who have never used this medication.

In 2014, another study again highlights the lack of a relationship between OC use and breast cancer mortality rates, also mentioning a reduction in ovarian cancer risk. A study by Sernaqué indicates that breast cancer risk decreases in premenopausal women who use OCs compared to women who have never used contraceptives. However, long-term studies are needed to confirm this conclusion (25).

Regarding the use of combined hormonal contraceptives, Hernández's article (26) indicates a positive relationship with the likelihood of having endometrial and colon cancer, as a decrease in such neoplasias was found. Similarly, it mentions no significant difference in the results obtained in the study conducted with women who have used OCs and those who have never used them. Different bibliographies reviewed show differences in the conclusions obtained at the end of the study of the selected articles for this bibliographic review. However, it is worth noting that the bibliographies considered for this discussion were not chosen and filtered in the same manner.

The most common results indicate no significant relationship between hormonal contraceptive use and breast cancer, although they mention a short study duration. It is also mentioned that the factors most associated with breast cancer are genetic, with a family history of this neoplasia, and environmental factors such as diet, substance use, etc.

Limitations

The limitations of this article include the use of bibliographies in English and Spanish, limiting the number of articles available for information on the research conducted by other investigators in this field and expanding the number of bibliographies consulted that could have strengthened the obtained results.

CONCLUSION

Therefore, although some evidence suggests a possible association between the use of oral contraceptives and breast cancer, more research with large populations is needed to better establish the relationship between contraceptive use and breast cancer. However, it is noteworthy that long-term use, especially for more than 5 years, may be related to an increased risk of developing breast cancer in women aged 20 to 44 years. It is also important to consider that other risk factors, such as body mass index (BMI), family history of breast cancer, and smoking, may also influence the likelihood of developing this disease.

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