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Ovarian cancer and oral contraceptives: a systematic review

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RESUM

El càncer d'ovari és un important problema de salut que afecta les dones a tot el món. Tot i que en estudis previs s'ha suggerit un possible efecte protector dels anticonceptius orals contra el càncer d'ovari, cal encara aprofundir en el coneixement sobre aquesta relació i la influència de factors específics. Tenint en compte que no s'han fet revisions sistemàtiques recents sobre aquest tema, l'objectiu d'aquest treball és resumir l'evidència científica actual publicada respecte l'associació entre l'ús d'anticonceptius orals i el risc de càncer d'ovari.

Seguint la guia descrita al Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) es va dur a terme una revisió sistemàtica de la literatura publicada emprant la base de dades MEDLINE-PubMed fins al desembre de 2022. Com a resultat, es van incloure un total de 38 estudis.

La revisió sistemàtica va trobar evidències que donen suport a un possible efecte protector dels anticonceptius orals contra el càncer d'ovari. Diversos estudis inclosos van demostrar una disminució del risc de càncer d'ovari entre les dones que feien servir anticonceptius orals en comparació amb les que no els feien servir. A més, la revisió va identificar que l'efecte protector dels anticonceptius orals pot variar entre diferents poblacions o subgrups específics de dones. Factors com la distribució geogràfica, la mida de la mostra de l'estudi, l'edat, els factors reproductius i hormonals, la predisposició genètica i diferents estil de vida poden influir en la magnitud de l'efecte protector.

En conclusió, els resultats obtinguts en aquesta revisió sistemàtica suggereixen que els anticonceptius orals poden tenir un efecte beneficiós en la reducció del risc de càncer d'ovari, no obstant, cal destacar la necessitat de fer més investigacions per comprendre millor els mecanismes subjacents i explorar-ne les possibles interaccions amb els factors de confusió.

RESUMEN

El cáncer de ovario es un importante problema de salud que afecta a las mujeres en todo el mundo. En estudios previos se ha sugerido un posible efecto protector de los anticonceptivos orales contra el cáncer de ovario; sin embargo, aún existen lagunas de conocimiento sobre esta relación y la influencia de factores específicos. Teniendo en cuenta que no se han realizado revisiones sistemáticas recientes sobre ese tema, el objetivo de este trabajo es resumir la evidencia científica de los estudios publicados que investigan posibles asociaciones entre el uso de anticonceptivos orales y el riesgo de cáncer de ovario.

Siguiendo la guía descrita en el Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) se realizó un estudio sistemático de la literatura publicada utilizando la base de datos MEDLINE-PubMed hasta diciembre de 2022. Como resultado, se incluyeron un total de 38 estudios en esta revisión sistemática.

La revisión sistemática halló evidencias que respaldan un posible efecto protector de los anticonceptivos orales contra el cáncer de ovario. Varios de los estudios incluidos observaron una disminución del riesgo de padecer cáncer de ovario entre las mujeres que usaban anticonceptivos orales en comparación con las que no los usaban. Además, el trabajo identificó que el efecto protector de los anticonceptivos orales puede variar entre diferentes poblaciones o subgrupos específicos de mujeres. Factores como la distribución geográfica, el tamaño de la muestra de estudio, la edad, los factores reproductivos y hormonales, la predisposición genética y distintos estilos de vida pueden influir en la magnitud del efecto protector.

En conclusión, los resultados de esta revisión sistemática sugieren que los anticonceptivos orales pueden tener un efecto beneficioso en la reducción del riesgo de padecer cáncer de ovario. No obstante, también se destaca la necesidad de realizar más investigaciones para comprender mejor los mecanismos subyacentes y explorar las posibles interacciones con los factores de confusión.

ABSTRACT

Ovarian cancer is a significant global health concern affecting women worldwide. Previous studies have suggested a possible protective effect of oral contraceptives against ovarian cancer, however, there are still knowledge gaps regarding this relationship and the influence of other specific factors remains unknown. Considering that no recent systematic review on the topic has been published, the aim of this study is to summarize the outcomes from updated literature investigating the potential associations between oral contraceptive use and ovarian cancer risk.

Following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) a systematic search of the literature published in the MEDLINE-PubMed database until December 2022 was conducted. As a result, a total of 38 studies were finally included in this systematic review.

The systematic review found evidence supporting a potential protective effect of oral contraceptives against ovarian cancer. Several studies included in the review reported a decreased risk of ovarian cancer among women who used oral contraceptives compared to non-users. Additionally, the review identified that the protective effect of oral contraceptives may vary among different populations or specific subgroups of women. Factors such as geographic distribution, sample size of the study, age, reproductive and hormonal factors, genetic predisposition and lifestyle choices may influence the magnitude of the protective effect.

In conclusion, the overall findings of this systematic review suggest that oral contraceptives may have a beneficial effect in reducing the risk of ovarian cancer. Yet, further research to better understand the underlying mechanisms and explore the potential interactions with confounding factors is warranted.

SUMMARY

1 INTRODUCTION

Cancer refers to diseases in which certain cells in the body start dividing and growing uncontrollably; these cells are able to migrate to other parts of the body, infiltrating and destroying normal tissues. This disorder can be caused by different factors, such as lifestyle factors (exposure to carcinogenic agents such as tobacco), genetic changes or chronic inflammation (1). In 2020, there were estimated 19.3 million new cancer cases and 10 million deaths around the world (2), thus indicating that this is a global public health concern.

Ovarian cancer is still the leading cause of death from gynecological cancers in most of the developed countries, which significantly contributes to the mortality of cancer in women (3). Less than 35% of women with epithelial ovarian cancer survive for at least 10 years, while around 50% of cases are fatal within 3 years; unfortunately, given the absence of symptoms in early-stage disease and lack of effective screening, ovarian cancer is typically diagnosed at late stages, resulting in a low survival rate (4). Global incidence of ovarian cancer has, nevertheless, been stable during the last decades, but it is still a disease that has contributed to a considerable number of deaths around the world (2).

1.1 Classification of ovarian cancer types

Ovarian cancer is classified into different subtypes (Figure 1), with the epithelial subtype being the prevalent, since only a 10% of the cases has a non-epithelial origin. Among epithelial ovarian cancer, 97% are non-mucinous and 3% mucinous: non-mucinous tumors present different histotypes like serous (70%), endometroid (10%), clear cell (10%), and unspecified (5%) (5).

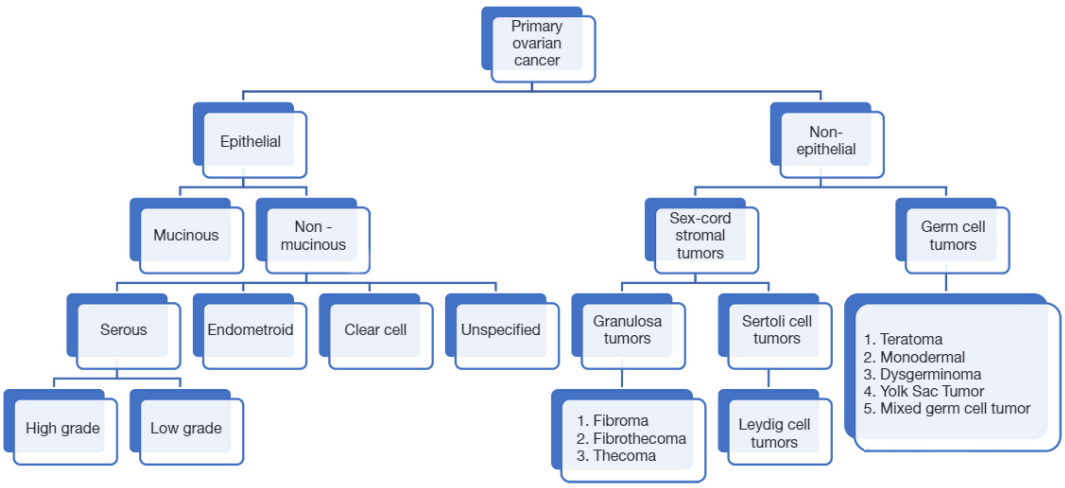

Figure 1. Classification of ovarian cancer types and subtypes. Extracted from: Gaona-Luviano et al. (2020).

Ovarian cancer is a group of diseases that originates in the ovaries or in the related areas of the fallopian tubes and the peritoneum (Figure 2). The two ovaries that women have in the pelvis – one on each side of the uterus – produce female hormones and oocytes for reproduction. Two long slender tubes called fallopian join both ovaries and carry the oocytes from the ovaries to the uterus. The peritoneum is the tissue lining that covers organs in the abdomen (6).

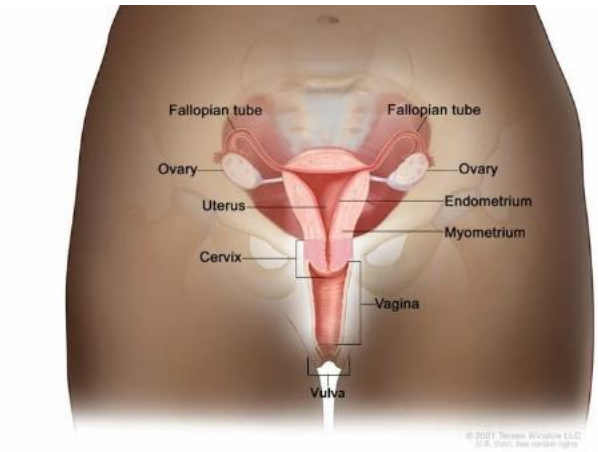

Figure 2. Diagram of different parts of a woman's reproductive system. Extracted from: www.teresewinslow.com.

1.2 Detection of ovarian cancer

The lack of effective screening and the generalized symptoms of ovarian cancer, which include abdominal, back or pelvis pain, fatigue, diarrhea, nausea and changes in urinary function (7) are the main confounding factors for the delay in detection.

In order to improve the diagnosis and reduce the mortality of this disease, it is crucial to promote an early detection, since only 20% of the ovarian cancers are currently diagnosed in the first stages. The most common strategies used to forecast an ovarian cancer include a screening with transvaginal sonography and the measurement of the tumor marker CA-125 by an antigen test. These approaches, nevertheless, have limited sensitivity and specificity, and have a significant rate of false positive results. Most recent approaches, including the identification of new biomarkers and the use of artificial intelligence, are currently being investigated to improve the accuracy of ovarian cancer diagnosis (8).

1.3 Ovarian cancer risk factors and attenuators

There are different risk factors that have been found to potentially raise the chance of developing this disease, which include both genetic and environmental factors. Identifying these risk factors can be fundamental in both understanding the disease and developing strategies for prevention and early detection.

On the one hand, environmental risk factors might include factors such as age (risk increases with age), reproductive history (risk decreases with increasing number of pregnancies), exposure to environmental toxins (talc, pesticides, and herbicides) or certain dietary factors. Additionally, the use of hormonal contraceptives and parity has been shown to decrease the risk of ovarian cancer, while the use of hormone replacement therapy after menopause may increase the risk. On the other hand, genetic mutations in *BRCA1* and *BRCA2* genes are associated with a high risk of ovarian cancer (9).

1.4 Etiology of ovarian cancer

Although much is known about risk factors for ovarian cancer, its underlying mechanisms are not perfectly described. There are two hypotheses, the incessant ovulation and the gonadotropin theories; both propose that repeated ovulation and gonadotropin hormones (follicle-stimulating hormone or luteinizing hormone) increase mitotic activity and malignant transformation of the ovarian epithelium (10). It has also been seen that chronic inflammation, which leads to rapid cell division and DNA replication errors, may be an important precursor to ovarian cancer (11).

According to the 'incessant ovulation' hypothesis, the ovarian surface epithelium suffers micro-trauma from continuous, repetitive ovulation throughout the reproductive years. As a result, the cell division of the ovarian surface epithelium raises the opportunity for genetic mutations that could trigger the development of tumors (12). In numerous studies, an increased risk of ovarian cancer has been linked to factors that increase the number of ovulatory cycles, such as early menarche age, late menopause age and nulliparity, never having given birth. Not all ovarian cancer cases, however, can be explained by the incessant ovulation hypothesis, as some women who have never ovulated or who have had few ovulations still develop ovarian cancer. Therefore, the exact mechanism by which ovulation contributes to increase the chance of developing ovarian cancer is not fully understood (13).

Emerging research suggests that pelvic serous ovarian cancer arises from the fallopian tubes. This hypothesis is supported by studies that have shown that many high-grade serous ovarian cancers have early molecular alterations in the fallopian tube epithelium (14). In addition, a

nationwide population-based study found that women who have had their fallopian tubes removed through salpingectomy, have a significantly reduced risk of ovarian cancer (15).

In consequence of the damage and subsequent wound healing that the ovarian epithelium experiences during ovulation, ovaries and fallopian tubes are constantly exposed to a variety of oxidative and inflammatory reactive substances, such as reactive oxygen species, *TP53* expression and apoptosis, which all take place simultaneously at the site of ovulation. Oxidative DNA damage and the expression of the *TP53* suppressor gene are associated with ovulatory follicles, and the downregulation of *TP53* can block the repair or clearance of DNA damage, potentially increasing the risk of ovarian cancer (10).

1.5 Association between oral contraceptives and ovarian cancer

Oral contraceptives (OC) generally known as birth control pill, which contain a combination of estrogen and progestin or progestin alone, have been used as a highly effective method of contraception for decades. In addition to their contraceptive properties, they have also been shown to provide some protective effects against certain types of cancer, including ovarian cancer.

Part of the protective effect of OC with regard to ovarian cancer has been linked to the suppression of gonadotropin secretion (suppressing the ovulation) at the level of the pituitary gland and the hypothalamus (16). However, the decreased risk of ovarian cancer associated with OC use may not be related to anovulation alone, since it is also suggested that both follicle-stimulating[1] and luteinizing hormones[2] raise ovarian cancer risk by increasing cell growth and inhibition of apoptosis (17). Follicle stimulating hormone is a type of gonadotropin that is inhibited by the estrogen component of OC, whereas luteinizing hormone is another gonadotropin that it is inhibited by the progestin component of OC (18).

Hormonal levels increase dramatically during ovulation, including those of estrogen and progesterone (Figure 3 and 4). As hormones regulate growth and differentiation of many tissues (19), they have been suggested to trigger cancer development when excessively high during ovulation. Additional modifying effects from the exogenous hormones present in OC pills are also possible, and the protective effect of having fewer ovulations as caused by the pills could be weakened by hormone content. For instance, some ovarian cancers are hormone dependent,

[1] In women, FSH stimulates the growth of ovarian follicles in the ovary before the release of an egg from one follicle at ovulation (18).

[2] In women, LH carries out different roles in the two halves of the menstrual cycle. In weeks 1-2 of the cycle, LH stimulates the ovarian follicles in the ovary to produce the female sex hormone, estradiol. Around day 14 of the cycle, a surge in LH levels causes the ovarian follicle to rupture and release a mature oocyte (egg) from the ovary (18).

particularly those classified as epithelial ovarian cancers; these cancers can have estrogen and/or progesterone receptors on their cells, which can promote their growth (20).

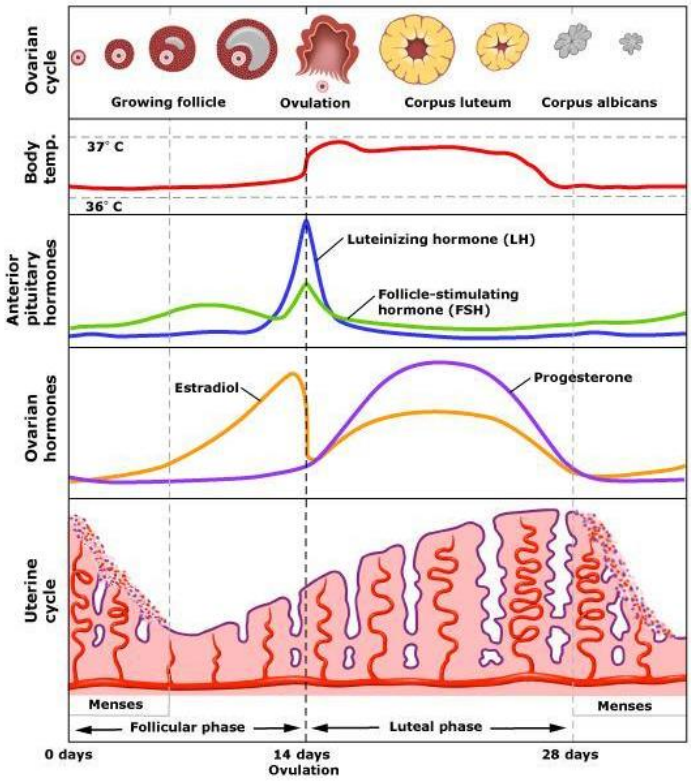

Figure 3. Hormonal fluctuation during a normal menstrual cycle. Extracted from: Medbullets team (3rd May 2023). *Step 1 medbullets*. Combined Oral Contraceptive Pill (COCP). https://step1.medbullets.com/reproductive/116064/combined-oral-contraceptive-pill-cocp

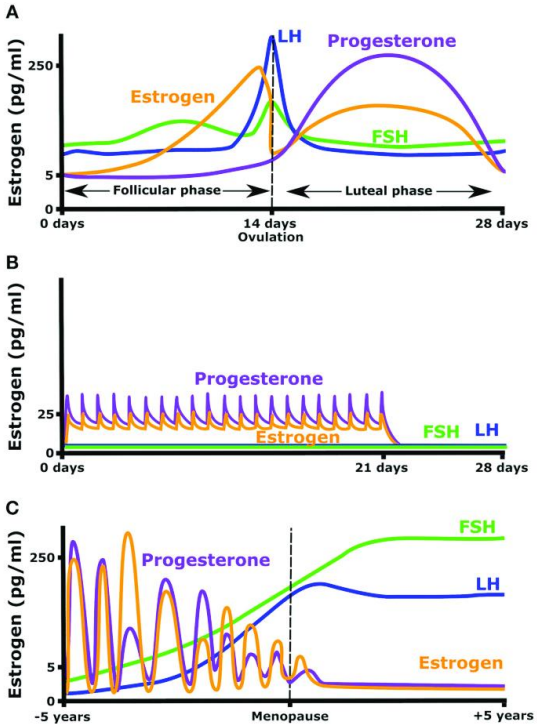

Figure 4. Hormonal fluctuations during (A) a normal menstrual cycle, (B) while taking an oral contraceptive containing both estrogen and progesterone, and (C) in the years before and after menopause. Extracted from: Chidi-Ogbolu, N. et al (2019).

1.6 Oral contraceptives as chemoprevention for ovarian cancer

Ovarian cancer risk and OC pills have been linked in previous publications. A study investigating associations between hormonal factors and the risk of epithelial invasive ovarian cancer from data of the Netherlands Cohort Study on cancer and diet (21), found that women who ever used OC had an almost 30% less ovarian cancer risk compared to those who never took these pills. Additionally, another study investigating the same association from data of the European Prospective Investigation into cancer and nutrition, revealed that women who used OC for 10 or more years had a significant 45% lower risk compared with users of 1 year or less (22). Nevertheless, not all studies found this significant positive correlation between OC and ovarian cancer: a retrospective cohort study including data from 1398 ovarian cancer patients involved

in a specific clinic from Rochester (Minnesota) did not reveal an improvement in overall survival with OC (23).

In short, studying the impact that OC has on ovarian cancer can be crucial from a public health point of view; it can help better understand the development and progression of ovarian cancer, as well as identify new targets for prevention and treatment. In this context, this systematic review aims to summarize the existing evidence on the protective effect of OC against ovarian cancer, including what is known about the underlying mechanisms. With this purpose, the current work specifically assesses the size of the studied population, focuses on the parameters evaluated, and tries to provide a clear picture about the principal outcomes reported in the literature.

2 OBJECTIVES

The goal of the present study is to review the main results of the available modern literature on the protective effect of oral contraceptives against ovarian cancer, and to provide an updated and comprehensive assessment of this potential association. For this purpose, a review of the recent scientific literature was conducted using articles available since January 2005 from the MEDLINE-PubMed database. Based on a critical review of the literature, the specific aims were:

- To provide a comprehensive overview of the current evidence on the protective effect of oral contraceptives against ovarian cancer, as well as to identify gaps in knowledge and areas for future research.
- To explore potential sources of heterogeneity among studies, including differences in design, population characteristics, and exposure and outcome definitions.
- To investigate the effect of different factors on the association between oral contraceptive use and ovarian cancer risk, assessing different tumor typologies, formulations in oral contraceptives and individuals with *BRCA* gene mutations.

3 MATERIAL AND METHODS

3.1 Literature search strategy

The review was conducted following the guidelines provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). This resource primarily focuses on the prospective reporting of reviews and the evaluation of the effects of interventions or observational relationships (24). Table 1 shows the search strategy conducted.

Table 1. Strategic search for the articles screening (organized by dates).

21st December	23rd January	17th February	27th February
Key words screening	Selection of articles based on their title	Selection of articles based on their abstract	Final selection of the articles for the systematic review

The systematic literature search was conducted using MEDLINE-PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) to identify relevant studies published between January 2005 and December 2022. The following search terms were used: ("Ovarian cancer" AND "Contraception") and ("Ovarian cancer" AND "Contraceptives").

3.2 Eligibility criteria and study selection

Inclusion criteria for studies relevant to this systematic review were: (i) studies that comprised women taking oral contraceptives for contraception or ovarian cancer prevention that included a comparison group with no oral contraceptive use; (ii) studies reporting quantitative associations between oral contraceptive exposure and ovarian cancer; (iii) controlled studies (cohort studies, case–control studies); (iv) studies that were peer-reviewed and were written in English; and (v) studies published on or after January 2005.

3.3 Data extraction

The following data were extracted and summarized from each study: first author surname, year, location, population studied, age of participants, study design, exposure measured and main outcomes.

3.4 Study characteristics (overview of included studies)

The MEDLINE-PubMed research with the keywords previously described resulted in a first identification of 1021 articles (Figure 5).

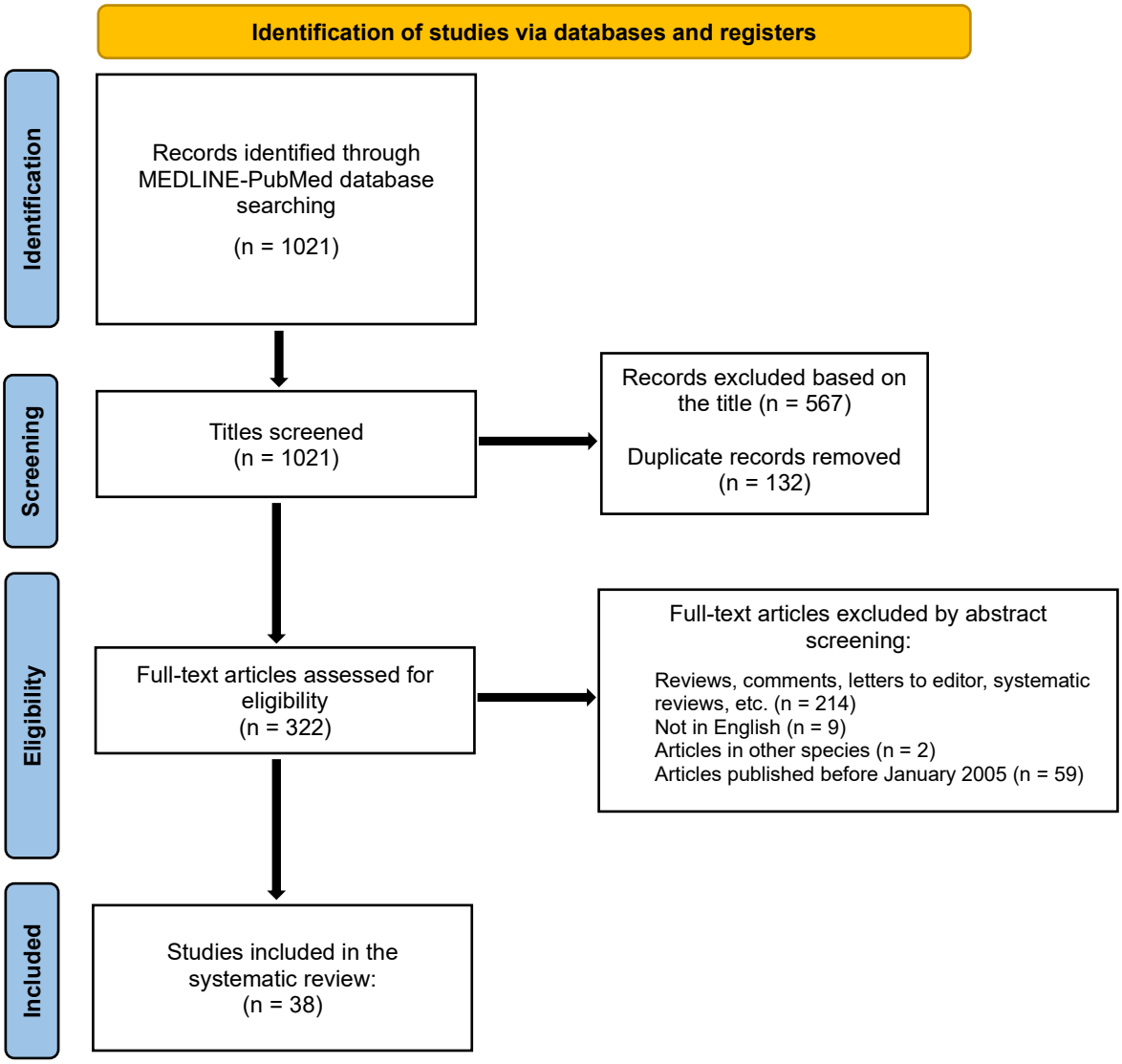

Figure 5. Flow-chart of the bibliographic search and reasons for the study selection. Extracted from: Page et al. (2021).

After a first selection, n=322 articles were retrieved, excluding a total of n=699 articles based on their title. Articles not relevant (such as reviews, comments, letters to editor or systematic reviews), studies in other species, in languages other than English, and literature published before January 2005, were excluded with the aim of only including the most updated literature. Secondly, after reviewing the abstract and other parts of the article, n=284 articles were excluded. These eligibility criteria finally resulted in the selection of 38 full-text articles, which were assessed in detail to provide the systematic review results.

4 RESULTS

4.1 Oral contraceptives and ovarian cancer

Table 2. Details about population included in each article assessed. Abbreviations: ND, non-determined.

Reference	Type of study	Total population	Ovarian cancer cases	Controls
12	Population-based case-control study	1805	813	992
35	Case-control study	1017	262	755
36	Cohort study	70259	174	70085
37	Cohort study	110929	281	110648
38	Cohort study	ND	1025	ND
39	Population-based case-control study	1863	896	967

Several studies included in this systematic review reported consistent findings regarding the significant reduction in ovarian cancer risk associated with oral contraceptive (OC). The study of Lurie et al. (12) observed a strong inverse trend associated with the duration of OC (OR = 0.59; 95% CI = 0.42–0.84), where women who used OC for less than a year had a modest reduction, but each year of OC use provided an average 5% reduction in the odds ratio (OR = 0.95; 95% CI = 0.92–0.98). A substantial reduction in ovarian cancer risk was, however, observed among women who used OCs for <1 year if they were recent users (time since the first or last OC use within 20 years). The risk reduction waned among short-term users who stopped using OC 20 or more years before the reference date. Other studies that demonstrated the significant protection of OC towards ovarian cancer are 13, 21, 22, 23, 25, 26, 27, 29, 30, 31, 32, 33, 34.

Despite the aforementioned observations, Le et al. (35) found a non-significant protective effect of OC against ovarian cancer in Vietnamese women. The authors acknowledged that the limited duration of OC use among their participants (<5 years of OC use for the majority) might resulted in an insufficient assessment of the protective effect. Thus, it is possible that the protective effect of OC on ovarian cancer takes longer to manifest. Similarly, Huang et al. (36) reported a non-significant reduction in the overall risk of ovarian cancer among Chinese OC users. However, this study faced a similar limitation, with only 20.4% of participants having ever used OC, and a 24.5% of users having a duration of use exceeding 5 years, resulting in a low prevalence of long-term OC users. Moreover, the mean age at recruitment was 52.5 years, far from the usual period of

OC intake (early reproductive years). Consequently, due to the low prevalence of long-term OC use and the long duration since cessation of OC use in the studied population, the protective effect of OCs could have been too small to detect or potentially already attenuated.

The study Shafrir et al. (37) also revealed a non-significant decreased risk (57%; 95% CI = 0.18–1.03) after ≥15 years of OC use. Nevertheless, an increased risk of ovarian cancer with ≤6 months of OC use (HR = 1.82; 95% CI = 1.13–2.93) was found among short-term users (≤1 year), which was restricted to OCs containing mestranol (HR = 1.83; 95% CI = 1.16–2.88) and first-generation progestin (HR = 1.72; 95% CI = 1.11–2.65). These results are in stark contrast to results of other studies included in this systematic review that assessed short-term use of OCs: some observed no significant association (28, 31, 39), while others reported a suggestive (10, 12) or significant (40) decreased risk of ovarian cancer. Briefly, the associations observed for this younger birth cohort differed substantially from the results of previous cohort studies, possibly reflecting changes in OC formulations and patterns of use over time, although authors did mention that these results could be due to chance. Yet, an important limitation of the study was the relatively limited number of ovarian cancer cases (n = 281) included. Therefore, further research is needed including larger studies that evaluate newer OC formulations and ovarian cancer risk.

On the other hand, Bešević et al. (38) observed that ever using OC was not associated with epithelial ovarian cancer survival (HR = 0.96; 95% CI = 0.79–1.17). In fact, longer duration of OC use among ever users was unexpectedly associated with a worse survival: >10 years vs ≤1 year of use (HR = 1.74; 95% CI = 1.10–2.75). The main strengths of this study were the large number of cases and the representation of findings from 10 European countries, which were identified in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Furthermore, a potential limitation was that exposure data was collected on average 6 years prior to diagnosis; however, the impact of this was likely limited since the majority of the cases in the study (63%) were postmenopausal at recruitment and had completed their reproductive history.

Finally, the study conducted by Moorman et al. (39) which examined how reproductive risk factors vary between pre- and postmenopausal ovarian cancer, found an inverse dose-response relationship with years of OC use for premenopausal women (OR = 0.3; 95% CI = 0.2–0.6) in the case of those that took OC for >10 years. Among postmenopausal women, no significant associations were observed for the duration of OC use; the authors claimed that OC exposure generally occur only in premenopausal women, which means that postmenopausal women would have experienced this exposure in the more distant past. Hence, the stronger associations

found for premenopausal women could simply reflect time since exposure rather than differences in risk associated with the hormonal milieu.

Considering the existing research inconsistencies (Table 2) and the need for a more comprehensive understanding of the relationship between oral contraceptives and ovarian cancer, further studies are warranted to explore specific topics in this realm.

4.2 Oral contraceptive formulations and ovarian cancer risk

Five studies included in the systematic review (17, 25, 40, 41 – Table 3) investigated how the potency and type of OC formulation are linked to the risk of ovarian cancer. Related to this, it is worth mentioning that most OC pills contain a combination of estrogen (ethinylestradiol or mestranol) and progestin, but progestin-only preparations also exist. Since they became available, considerable changes have been made in the estrogen and progestin content of combined OC regarding generic substance, dose and potency (i.e., the amount required to produce an effect of given intensity), that aimed to decrease the undesirable side effects (29).

The first OC introduced contained 50 µg ethinylestradiol (or an equivalent 100 µg mestranol) and are referred as ‘‘high-dose’’, whereas those called ‘‘low-dose’’ were introduced in the late 1970s and contained 20-40 µg ethinylestradiol. At the same time as the reduction in estrogen dose, new types of progestins were developed, such as desogestrel, gestodene and drospirenone (29). These modifications were aimed at improving the safety and tolerability of OC, notwithstanding concerns were raised that the newer types of OC did not protect against ovarian cancer to the same degree as the older high-dose formulations (17). However, relatively few observational studies have addressed whether the specific hormone content of OC affects the degree of protection against ovarian cancer (17, 25, 40, 41).

Changes made in formulations of combined OC (reductions in oestrogen dose and introduction of newer progestogens) also included new patterns of administration (continuous versus monthly cycles in which 21 days of combined hormonal contraception is followed by seven hormone-free days during which a withdrawal bleed occurs), new non-oral routes of administration, and an increased use of progestogen only preparations (22). As a result, it is essential for users of contemporary OC to ascertain whether they can expect a similar reduction in the risk of ovarian cancer as observed in older studies and determine if any specific formulation offers a distinctive benefit.

To better understand the position of available literature on this association, a comparison of the outcomes from the different studies mentioned before was done in this study.

Table 3. Details about population included in each article assessed in the study of oral contraceptive formulations and ovarian cancer.

Reference	Type of study	Total population	Ovarian cancer cases	Controls
17	Population-based case-control study	2118	554	1564
25	Cohort study	1879227	1249	1877978
40	Population-based case-control study	1594	568	1026
41	Population-based case-control study	1688	745	943

Greer et al. (40) explored whether the protection associated with OC might be altered by the androgenicity of the progestin component. An excess of androgen exposure may be particularly important in cancer risk, since more than 90% of ovarian cancer tumors express androgen receptors, and androgens play a role in follicular growth, maturation, and atresia[3]. This study found that independent from the androgenicity of its progestin component, OC use was associated with approximately an overall decrease of 40–50% in ovarian cancer risk. A negative association was observed for androgenic-only OC formulations (OR = 0.52; 95% CI = 0.35–0.76) as well as for nonandrogenic-only OC formulations (OR = 0.59; 95% CI = 0.45–0.78). Increasing duration of use, early age at first use, and recentness of OC use all provided an increased protection against ovarian cancer, regardless of the androgenic potential of the progestin in the OC formulation employed.

The study conducted by Iversen et al. (25) assessed whether the use of contemporary combined OC (containing newer progestogens) or the use of progestogen-only contraceptives was associated with a reduction in the risk of ovarian cancer; however, few women in the study were exclusive users of progestogen-only contraceptives, so evidence was limited. As a result, a reduced risk was observed for current or recent use of combined OC, whereas current or recent users of progestogen-only products seemed to have a smaller, non-significant reduction in ovarian cancer risk. Similarly, Faber et al. (17) revealed that the use of combined OC or mixed use (combined and progestin-only pills) decreased the risk of ovarian cancer, whereas no association was found for exclusive intake of progestin-only pills.

[3] During a menstrual cycle, multiple immature follicles continue to develop. Nevertheless, there is only one follicle that completes the development and releases a fully mature oocyte. The other follicles go through a programmed process of cell death degenerate/regress (40).

Additionally, the study of Faber et al. (17) evaluated the effect of high and low potency contraceptives. Results showed no significant differences in ovarian cancer risk between high and low potency OC containing estrogen and progestin. In parallel, Lurie et al. (41) found a significantly reduced ovarian cancer risk in all categories of OC by potency, with ORs ranging from 0.62 for high estrogen and high progestin to 0.19 for low estrogen and low progestin users, when compared with participants who never used hormonal contraception. Although the odds of ovarian cancer were lower in users of low potency OC than in those of high potency OC, the difference in risk reduction among them was not statistically significant, in agreement with the results of Faber et al. (17).

4.3 Oral contraceptives and ovarian cancer risk by tumor typology

Ovarian cancer, the most deadly gynecologic malignancy in women, is a highly heterogeneous disease. Each histotype of ovarian cancer is likely to originate from a different etiologic pathway, displaying a high level of heterogeneity in clinical behavior and disease progression (42).

Ovarian tumors can be further divided into benign, borderline and invasive; this division is very important because it relates to behavior. Borderline ovarian tumors show greater epithelial proliferation than their benign counterparts and variable nuclear atypia; nonetheless, unlike carcinomas, there is no destructive stromal invasion and their prognosis is much better (43). Recent evidence suggests that invasive tumors can be classified as (44, 45, 46):

- Type I ovarian tumors, which are more likely to arise from the ovarian surface epithelium, can be histologically classified as low-grade tumors (grade 1, well differentiated) and present mutations in the genes of *KRAS*, *BRAF, CTNNB1* (β-catenin), and *PTEN*.
- Type II tumors are more likely to be high-grade tumors (grade 2 or 3, moderately or poorly differentiated) with a distal fallopian tube origin and *TP53* mutations.

Prior work indicated that tumors originating from the ovarian surface (those with type I tumor characteristics) tend to present a dominant tumor mass with tumor growth primarily confined to one ovary, whereas tumors of fallopian tube origin (those with type II tumor characteristics) tend to be non-dominant resulting in bilateral tumors with a similar extent of growth or peritoneal tumors (47, 48). Recent findings indicate that endometrioid and clear cell epithelial ovarian tumors have a tendency to be dominant (type I) and potentially originate from endometriotic tissues, whereas serous epithelial ovarian tumors are characterized by a greater proportion of non-dominant (type II) cases (15, 49). Thus, tumor dominance can be considered

as an indicator of cancer origin, distinguishing ovarian or endometriotic from fallopian tube cancer.

Identifying differences between the most rapidly fatal versus less aggressive cancer, as well as for tumor dominance, could improve our understanding of ovarian carcinogenesis etiology and better target prevention. Hence, a review of the available literature assessing this subject was done, to better understand if there was a general agreement regarding the effect that OC has on the different ovarian tumors described (Table 4).

Table 4. Details about population included in each article assessed in the study of oral contraceptives and ovarian cancer risk by tumor typology. Abbreviations: ND, non-determined.

Reference	Type of study	Total population	Ovarian cancer cases	Controls
4	Case-control study	110493	ND	ND
		153180	ND	ND
		3370	1861	1509
		4303	2203	2100
14	Cohort study	434233	1058	435291
50	Cohort study	334126	1245	332881
51	Population-based case-control	1404	496	908
52	Nationwide population-based case-control study	≈ 14160	885	15 controls per case
53	Case-control study	82528	5158	77370

Poole et al. (4) conducted an analysis comparing risk factor associations between women who died within 3 years of diagnosis and women who survived at least 3 years postdiagnosis, using data from four different studies (*Nurses' health study*, *NIH-AARP diet and health study*, *Australian ovarian cancer study* and *The New England case-control study*). The main finding was that OC use within the last 20 years was associated with a significantly decreased risk of rapidly fatal (high grade, type II: RR = 0.48; 95% CI = 0.38–0.61), but not less aggressive disease (low grade, type I: RR = 0.86; 95% CI = 0.72–1.03). In contrast, Huang et al. (14) assessed the effects of OC use on dominant and non-dominant tumors, finding a decreased risk of dominant tumors (low grade, type I: HR = 0.70; 95% CI = 0.59–0.83), while no risk reduction was observed for non-dominant tumors (high grade, type II: HR = 1.05; 95% CI = 0.80–1.39).

The study of Fortner et al. (50) found that duration of OC use (≥10 years vs. never use) was inversely associated with the risk of suffering from a type I or type II tumor (Type I: RR = 0.54;

95% CI = 0.31–0.94, Type II: RR = 0.71; 95% CI = 0.51–0.97), while no association was observed for borderline tumor (RR = 0.75; 95% CI = 0.35–1.61). However, case numbers were limited in some subgroups (borderline n = 106, type I n = 184 and type II n = 480), so further larger studies investigating risk factors by tumor aggressiveness were proposed, to obtain a better characterization of epithelial ovarian cancer risk. Similarly, Koushik et al. (51) revealed a significant reduced risk of type I and type II invasive tumors with ≥10 years of OC use compared to never use (OR = 0.73; 95% CI = 0.54–0.99), whereas no apparent association was observed for borderline tumors (OR = 1.41; 95% CI = 0.81–2.44). On the other hand, Rasmussen et al. (52) estimated the association of OC use with serous ovarian borderline tumor (SBT) and found a decreased risk (OR = 0.40; 95% CI: 0.26–0.62); this was the first study to report a strong and significantly decreased SBT risk associated with OC use, supporting that SBTs and serous ovarian cancer share similar risk factors.

A plausible hypothesis for the lack of association between the use of OC and borderline tumors could be that the latency period for OC use is shorter in borderline tumors, approximately around 10–15 years, and therefore a reduced risk would not be expected for older women (28, 54). In the study of Koushik et al. (51), about 59% of participants with borderline tumors reported that they spent at least 20 years without taking OC, thus, the observed lack of inverse association would be consistent with the hypothesis that use of OC among participants did not occur during the etiologically relevant period for borderline tumors.

Finally, Fortner et al. (50) and Hemmingsen et al. (53) conducted separated studies examining the relationship between OC use and the risk of ovarian cancer across various histologic subtypes. Fortner et al. (50) focused on epithelial histologic subtypes (Table 5) and found that duration of OC use was only significantly associated with reduced risk of serous tumors (OC use ≥10 years vs. never user, RR = 0.61; 95% CI = 0.46–0.82). Alternatively, Hemmingsen et al. (53) examined the risk of non-epithelial and serous ovarian cancer with OC intake. Results revealed that OC use decreased the odds for all the three tumor types: sex cord-stromal tumors (OR = 0.40; 95% CI = 0.13–1.22), germ cells tumor (OR = 0.50; 95% CI = 0.29–0.87) and serous tumor (OR = 0.50; 95% CI = 0.40–0.62). However, the authors indicated that despite the nationwide design, the number of cases was moderate (germ cell n = 188, sex cord-stromal n = 116 and serous n = 4854); therefore, results should thus be interpreted with caution, and eventually, more studies are needed on non-epithelial ovarian cancer to establish firm conclusions in regard to etiology and risk factors.

Table 5. OC use and risk of invasive epithelial ovarian cancer by main histologic subtypes: EPIC cohort, 1992–2010. Extracted from: Fortner et al. (2015).

	Invasive EOC ($n = 1,139$)		Serous ($n = 631$)		Mucinous ($n = 79$)		Endometrioid ($n = 131$)		Clear cell ($n = 57$)	
	Case *n*	HR1 95% CI	Case *n*	HR[1] 95% CI	Case *n*	HR[1] 95% CI	Case *n*	HR[1] 95% CI	Case *n*	HR[1] 95% CI
Oral contraceptive use										
Never	574	Reference	298	Reference	35	Reference	56	Reference	26	Reference
Ever	530	0.84 (0.73–0.96)	316	0.92 (0.77–1.10)	41	0.88 (0.53–1.47)	71	1.12 (0.75–1.67)	27	0.87 (0.47-1.63)
Duration ≤1 year	122	1.02 (0.83–1.25)	75	1.13 (0.87–1.47)	7	0.89 (0.39–2.07)	14	1.15 (0.62–2.12)	11	2.15 (1.01-4.58)
2–4 years	135	0.96 (0.78–1.17)	76	0.98 (0.75–1.28)	14	1.43 (0.73–2.81)	17	1.16 (0.65–2.07)	6	0.81 (0.32–2.09)
5–9 years	116	0.88 (0.71–1.09)	70	0.96 (0.73-1.27)	7	0.75 (0.31–1.78)	18	1.35 (0.76–2.41)	2	0.31 (0.07–1.35)
≥10 years	113	0.57 (0.45–0.70)	68	0.61 (0.46–0.82)	10	0.70 (0.32–1.51)	13	0.62 (0.32–1.20)	5	0.47 (0.17–1.32)
p for trend[2]		*< 0.01*		*<0.01*		*0.15*		*0.09*		*0.07*
p for subtype heterogeneity[3]: Ever OC use										*0.82*
p for subtype heterogeneity[3]: Duration of OC use										*0.86*

4.4 Oral contraceptives and ovarian cancer among *BRCA* mutation carriers

The following analysis was limited to studies that assessed ovarian cancer risk in a population of mutation carriers to reflect the following clinical question: if a woman bears a *BRCA1/2* mutation, can she reduce her risk for ovarian cancer by using OC? Six studies were identified (55, 56, 57, 58, 59, 60 – Table 6) that evaluated the association between OC use and ovarian cancer exclusively among *BRCA* mutation carriers.

Women with pathogenic mutations in *BRCA1* or *BRCA2* have a high lifetime risk of ovarian cancer. For carriers of *BRCA1* mutations, the lifetime risk of ovarian cancer is around 40%, whereas for those with *BRCA2* mutations the risk is about 20%, compared to less than 2% for women in the general population. The high risk of ovarian cancer among mutation carriers underscores the importance of assessing crucial factors that affect the likelihood of developing the disease (39).

Primary prevention strategies are of great interest to women with known genetic mutations or a family history of breast and ovarian cancer. Among *BRCA1/2* mutation carriers, bilateral salpingo-oophorectomy[4] can reduce the risk of ovarian and breast cancers by 80% and 50%, respectively (61). Although health-economic decision models suggest that this surgery is both effective and cost-effective in *BRCA* carriers (62, 63), it results in premature menopause and is accompanied by potential harms, including increased risk of cardiovascular disease (64, 65). Therefore, some high-risk women prefer alternatives that are less invasive and preserve ovarian function and fertility.

[4] Salpingo-oophorectomy: the removal of one (unilateral) or both (bilateral) of the ovaries or fallopian tubes (66).

A potential means for women at high genetic risk to reduce their likelihood of developing ovarian cancer could be chemoprevention with OC. Ever use of OC is associated with reduction in the incidence of ovarian cancer in the general population, with greater reduction of risk with longer duration of use. If OC use reduces ovarian cancer incidence similarly in women at high risk, these drugs may be a viable prevention strategy for women who have not completed childbearing or who wish to avoid surgery. Yet, the chemopreventive effect of OC for ovarian cancer must be weighed against the possible increased risk of thromboembolism and long-term risks such as breast cancer (40).

Comparing outcomes from the articles mentioned above, the effect that OC have on ovarian cancer among *BRCA* mutation carriers was evaluated.

Table 6. Details about population included in each article assessed in the study of oral contraceptives and ovarian cancer among *BRCA* mutation carriers.

Reference	Type of study	Total population (*BRCA*)	Ovarian cancer cases	Controls
55	Case-control study	3223 (2713 *BRCA1* vs. 508 *BRCA2*)	799 (670 *BRCA1* vs. 128 *BRCA2*)	2424 (2043 *BRCA1* vs. 380 *BRCA2*)
56	Case-control study	6596	1329	5267
57	Case-control study	14199	2221	11978
58	Cohort study	6434 (3989 *BRCA1* vs. 2445 *BRCA2*)	452 (346 *BRCA1* vs. 106 *BRCA2*)	5982 (3643 *BRCA1* vs. 2339 *BRCA2*)
59	Cohort study	3319 (2281 *BRCA1* vs. 1038 *BRCA2*)	253 (201 *BRCA1* vs. 52 *BRCA2*)	3066 (2080 *BRCA1* vs. 986 *BRCA2*)
60	Case-control study	6032	389	5643

McLaughlin et al. (55) found a highly significant reduced risk of ovarian cancer for the use of OC in carriers of *BRCA1* mutations (OR = 0.56; 95% CI = 0.45–0.71) and carriers of *BRCA2* mutations (OR = 0.39; 95% CI = 0.23–0.66); in both univariable and multivariable analyses. Similarly, Kotsopoulos et al. (56) agreed on the risk reduction for the two *BRCA* mutation carries, and found that for OC use, maximum benefit was seen with five or more years of use among *BRCA1* mutation carriers (OR = 0.50; 95% CI = 0.40–0.63) and three or more years for *BRCA2* mutation carriers (OR = 0.42; 95% CI = 0.22–0.83). Overall, it was estimated that a history of OC use was associated with a 40% reduction in ovarian cancer (OR = 0.60; 95% CI = 0.50–0.71), which is close

with the 37% risk reduction that Xia et al. (57) stablished when OC was used among *BRCA* mutation carriers.

On the other hand, the study of Schrijver et al. (58) also found an inverse association between OC use and ovarian cancer risk which persisted for >15 years after use, but this correlation was not significant in carriers of *BRCA2* mutation that used OC for <5 years; authors mentioned that it could be due to the small sample size in this group. Similarly, Antoniou et al. (59) observed that mutation carriers who had ever used OC were at a significantly reduced risk of developing ovarian cancer (HR, 0.52; 95% CI, 0.37–0.73), and this effect was mainly driven by *BRCA1* mutation carriers. Again, nevertheless, the number of *BRCA2* mutation carriers in individual categories was too small to draw reliable conclusions.

Ferris et al. (60) included participants from the three clinic-based sites (New York, Philadelphia and Utah) of the Breast Cancer Family Registry (BCFR) who had detailed information on ovarian cancer incidence within families, assessing the effect measure modification by *BRCA1/2* status. Figure 6 shows the OC results stratified by *BRCA1/2* mutation status.

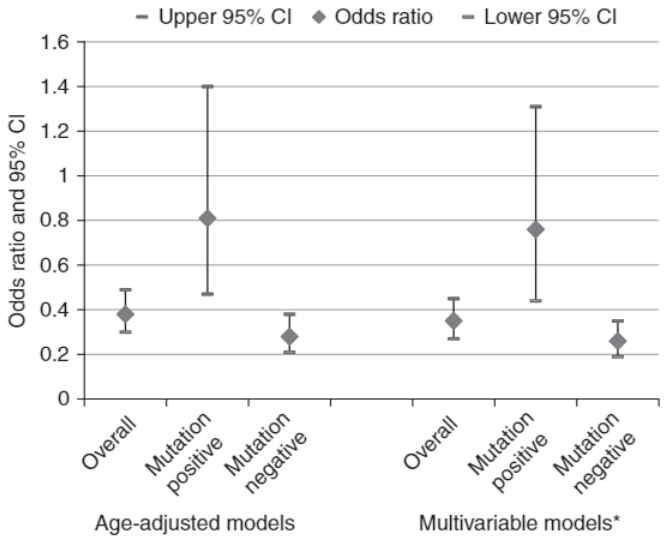

Figure 6. Risk of ovarian cancer by oral contraceptive use among all cases and controls by *BRCA1/2* mutation status among women included in the Breast Cancer Family Registry (Mutation negative imputed). **Adjusted for age, race, parity. Age-adjusted models: overall: n = 5780, case mutation positive: n = 76, case mutation negative: n = 277, control mutation positive: n = 566, control mutation negative: n = 4861. Multivariable models: overall: n = 5749, case mutation positive: n = 75, case mutation negative: n = 276, control mutation positive: n = 564, control mutation negative: n = 4834.* Extracted from: Ferris et al. (2014).

In both the age-adjusted and multivariable models, the inverse association between OC and ovarian cancer was stronger and only statistically significant in those who were *BRCA1/2* mutation negative compared with those who were *BRCA1/2* mutation positive (60).

5 DISCUSSION

This systematic review of literature investigating the relationship between oral contraceptives (OC) and ovarian cancer reveals a general consensus among different researchers regarding the significant reduction risk in ovarian cancer associated with the use of OC. Multiple studies, including population-based case-control studies and cohort studies, have consistently demonstrated this association, highlighting the potential benefits of OC use in reducing the incidence of ovarian cancer. The observed inverse trend, which indicates a dose-response relationship where longer durations of OC use are associated with a greater reduction in risk, further supports the overall agreement on the protective effect of OCs.

Yet, it is important to acknowledge that despite this general consensus along the literature cited, there are studies included in this systematic review that reported conflicting findings. These discrepancies could be attributed to disparities in the presence of different study designs and the influence of potential confounding factors. Factors such as geographic distribution, the sample size of the study, age, reproductive and hormonal factors, genetic predisposition, and lifestyle choices may certainly confound the association between OC use and ovarian cancer risk (67). Considering the complex role of these factors, it becomes crucial to carefully examine their potential influence on the observed relationship between OC use and ovarian cancer risk in order to gain a more comprehensive understanding of this topic.

An important consideration when interpreting the results of studies investigating the relationship between OC and ovarian cancer is the potential influence of the sample size. Sample size plays a critical role in the statistical analysis of a study and its ability to detect significant associations; studies with larger sample sizes are generally more robust and have a higher possibility of discovering actual effects. Therefore, studies with smaller sample sizes, like some of those included in this systematic review, may have limited statistical power to detect significant associations, potentially leading to conflicting or inconsistent findings.

Furthermore, the type of study design, including population-based case-control studies, case-control studies, and cohort studies, can introduce different biases and limitations that may impact the observed associations. For instance, case-control studies are susceptible to recall bias, where cases may recall OC use differently than controls, leading to misclassification. In population-based case-control studies and cohort studies, on the other hand, the cases and controls are derived from the same underlying well-defined population (Figure 7). As a result, the goal is to ensure that cases and controls are drawn from the same population base, reducing potential biases that may arise from selecting cases and controls from different sources, but may

still be influenced by selection bias or confounding factors due to unmeasured variables (68). Thus, the presence of confounding factors can vary across different study designs, making it challenging to reconcile and draw unanimous conclusions.

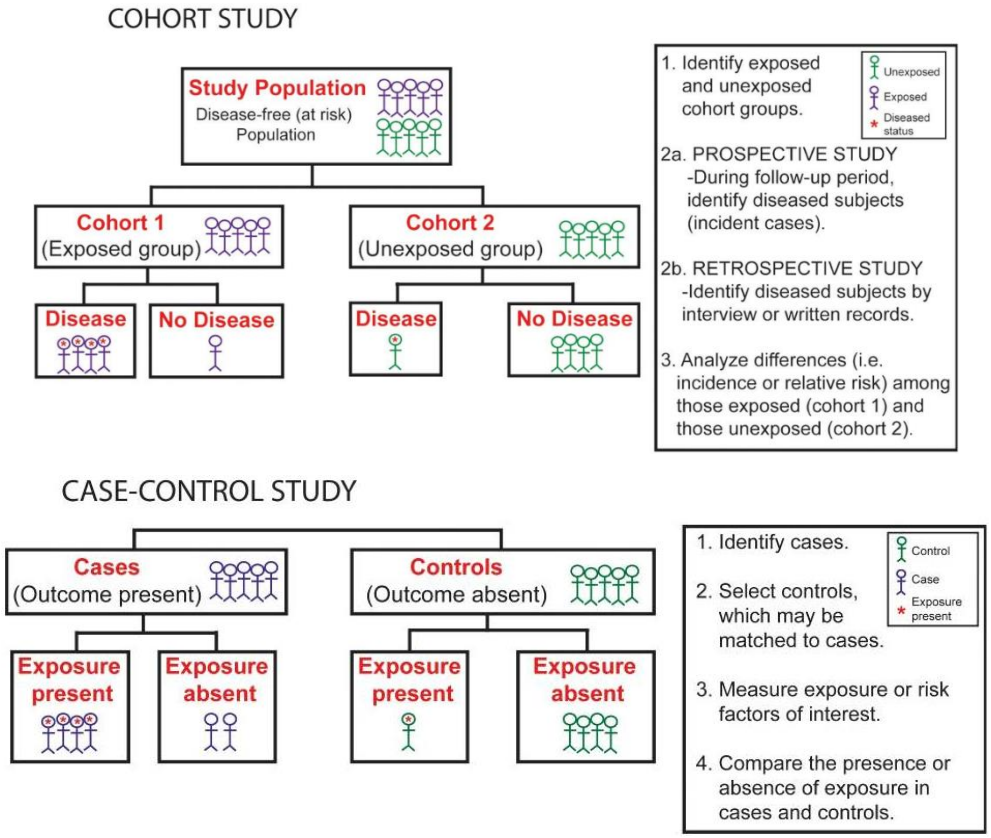

Figure 7. Cohort and Case-Control Study Designs. Extracted from: Song et al. (2010).

The age of the population in the different studies included in this systematic review can also be a confounding factor due to the well-established relationship between age and ovarian cancer risk. Ovarian cancer primarily affects postmenopausal women, with the incidence of the disease increasing with age (7). Therefore, if the age distribution differs significantly between the study populations, it can introduce bias and confound the association between OC use and ovarian cancer risk. Yet, to account for the potential confounding effect of age, some studies have employed statistical techniques, such as age adjustment, to control for the age-related differences between groups. By doing so, researchers can better assess the independent effect of OC use on ovarian cancer risk while minimizing the influence of age as a confounding factor (60).

The different geographical locations of the sample sizes, including different nationalities, can also introduce confounding factors in this research for several reasons. Firstly, there can be variations in the prevalence of both OC use and ovarian cancer across different countries and populations. Cultural, socioeconomic, and healthcare factors can influence the prevalence of OC use, as well

as the availability and utilization of healthcare services for ovarian cancer screening and diagnosis. Secondly, environmental factors such as diet, lifestyle, and exposure to certain chemicals or toxins can vary across different geographic regions, potentially confounding the association between OC use and ovarian cancer risk (69). Thus, when comparing study results across different populations, it is crucial to consider these contextual factors that can influence both the OC use and ovarian cancer incidence.

Additionally, there may be differences in genetic and environmental factors across populations that can interact with OC use and modify the risk of ovarian cancer. Genetic variations, including polymorphisms in genes related to hormonal metabolism or DNA repair mechanisms, can contribute to differences in individual susceptibility to the effects of OC use on ovarian cancer risk (70).

The findings from the studies by Faber et al. (17), Iversen et al. (25), Greer et al. (40) and Lurie et al. (41) contribute to the understanding of the association between ovarian cancer and the different OC formulations. Overall, the results suggest that OC use is associated with a significant reduction in the risk of ovarian cancer. This protective effect remains consistent irrespective of the androgenicity of the progestin component in OCs. Regarding the specific types of OC formulations, combined OC and mixed use of combined and progestin-only pills showed a decreased risk of ovarian cancer. However, exclusive use of progestin-only pills did not demonstrate a significant association with ovarian cancer risk reduction, although, as few women were exclusive users of progestogen-only contraceptives in the studies, results must be interpreted carefully. In terms of hormone potency, no major differences in ovarian cancer risk were observed between high and low potency estrogen and progestin combinations in combined OC.

The studies from Poole et al. (4), Huang et al. (14), Fortner et al. (50), Koushik et al. (51), Rasmussen et al. (52) and Hemmingsen et al. (53) investigated the relationship between OC use and ovarian cancer risk, particularly in relation to tumor aggressiveness and histologic subtypes. Overall, literature suggests a potential protective effect of OC use against certain subtypes of ovarian cancer but fails to establish a unanimous association. For instance, Poole et al. (4) and Huang et al. (15) both found a reduced risk of invasive tumors with OC use, however, results were conflicting with regard to the invasive type (type I and II / dominant and non-dominant) that benefited from the effects of OC use. On the other hand, Fortner et al. (50) and Koushik et al. (51) established a significant reduced risk of OC use compared to never use, for both Type I and II of invasive tumors, but did not find a significant reduction risk among borderline tumors.

In contrast, Rasmussen et al. (52) proved a significantly reduced risk of serous ovarian borderline tumor (SBT) associated with OC use, supporting that SBTs and serous ovarian cancer share similar risk factors. It is important to acknowledge that the studies conducted in this area have limitations, including small sample sizes in certain subgroups. Additionally, the effects of cofounding factors mentioned before further complicate the interpretation of the findings.

Finally, the works from McLaughlin et al. (55), Kotsopoulos et al. (56), Xia et al. (57), Schrijver et al. (58), Antoniou et al. (59) and Ferris et al. (60) reveal a range of findings, highlighting the lack of a unanimous position, therefore, variations and limitations in the studies should be noted. While McLaughlin et al. (55), Kotsopoulos et al. (56) and Xia et al. (57) all revealed a highly significant reduced risk of ovarian cancer for the use of OC in carriers of *BRCA1* and *BRCA2* mutations, the studies of Schrijver et al. (58) and Antoniou et al. (59) only found a significant reduction risk in *BRCA1* mutation carriers. Yet, the small sample sizes of *BRCA2* mutation carriers in these studies may limit the ability to draw definitive conclusions for this subgroup. On the contrary, the outcomes of Ferris et al. (60) indicated a stronger, statistically significant inverse association between OC use and ovarian cancer in individuals who did not carry any *BRCA1/2* mutation, compared to those who did, suggesting a potential interaction between OC use and *BRCA1/2* mutation status in modifying ovarian cancer risk.

Overall, and except the study of Ferris et al. (60), the literature cited shows a consistent trend that OC are associated with a decreased risk of ovarian cancer in women with *BRCA* mutations. However, before using OC as preventive measure for ovarian cancer, it is important to consider individual factors such as personal risk factors, medical history, lifestyle and the potential increase in breast cancer risk attributed to OC use. Moreover, while OC can reduce the risk of ovarian cancer, they do not completely eliminate it, so women with *BRCA* mutations may still be advised to undergo risk-reducing surgery, such as bilateral salpingo-oophorectomy.

6 CONCLUSION

In conclusion, this comprehensive review of the literature provides the most up to date synthesis of the associations on the relationship between oral contraceptives (OC) and ovarian cancer. While it has revealed a consistent trend indicating a significant reduction in ovarian cancer risk associated with OC use, as multiple studies have demonstrated this association, it is important to note that conflicting findings among the reviewed studies exist. Some of them can be attributed due to variations in study design and the influence of confounding factors such as geographic location, sample size, age, reproductive and hormonal factors, genetic predisposition, and lifestyle choices. Therefore, additional research is necessary to resolve these discrepancies and identify the underlying mechanisms to have a complete understanding of the subject. For future studies, larger sample sizes, robust study designs, and careful evaluation of confounding factors is needed to establish before selecting the articles included in the review to draw more conclusive evidence.

7 ETHICAL CONSIDERATIONS OF CONDUCTING A SYSTEMATIC REVIEW STUDY

The basis of scientific evidence can be stablished, by conducting systematic reviews or other extensive epidemiologic literature studies. While this can be a powerful tool to communicate research findings, it also come with ethical obligations. Unlike primary researchers, systematic reviewers do not collect personal, sensitive, or confidential information from participants; they use publicly accessible documents as evidence and are required to ensure different criteria (71).

When conducting a systematic review, it is mandatory for researchers to adhere to accepted research practices and avoid malpractices. This commitment to ethical guidelines ensures the integrity of the research process and the reliability of the findings. Adhering to established protocols is another important aspect of ethical research: researchers should follow rigorous methodologies and standardized procedures to ensure the reliability and validity of the systematic review. Differing from established protocols without appropriate justification can introduce biases and compromise the quality of the research. In this study, in order to make sure that all the data on the topic of interest was included, we used a reproducible and transparent methodology described in PRISMA.

In addition, accurate reporting of data is crucial for maintaining research integrity. Researchers should present their findings honestly and transparently, without manipulating or selectively omitting data to support a particular hypothesis or desired outcome. This includes reporting both positive and negative results, as well as any limitations in the findings.

Another important consideration is avoiding plagiarism. Plagiarism refers to the inappropriate authorship and is a serious ethical violation that should be strictly avoided. It involves the use of someone else's ideas, words, or work without proper attribution. Researchers conducting a systematic review should do a comprehensive analysis and synthesis of existing literature, providing proper citations and references to acknowledge the contributions of others. This is the criteria that this study has firmly followed.

8 SUSTAINABILITY AND ORAL CONTRACEPTIVE USE

When discussing sustainability in the context of oral contraceptive use, it is essential to consider the potential environmental impacts associated with the production, use and disposal of oral contraceptives.

1. Waste management:
    a. The production and packaging of oral contraceptives generates waste, which includes the plastic packaging, blister packs and discarded pills. A proper management should be carried out, such as recycling and appropriate disposal methods, to help minimizing the environmental impact of this waste.
    b. The safe disposal of unused or expired oral contraceptives is important to prevent the release of the active pharmaceutical ingredients into the environment, which would have ecologic consequences.
2. Pollution prevention: the manufacturing processes involved in producing oral contraceptives involve the use of chemicals, solvents, and energy sources. A measure that can be implemented to reduce the pollution could be adopting cleaner production technologies to reduce the emissions. This can include changes to a packaging eco-friendlier or eventually including the use of green energy sources. When implementing a cleaner production, senior management support, staff awareness, participation and impute are essential (72).
3. Health and environmental impact: evaluating the long-term health and environmental impact of the hormones present in oral contraceptives is also important. A study of the potential effects on aquatic ecosystems should be done to provide insights into the sustainability considerations that are associated with their use.

Although the oral contraceptive use and ovarian cancer research might not be directly connected to a broader sustainability discussion, exploring the potential environmental implications of oral contraceptive production, use and disposal can contribute to a more comprehensive approach to the topic.

9 GENDER BIAS IN RESEARCH STUDIES

Gender biases refer to unfair preferences based on gender: it can manifest in favoring one gender over the other in research design, data collection, analysis, or interpretation. Addressing these biases is crucial for ensuring reliable and equitable research outcomes.

Gender stereotypes in medicine can have a significant impact on the diagnosis and treatment of both men and women. One common stereotype is the assumption that diseases and conditions present and progress similarly in both genders, despite potential biological and physiological differences. This assumption can lead to biased research studies where predominantly male subjects are included, and findings are generalized to both genders, therefore, resulting in a lack of understanding about how diseases and treatments affect women (73). This gender bias in research can lead to misdiagnosis, delayed diagnosis, or ineffective treatments for women. For instance, certain symptoms or risk factors that may be more prevalent or distinctive in women could be overlooked or not thoroughly investigated due to the narrow focus of research. However, as ovarian cancer is a disease that can only occur in women, the equality between genders in the research to avoid stereotypes has not been possible to demonstrate in this study.

Moreover, citations play a crucial role in acknowledging the contributions of previous studies/researchers and providing evidence to support arguments. One aspect of citation bias is the underrepresentation of women's research in scholarly publications. Studies have shown that articles authored by women tend to receive fewer citations compared to those authored by men, even when controlling for other factors such as publication venue or topic. This discrepancy may result from several factors, including gender biases in the peer review process, implicit biases among researchers, or a lack of visibility and opportunities for women in academia (74).

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