

The association between oral contraceptive pills and ovarian cancer risk: A systematic review and meta-analysis

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Keywords

Ovarian cancer
OCPs
Systematic review
Meta-analysis

Summary

Introduction > Previous study results have been inconclusive, so this meta-analysis aims to evaluate the association between ovarian cancer and oral contraceptive pills (OCPs).

Methods > PubMed, EMBASE, Scopus, and Web of Science were searched to identify studies on the association between OCPs and ovarian cancer from January 1, 2000 through February 5, 2023. The pooled relative risk (RR) and odds ratio (OR) were used to measure this relationship.

Results > A total of 67 studies were included. In the association between ever-use compared with never-use of OCPs and ovarian cancer risk, the pooled RR in cohort studies was 0.69 [95% CI: 0.61, 0.78]. For the relationship between duration of OCPs use and ovarian cancer in the cohort studies, no association between duration of use 1–12 months 0.92 [95% CI: 0.82, 1.03] and duration of use 13–60 months 0.87 [95% CI: 0.73, 1.04], but there is a statistically significant inverse relationship between duration of use 61–120 months 0.62 [95% CI: 0.48, 0.81] and more than 120 months 0.51 [95% CI: 0.32, 0.80] and ovarian cancer. For the relationship between OCPs and histological subtype of epithelial ovarian cancer in the cohort studies, the pooled RR for invasive was 0.70 [95% CI: 0.56, 0.87], but no association between OCPs and borderline ovarian cancer 0.64 [95% CI: 0.31, 1.31].

Conclusion > Our analysis shows a statistically significant inverse relationship between ever-use compared to never-use of OCPs and ovarian cancer risk, and also between invasive cancer and OCPs. By increasing the duration of OCPs use, the risk of ovarian cancer decreased.

Mots clés

Cancer de l'ovaire
OCP
Revue systématique
Méta-analyse

■ Résumé

Association entre pilules contraceptives orales et risque de cancer de l'ovaire: une revue systématique et une méta-analyse

Introduction > Les résultats d'études précédentes n'ayant pas été concluants, cette méta-analyse vise à évaluer l'association entre le cancer de l'ovaire et les pilules contraceptives orales (oral contraceptive pills - OCP).

Méthodes > Des recherches ont été effectuées dans PubMed, EMBASE, Scopus et Web of Science pour identifier des études sur l'association entre les OCP et le cancer de l'ovaire du 1^{er} janvier 2000 au 5 février 2023. Le risque relatif (RR) et l'odds ratio (OR) regroupés ont été utilisés pour mesurer cette relation.

Résultats > Un total de 67 études ont été incluses. Dans l'association entre l'utilisation antérieure et la non-utilisation d'OCP et le risque de cancer de l'ovaire, le RR groupé dans les études de cohorte était de 0,69 [IC à 95 %: 0,61, 0,78]. Pour la relation entre la durée d'utilisation des PCO et le cancer de l'ovaire dans les études de cohorte, aucune association entre la durée d'utilisation de 1 à 12 mois 0,92 [IC à 95 %: 0,82, 1,03] et la durée d'utilisation de 13 à 60 mois 0,87 [IC à 95 %: 0,73, 1,04], mais il existe une relation inverse statistiquement significative entre la durée d'utilisation de 61 à 120 mois 0,62 [IC à 95 %: 0,48, 0,81] et plus de 120 mois 0,51 [IC à 95 %: 0,32, 0,80] et le cancer de l'ovaire. Pour la relation entre les OCP et sous-type histologique du cancer de l'ovaire dans les études de cohorte, le RR global pour le cancer invasif était de 0,70 [IC à 95 %: 0,56, 0,87], mais aucune association entre les OCP et le cancer de l'ovaire limite 0,64 [IC à 95 %: 0,31, 1,31].

Conclusion > Notre analyse montre une relation inverse statistiquement significative entre l'utilisation constante et la non-utilisation d'OCP et le risque de cancer de l'ovaire ainsi qu'entre cancer invasif et OCP. En augmentant la durée d'utilisation des OCP, le risque de cancer de l'ovaire a diminué.

Introduction

Ovarian cancer is increasingly recognized as a heterogeneous disease with subtypes of epithelial ovarian: invasive epithelial ovarian and borderline epithelial ovarian. It is also one of the most common gynecologic cancers, ranking third after cervical and uterine cancer [1]. The incidence of ovarian cancer varies widely among different populations worldwide [2] and the highest incidence of ovarian cancer has been reported in the Scandinavian countries, Eastern Europe, Canada, and Africa [3]. The lowest rates have been reported from Asia (except for Japan) and also the worst prognosis and the highest mortality rate have been reported [4]. Although ovarian cancer is less common than breast cancer [5], it is three times more deadly and is predicted to increase significantly by 2040 [6]. The high mortality of ovarian cancer is due to the asymptomatic and latent growth of the tumor, delayed onset of symptoms, and lack of appropriate screening, leading to its diagnosis in the advanced stages. Therefore, the silent killer is the name given to this cancer [7,8]. Due to the high mortality rate of the disease and the costs incurred by the health care system, physicians are trying to prevent women from contracting the disease [9]. There are modifiable factors that

are associated with the risk of ovarian cancer. Studies suggested that obesity increased the risk of ovarian cancer [10,11]. Vegetables including cooked cauliflower, cooked greens, and cooked cruciferous have been found to be inversely associated with ovarian cancer [12] and also shown an association between smoking and the risk of mucinous ovarian cancer [13].

There is also conflicting evidence regarding the next risk factor, the use of oral contraceptives. [14,15]. Previous studies have examined the association between ovarian cancer and oral contraceptives via two pathways. These studies found considerable heterogeneity in outcomes between type I and type II tumors. For example, oral contraceptives showed a stronger protective effect against type I tumors, while the association between duration of oral contraceptive use (OC) and type II tumors was stronger [16].

Some other studies have considered OCPs to be one of the most potent preventive agents known for ovarian cancer [17-19], therefore, understanding the impact of OCPs use on the risk of ovarian cancer in the future has important public health implications [20]. but some studies have not found such a link or considered it a risk factor [21-23].

From 2014 until now, no other meta-analyses were conducted in this field, and in the meantime, up-to-date articles with accurate scientific evidence have been published. On the other hand, A study published in 2017 showed that using OCPs for almost a year increased the risk of ovarian cancer [24], so we performed a meta-analysis to resolve the inconsistencies. In our meta-analysis, we did a more extensive search than the previous meta-analysis, and we also searched more databases. Finally, the purpose of our meta-analysis was to evaluate the association between ovarian cancer and OCPs and the association between OCPs and histological subtype of epithelial ovarian cancer too.

Methods

Literature search strategy

To identify observational studies on the association between OCPs and ovarian cancer, a comprehensive search was performed of several electronic databases including PubMed, EMBASE, Scopus and Web of Science from January 1, 2000 through February 5, 2023. The search term comprised the following keywords: "oral contraceptives pill", "combined oral contraceptives", "oral contraceptives", "ovarian cancer", "ovarian neoplasms", "epithelial ovarian carcinoma" and "granulosa cell tumor of the ovary". Also, we investigated references of all the articles to identify studies that were not included during the initial search. We conducted a systematic review and meta-analysis to search for the association between oral contraceptive pills and ovarian cancer risk in the general population, not this sub-group of the population that had an excess risk for ovarian cancer like in BRCA1/2 mutation carriers. The following inclusion criteria were selected for meta-analysis: the study comprised a case-control or cohort study design, the primary outcome was a risk of ovarian cancer, the relative risk (RR) or odds ratio (OR) or hazard ratio (HR) and the corresponding 95% confidence interval (CI) of ovarian cancer associated with OCPs were presented, studies published in English. Furthermore, the exclusion criteria included intervention studies, letter to the editor, report, case report, review and meta-analysis.

Study selection

Initially, we screened the titles and abstracts of all studies to identify those that met the inclusion criteria by two authors (MA and FKH) independently. Full-text assessment was conducted for those that were difficult to determine with titles and abstracts only. After reading the full text of all potentially eligible articles, two authors (MA and FKH) screened full text final, and decision was made for each study. In cases of disagreement, a third review author was consulted or was resolved by discussion. Totally, 2122 articles were retrieved (239 from PubMed, 305 from EMBASE, 1029 from Scopus and 549 from Web of Science. A total of 67 articles remained after the review process shown in [figure 1](#).

Data extraction

A structured data extraction form was used to extract data from the papers. The extracted data included: the last name of the first author, publication year, country, study design, study purpose, sample characteristics, sample size, mean age, main measurements and confounder. Extraction of data was done by the same two review authors (MA and FKH) who conducted the study selection independently.

Evaluating the quality of articles

The quality of studies was assessed using Newcastle- Ottawa quality assessment scale (NOS) adapted for observational studies [25]. The NOS is based on three domains including the selection of study groups, comparability of groups and description of exposure and outcome. This scale including eight items and star scores assesses the quality of each study in each domain. All items except the comparability domain have one star (the maximum score based on stars for the comparability domain is two). Totally, earned stars are calculated as the total quality score for each study. Based on these criteria, study quality was rated on a scale from one star, very poor, to 10 stars, high quality. Studies are rated as high (7–10), medium (5–6) or low quality (< 4). Two review authors (EH and FKH) completed the quality assessment independently. In cases of disagreement or items that remained unclear, a third review author was consulted.

Statistical analysis

The pooled OR and RR and the 95% confidence intervals were used to measure the association between OCPs and the risk of ovarian cancer by assuming a random effects meta-analytic model. We used estimates adjusted. Statistical heterogeneity was evaluated using Cochran's Q-test and I^2 statistic. subgroup analysis was carried out according to the intensity (invasive and borderline), and duration of taking the OCPs. Leave-one-out sensitivity analysis was performed to identify influential studies in meta-analysis. Publication bias was determined by funnel plot and Begg's and Egger's tests. The P -value of < 0.05 is considered statistically significant. The analyses were performed using Stata software version 14.

Results

Study characteristics

The search strategy and the algorithm of study selection are shown in [figure 1](#). According to the keywords and MeSH terms and Emtree terms a total of 2122 studies were identified. Subsequently, after identifying relevant studies and removing duplicates and considering the inclusion and exclusion criteria, 1022, 260, and 57 studies were excluded after reviewing their titles, abstracts, and full-texts, respectively. Finally, 67 articles met the inclusion criteria and quality assessments were performed for all of them. Of these, twenty-eight studies were conducted in the United States, six studies in Denmark, eight

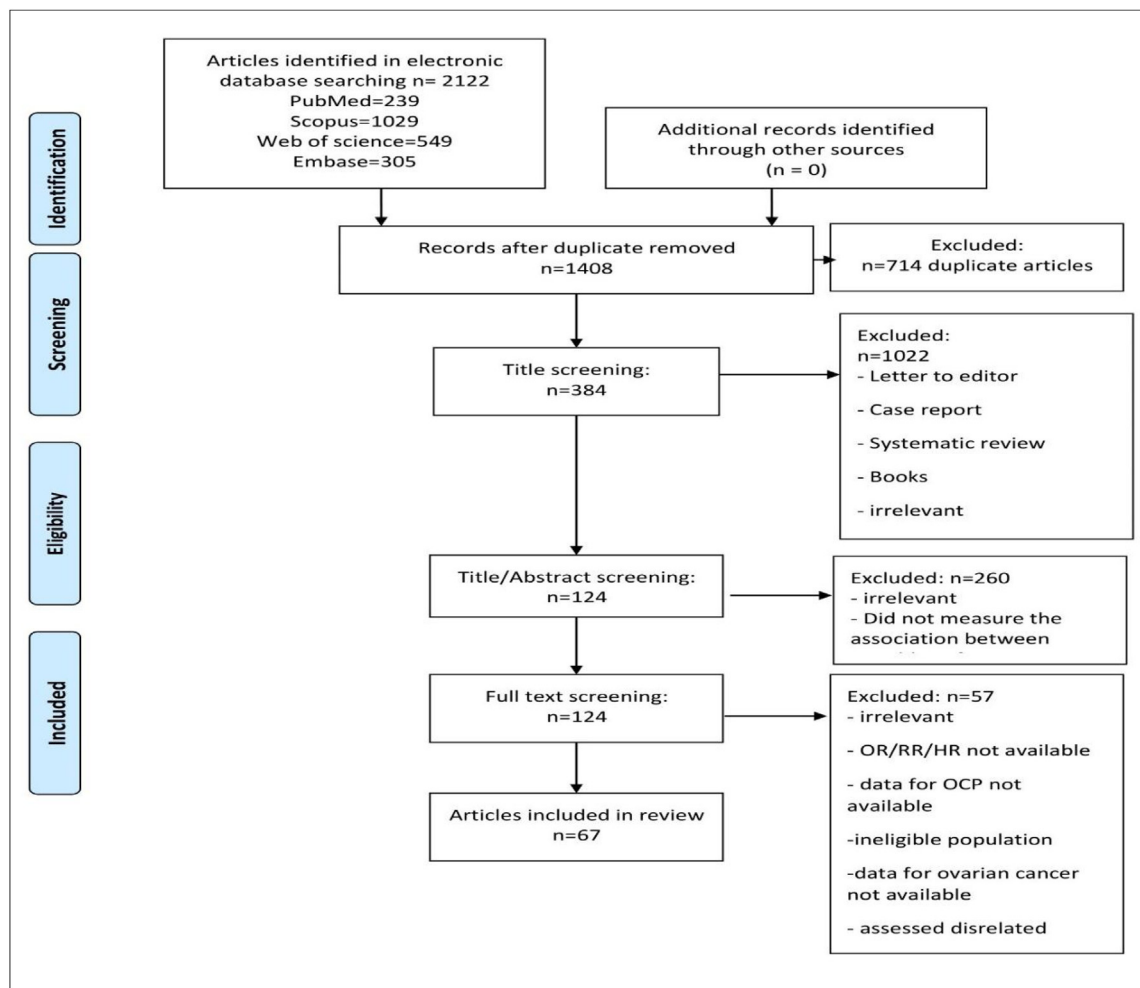


FIGURE 1
Flow chart depicting the study selection process (screening)

studies in Italy, six studies in Sweden, eight studies in the United Kingdom, two studies in Australia and other studies were in other parts of the world. The cut-offscore of 7 or higher was considered as the studies considered as having high level of quality, 5–6 was considered as the studies with moderate quality and 4 or lower was considered as the studies with low quality. Thirty studies were in range of 7–10, that they had high levels of quality. twenty-seven studies range of 5–6, that had moderate levels of quality. Ten studies were in range of 4 or lower that had low levels of quality. [Supplementary Table 1](#) summarizes the characteristics of selected studies.

Use of OCPs and ovarian cancer risk

[figure 3](#) presents the results of the random-effects meta-analysis and the pooled adjusted RR among a total of twelve cohort studies included for examining the association between ever-

use compared with never-use of OCPs and ovarian cancer risk. Based on results, the pooled RR was 0.69 [95% CI: 0.61, 0.78] which represent 31% reduction in ovarian cancer risk in women who have ever used OCPs. However, there is significant heterogeneity among studies ($I^2 = 77.2\%$; $P = 0.0001$). See [supplementary Figure 1](#) for the results of thirty-two case-control studies. Based on these results, the pooled OR of the case-control studies was 0.64 [95% CI: 0.59, 0.69] which represents a 36% reduction in ovarian cancer risk in women who have ever used OCPs. There is significant heterogeneity among case-control studies ($I^2 = 90.6\%$; $P = 0.0001$). Sensitivity analysis showed that there is no single study as a potential source of heterogeneity in cohort and case-control studies. We determined the possibility of publication bias using the funnel plot ([figure 2](#)) as well as Begg's and Egger's tests in cohort and case-control studies. The studies are almost symmetrical scattered on both

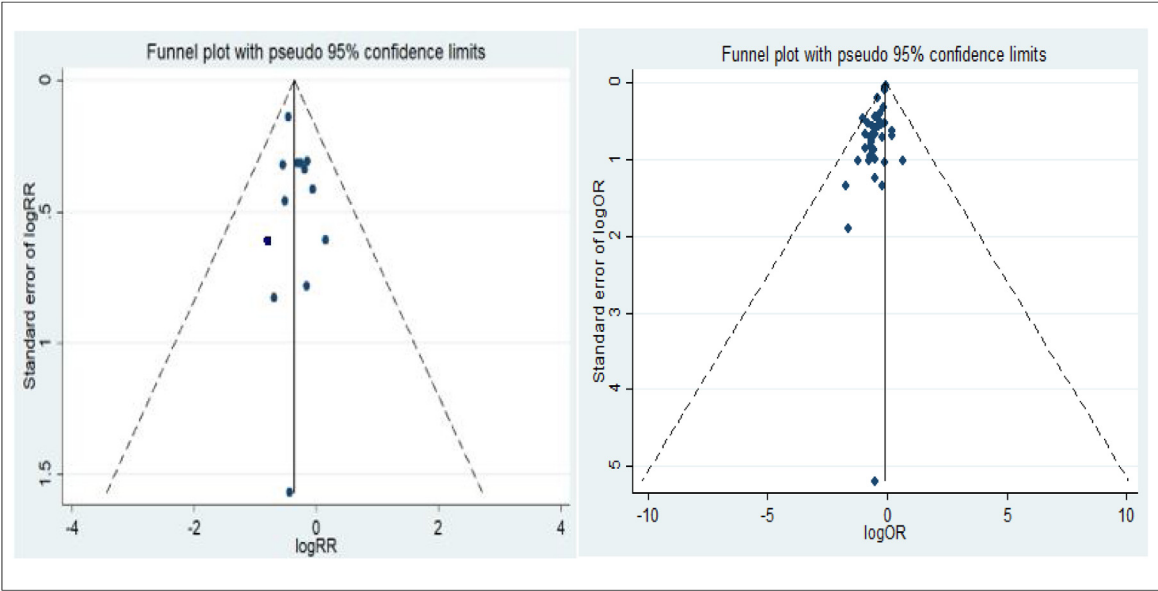


FIGURE 2
Funnel plot of included studies by study design

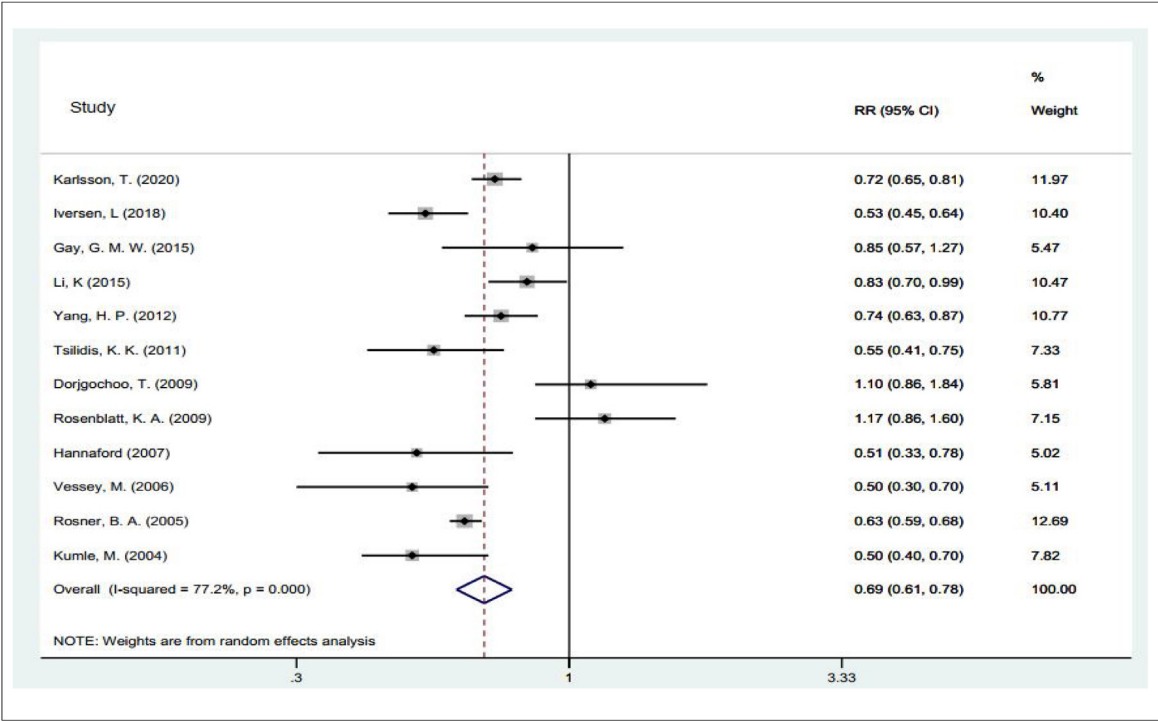


FIGURE 3
Forest plot of the association between ever-use compared with never-use of OCPs and ovarian cancer in cohort studies

sides of the vertical line showing the absence of publication bias. Based on Begg's ($P = 0.732$) and Egger's ($P = 0.602$) tests in cohort studies and Begg's ($P = 0.770$) and Egger's ($P = 0.133$) tests in case-control studies we found no evidence of publication bias.

Duration of OCPs use and ovarian cancer risk

The results of the relationship between duration of OCPs use and ovarian cancer stratified by duration of use (1–12 months, 13–60 months, 61–120 months and more than 120 months) in the cohort studies shown in [figure 4](#), a total of 12 studies were included in parts A and B. With respect to results, no significant association between duration of use 1–12 months 0.92 [95% CI: 0.82, 1.03] and duration of use 13–60 months 0.87 [95% CI: 0.73, 1.04], but there is a statistically significant inverse relationship between duration of use 61–120 months 0.62 [95% CI: 0.48, 0.81] and more than 120 months 0.51 [95% CI: 0.32, 0.80] and ovarian cancer. See supplementary [figure 2](#) a total of 42 studies were included in parts A (duration of use 1–12 months), B (duration of use 13–60 months), C (duration of use 61–120 months) and D (duration of use more than 120 months). Based on these results, the pooled OR of the case-control studies for duration of use 1–12 months was 0.82 [95% CI: 0.76, 0.89], duration of use 13–60 months was 0.71 [95% CI: 0.63, 0.81], duration of use 61–120 months was 0.59 [95% CI: 0.51, 0.70] and more than 120 months was 0.45 [95% CI: 0.39, 0.52] which represent 18%, 29%, 41% and 55% reduction in ovarian cancer risk, respectively. However, there is evidence of significant heterogeneity among cohort studies and case-control studies. Sensitivity analysis in the cohort studies showed that the studies by A, J, Shafrir, A. L, Rosner, B. A and Vessey, M. were sources of observed heterogeneity [24,26,27] and the case-control studies showed that the study by Ferris, J. S was sources of observed heterogeneity [28]. Based on Begg's ($P = 0.487$) and Egger's ($P = 0.157$) tests in cohort studies and Begg's ($P = 0.304$) and Egger's ($P = 0.126$) tests in case-control studies we found no evidence of publication bias.

OCPs and histological subtype of epithelial ovarian cancer

[figure 5](#) presents the results of the random-effects meta-analysis and the pooled adjusted RR among a total of five studies included for the relationship between OCPs and ovarian cancer stratified by the histological subtype of epithelial ovarian cancer (invasive, borderline) in the cohort studies. Based on the results, the pooled RR for invasive was 0.70 [95% CI: 0.56, 0.87] which represents a 30% reduction in invasive ovarian cancer risk in women who used OCPs, but no significant association between OCPs and borderline ovarian cancer 0.64 [95% CI: 0.31, 1.31]. [figure 6](#) presents the results of a total of ten studies included the relationship between OCPs and histological subtype of epithelial ovarian cancer in the case-control studies. Based on results, the pooled OR for invasive was 0.87 [95% CI: 0.80, 0.94] which

represents a 13% reduction in invasive ovarian cancer risk in women who used OCPs, but no significant association between OCPs and borderline ovarian cancer 0.90 [95% CI: 0.75, 1.08]. However, there is evidence of significant heterogeneity among cohort studies ($I^2 = 74.8\%$; $P = 0.001$) and case-control studies ($I^2 = 77\%$; $P = 0.006$) for invasive ovarian cancer, but for borderline ovarian cancer in case-control study we found evidence of moderate heterogeneity ($I^2 = 52.1\%$; $P = 0.100$). Sensitivity analysis in the cohort studies showed that the study by A, Fortner, R was source of observed heterogeneity [29] and the case-control studies showed that the study by Tung, K. H. was source of observed heterogeneity [30]. Based on Begg's ($P = 0.902$) and Egger's ($P = 0.395$) tests in cohort studies and Begg's ($P = 0.631$) and Egger's ($P = 0.282$) tests in case-control studies we found no evidence of publication bias.

Discussion

In the present study, 67 studies were identified and included from PubMed, ISI, Embase and Scopus for a meta-analysis that concerns the association between OCPs use and the risk of ovarian cancer.

Previous studies have shown different results. Some of them have confirmed that OCPs is a protective factor for ovarian cancer and some of them did not confirm this [17,31–34]. Basically, ovarian cancer depends on many factors, and in different studies, only some of these factors have been adjusted. This is one of the reasons for the different results. For example, residence in North America or northern Europe [35], and having a mother or sister with ovarian cancer is associated with an elevated risk [36], and that increasing number of pregnancies (whether or not full term) [37], increasing length of oral contraceptive use [38], and increasing duration of lactation are protective [39]. A history of breast or endometrial cancer appears to be associated with a slight elevation in risk [40]. Apart from oral contraceptive use, none of these characteristics can be modified easily [41]. Also, ethnic background, germline tumor suppressor gene mutations, unexplained infertility, obesity and positive family history as risk factors, and number of full-term pregnancies, time spent breastfeeding, tubal ligation and prior hysterectomy, and healthy diet as protective factors can play a role in ovarian cancer that is difficult to remove the effect of these confounders [42–44]. In addition, different studies differed in mean age, duration of OCPs use, and follow-up time of patients and study design which could be another reason for the difference in results between studies.

In this study, we examined the three sections including the effect of duration of OCPs use, and OCPs and intensity of ovarian cancer. Our result demonstrated that OCPs is a protective factor for ovarian cancer which represents a reduction in ovarian cancer risk in women who have ever used OCPs. This association was not observed with the low duration of use and only

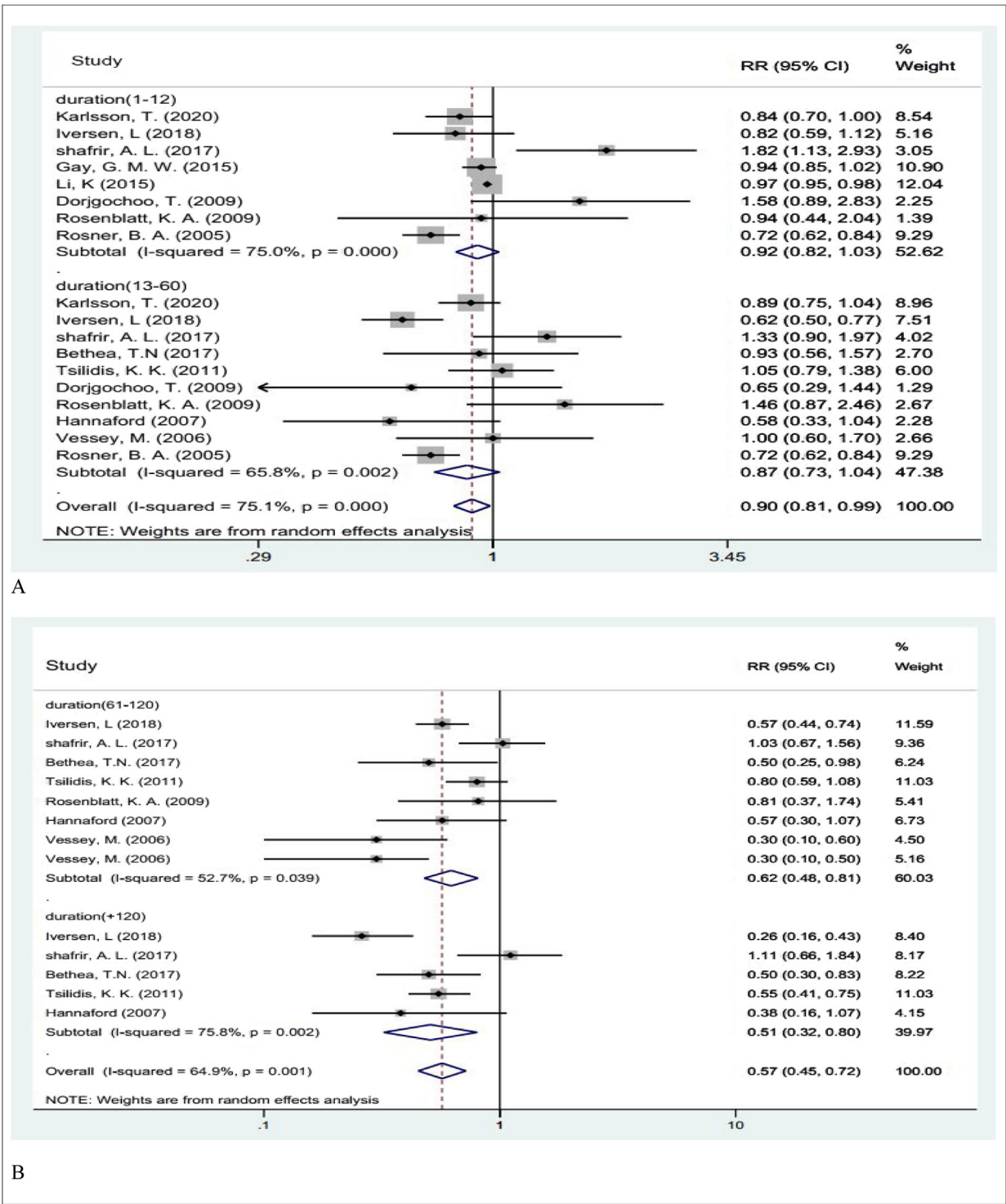


FIGURE 4
Forest plot of relationship between duration of OCPs use and ovarian cancer in cohort studies. A. duration of use 1-12 months, 13-60 months. B. duration of use 61-120 months and more than 120 months

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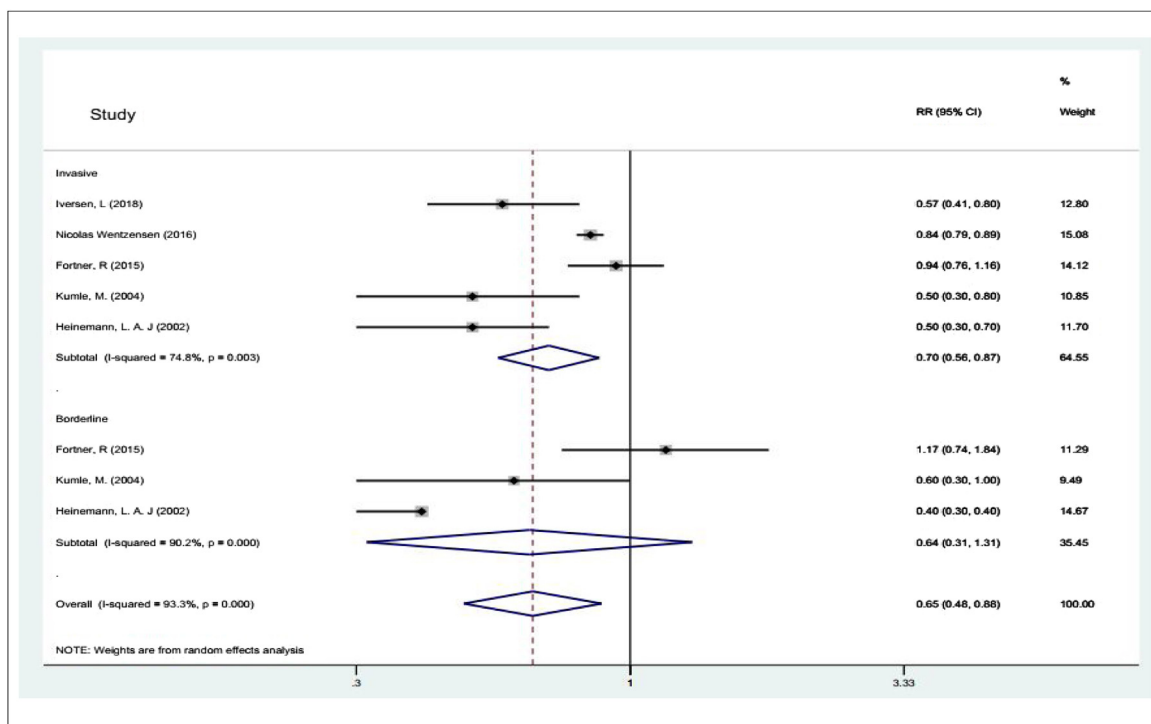


FIGURE 5
Forest plot of relationship between OCPs and histological subtype of epithelial ovarian cancer in cohort study

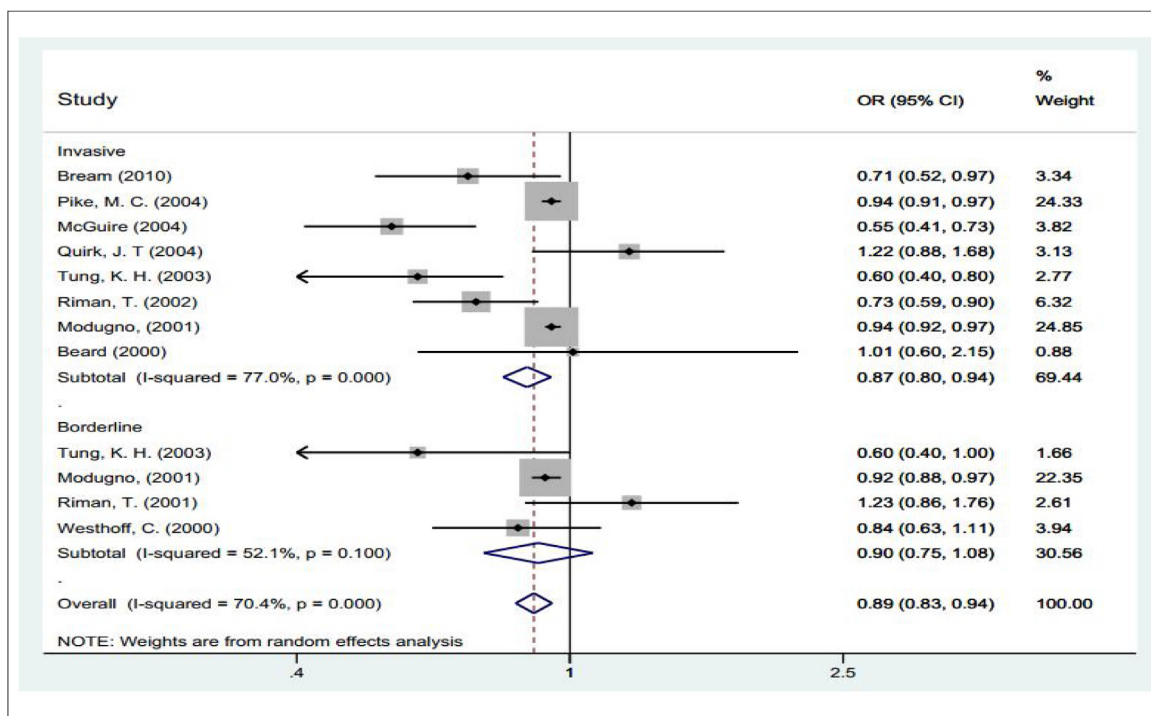


FIGURE 6
Forest plot of relationship between OCPs and histological subtype of epithelial ovarian cancer in casecontrol study

observed in the duration of use 61–120 months and more than 120 months.

This finding is consistent with previous studies [17,45–47]. The results of our study were similar to previous meta-analyses which reported OR forever use compared with never use of OCPs (OR 0.73, 95% CI 0.66–0.81) [48]. In R B Ness et al. population-based case control study, the risk of ovarian cancer was reduced by about 40 percent for oral contraceptive users overall after adjustment for age, gravidity, family history of ovarian cancer, and race [49]. This suggests that by adjusting various factors, the risk of ovarian cancer is reduced. Contrary to our study, in a follow-up OCPs users compared to never use, reported an increased risk of ovarian cancer with ≤ 6 months of OC use (HR 1.82; 95% CI 1.13–2.93). Alternatively, OCs may influence ovarian cancer development through mechanisms other than ovulation inhibition as, for example, OCs decrease ovarian production of androgens and higher levels of androgens may be associated with increased ovarian cancer risk [50,51]. It has been suggested that a decreased risk for ovarian cancer is most probably due to ovulations being prevented in oral contraceptive users [52]. This effect would be achieved by contraceptives inhibiting gonadotropin secretion both at the level of the pituitary gland and the hypothalamus [53].

Furthermore, our results showed a significant relationship between duration of OCPs use and ovarian cancer risk. Previous studies reported that the reduction in risk is greater when women used oral contraceptives longer [38,54,55]. The previous meta-analysis reported that there is a positive relationship between the duration of OCPs use and the degree of the protective effect reported [48].

The relative decline in ovarian cancer risk with increasing duration of use does not vary substantially by women's ethnicity, education, age at menarche, parity, family history of breast cancer, use of hormone replacement therapy, body mass index, height, or their consumption of alcohol and tobacco [56]. In Cristina Bosetti study a stronger reduction was observed for women who had used OCPs for > 5 years (OR = 0.50, 95% CI 0.33–0.76) compared to those who had used them for < 5 years. women who started using OCs at younger ages and reported a longer time since first use had an apparent stronger protection, which, however, appeared to be mainly attributable to a longer duration of use [57].

In relation to the histological subtype of epithelial ovarian cancer, our results indicated that the use of OCPs reduced the risk of invasive ovarian cancer but not borderline ovarian cancer. Our study confirms previous reports of an inverse association of invasive ovarian cancer risk with oral contraceptive use [58–60]. However some evidence reported that the use of OCPs had an inverse association with borderline ovarian tumors [61,62], but Ovarian borderline tumors seem to have similar epidemiological patterns with regard to reproductive events such as parity and lactation but the association was not dependent on the use of

OCPs [63,64]. The association between oral contraceptive (OC) use and ovarian cancer risk can vary depending on the histological subtype of the tumor [65]. In terms of borderline ovarian tumors (BOTs), these are a subgroup of ovarian malignancies with low malignant potential [66–68]. There is a assumption that use of OCP may be more effective in preventing invasive ovarian cancer compared to borderline ovarian cancer. This can be because of OCPs work by suppressing ovulation and reducing the number of ovulatory cycles a woman has, which can decrease the risk of developing certain types of ovarian cancer. Invasive ovarian cancer is more aggressive and has a higher likelihood of spreading beyond the ovaries, so the preventive effect of OCPs may be more significant in this type of cancer [69]. While the studies highlights the effectiveness of OCPs in reducing the risk of ovarian cancer, they does not specifically compare the effectiveness between invasive ovarian cancer and borderline ovarian tumors (BOT). What is clear is that borderline ovarian cancer is related to other factors such as lifestyle, cancer stage, age at childbirth and ovarian cysts [70].

In different studies, some factors have been adjusted and have caused different results. This may be because of the degree of risk reduction can vary based on the specific formulation of the OC, which has evolved over time [71]. Early OC formulations typically contained higher doses of hormones (both estrogen and progestin) compared to more recent formulations. The potency of these hormones in OCs can influence their impact on ovarian cancer risk [72]. A study published in the Journal of the National Cancer Institute found that OC formulations with high-progestin potency appear to be associated with a greater reduction in ovarian cancer risk than those with low-progestin potency. This suggests that the progestin component of OCs may play a key role in reducing ovarian cancer risk [73]. As for newer OC formulations, they often contain lower doses of hormones and may include different types of progestin compared to older formulations. The impact of these newer formulations on ovarian cancer risk is still being studied. However, it's important to note that even with these changes, the use of OCs is still generally associated with a reduction in ovarian cancer risk [74]. We used the Q-test and I^2 statistic to detect heterogeneity. There is significant heterogeneity among case-control studies. There can be various reasons for heterogeneity between studies. The first reason could be the difference in sample size of different studies. The second reason for heterogeneity could be the publication year. The eligible studies were published from 2000 to 2021. The third reason could be related to the geographical area of the published studies. Most of the studies were in the United States. The fourth reason, the differences might be due to the lack of adjustment on well-known risk factors. Also, differences in instrumental, methodology (because our meta-analysis was cohort and control case studies) and study population may be other sources of heterogeneity.

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Our study had some limitations. First, we used studies written in English language and exclude other languages. Second, the studies we reviewed were from 2000 to 2021 and we did not include studies before 2000. Third, some variables, such as age, that may affect heterogeneity due to limited information have not been studied. Another limitation of the current analysis is that the included studies almost never specifically reported the reasons for OCPs use. It is likely that most women used OCPs for contraception or to treat conditions such as dysmenorrhea, whereas few used them for ovarian cancer prophylaxis. Also, in this study we discussed about association between ever-use compared with never-use of OCPs and ovarian cancer while differences between studies might be explained by a differential impact of oral contraceptive use depending on recency of use, of OC type, of OC use duration.

Conclusion

Our analysis demonstrated a statistically significant reduction in ovarian cancer risk among women with a history of OCPs use,

with greater reductions in risk with a longer duration of use. This risk reduction is only observed in invasive ovarian cancer. The results of meta-analysis studies are valuable. Therefore, researchers can use this study for future research.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.bulcan.2024.05.010>.

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