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Original Article

# The Association between Oral Contraceptive Pills and Subtypes of Ovarian Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

**Introduction:** Limited studies have been conducted on the effect of oral contraceptive pills on the subgroups of ovarian cancer, so we decided that conduct a systematic review and meta-analysis to investigate the effect of preventive pills on ovarian cancer subgroups.
**Methods:** Scopus, PubMed, Web of Science and EMBASE were searched to identify studies on the association between OCPs and subtypes of ovarian cancer from January 1, 2000, through February 5, 2023. The pooled relative risk (RR) and odds ratio (OR) were used to measure this association.
**Results:** A total of 48 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], and the pooled OR of the case-control studies was 0.64 [95% CI: 0.59, 0.69]. For the association between OCPs and subtypes of ovarian cancer, there is a significant inverse association between OCPs and serous 0.72 [95% CI: 0.23, 0.82] and endometrioid 0.74 [95% CI: 0.64, 0.86], but no association between OCPs and clear cell 0.84 [95% CI: 0.60, 1.16] and mucinous 0.80 [95% CI: 0.63, 1.01].
**Conclusion:** This study shows a statistically significant inverse association between ever-use compared to never-use of OCPs and ovarian cancer risk. Also shows a statistically significant inverse association between serous and endometrioid cancer and OCPs, but no association between OCPs and clear cell and mucinous.

## Introduction

Ovarian cancer is a complex disease that is more common in postmenopausal women and is associated with poor survival. It is the sixth most common cancer and the fifth leading cause of cancer death in women in developed countries. Thus, although it accounts for less

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than a third of all female cancers, ovarian cancer deaths account for more than two-thirds of cancer deaths in women. Its prevalence is higher in Western Europe and North America than in Asia and Africa.[1] Although the incidence of ovarian cancer is less than that of breast cancer, it is three times more lethal. It is predicted that by 2040, the death rate of this cancer will increase significantly.[2] This cancer has a poor prognosis, and a five-year survival rate of 17% has been reported for the advanced stage of the tumor.[3] Its high lethality rate is due to the asymptomatic growth of the tumor, delay in diagnosis and lack of appropriate screening, which results in diagnosis in the advanced stages of the tumor.[2, 4, 5] The results of previous studies have shown that the ovarian cancer risk increases with age, family history, and BRCA1 gene mutation. Also, the risk of this cancer increases with fertility-related factors, such as: late pregnancy or not getting pregnant, late menopause, hormone therapy after menopause, and ovulation. Other modifiable metabolic and lifestyle risk factors include smoking, alcohol consumption, physical inactivity, unhealthy diet, low vitamin D levels, obesity, and diabetes.[3, 6-8] Epidemiological studies have repeatedly shown the effect of contraceptive pills in reducing the risk of ovarian cancer.[9-11] The exact mechanism is unknown, but there are many hypotheses in this regard. These hypotheses include: inhibiting ovulation, reducing exposure to gonadotropins, and increasing progesterone levels.[10] Although ovarian cancer was once investigated as a single entity, it can be divided into different histologic subtypes with different risk factors, cells of origin, molecular compositions, clinical features, and treatments. These histologic subtypes include epithelial cancers, which account for about 90% of ovarian cancers, and include serous, endometrioid, clear cell, and mucinous cancers. Only ten percent of them are non-epithelial cells.[12, 13] Serous tumors are classified into two categories: high-grade serous carcinomas (HGSC) and low-grade serous carcinomas (LGSC). HGSCs comprise 70-80% of epithelial ovarian cancer subtypes, whereas LGSCs comprise less than 5%. endometrioid, mucinous, and clear cell subtypes constitute 10, 3, and 10%, respectively8. Epithelial cell carcinoma is diagnosed at an average age of 63 years, and more than 70% of cases are diagnosed at advanced stages with a 5-year survival rate of 48%.[14] There is evidence that shows that birth control pills reduce ovarian cancer in subtypes of this cancer. A case-control study (2017) showed that the use of combined pills before term pregnancy also reduces the risk of epithelial cell by 9%. It also showed similar results regarding endometrioid, serous and clear cells.[15, 16] Studies have investigated the effect of preventive pills on all ovarian cancers, but the studies that have been conducted on the effects of the mentioned pills on the subgroups of ovarian cancer are limited, so we decided that conduct a systematic review and meta-analysis to investigate the effect of preventive pills on ovarian cancer subgroups.

## Methods

### Literature search strategy

A comprehensive search was conducted to identify studies on the association between OCPs and ovarian cancer and ovarian cancer subtype in several electronic databases including Scopus, PubMed, Web of Science

and EMBASE 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 reviewed the references of all articles to identify studies that were not included in the initial search. We conducted a systematic review and meta-analysis to realize the association between oral contraceptive pills and ovarian cancer and subtype of ovarian cancer in the general population not the subgroups of the population that have a higher risk of ovarian cancer, such as 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 to select studies that met the inclusion criteria by two authors (MA and FKH) independently. For studies that were difficult to select with only titles and abstracts, full-text assessment was conducted. Two authors (MA and FKH) reviewed the full text and decision was made for each study after reading the full text of eligible articles. The third author was consulted in case of disagreement or resolved through discussion. Totally, 2122 articles were retrieved (239 from PubMed, 305 from EMBASE, 1029 from Scopus and 549 from Web of Science. A total of 48 articles remained after the review, which is shown in Figure 1.

**Data Extraction**

We extracted the data of the articles using the data extraction form. 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. Data extraction was performed by two review authors (MA and FKH).

**Evaluating the Quality of Articles**

The quality of the studies was assessed using the Newcastle-Ottawa Quality Assessment Scale (NOS). 17. NOS has three domains, including: the selection of study groups, comparability of groups and description of exposure and outcome. This scale includes eight items and the star scores assesses the quality of each study. All items except the comparability domain have one star (the maximum score for the comparison domain is two). Totally, a total quality score is obtained for each study. Based on these criteria, study quality was rated from one star, very poor, to 10 stars, high quality. Studies are rated as high (7–10), medium (5–6) or low quality (< 4). Quality assessment was independently reviewed by two review authors (MA and FKH). In cases of disagreement, a third review author was consulted.

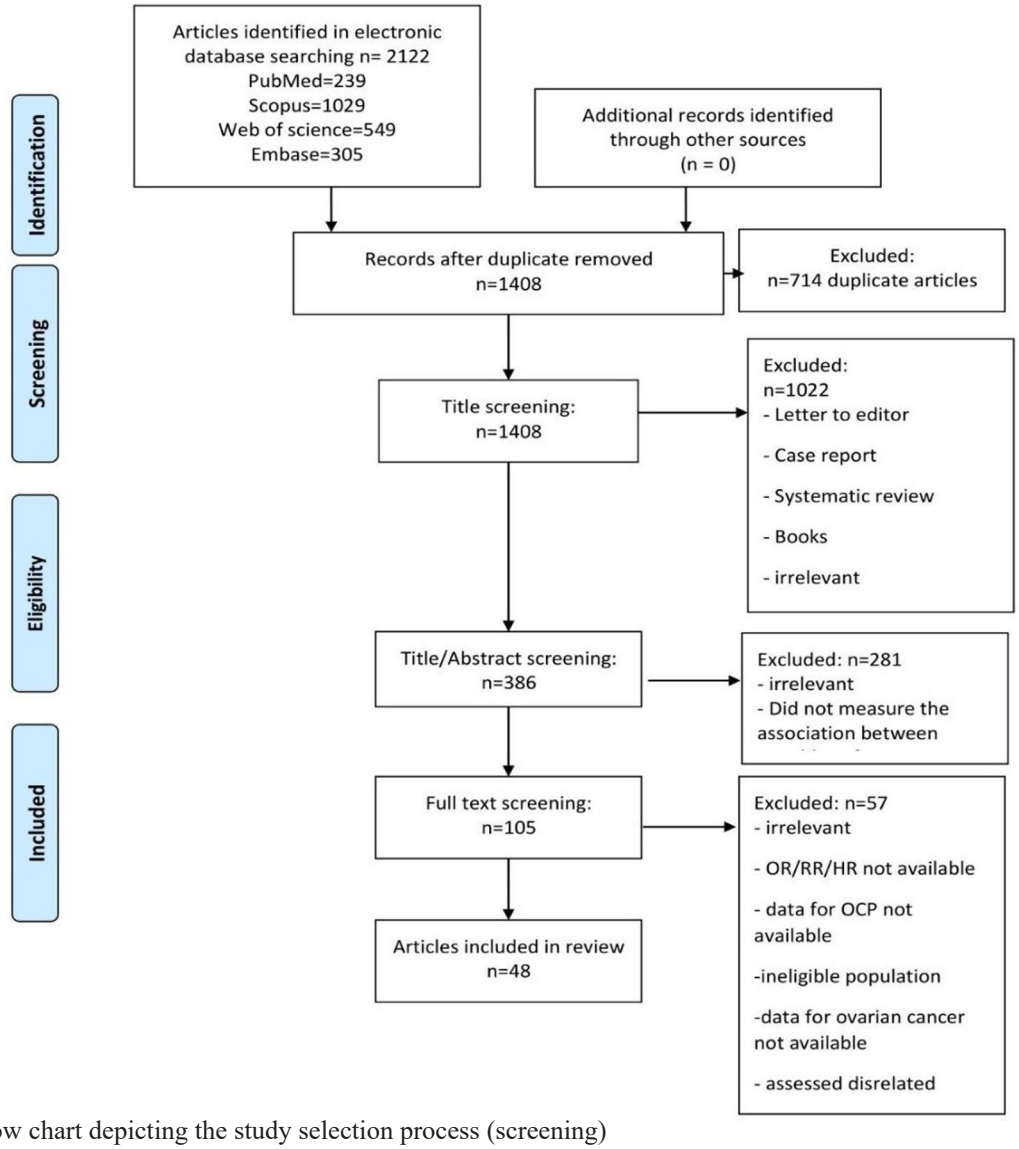


Figure 1. Flow chart depicting the study selection process (screening)

## Statistical analysis

The pooled OR and RR and the 95% confidence intervals were used to evaluate the association between OCPs and 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 carried out according to the subtype of ovarian cancer (serous, clear cell, endometrioid and mucinous). Leave-one-out sensitivity analysis was performed in order to identify influential studies in meta-analysis. Publication bias was determined using a funnel plot and Begg's and Egger's tests. Statistical significance is considered p-value <0.05. Stata software version 14 was used for analysis.

## Results

### Study characteristics

Figure 1 shows the search strategy and study selection algorithm. A total of 2122 studies were identified according to keywords and MeSH terms and Emtree terms. Subsequently, after removing duplicates and considering the inclusion and exclusion criteria, 1022, 281, and 57 studies were excluded after reviewing their titles, abstracts, and full-texts, respectively. Finally, 48 articles were included in the study and quality assessments were performed for all of them. Of these, fifteen studies were conducted in the United States, six studies in Denmark, seven studies in Italy, five studies in the United Kingdom, three studies in Australia, two studies in Sweden and other studies were in other parts of the world. High, medium, and low quality studies were considered with a cut-off score of 7 or higher, 5-6, and 4 or less, respectively. Twenty-two studies with a range of 7 to 10 were of high quality. Nineteen studies with a range of 5-6, were of moderate quality. Seven studies were in the range of 4 or lower that had low levels of quality. Characteristics of selected studies are summarized in Supplementary Table 1

### 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 the 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 considerable heterogeneity among studies ($I^2$=77.2%; P=0.0001). See Figure 4 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 considerable heterogeneity among case-control studies ($I^2$=90.6%; P=0.0001). Sensitivity analysis showed that there is no single study as a

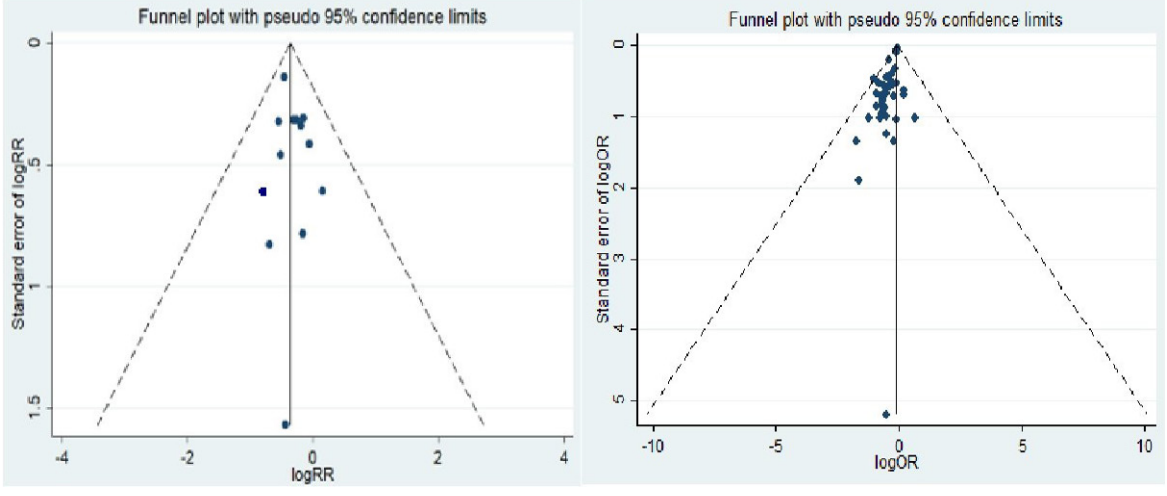


Figure 2. Funnel plot of included studies by study design.

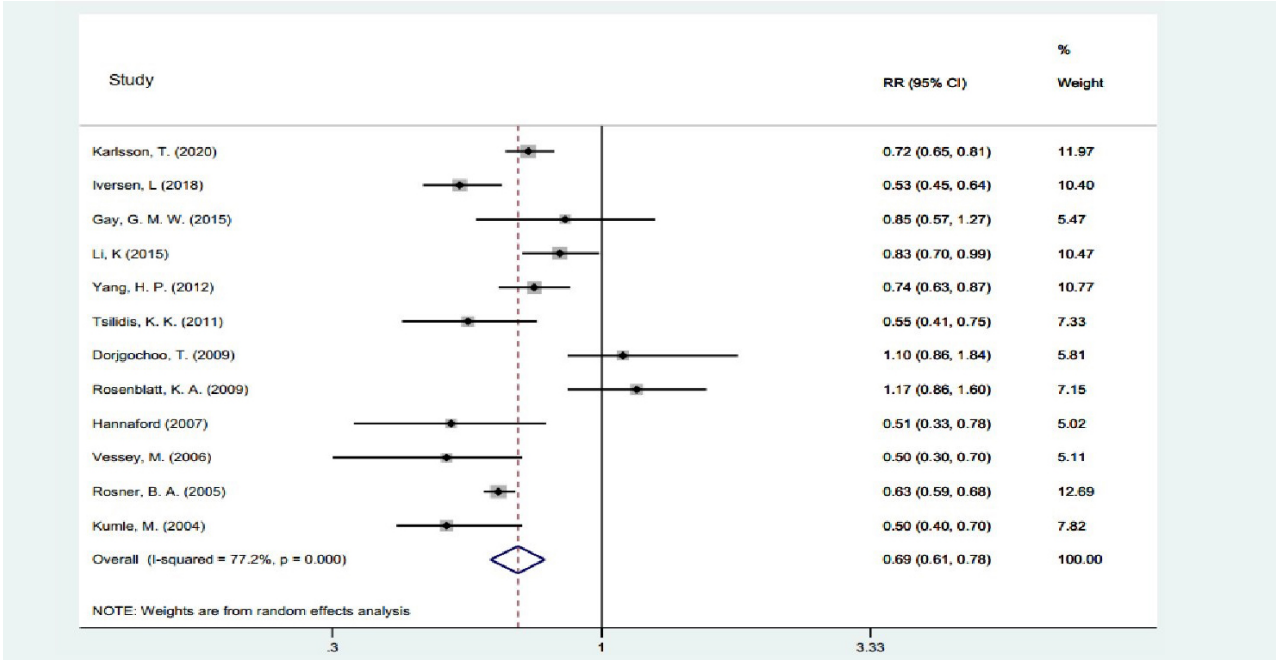


Figure 3. Forest plot of the association between ever-use compared with never-use of OCPs and ovarian cancer in cohort studies

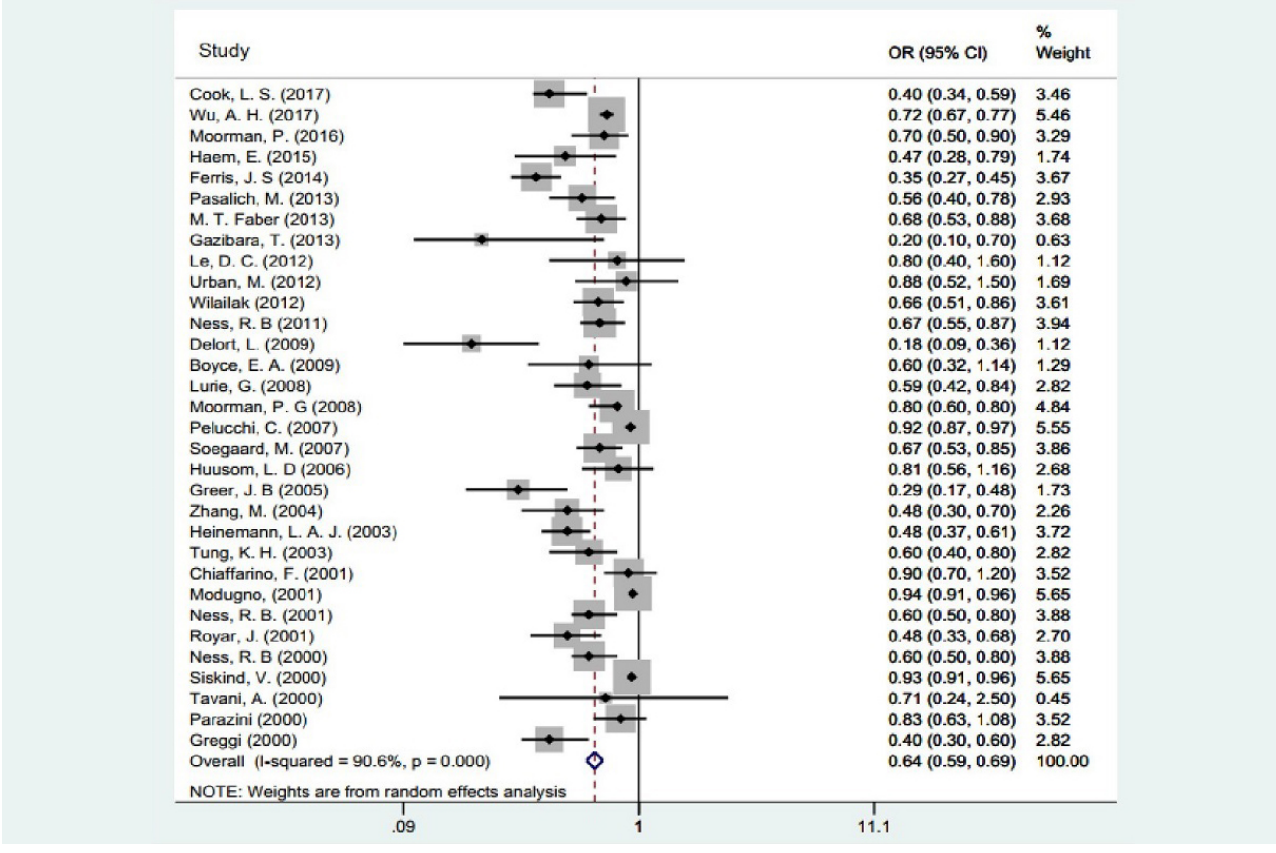


Figure 4. Forest plot of the association between ever-use compared with never-use of OCPs and ovarian cancer in case-control studies

potential source of heterogeneity in cohort and case-control studies. The publication bias was determined 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 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.

## OCPs and subtypes of ovarian cancer

Figure 5 shows the results of the random-effects meta-analysis and the pooled adjusted OR among a total of thirteen studies included for the association between OCPs and subtypes of ovarian cancer (serous, clear cell, endometrioid and mucinous). Based on the results, there is a significant inverse association between OCPs and serous 0.72 [95% CI: 0.23, 0.82] and endometrioid 0.74 [95% CI: 0.64, 0.86] which represent a 28% and 26% risk reduction of these ovarian cancer subgroups, respectively, but no association between OCPs and clear cell 0.84 [95% CI: 0.60, 1.16] and mucinous 0.80 [95% CI: 0.63, 1.01]. However, there is evidence of heterogeneity in subgroups serous ($I^2$=89.3%; P=0.001), clear cell ($I^2$=66.6%; P=0.030) and mucinous ($I^2$=69.3%; P=0.002), but for endometrioid there is no evidence of heterogeneity ($I^2$=25.9%; P=0.231).

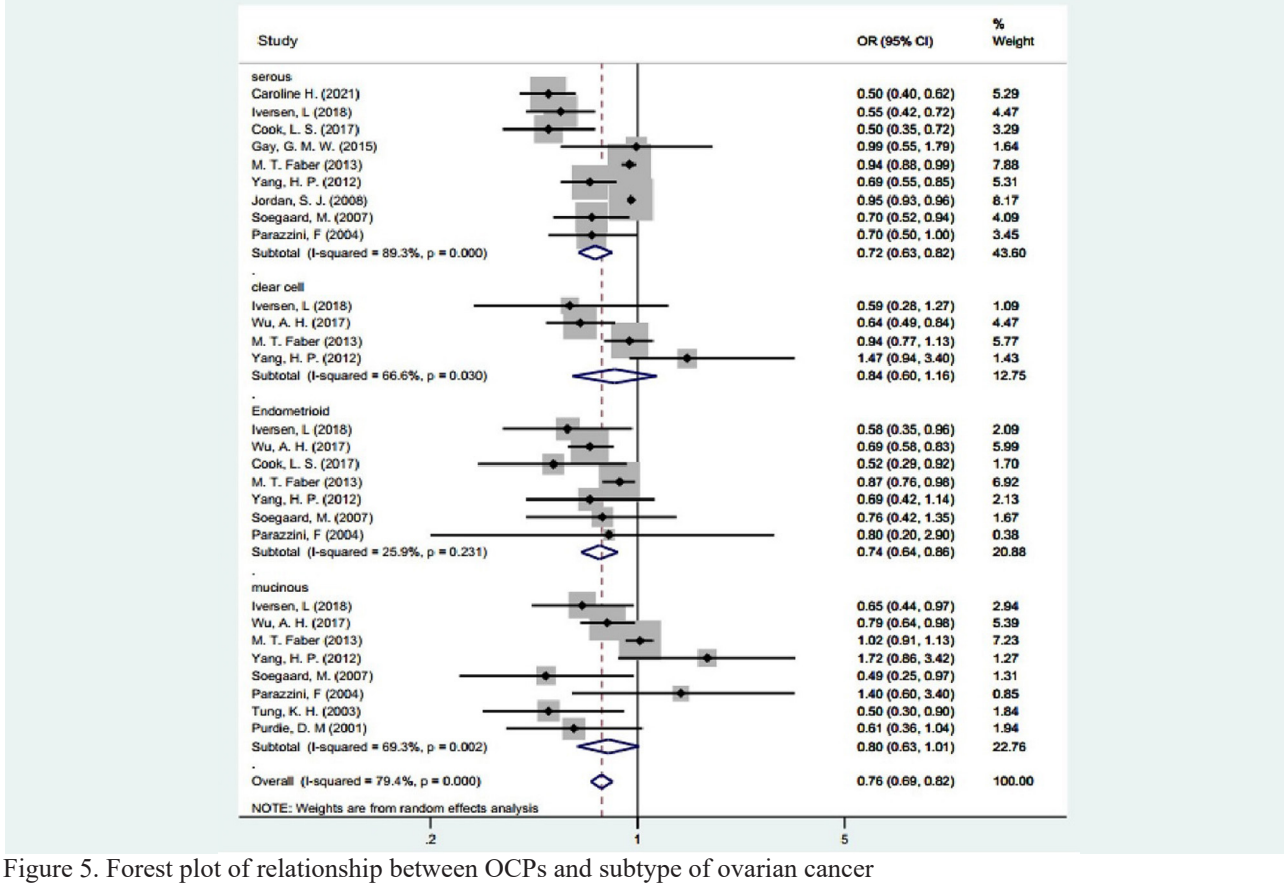

Figure 5. Forest plot of relationship between OCPs and subtype of ovarian cancer

Sensitivity analysis showed that the studies by Wu, A. H. and M. T. Faber were sources of observed heterogeneity18 19. Based on Begg (P=0.385) and Egger (P=0.138) tests, there was no evidence for publication bias.

## Discussion

In this meta-analysis, 48 studies were examined to determine the association between the use of OCPs and the risk of ovarian cancer and its subtypes. The results obtained from cohort and case-control studies showed a significant reduction in the risk of ovarian cancer in women who used OCPs. Also, regarding the subtypes, the results showed an inverse association between the use of OCPs and the two subtypes of serous and endometrioid (ENOC), but no significant association was found between the use of OCPs and the incidence of clear cell and mucinous subtypes.

The inverse association of OCPs with ovarian cancer has been seen by many studies,[20-23] but some of them did not show accurate evidence.[24]

The exact mechanism of the protective effect of OCPs on ovarian cancer has not been clearly defined. Genetic history, obesity, nutrition, smoking and alcohol consumption, pregnancy and breastfeeding, and hysterectomy are among the confounders that can affect this association. Also, people who used OCPs for a longer period showed a higher level of protection, and sometimes this effect remains for about 15 years after stopping use, which shows the effect of the duration and dosage of OCPs on this association.[25-27]

According to the behavior and growth of cells, ovarian cancer is divided into four subgroups: serous, endometrioid, clear cell, and mucinous. For the primary prevention of ovarian cancer, the use of OCPs has been shown to be one of the most effective methods, but for the subtypes, due to the difference in tissue origin, studies showed different results. According to the results of several studies, all kinds of OCPs, regardless of the specific formula, have the inverse effect on serous, endometrioid, and clear cell subtypes, but there is a difference of opinion regarding the mucinous subtype.[22, 27-30]

Our meta-analysis, similar to previous studies, revealed an inverse association between the use of OCPs in serous and endometrioid types. Studies have shown that high-grade serous carcinomas have a pseudo-endometrioid morphology,[31, 32] and this similarity can be one of the reasons for the same response to the use of OCPs. However, unlike some previous studies, the results of our study did not show an association between the use of OCPs and clear cell subtype. A recent study stated that compared to other subtypes of ovarian cancer, clear cell carcinomas have a unique epigenetic mechanism.[33, 34] This characteristic can be one of the explanations for the lack of association. Also, over time, with significant improvement in pathology, serum markers, and imaging, the diagnosis of subtype has become more accurate and has prevented the misclassification of cases. However, there were two studies as sources of heterogeneity for clear cell in our analysis that stated the inverse association between OCPs and clear cell tumors, and this could be another reason for the non-significance of the association investigated in the present study. The results of our study, similar to other studies, did not show an effect on the use of OCPs and reducing the risk of mucinous subtype.[26, 35] Due to the rarity of the mucinous subtype, most studies reported a small sample size of this

subtype, and insufficient sample size can be one of the reasons for ignoring the association of mucinous tumors. In general, mucinous tumors were not associated with factors related to ovulation (except for parity).[36]

## Study limitations

Our study had several limitations: The studies included in the meta-analysis were from 2000 to 2023, and we did not consider studies before 2000. Second, the studies that were reviewed were only English language studies, and we did not consider articles in other languages. Another limitation of the current study is that none of the studies we reviewed specifically mentioned the reasons for using OCPs. Probably because most of the uses of OCPs are for contraception or treat diseases like dysmenorrhea and few people used OCPs for ovarian cancer prophylaxis. The absence of a randomized trial to investigate the association between ovarian cancer and the use of OCPs was one of our other limitations. Biological plausibility, biological gradient, consistency across studies, the strength of association, coherence, and temporality are criteria for causal inference in epidemiology, this observed association between OCP and ovarian cancer fulfills many of them.

## Conclusion

In conclusion, this systematic review showed a statistically significant inverse association between ever-use compared to never-use of OCPs and ovarian cancer risk. Also shows a statistically significant inverse association between serous and endometrioid cancer and OCPs, but no association between OCPs and clear cell and mucinous. However, to better understand the effect of OCPs on this deadly disease, especially the clear cell and mucinous subtypes, it is recommended to conduct more extensive research with the aim of effective prevention.

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## Authors' contributions

MA. conducted research, FKH. provided essential reagents or provided essential materials. FKH. Performed the statistical analysis. FKH., MA., FSS., ZB., FE. And HA wrote the paper. FKH. had primary responsibility for final content; FKH. and MA had responsibility for all parts of the manuscript. All authors have approved the final article should be true and included in the disclosure.

## Conflicts of interest

The authors declare that they have no conflict of interest.

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Supplementary Table 1. Characteristics of studies

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Boyce, E. A. Et al 2009[1] | USA | case-control | identify risk factors for ovarian granulosa cell tumors (GCT) through a case-control study comparing women with GCT to women with epithelial ovarian cancers (OC) and general population (GP) controls. | Women with GCT and OC were identified from our hospital tumor board and the Massachusetts and New Hampshire Statewide Cancer Registries between January, 1988 and November, 2008. | 72 women with GCT, 1578 GP controls, and 1511 OC controls were identified. | NA | OR for oral contraceptive pills 0.32, 95% CI (0.17, 0.63) | Age and Race | 7 |
| 2 | Chiaffarino, F. et al 2001[2] | Italy | case-control | Menstrual, reproductive and hormonal factors have been related to ovarian cancer risk, but further quantification of their role in various populations is required. They have considered data on these issues from a uniquely large, multicentric case-control study from Italy. | Cases were below age 79, with incident, histologically confirmed epithelial ovarian cancer, and controls admitted between 1992 and 1999 to a network of hospitals in 4 Italian areas for acute, nonneoplastic, diseases. | Cases 1031 controls 2411 | Cases were 1031 women (median age 56, range 18-79 years) Controls were 2411 women (median age 57, range 17-79 years) | OR for OC users was 0.9,95% CI( 0.7-1.2) | Age and center | 5 |
| 3 | Caroline H. Hemmingsen[3] 2021 | Denmark | Case-control | To examine the association between reproductive factors and risk of non-epithelial ovarian cancer and to compare the associations with those in serous ovarian cancer | In the Danish Cancer Registry, all women with a diagnosis of ovarian cancer of germ cell, sex cord-stromal or serous histology during 1982–2016 were identified. | Cases n = 4854 Controls n= n = 72,810 | 20-39 | use of oral contraceptives decreased the odds for all three tumor types (germ cell: OR = 0.50, 95% CI: 0.29–0.87; sex cord-stromal: OR = 0.40, 95% CI: 0.13–1.22; serous: OR = 0.50, 95% CI: 0.40–0.62). | Adjusted for age (by design), calendar year, and highest attained level of education. | 7 |
| 4 | Cook, L. S. Et al 2017[4] | Canada | population-based case–control | Combined oral contraceptive (COC) use reduces epithelial ovarian cancer (EOC) risk. We therefore investigated the EOC risk associated with COC use, focusing on COC use before the first full-term pregnancy (FFTP). | This Canadian population-based case–control study (2001–2012) included 854 invasive cases/2139 controls aged X40 years who were parous and had information on COC use. | 854 invasive cases/2139 controls | 40-79 | OR for COC use exclusively before the first full-term pregnancy was 0.91, 95% CI (0.86–0.96). In contrast, per year of use exclusively after the FFTP was not associated with risk (OR = 0.98, 95% CI = 0.95–1.02). | study site age parity age at FFTP breastfeeding, first degree female family history of breast or ovarian cancer, tubal ligation and BMI | 7 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 5 | Delort, L. et al 2009[5] | France | Case-control | The aim of this study was to evaluate the role of factors influencing hormonal levels such as body mass index (BMI), BMI at age 20, waist-to-hip ratio (WHR), oral contraceptive (OC) use, and risk of ovarian cancer | Cases aged 24-84 years who had ovarian cancer with no BRCA mutation were enrolled in the COSA (Breast and Ovarian Cancer in Auvergne) program between November 1996 and November 1999 in different hospitals within the Auvergne region of France. A control population was gathered in 2005 and 2006 in a mammographic screening center | Cases (n=55) Controls (n=857) | Cases 58.4 years and controls 57.7 years. | OR for use of OCs was 0.18, 95% CI (0.09-0.36). | age | 5 |
| 6 | Dorjgochoo, T. et al 2009[6] | China | Prospective cohort | we examined the role of OC, IUD and TS use in the etiology of all cancers combined and in cancers of the breast, uterine body, ovary, thyroid, colon, rectum, liver, gallbladder, pancreas, stomach and lung | The Shanghai Women's Health Study is a population-based, prospective study of women 40–70 years of age at recruitment who resided in 7 urban districts of Shanghai, China. | 74,942 women | 53.4 | HR for 2 years of use OC was 0.65, 95% CI (0.29–1.44). | education, age at menarche, number of live births, BMI, regular exercise in the 5 years preceding the interview, cigarette smoking, menopausal status, and first degree family history of any cancer. | 7 |
| 7 | Faber, M. T. Et al 2013[7] | Denmark | population-based case–control | we examined the association between oral contraceptive use and risk of ovarian cancer. We collected comprehensive information on the estrogen and progestin doses derived from oral contraceptives and were thus able to examine the impact of cumulative intake of estrogen and progestin on ovarian cancer risk. | We used data from a population-based case– control study conducted in Denmark in 1995–1999 among women aged 35–79 years | 554 cases and 1,564 controls | 35–79 | OR for Exclusive use of combined oral contraceptives was 0.68, 95 % CI (0.53–0.88). OR for solitary use of progestin-only pills was 0.97,95 % CI (0.45–2.14). OR for mixed use of combined and progestin-only pills was 0.50, 95 % CI (0.28–0.87) | Age Pregnancy Breast feeding Menopausal status Hormone replacement therapy use Family history of breast and/or ovarian cancer Hysterectomy Tubal ligation Education Body mass index Smoking status | 6 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 8 | Ferris, J. S. Et al 2014[8] | USA | case–control | Oral contraceptive use has been consistently associated with a reduced risk of ovarian cancer in unrelated, average risk women; however little data exist on whether this benefit extends to higher risk women from cancer families. To examine this, we conducted family-based analyses using the Breast Cancer Family Registry. | We included participants from the three clinic-based sites of the Breast Cancer Family Registry (BCFR) (New York, Philadelphia and Utah) who had detailed information on ovarian cancer incidence within families). Overall, there were 2375 families from the three clinic based sites, and 101 families who have at least two sisters discordant for ovarian cancer status. | 389 cases, 5643 controls<br><br>109 cases, 149 unaffected sister controls | NA | OR for ever use of oral contraceptives in the multivariable generalized estimating equation model was 0.58, 95% CI (0.37, 0.91). | age, parity, race, age at last birth. | 5 |
| 9 | Gay, G. M. W. Et al 2015[9] | Singapore | retrospective cohort | The aim of this study was to assess associations of breastfeeding, adiposity and reproductive risk factors with ovarian cancer risk in a Singaporean population. | 28,234 women aged 50–64 who participated in the mammography project answered a detailed questionnaire on reproductive factors, as well as breastfeeding and oral contraceptive use. | 28,234 | 57.4 | HR for ever oral contraceptive use was 0.85, 95% CI (0.57, 1.27). HR for each year increase in total duration of oral contraceptive use was 0.94, 95 % CI (0.85, 1.02). | Adjusted for age, housing type and family history of breast cancer. Stratified by race BMI status and smoking status | 7 |
| 10 | Gazibara, T. et al 2013[10] | Serbia | case-control | The aim of this case-control study was to determine the risk factors for OC in the female population of Belgrade, Serbia. | Cases treated and followed in the Department of Gynecology and Obstetrics of the Clinical Center of Serbia and the Clinic of Gynecology and Obstetrics «Narodni Front» in Belgrade, between 2006 and 2008. The control group consisted of 160 women, double matched according to age and municipality of residence. | Cases (n = 80) Controls(n = 160) | Case 56.1 Control 56.7 | OR for oral contraceptives use was 0.2, 95% CI (0.1–0.7). | NA | 7 |
| 11 | Greggi, S. et al 2000[11] | Italy | Case -control | We conducted a case–control study to analyze risk factors for ovarian cancer. | Cases included 440 women (age range 13–80 years)with a histologically confirmed diagnosis of epithelial ovarian cancer who were admitted to the Gynecological Oncological Department of Gynecologic Oncology at the Catholic University Hospital in Rome, Italy. Controls were women admitted to the same hospital. | Cases 440 and 868 control | NA | OR for ever users was 0.4, 95% CI (0.3–0.6). | age | 6 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 12 | Greer, J. B. et al 2005[12] | USA | case-control | Oral contraceptives (OCs) have been consistently linked to reduced risk of ovarian cancer. The authors investigated whether OC efficacy might differ according to androgenicity by using data from a large, population-based, case-control study | Cases, aged 20 – 69 years, with epithelial ovarian cancer diagnosed and were ascertained from 39 hospitals in the Delaware Valley surrounding Philadelphia. Controls, aged 65 or younger, were ascertained by random-digit dialing and frequency matched to cases. | 568 cases and 1,026 controls | 20-69 | OR for Androgenic and non-androgenic OCs (0.52, 95% CI 0.35–0.76 and odds ratio 0.59, 95% CI 0.45–0.78, respectively). | Age, number of live births, family history of ovarian cancer, and tubal ligation. | 6 |
| 13 | Haem, E. et al 2015[13] | Iran | Case -control | This study evaluated the role of family history of cancer and gynecologic factors in relation to the etiology of ovarian cancer in a low socioeconomic population in Iran. | A total of 26788 women participated in the screening program of whom 76 had ovarian cancer. The control group included 26712 subjects. Women in this study were mainly from poor and low socioeconomic classes. The present study was conducted on women who resided in Tehran and other Iranian provincial capitals. | Case (n=76) control (n=26712) | The mean±SD age of subjects with ovarian cancer was 48±10.41 years; for healthy controls it was 45.73±10.15 years | OR for the use of oral contraceptive pills was 0.47, 95% CI(0.28-0.79). | NA | 4 |
| 14 | Hannaford 2007[14] | UK | Cohort | To examine the absolute risks or benefits on Ovarian cancer associated with oral contraception. | Directly standardized data from the Royal College of General Practitioners' oral contraception study. | Exposed: 744,000 person-years of observation Unexposed: 339,000 person-years of observation | 29 | RR for the use of oral contraceptive pills was 0.51, 95% CI(0.33-0.78). | Age, parity, smoking, social status | 4 |
| 15 | Heinemann, L. A. J. 2003[15] | German | Case-control | There has been convincing evidence from cohort and case-control studies that OC use reduces the risk of cancer of the uterine corpus and ovary. The effect of OCs with low estrogen content is less clear. We addressed this question within a case-control study | cases were women up to 65 years of age at the time of newly diagnosed cancer of the uterine corpus or ovary. For each cancer case four woman from the same region and of the same year of birth were searched for in the database of the German cohort study on Women's health as controls. | 419 cases 1518 controls | 51.4 for case 50.5 for control | OR for OC use was 0.48, 95% CI ( 0.37 to 0.61). | Adjustment for 10-year age groups and other co-variables: other sex steroids, parity, gynecological conditions | 6 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 16 | Huusom, L. D. et al 2006[16] | Den-mark | case-control | The aim was to examine risk factors for ovarian borderline tumors overall, and according to histological subtype (serous vs. mucinous), in a large Danish population-based case-control study | we included women 35–79 years of age. Controls were frequency-matched in 5-year intervals by using the age distribution of women with ovarian cancer (1987–92) registered in the Danish Cancer Registry, which contains information on all persons in Denmark diagnosed with cancer since 1942 | Cases (n=202) Controls (n=1564) | 35–79 | OR for use of OC was 0.81 ,95% CI(0.56 – 1.16). | Adjusted for age (in categories), childbirth (ever/never), number of additional births (linear), age at first birth (linear), breast-feeding (linear), smoking (ever/never), intake of milk (linear) | 6 |
| 17 | Iversen, L. et al 2018[17] | Den-mark | prospective, nationwide cohort study | To investigate the association between contemporary combined hormonal contraceptives (including progestogen types in combined preparations and all progestogen-only products) and overall and specific types of ovarian cancer. | All women aged 15-49 years during 1995-2014 were eligible. Women were excluded if they immigrated after 1995, had cancer (except non-melanoma skin cancer), had venous thrombosis, or were treated for infertility before entry (final study population included 1 879 227 women). | 1879227 | 15-49 | Compared with never users, reduced risks of ovarian cancer occurred with current or recent use and former use of any hormonal contraception (relative risk 0.58 (95% confidence interval 0.49 to 0.68) and 0.77 (0.66 to 0.91), respectively). | Adjusted for calendar year, parity, age, education, tubal sterilisation, hysterectomy, endometriosis, polycystic ovary syndrome, and family history of breast or ovarian cancer. | 7 |
| 18 | Jordan, S. J. et al 2008[18] | Austra-lia | Case-control | We have therefore investigated the risk factors for fallopian tube and primary peritoneal cancers individually and have compared them with those for invasive serous ovarian cancer using data from an Australian case control study conducted between 2002 and 2005. | The Australian Ovarian Cancer Study (AOCS) was an Australia-wide population-based case-control study. women aged 18–79 years with suspected epithelial ovarian cancer were recruited primarily in gyneco-logic-oncology units by research nurses. | incident invasive serous ovarian (n 5 627), 1,508 control women | For Controls 56.4 . for Ovary 59.7 | OR for Per year of use of hormonal contraceptives was 0.95, 95% CI (0.93–0.96). | Parity, history of breast or ovarian cancer in first degree relatives, age, education | 8 |
| 19 | Karlsson, T. Et al 2020[19] | UK | Prospective and retrospective cohort | The purpose of this study is to clarify the time-dependent effects between long-term oral contraceptive use and cancer risk | We performed an observational study in 256,661 women from UK Biobank, born between 1939 and 1970. Information on cancer diagnoses were collected from self-reported data and from national registers until March 2019. | 256,661 women | 56 | OR for long-term oral contraceptive use was 0.60, 95% CI(0.48–0.75). | Age, Year of birth (YOB), smoke, BMI, Townsend's deprivation index TDI, age at menarche, had menopause, had hysterectomy, number of live births, hormone replacement therapy. | 7 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | Kumle, M. et al 2004[20] | Sweden Norway | prospective Cohort | We present here results from a large, population-based, prospective study: the Norwegian– Swedish Women's Lifestyle and Health cohort – with detailed assessment of HC use and complete follow-up | The risk of ovarian epithelial neoplasia following use of hormonal contraceptives (HC) was examined in data from the Norwegian– Swedish Women's Lifestyle and Health cohort including 103 551 women aged 30–49 years in 1991–92 | 103 551 | 30-49 | RR for ever use of hormonal contraceptives was 0.6, 95% CI(0.5–0.8). | Age, parity, , use of postmenopausal hormone therapy, menopausal status, country (Sweden/Norway | 7 |
| 21 | Le, D. C. Et al 2012[21] | Vietnam | case-control | we conducted a case–control study to examine the association between reproductive and menstrua factors and ovarian cancer among women in Northern Vietnam. | We analyzed 262 ovarian cancer patients recruited from 27 hospitals in 12 provinces and Ha Noi City from April 2001 to May 2006, plus 755 controls matched by age and residential address. | 262 case 755 controls | NA | OR for ever use of Oral contraceptives was 0.8, 95% CI (0.4–1.6). | age, education level (primary school, basic school, secondary school or higher), parity (para 1–5), body mass index (BMI; b20.00, 20.00–22.45, 22.50–24.99, ≥25.00 kg/m2) , menopausal status, age at menarche (≤13, 14–15, ≥16 years) | 4 |
| 22 | Li, K. Et al 2015[22] | UK | Prospective cohort | In the present study, we aimed to build an ovarian cancer risk prediction model for women in Western Europe using data from the European Prospective Investigation into Cancer and Nutrition (EPIC), with particular interest in examining whether the discriminatory power could be improved by considering more epidemiological risk factors. | The EPIC study is a multicenter, population-based cohort study including 4520 000 participants (367 903 women), recruited between 1992 and 2000 in 23 study canters across 10 European countries | (n = 20 2206) | 46–55 | HR for ever use of OC in a full model was 0.83, 95% CI (0.70, 0.99). HR for duration of OC use (1-year increase) was 0.97, 95% CI (0.95, 0.98). | competing risk of death or other incident cancer | 6 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 23 | Lurie, G. Et al 2008[23] | USA | case-control | The objective of this analysis was to re-examine time related characteristics of OC use while accounting for the confounding effects of formulation potency and age at first and last pregnancy | Cases were histologically confirmed, age 18 years or older. controls were randomly selected from participants in an annual survey of representative households, and in Los Angeles20 they were selected by random-digit dialing. | 813 cases 992 controls | 18<_ | OR for ever use of oral contraceptives was 0.59, 95% CI ( 0.42–0.84).OR for 5 or more years after initiation of OC use was 0.18, 95% CI (0.08–0.39). | Adjusted for age, ethnicity, education, family history of ovarian cancer, tubal ligation, gravidity, age at last pregnancy, menopausal status and type of menopause, age at menopause, and use of menopausal hormone | 7 |
| 24 | Modugno, F.et al 2001[24] | USA | case-control | Differences in histology among the subtypes of epithelial ovarian tumors suggest possible differences in their etiologies. We examined reproductive risk factors for epithelial ovarian cancer according to histologic subtype and tumor invasiveness | Briefly, cases were women age 20 to 69 who were diagnosed with incident epithelial ovarian cancer within the 6 months before interview. Controls age 65 or younger were ascertained by random digit dialing and frequency matched to cases by 5-year age groups and 3-digit telephone exchanges | Cases recent diagnosis of epithelial ovarian cancer (n 767) were compared to community controls (n 1367) frequency matched by age | 20-69 | OR for use of OC for invasive ovarian cancer and Borderline ovarian cancer was (0.94, 95% CI 0.92–0.97, and 0.92, 95% CI 0.88–0.97 respectively). | adjusted for age, number of live births, years of oral contraceptive use, years of non contraceptive estrogen use and months breastfed as continuous variables, tubal ligation, hysterectomy, family history of ovarian cancer, and family history of breast cancer as dichotomous variables, and ethnicity as a polychotomous variable | 7 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 25 | Moorman, P. G.et al 2016[25] | USA | case-control | This analysis examined associations between number, duration, and timing of reproductive events and epithelial ovarian cancer among African-American women. | cases were African American/ black race, aged 20-79 years, diagnosis of invasive, epithelial ovarian cancer, no prior history of ovarian cancer, and ability to complete an interview in English. Eligibility criteria for controls were similar to cases plus they must not have had bilateral oophorectomy or a prior history of ovarian cancer. | 641 cases 752 controls | 20-79 | OR for OC user was 0.7,95% CI (0.5-0.9). | * OR adjusted for study site, age, family history of breast or ovarian cancer in first degree relative, age at menarche, tubal ligation, body mass index, and number of full-term pregnancies. | 7 |
| 26 | Moorman, P. G.et al 2008[26] | USA | case-control | In this paper, we report data from a case-control study of ovarian cancer in North Carolina to evaluate whether associations with pregnancy and OCs differ by menopausal status. | cases were aged 20–74 years, had no prior history of ovarian cancer, and resided in the 48-county study area. Controls from the same 48-county region were identified by using random digit dialing and were frequency matched to cases. | These analyses were based on 896 cases (314 premenopausal, 582 postmenopausal) and 967 controls (360 premenopausal, 607 postmenopausal) | 20-74 | OR for use of OC in premenopausal women was 0.5, 95% CI (0.3, 0.8). And for >10 years of use was 0.3, 95% CI (0.2, 0.6). | Adjusted for age (cubic spline), race (African American, non–African American), family history of breast or ovarian cancer, age at menarche, tubal ligation, infertility, body mass index, number of full-term pregnancies, and age at last pregnancy. | 7 |
| 27 | Ness, R. B.et al 2011[27] | USA | Case-control | Few studies have examined methods of contraception, beyond oral contraceptives (OCs) and tubal ligation, in relation to ovarian cancer risk. | Both invasive and borderline tumors were included. Eligible women were at least 25 years of age and within 9 months of initial diagnosis. Controls consisted of women at least age 25 who lived in telephone exchanges wherein cases resided. | 900 cases 1800 population-based control | 25<_ | OR for ever use of OCs versus never use was 0.75, 95% CI (0.61-0.93). | Adjusted for age, number of pregnancies, race, infertility, family history of ovarian cancer, ever use of oral contraceptives, ever use of IUDs, ever use of barriers, tubal ligation, and vasectomy | 7 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 28 | Ness, R. B. Et al 2000[28] | USA | case-control | We report the results of a population-based, case-control investigation designed to address further the impact of dose of oral contraception on its association with ovarian cancer. | Cases were women aged 20–69 years who had been diagnosed with epithelial ovarian cancer within the 6 months prior to interview. Controls aged 65 years or younger were ascertained by random digit dialing and were frequency matched by 5-year age groups and three-digit telephone exchanges to cases | Cases 767 Controls 1367 | 20-69 | OR for use of OCP was 0.6, 95% CI (0.5-0.8). | Adjusted for age, number of pregnancies, family history of ovarian cancer, and race | 6 |
| 29 | Ness, R. B.et al 2001[29] | USA | Case-control | Here we report results from a population-based, case control study in which we examined the specificity of contraceptive effects on risk reduction for ovarian cancer. | Cases were women aged 20–69 years who had been diagnosed with epithelial ovarian cancer within the 6 months prior to interview. Controls aged 65 years or younger were ascertained by random digit dialing and were frequency matched to cases. | cases (N = 727) with community controls (N = 1,360). | 20-69 | OR for ever use of oral contraceptives for contraception, was 0.6, 95%Cl (0.5–0.8). | Adjusted for age, pregnancies, race, and family history of ovarian cancer. | 6 |
| 30 | Pasalich, M. Et al 2013[30] | China | Case-control | To investigate the association between reproductive factors and the risk of ovarian cancer among southern Chinese women. | Cases were incident patients who had been histopathologic ally diagnosed with an epithelial ovarian tumor. Controls were patients who were recruited from wards of the departments of physiotherapy, respiratory disease, gastroenterology, ophthalmology and orthopedics | 500 incident ovarian cancer patients and 500 controls | Cases 59.0±5.6 Controls 59.7±6.4 | OR forever use of oral contraceptives was 0.56, 95% CI (0.40 to 0.78). | Age at interview, smoking status, alcohol drinking, education level and body mass index. In addition, mutual adjustment was made for parity, oral contraceptive use, hormone replacement therapy, menopausal status, hysterectomy and family history of ovarian and/or breast cancer. | 6 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| | Parazzini 2000[31] | Italy | Case-control | To investigate the association between reproductive factors and the risk of ovarian cancer. | This study was applied in Italy between 1983 and 1991 on 971 ovarian cancer cases and 2758 control women to computation the multivariate relative risk estimates, and population attributable Risks (PARs). | 971 ovarian cancer cases and 2758 control women | NA | OR for ever use of oral contraceptives was 0.83, 95% CI(0.63 to 1.08). | Age, parity, calendar year of interview, age at menopause, family history of breast or ovarian cancer, green vegetable consumption, fat intake score | 7 |
| 32 | Parazzini, F et al 2004[32] | Italy | Case-control | The aim of the study was to examine the overall risk factors for epithelial ovarian cancer according to histologic subtypes. | Data separated by histological subtypes collected in the framework of a large case-control study on ovarian cancer conducted in Italy were analyzed. The cases were women below the age of 75 years, admitted to a network of hospitals in Milan. | Cases mucinous tumor (n = 52), serous tumor (n = 680), endometrioid tumor (n = 41). Controls were 2758 | 0-75 | Oral contraceptive use was associated with OR lower than unity for serous (OR = 0.7) and endometrioid (OR = 0.8) ovarian cancers but not for mucinous (OR = 1.4) and other histologies (OR = 1.6) | terms for age, education, parity, and family history of ovarian cancer. | 5 |
| 33 | Pelucchi, C. Et al 2007[33] | Italy | Case-control | Several factors that are related to ovulation are relevant to ovarian cancer risk, but it is unclear whether they can be included in a single definition of years of ovulation | In the first study, data were collected in the greater Milan area, women aged 22 to 74 years .The second study was conducted in 4 Italian areas. In both studies, cases were women who were admitted for incident, histologically confirmed ovarian cancer to the major teaching and general hospitals in the areas under surveillance; control subjects were women who were admitted to the same hospitals as case | 1822 histologically confirmed cases and 4631 control | 22-74 | OR for oral contraceptive use, was 0.92, 95% CI(0.87-0.97). | ORs adjusted for study, calendar year at interview, age, center, education, hormone replacement therapy use, and family history of ovarian and breast cancer in first degree relatives. | 4 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 34 | Purdie, D. M. et al 2001[34] | Austra-lia | Case-control | The proposition that mucinous ovarian cancer has an etiology distinct from that of other histologic types has been evaluated using data from a population-based case-control study of epithelial ovarian cancer conducted in 1990-1993 among Australian women aged 18-79 years. | Women diagnosed in 1991 and 1992 were recruited in New South Wales and Victoria; in Queensland, where the cancer registry was an additional source, women diagnosed in these 2 years and also in 1993 and the latter part of 1990 were eligible for enrollment. | Mucinous (n = 114) Controls (n = 853) | 18-79 | OR for ever oral contraceptive use was 0.61, 95% CI (0.36, 1.04) for mucinous ovarian cancer. | age in years, age squared, body mass index, smoking, and alcohol consumption | 6 |
| 35 | Rosenblatt, K. A.et al 2009[35] | China | Cohort | No associations were observed between OCs and the risk of all cancers combined or for any of the nine other cancers. It is unlikely that the use of OCs has contributed to the temporal trends in cancer incidence in China in recent decades. | From 1998 to 1991, an in-person baseline interview was administered to approximately 267,400 female textile workers in Shanghai, China. The cohort was followed until July 2000 for incident cancer cases. | Included in this analysis were the 258,956 women who answered the question on ever use of oral contraceptives and had at least one month of follow-up time. Of these women, 37,319 had ever used oral contraceptives | NA | RR for ever use of OCs was 1.17, 95% CI (0.86- 1.60). | Adjusted for parity and age using linear splines unless otherwise noted | 4 |
| 36 | Rosner, B. A.et al 2005[36] | USA | cohort | we evaluated a range of models regarding ovarian cancer incidence within the prospective Nurses' Health Study and Nurses' Health Study II. We began with the established reproductive risk factors and sought a succinct and relevant summary applicable to ovarian cancer. | The Nurses' Health Study (NHS) cohort was established in 1976, when 121,700 female U.S. registered nurses between the ages of 30 and 55 years responded to a mailed study questionnaire. Data on parity were updated through 1984. The Nurses' Health Study II (NHS II) cohort was established in 1989, when 116,678 women 25–42 years of age returned a baseline questionnaire. | 78,504+ 106,618 | 25-55 | RR for use of oral contraceptives for 5 years before age 30 to age 70 was,0.63 (32-41%). (0.59 to 0.68) . (Similar results were obtained with oral contraceptive use after age 30.) RR for five years of use was 0.72, (0.62- 0.84). | Age at first birth, age at menarche and birth index, parity | 4 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 37 | Royar, J. Et al 2001[37] | German | Case-control | Our study thus provides the first European data on the relationship between ovarian cancer risk and low-dose oral contraceptives with 35mg or less ethinyl estradiol content. | We attempted to recruit all women up to the age of 75 years who were newly diagnosed of either primary invasive ovarian cancer or borderline tumor. For each case we attempted to recruit 2 population controls individually matched by age and study area. | 282 cases 533 controls | The mean age of the patients and the controls were 55.2 years (range 21–75, SD 12.4) and 55.1 years (range 23–75, SD 12.2), respectively. | OR for per year of use was 0.93, 95% CI (0.90–0.96). OR being 0.86, 95% CI (0.77– 0.94), 0.91, 95% CI(0.83–1.00), and 0.95,95% CI (0.91–0.99) per year of using OC containing <35 mg, 35–<50 mg, and >50 mg ethinyl estradiol, respectively. | parity, breast-feeding , first degree family history of ovarian cancer, tubal ligation and hysterectomy. | 6 |
| 38 | Siskind, V. Et al 2000[38] | Australia | case-control | we examined the effects of oral contraceptive use after controlling for estimated number of ovulatory cycles | three Australian states that included 794 women with epithelial ovarian cancer and 853 community controls for whom we had adequate contraceptive and reproductive histories. | 794 women with epithelial ovarian cancer and 853 community controls | NA | OR for use for up to 1 year was, 0.57 95% CI (0.40-0.82). OR for use before the first pregnancy was 0.95, 95% CI (0.87-1.03). | number of ovulatory cycles parity, smoking, and history of pelvic surgery. | 7 |
| 39 | Soegaard, M. Et al 2007[39] | Denmark | Case-control | The aim of the study was to examine the overall risk factors for epithelial ovarian cancer and according to histologic subtypes. | Cases were women 35 to 79 years of age and recruited from 16 gynecologic departments in Denmark. A random sample from the general female population, 35 to 79 years of age in the study area, was drawn by means of the computerized Civil Registration System. | 554 cases 1,564 controls | 35-79 | OR for use of oral contraceptives was 0.67, 95% CI (0.53-0.85). | age, pregnancy and additional pregnancies. | 7 |
| 40 | S Wilailak. et al 2012[40] | USA | Case-control | To evaluate the effect of depot medroxyprogesterone acetate (DMPA) in protecting against epithelial ovarian cancer (EOC) and to evaluate factors associated with the risk of EOC. | Three hundred and thirty patients with EOC (‘cases’) and 982 matched controls were recruited from the 12 hospitals. Cases were newly diagnosed patients with EOC, demonstrated pathologically. Controls were age-matched patients admitted to different wards in the same hospital. | Cases= 330 Controls=391 | 20-70 | OR for use of combined oral contraceptive pills (OR 0.66; 95% CI 0.51–0.86) | sociodemographic factors, personal history, current disease, family history, reproductive history, contraceptive history and use of female hormones | 8 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 41 | Tavani, A. Et al 2000[41] | Italy | Case-control | As women with a family history of ovarian and/or breast cancer possibly inherit genetic changes that alter their risk of ovarian cancer, other established risk factors for ovarian cancer may influence the risk differently in women with and without a family history of the disease. | Cases were under 75 years, with incident, histologically confirmed epithelial ovarian cancer, and controls were under 75 years, admitted to hospitals for non-malignant, non-hormone-related conditions, who had not undergone bilateral oophorectomy. | Cases 971 controls 2758 | <75 | OR for use of oral contraceptive in woman with family history of ovarian or breast cancer and without family history were 1.4 ,95% CI (0.4-4.4) and 1.2,95% CI (0.9-1.7) respectively. | Age Area of residence | 5 |
| 42 | Tsilidis, K. K. Et al 2011[42] | Denmark France Germany Greece Italy Netherlands Norway Spain Sweden UK | Prospective cohort | We examined the associations of oral contraceptive use and reproductive factors with ovarian cancer risk in the European Prospective Investigation into Cancer and Nutrition. | The European Prospective Investigation into Cancer and Nutrition (EPIC) includes approximately 370 000 women and 150 000 men. The participants were recruited between 1992 and 2000 in 23 centers in 10 European countries. | 327,396 | The mean age at recruitment and diagnosis for the ovarian cancer cases was 55 and 60 years, respectively | HR for used oral contraceptives for 10 or more years 0.55, 95% CI(0.41-0.75). | smoking status, body mass index, unilateral ovariectomy , simple hysterectomy, menopausal hormone therapy, age at menarche , number of full-term pregnancies and age at menopause. | 7 |
| 43 | Tung, K. H. Et al 2003[43] | USA | Case-Control | In this paper, we emphasize histologic-specific differences in the association of reproductive factors with the risk of epithelial ovarian cancer. | Cases were 18 or more years of age, having no prior history of ovarian cancer, and having at least one intact ovary for controls. Population controls were randomly selected from a from lists of participants in a Department of Health statewide annual survey in Hawaii. | 558 histologically confirmed epithelial ovarian cancer cases and 607 population controls | The mean age at diagnosis for women with borderline tumors (48 years of age) was younger than the mean age for women with invasive tumors (56 years of age). | Inverse relations were generally similar for borderline 0.6 (0.4, 1.0) and invasive tumors0.6 (0.4, 0.8) | age, ethnicity, study site, education, pregnancy status, and tubal ligation. | 7 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 44 | Urban, M. Et al 2012[44] | United Kingdom | case–control | to investigate the relationship between use of oral and injectable hormonal contraceptives and cancers of the breast, cervix uteri, ovary, and endometrium. | Cases for this study were women with a newly diagnosed invasive breast, cervical, ovarian, or endometrial cancer. Controls consisted of women diagnosed with cancer types that have no known relationship to oral or injectable contraception, based on data from the International Agency for Research on Cancer. | Controls 1,492 case 182 | 49 case 48 control | For durations of use ≥5 y versus never use, the ORs of ovarian cancer were 0.60 (0.36–0.99, p = 0.04) for oral and/or injectable contraceptive use | age at diagnosis, year of diagnosis, education, tobacco smoking, alcohol consumption, parity/age at first birth, number of sexual partners, urban/ rural residence, and province of birth. | 6 |
| 45 | Vessey, M. Et al 2006[45] | UK | Prospective cohort | We examined cancer incidence in relation to oral contraceptive (OC) use in the Oxford Family Planning Association contraceptive study | The study includes 17032 women, recruited at family planning clinics at ages 25–39 years between 1968 and 1974, who were using OCs, a diaphragm, or an intrauterine device. | 17032 | 25-39 | RR for OC use was 0.5, 95% CI(0.3-0.7). | age, social class, smoking, body mass index, parity, height, age at first-term pregnancy, age at first marriage | 4 |
| 46 | Wu, A. H. Et al 2017[46] | USA | Case-control | we examined the effects of age at first and last births and age at use of COCs using data from studies conducted in Los Angeles County, California, USA | Cases were eligible for inclusion in the study if they were between 18 and 74 years of age at diagnosis and up to age 79 for cases diagnosed between 2003 and 2008. Controls were individually matched to cases on race/ethnicity and year of birth (±5 years). | (1,632 cases, 2,340 controls) | 18-74 | OR for use of COC before age 25 was 0.62, 95% CI (0.52-0.80) and for ages 25-34 was 0.71, 95% CI(0.60-0.83). | (family history of ovarian cancer, history of endometriosis, talc use, tubal ligation, infertility, number of incomplete pregnancies, age at menarche, BMI, education, SES, age and type of menopause, type and duration of menopausal hormone therapy. plus number of births (continuous) and age at first birth category (continuous). | 7 |

Continued from Supplementary Table 1.

| row | Author/year | country | Study design | Study purpose | Sample characteristics | Sample size | Mean Rang\ age | Main measurements | confounder | NOS |
|---|---|---|---|---|---|---|---|---|---|---|
| 47 | Yang, H. P. Et al 2012[47] | USA | prospective cohort | To further assess these relationships, we examined risk factors for ovarian carcinoma by histological subtype in the large prospective NIH-AARP Diet and Health Study with on average 10 years of follow-up. | In brief, the NIH-AARP Diet and Health Study was established in 1995– 1996 by inviting 3.5 million AARP members aged 50–71 years in six states. | 169,391 | 62.8 | risk for epithelial ovarian carcinoma inversely associated with OC use (RR = 0.74; 95% CI: 0.63-0.87). Ever OC users were at significantly decreased risk for serous (RR = 0.69, 95% CI: 0.55, 0.85) and other epithelial cancers (RR = 0.70, 95% CI: 0.52- 0.94) | age, parity and menopausal hormone therapy Unknown/missing set as a separate category within each factor. duration of menopausal hormone therapy use, excluded dichotomous ever/never use variable accordingly, as done for parous for categories of parity | 6 |
| 48 | Zhang, M. Et al 2004[48] | China | case-control | A case-control study was conducted to investigate the effects of reproductive and dietary risk factors on ovarian cancer risk in China | Cases were histologically confirmed epithelial ovarian cancer. Controls were without neoplasm and long-term dietary modifications. | Cases (n = 254) Controls (n = 652) | 62.8 | OR for oral contraceptive use was 0.48, 95% CI (0.3 – 0.7). | Estimates from fitting logistic regression models include terms for age, locality (urban, rural), education, family income, BMI, total energy intake, tobacco smoking ,alcohol consumption, ovarian cancer in first degree relatives. | 5 |

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