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THE ASSOCIATION BETWEEN ASSORTED HORMONAL CONTRACEPTIVE METHODS AND ADVANCED-STAGE EPITHELIAL OVARIAN CANCER: A SYSTEMATIC REVIEW

CHENG CHENG

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SYSTEMATIC REVIEW

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DEDICATION

To Weihua Li

Thank you for being a role model and giving me the example of unconditional love and support to guide me through life. Thank you for your genuine encouragement in my academic pursuit, even if it keeps us afar. I cannot ask for a better mother or a better mentor.
I love you.

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SYSTEMATIC REVIEW

by

CHENG CHENG
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TABLE OF CONTENTS

Background.....	6
Literature Review	6
Public Health Significance	4
Descriptive Epidemiology	5
Research Objectives	5
Specific Aim	5
Methods	6
Study Design	6
Key Word Search	6
Study Subjects	7
Eligibility Criteria.....	7
Data Collection	7
Human Subjects Considerations	10
Results	11
Quality Assessment	11
Study Characteristics	12
Discussion.....	14
Strengths and Limitations.....	15
Conclusion.....	17
Appendix A	18
Appendix B.....	21
Appendix C.....	22
Appendix D	24
References	25

BACKGROUND

Literature Review

Epithelial ovarian cancer, the most lethal of the gynecological cancers¹⁷, is typically diagnosed at advanced stages¹⁹. Women diagnosed with advance-staged (i.e., stage III and IV according to the International Federation of Gynecology and Obstetrics) epithelial ovarian cancer are more likely to have recurrent episodes within 18 months¹⁷. According to a 2012-2016 case analysis conducted by the surveillance, epidemiology, and end results, or SEER program, the incidence of ovarian cancer was 11.4 per 100,000 women in all races per year with the highest incidence in non-Hispanic whites, of 11.9 per 100,000 women and the lowest incidence in Asians / Pacific Islanders women, of 9.4 per 100,000 persons per year. The mortality incidence was 7.0 per 100,000 persons in all races per year in the United States⁴³.

Many cancers originate from genetic mutations, including ovarian cancer²⁶. Studies indicate epithelial ovarian tumors develop in two distinctive pathways with type I arising from ovarian epithelium and inclusion germ cell layers and type II deriving from fallopian tubular epithelial origins. The mutation product of p53 results in various clinical symptoms and end points^{20,33}. Clinicians also have recognized the association of BRCA1 and BRCA2 genes with both of ovarian cancer and breast cancer². A multivariate analysis conducted by Gallagher et al.¹⁴ revealed that multiple organ systems are prone to be involved during an ovarian malignancy, because there is a lack of distinct symptomatology, which allows the cancer to spread prior to detection.

Numerous studies also have indicated assorted risk factors contribute to the incidence and survival rate identifying racial/ethnic differences, genetic risk factors as the BRCA genes, and nongenetic risk factors including reproductive and hormonal factors, environmental and lifestyle factors. The racial differences in incidence and survival rates within the United States resemble the global pattern, with the highest incidence and mortality rates among non-Hispanic whites, followed by Hispanics, and the lowest incidence and mortality rates are among non-Hispanic blacks and Asians^{25,43}. The exact causes of racial disparities of epithelial ovarian cancer is still left unclear, the reasons are likely to be diverse^{5,21}.

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) both stimulate the ovaries to produce steroids in females²⁵. Simon et al (1983) concluded, based on in vitro studies, that these hormones contribute to the malignant epithelial tumors. Aside from the oral contraceptive use research conducted by CDC³², several hormonal factors also have been associated with the development of epithelial ovarian cancer. Studies have suggested an association between lower parity and an increased risk of developing aggressive epithelial ovarian cancer^{6,23}. Women with longer ovulatory history are exposed to a greater risk of advanced epithelial ovarian cancer as well²³. Women who have had a hysterectomy or experienced early-age menopause are at reduced risk of epithelial ovarian cancer³. Menstrual cycle irregularity and younger age at menarche also have been associated with lower risk of deaths from high-grade epithelial ovarian cancer²⁹.

From 1990s to 2000s, there had been seven new hormonal contraceptive regimens approved by the Federal Drug and Administration (FDA). The birth control shot, depot medroxyprogesterone acetate (DMPA) along with the arm implant were introduced in the 1990s. The intrauterine device (IUD) that releases levonorgestrel daily was approved in 2000. The following year, transdermal patch and vaginal ring were brought to the market. In 2003, combined oral contraceptive were introduced to the public and became common and popular^{7,39}. All these various types of hormonal contraceptives differ in effectiveness and availability, but they all introduce hormones to regulate ovulation and inhibit body's natural cyclic hormones to prevent pregnancy⁴⁴.

Decades of research suggest that there are many factors related to the prognostic characteristics of epithelial ovarian cancer; in fact, abundant sources have investigated the association of hormonal factors to epithelial ovarian cancer. Thigpen et al (1993) analyzed a pooled database from the Gynecologic Oncology Group and specified age as a determinant for pathological outcome in which women aged 69 and older had a poorer prognosis than younger women³⁴. One of the early studies, conducted in the 1980s by the United States Centers for Disease Control and Prevention (CDC), the Cancer and Steroid Hormone Study (CASH), revealed that regular users of contraceptive pills for 10 years or more had a lower lifetime risk of epithelial ovarian cancer³⁸. Based on such findings, a World Health Organization collaborative study further indicated that there were no remarkable differences in the level of protection based on the levels of dosage in contraceptive pills²⁷. Furthermore, a meta-analysis conducted by Wheeler et al (2019) identified that any type of intrauterine device they investigated was associated with a lower incidence of ovarian cancer³⁶.

Public Health Significance

Ovarian cancer is the fifth leading cause of death from cancer among adult females and the second most common gynecologic cancer in the United States⁴². Ovarian cancer usually goes undetected until it has already developed into an advanced stage and has spread to the pelvis and abdomen. The survival rate for ovarian cancer is generally as high as 92% when detected in the early stage, however, due to the non-specific symptoms of ovarian cancer and the lack of early detection tests, the 5-year survival rate for advanced stages can be low as 30% in the United States⁴⁰. Moreover, about 75% of patients are diagnosed at advanced stages because of the asymptomatic nature of EOC¹⁹. EOC is the most predominant pathological subtype accounting for more than 90% of all ovarian cancer³³. According to the global statistics report published by the World Ovarian Cancer Coalition in 2018, the risk of ovarian cancer increases in more developed countries and urbanized areas, though the survival rates in higher income countries vary by stage of diagnosis, awareness of the disease, attitude and accessibility towards treatment⁴¹.

As noted, the development of EOC is associated with hormone-related risk factors, disparity in the EOC development may be induced by various hormonal contraceptives¹³. This study was designed to enhance our understanding of the hormonal factors associated with the development of EOC by examining across various contraceptive methods. Identifying unique and shared risk factors that contribute to increased risk for EOC will allow public health professionals targeted programs to combat this deadly cancer.

Descriptive Epidemiology

As stated above, multiple studies, including population-based studies have been conducted that reveal an association between use of hormonal contraceptives and the development of EOC. All studies considered for this review were screened using predetermined inclusion and exclusion criteria. This systematic review analyzed all eligible studies, examined the study measures used, and evaluated the validity and reliability of each source.

Research Objectives

The overall goal of this study is to systematically analyze peer reviewed publications, published between 2009 and 2019, that examined associations between hormonal risk factors related to various types of contraceptive use and the subsequent development of epithelial ovarian cancer.

Specific Aim

To identify potential hormonal risk factors induced by various hormonal contraceptive use that influence the development of advanced stage II, III and stage IV (FIGO) epithelial ovarian cancer.

METHODS

Study Design

To meet the study objective and aim, I completed a systematic literature review. All articles have been identified through a key word search (see Key Word Search next). The purpose of this study is to methodically identify publications between 2009 and 2019, which include analytical studies that examined advanced stage II, III and stage IV epithelial ovarian cancer and use of hormonal contraceptives. The 10-year span for publications was set considering the innovative emergence of hormonal contraceptive methods³⁸. This systematic review will analyze the differences in the development of ovarian cancer across various types of hormonal contraceptive. Acquired data were secondary, sources were identified from online academic databases, including using pre-determined inclusion and exclusion criteria.

All selected articles have been reviewed systematically. Articles that employed nonrandomized samples and meta-analyses were analyzed using the Newcastle-Ottawa Scale (NOS). The NOS has two assessment scales that have been designated for case-control studies and cohort studies. The cross-sectional studies for this review were analyzed based on the case-control studies considering the analytical parameters. The instruments used the intraclass correlation coefficient (ICC)- and normative score to evaluate the extracted data for internal reliability through Spearman rho to calculate the between-scale correlation¹⁰.

Key Word Search

Epithelial ovarian cancer, hormonal contraceptive, contraceptive skin patch, birth control pill, vaginal ring, hormone-releasing contraceptive coils, hormone injection, hormonal birth control implant, tubal ligation.

Study Subjects

1. **Subjects:** published peer-reviewed articles
2. **Time:** January 1, 2009 to December 31, 2019
3. **Study design:** systematic review

Eligibility Criteria

1. Inclusion

- a. Study design: randomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and statistical analyses.
- b. Research type: quantitative research
- c. Study outcome measures: incidence rate, incidence rate ratio, percentage attributable risk, hazards ratio, odds ratio, mortality risk
- d. Risk factors: hormonal contraceptive methods including birth control pills, contraceptive skin patch, vaginal ring, hormone-releasing contraceptive coils, intrauterine device, arm implant, tubal ligation, and birth control injection.

2. Exclusion

- a. Sources: non-English sources
- b. Research type: qualitative research

Data Collection

Each database has been reviewed for journal titles, abstracts, and full-text articles to avoid compromising sensitivity. All reference lists from the selected journal articles were analyzed for potential inclusion of studies missed by the initial search. The selected studies

were screened for potential duplications of study populations in the Method section. In this case, the study with higher level of evidence, greater number of patients, longer follow-up period, or more thorough reporting of primary outcomes of interest would be used¹⁵. All the eligible peer-reviewed publications were recorded in an accrual log to extract the valid information suitable for the study objectives (See Accrual Log for Literature Review below).

Accrual Log for Literature Review

[illegible]

Human Subjects Considerations

Due to the characteristic of systematic-review analysis, the human subject's safety considerations will not be applied to this study.



Completion Date 21-Aug-2018
Expiration Date 20-Aug-2021
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RESULTS

A total of 24 records were identified from the primary searches; ten full reports were included in this review after full-text assessment^{3,8,9,11,13,16,18,31,35,37}. Seven of the ten comprised studies that investigated the association between oral contraceptive^{3,8,9,11,13,18,31,35,37}, the most common form of hormonal contraceptive³⁹, and the development of epithelial ovarian cancer ([Appendix A](#)). The three other reports examined tubal ligation³¹, depot medroxyprogesterone acetate (DMPA)³⁷ and IUD¹⁶, and were grouped for assessment in [Appendix B](#).

Out of the seven studies investigating the association between oral contraceptive use and the development of epithelial ovarian cancer ([Appendix A](#)), three yielded odds ratio, two yielded hazards ratio, one relative ratio, and one investigated mortality risk and overall survival time as measures of risk. For the studies that examined hormonal contraceptives other than OC ([Appendix B](#)), two studies yielded odds ratio and one used hazards ratio as measures of risk.

Quality Assessment

The ten selected studies had been divided into two groups based on the NOS scale for the study characteristics – cohort studies and case-control studies. The quality assessment for cohort studies have been recorded in [Appendix C](#), and [Appendix D](#) concludes the quality assessment for case-control studies and the derivatives.

As can be seen in Appendices C and D, the selected cohort studies in [Appendix C](#) are of higher quality based on NOS assessment scale than the selected cross-sectional studies in

[Appendix D](#). Only one out of the five selected cohort studies, published by Fortner et al (2015), did quality for full-credit because it did not conclude statement regarding adequacy of follow-up¹¹. Three of the five selected cross-sectional studies ([Appendix D](#)) defined the exposure using written self-reports^{8,11,31}, which can potentially lead to information bias¹.

Furthermore, three out of the five cross-sectional studies did not report or discuss the non-response rate^{8,31,37}; non-response bias can also impact the reliability for the included studies²⁹.

Study Characteristics

Seven out of the ten studies investigating the association between oral contraceptives and advance-stage ovarian cancer are summarized in [Appendix A](#). [Appendix B](#) summarizes the other three forms of hormonal contraceptives. Five of the ten studies were cohort studies ([Appendix C](#)), five were case-control studies or derivatives of case-control studies ([Appendix D](#)). Three out of the seven studies examining the association between oral contraceptive use and epithelial ovarian cancer analyzed odds ratio as the outcome measure^{8,9,11}; two analyzed hazards ratio as the outcome measure^{3,35}; one measured mortality risks¹⁸; and one measured relative risk¹².

Five out of the seven studies reported in [Appendix A](#) concluded a protective effect between oral contraceptive use and the development of ovarian cancer - three reported an association between OC use and lowered risk in ovarian cancer development^{9,11,35}; two reported an association between OC use and improved cervical cancer survival outcomes^{13,18}. In contrast, two other studies included in Appendix A. Chen et al (2016) described an

association between OC users and higher frequency of ovarian cancer compared to non-OC users⁸ and Besevic et al, (2015) reported an association between longer duration of OC use and worse ovarian cancer survival³.

The studies investigating the association between other methods of hormonal contraceptives and advance-stage ovarian cancer have been summarized in [Appendix B](#). One study, which investigated depot medroxyprogesterone acetate (DMPA), the birth control shot³⁷, reported a protective association between DMPA and EOC. Huang et al (2014) examined intrauterine devices (IUDs) and tubal ligation; their study results revealed a nonsignificant association between IUD use and ovarian cancer risk¹⁶ in contrast tubal ligation was association with reduced ovarian cancer risk³¹. Two of the three studies were based on case-control studies^{31,37} and the third study was cohort study¹⁶. Two out of the three studies investigating other forms of contraceptives measured odds ratio, the other use analyzed hazards ratio for the study outcome measure.

DISCUSSION

Seven out of the ten articles summarized in the current report described a significant reduction in risk of aggressive epithelial ovarian cancer development with the use of hormonal contraceptives in the form of oral contraceptives, tubal ligation, Depot medroxyprogesterone acetate (DMPA), Intrauterine Device (IUD). Specifically, a protective association of ever use and longer duration of hormonal contraceptive and the development of EOC was reported among these seven studies that concluded reduced risk. Two studies reported a nonsignificant result, but the direction of these associations suggested a protective association between contraceptive use and development of aggressive epithelial ovarian cancer^{9,16}. The study conducted by Besevic et al (2015), is the only study that reported a harmful effect³.

Based on the European Prospective Investigation into Cancer initiative (EPIC), they conclude that longer durations of OC use was associated with shorter survival time for advanced-stage EOC patients (>10 years vs \leq 1 year of use: HR=1.74 95% CI=1.10–2.75, Ptrend=0.01)³. However, Tsilidis et al.³⁵ and Fortner et al.¹³ also measured the association between oral contraceptive use and the risk of ovarian cancer using the EPIC data; both obtained conflicting results. Tsilidis et al concluded that women who used oral contraceptive for 10 or more years had a significant 45% (HR, 0.55; 95% CI, 0.41–0.75) lower risk compared with users of 1 year or less (P-trend, <0.01)³⁵. Fortner et al obtained a significant association between long duration of OC use and the risk of advanced-stage EOC¹³. The discrepancy between the Besevic study and the latter two studies was the identification of confounders in the process of statistical adjustment. Besevic et al controlled

for age, BMI, tumor stage, and smoking history; Tsilidis et al controlled for age, BMI, menopausal status and parity; Fortner et al controlled for age, menopausal status, parity, and menstrual cycle irregularity. The discrepancy of covariates may introduce a confounding bias into the association, therefore, Besevic concluded an inverse association when all three studies were derived from the same dataset.

All of selected studies suggested for a protective association between hormonal contraceptives and the development of EOC controlled for, menopausal status, parity, and age^{8,9,11,13,16,18,31,35,37}, which have all been reported as potential confounders for birth control use and epithelial ovarian cancer¹³. According to CDC (2019), women with higher socioeconomic status tend to have better survival and less incidence due to access to healthcare⁴². Furthermore, previous research has demonstrated that age, lower parity and post-menopausal status has been associated with higher risk epithelial ovarian cancer²⁸.

Out of the ten reported articles, four types of hormonal contraceptives were included, many other common forms of birth control such as birth control implant and birth control patch, have yet to be investigated with the association of EOC. Excluding OC, this study identified only one article investigating the association between each form of hormonal contraceptives and EOC.

Strengths and Limitations

As with most research, there are strengths and limitations of this review. One of the strengths of this systematic review is the well-defined eligibility criteria for data acquisition. The inclusion criteria for the publication year between 2009 and 2019 refined the relevancy

of the contraceptive methods that were assessed in the selected articles. Many of the published articles were based on large dataset from cancer registries and analyzed validated cases, which thereby eliminates information bias. Most of the reported studies did not disclose their follow-up rates, which can potentially induce selection bias into the studies. Four of the ten studies were conducted in Europe, and all analyzed OC use as the birth control method based on the EPIC study. Three studies were conducted in Asia and the remaining three were American studies based on data from cancer registries. This diversity of racial/ethnic groups can also bias the results in a comprehensive comparison such as this. The genomic variation between these racial/ethnic groups could also serve as a confounding factor in these studies and bias the measure of association.

The investigated study samples ranged from hundreds to hundreds of thousands, these large datasets can significantly impact the representative of the selected populations. However, all the selected articles did not analyze the measure of association with the considerations of potential confounders that would be contributed to the hormone levels of patients, such as the discrepant oral contraceptive forms combined estrogen-progesterone, progesterone only and the continuous or extended use pill¹². As a final limitation for this review, the selected articles analyzed three forms of hormonal contraceptive methods; thus, the association between other hormonal contraceptives, the skin patch and vaginal ring for instance, and ovarian cancer development, is yet to be known.

Conclusion

Various hormonal contraceptives were analyzed for their association with the development of ovarian cancer, and most revealed a protective effect among women. Future studies should analyze the association based on the stratification of race/ethnics, genomic variations, the specific form of oral contraceptive pills, and other topical hormonal contraceptive methods.

APPENDIX A

Source	Database	Study Design	Study Outcome Measures	Study Setting & Study Population	Study Intervention	Key Findings	Quality Assessment
Kolomeyevskaya, N. V. et al. (2015). Oral Contraceptive Use and Reproductive Characteristics Affect Survival in Patients with Epithelial Ovarian Cancer: A Cohort Study. International Journal of Gynecological Cancer. 25 (9): 1587-1592. DOI: 10.1097/IGC.0000000000000540	Journals@Ovid Complete	Cohort Study	Overall survival time, mortality risk	Women aged 18 to 99 years with newly diagnosed EOC, fallopian tube, or primary peritoneal carcinoma seeking care at Roswell Park Cancer Institute.	Overall survival time was calculated in months from the date of diagnosis until the date of death or of last follow-up. Patients alive at last contact were censored at the date of last contact. The Kaplan-Meier technique was used to compare survival across various exposures. Categorical exposures were tested using the log-rank test, whereas continuous variables were analyzed with Cox regression. A threshold of $P < 0.20$ was used to identify candidate variables for final models. Final models were selected using a forward selection process; for consistency, covariates identified for any model were included in all adjusted models. Cox regression was used to compute crude hazards ratios (HRs) and adjusted HRs (aHRs), as well as 95% confidence intervals (95% CIs). Linearity of associations between continuous variables and survival were confirmed using linear spline models. The proportional hazards assumption was verified for each factor of interest.	A history of OC use and parity are associated with improved survival in patients diagnosed with ovarian cancer. History of OC use was associated with a 35-month improvement in median overall survival (81 vs 46 months; HR, 0.51; 95% CI, 0.39–0.66), although this association was attenuated when analyses were adjusted for age at diagnosis, stage, and histologic subtype (aHR, 0.71; 95% CI, 0.53–0.97).	9/9
Cook, L. S. and Pestak, C. R. et al. (2017). Combined Oral Contraceptives Use Before the First Birth and Epithelial Ovarian Cancer Risk. British Journal of Cancer. 116: 265-269. DOI: 10.1038/bjc.2016.400.	PubMed Central	population-based case-control study	odds ratio	Briefly, cases were identified from the population-based BC and AB cancer registries who were: age 20–79 years (40–79 in AB); diagnosed with first primary, incident, histologically confirmed EOC (invasive EOC in AB); and able to complete study in English. A total of 1505 cases (60% of 2522 eligible) completed the study. Eligible controls identified from provincial health rosters and a mammography screening program (Eheman et al, 2014) were: aged 20–79 years (40–79 in AB); able to complete study in English; and, had at least one ovary. A total of 2564 (53% of 4838 eligible) completed the study.	Logistic regression to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) in R software. Final aORs included matching variables, age at FTTP, first degree family female breast or ovarian cancer, tubal ligation, and BMI. Histotype-specific analyses were restricted to high-grade serous and combined endometrioid/clear cell.	Any COC use was associated with a reduction in risk (aOR=0.58, 95% CI=0.49, 0.69). Among COC users, risk was most strongly reduced with longer durations of use overall, within more recent time since last use, and for younger ages at first use.	7/9

Appendix A – Literature review of other forms of hormonal contraceptives

Source	Database	Study Design	Study Outcome Measures	Study Setting & Study Population	Study Intervention	Key Findings	Quality Assessment
Tsilidis, K. K. and Allen N. E et al. (2011). Oral Contraceptive Use and Reproductive Factors and risk of ovarian cancer in the European Perspective Investigation into Cancer and Nutrition. British Journal of Cancer. 105 (9): 1436-42. DOI: 10.1038/bjc.2011.371.	PubMed Central	Cohort Study	Hazards ratio	Participants recruited between 1992 and 2000 in 23 centers in 10 European countries (Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden and the United Kingdom) for the European Prospective Investigation into Cancer and Nutrition (EPIC). Incident cancer cases were identified through linkage to population cancer registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the UK, or using a combination of methods.	Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard models stratified by centre and age, and adjusted for smoking status, body mass index, unilateral ovariectomy, simple hysterectomy, menopausal hormone therapy, and mutually adjusted for age at menarche, age at menopause, number of full-term pregnancies and duration of oral contraceptive use. including linkage to health insurance records, cancer and pathology registries, and active follow-up of study participants or their next of kin in France, Germany and Greece.	Women who used oral contraceptives for 10 or more years had a significant 45% (HR, 0.55; 95% CI, 0.41–0.75) lower risk compared with users of 1 year or less (<i>P</i> -trend, <0.01). Compared with nulliparous women, parous women had a 29% (HR, 0.71; 95% CI, 0.59–0.87) lower risk, with an 8% reduction in risk for each additional pregnancy. A high age at menopause was associated with a higher risk of ovarian cancer (>52 vs ≤45 years: HR, 1.46; 95% CI, 1.06–1.99; <i>P</i> -trend, 0.02). Age at menarche, age at first full-term pregnancy, incomplete pregnancies and breastfeeding were not associated with risk.	9/9
Fortner, R. T. and Ose, J. et al. (2015). Reproductive and hormone-related risk factors for epithelial ovarian cancer by histologic pathways, invasiveness and histologic subtypes: Results from the EPIC cohort. International Journal of Cancer. 137: 1196 - 1208. DOI: 10.1002/ijc.29471.	Wiley Online Library Database	Cohort study	Relative risks	The EPIC cohort was established between 1992 and 2000 at 23 centers in 10 countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden and the United Kingdom. Participants were excluded if they reported history of prior cancer at recruitment (except non-melanoma skin cancer), had incomplete baseline data, reported bilateral oophorectomy at baseline, or women missing data on all investigated reproductive and hormone-related risk factors, leaving a study population of 334,126 women.	Main exposure variables were categorized as follows: age at menarche: ≤13, 14, ≥15 years; age at menopause: ≤48, 49–50, 51–54, ≥55 years; full-term pregnancy: yes/no; number of full-term. All analyses were adjusted for OC use (ever/never), HRT use (ever/never), age at menopause (continuous; pre-/perimenopausal assigned median age at menopause), menopausal status at baseline (pre- or perimenopausal/postmenopausal), and full-term pregnancy (ever/never), except when the variable was the main effect. pregnancies: 0, 1, 2, 3+; breastfed: yes/ no; menstrual cycle regularity: ≤26 days, 27–29 days, 30+ days, none or irregular; OC use: yes/no; OC duration: never user, ≤1 year, 1–4 years, 5–9 years, ≥10 years; hysterectomy: yes/no; HRT use: yes/no; BMI: normal weight (<25 kg m ²), overweight (25–30 kg m ²), obese (≥30 kg m ²).	Duration of OC use and number of full-term pregnancies were inversely associated with both type I and type II, but not borderline, tumors (e.g., ≥10 years vs. never use of OC: borderline, RR: 0.75. duration of OC use was only significantly associated with reduced risk of serous tumors (e.g., OC use ≥10 years vs. never user, RR: 0.61 [0.46–0.82], <i>P</i> -trend < 0.01, <i>P</i> -het 5 0.86) [0.35–1.61], <i>P</i> -trend 5 0.22; type I, RR: 0.54 [0.31–0.94], <i>P</i> -trend 5 0.01; type II, RR: 0.71 [0.51–0.97], <i>P</i> -trend 5 0.01; <i>P</i> -het 5 0.22). Established protective factors, including duration of oral contraceptive use and full term pregnancy, were consistently inversely associated with risk across histologic subtypes (e.g., ever full-term pregnancy: serous, RR: 0.73 [0.58–0.92]; mucinous, RR: 0.53 [0.30–0.95]; endometrioid, RR: 0.65 [0.40–1.06]; clear cell, RR: 0.34 [0.18–0.64]; <i>P</i> -het 5 0.16).	8/9

Appendix A – Literature review of other forms of hormonal contraceptives

Source	Database	Study Design	Study Outcome Measures	Study Setting & Study Population	Study Intervention	Key Findings	Quality Assessment
Chen, Y., Tan, X., Ding, Y., Mai, B., Huang, X., Hu, G., & Luo, X. (2016). WWOX CNV-67048 Functions as a Risk Factor for Epithelial Ovarian Cancer in Chinese Women by Negatively Interacting with Oral Contraceptive Use. <i>BioMed research international</i> , 2016, 6594039. doi:10.1155/2016/6594039	PubMed Central	case-control study	odds ratio	549 EOC patients and 571 age (± 5 years) matched cancer-free controls were recruited from the Guangdong Provincial Maternity and Child Care Center in Guangzhou, China. Individuals with tumor history were excluded. Each participant was asked to donate 3 mL peripheral blood sample and complete a questionnaire to collect their data on sociodemographic, smoking status, alcohol consumption, menstrual and reproductive histories, and contraceptive use.	The chi-square test was used to assess differences in the distributions of CNV-67048 copy number between EOC cases and controls. The unconditional logistic regression model with or without adjustment for surrounding factors including age, age at menarche, number of births, menstrual history, oral contraceptive use, family history of cancer, smoking status, and alcohol intake was used to infer odds ratio (OR) and 95% confidence interval (95% CI) for each association between the CNV-67048 and EOC risk.	significantly higher frequency of menarche age less than 15 years, births number no less than 4, and reported null oral contraceptive use were observed in EOC cases than in controls (P values are 0.039, <0.001, and 0.039 in turn).	7/9
Clendenen, T. V. and Arslan, A. A. et al. (2013). Circulating prolactin levels and risk of epithelial ovarian cancer. <i>Cancer Causes & Control</i> . 24:741-8. DOI: 10.1007/s10552-013-0156-6.	SpringerLink	Nested case-control	odds ratio	The participants were recruited from the NYU Women's Health Study (NYUWHS), the Northern Sweden Health and Disease Study (NSHDS), and the ORDET cohort in Italy. In total, 230 ovarian cancer cases and 432 controls (~2 per case matched on age, menopausal status, and date of blood sampling) were included.	Cross-sectional analyses were preformed mutually adjusted for all factors significantly associated with prolactin levels in our study (age, parity, oral contraceptive use, and menopausal status). Multivariate conditional logistic regression models were adjusted for parity (ever/never had a full-term pregnancy) and use of oral contraceptives (OCs, past/never).	Cases were less likely ot have used OCs (64 vs. 70 %, $p = 0.26$). Past use of OCs was associated with lower prolactin levels in both pre- and post-menopausal women.	8/9
Bešević, J., Gunter, M. J., Fortner, R. T., Tsilidis, K. K., Weiderpass, E., Onland-Moret, N. C., ... Merritt, M. A. (2015). Reproductive factors and epithelial ovarian cancer survival in the EPIC cohort study. <i>British journal of cancer</i> , 113 (11), 1622–1631. doi:10.1038/bjc.2015.377	PubMed Central	cohort study	hazards ratio from death of EOC and EOC-related cause	Cases were identified through linkage with national cancer registries in Denmark, Italy, The Netherlands, Norway, Spain, Sweden and the UK. In France, Germany and Greece, cases were identified using insurance records, cancer registries and active follow-up of participants. Data on tumour invasiveness, histology, stage and grade were available from cancer registries and a pathology record review. A total of 1025 women diagnosed with EOC.	Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards regression models. Person-time was calculated as the number of days between EOC diagnosis and the date of death, emigration, loss to follow-up or censoring, whichever occurred first. Multivariable models were adjusted for covariates that were selected <i>a priori</i> because of their known influence on risk of EOC death; age at diagnosis (continuous), BMI (<23 kg m ⁻² , ≥ 23 –<25 (reference), ≥ 25 –<30, ≥ 30), tumour stage (local (reference), regional, metastatic, unknown) and smoking status (never (reference), former, current, unknown).	Among OC users a longer duration of use was associated with a worse survival (>10 years vs ≤ 1 year of use: HR=1.74 95% CI=1.10–2.75, $P_{trend}=0.01$). In a uniform subgroup of FIGO stage II/III cases (all histological subtypes), there was no association between OC use or OC duration of use with EOC-specific survival.	9/9

Appendix A – Literature review of other forms of hormonal contraceptives

APPENDIX B

Source	Database	Study Design	Study Outcome Measures	Study Setting & Study Population	Study Intervention	Key Findings	Quality Assessment
Sieh, W. and Salvador, S. et al. (2013). Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. <i>International Journal of Epidemiology</i> . 42(2): 578-89. DOI: 10.1093/ije/dyt042.	Oxford University Press Journals	Pooled analysis of case-control studies	Odds ratio and 95% confidence interval	Primary data from 13 population-based case-control studies. Cases were women newly diagnosed with invasive epithelial ovarian cancer (N = 7942) or borderline tumours (N = 2215). Eligible control women had at least one intact ovary and no history of ovarian cancer (N = 13 904).	Controls were matched to cases on geographical region and age in all sites, and when warranted on race/ethnicity. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression matched on sets determined by combinations of site, race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian, other) and 5-year age categories, and adjusted for age as a continuous variable, oral contraception use and number of full-term pregnancies.	Tubal ligation was associated with a 29% reduced risk of invasive ovarian cancer overall (OR, 0.71; 95% CI, 0.66-0.77; $P < 0.001$), after accounting for study site, age, race/ethnicity, oral contraceptive use and number of full-term births.	7/9
Wilailak, S. and Vipupinyo, C. et al. (2012). Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. <i>BJOG</i> . 119 (6):672-677. DOI: 10.1111/j.1471-0528.2012.03298.x.	Wiley Online Library Database	multicentre, case-control study.	The odds ratio (OR) and 95% confidence interval (95% CI) were calculated to assess the relationship between DMPA and EOC.	From 12 hospitals located across Thailand, 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 and controls were interviewed by trained interviewers using a standardised pre-tested questionnaire. The factors associated with EOC were evaluated using univariate and multivariate analyses.	The use of DMPA was found to be associated with a 39% reduction in the risk of EOC with an OR of 0.61 and a 95% CI of 0.44-0.85 ($P = 0.002$). A significant risk reduction (83%) was observed when the duration of DMPA use was >3 years (OR 0.17; 95% CI 0.07-0.39; $P < 0.001$). Other factors associated with a reduced risk of EOC were the use of combined oral contraceptive pills and breastfeeding. A factor associated with an increased risk of EOC was a family history of gynaecological cancer.	8/9
Huang, Z. and Gao, Y et al. (2014). Contraceptive methods and ovarian cancer risk among Chinese women: A report from the Shanghai Women's Health Study. <i>International Journal of Cancer</i> . 137 (3): 607-14. DOI: 10.1002/ijc.29412.	Wiley Online Library Database	population-based, prospective cohort study	Hazards ratio	at baseline from March 1997 to May 2000, adult Chinese women aged 40-70 years were recruited from seven urban communities of Shanghai, China. . Incident cancer cases were verified by home visits and medical chart review. Women who had a previous diagnosis of any cancer, an unverified diagnosis of cancer, a prior oophorectomy, unknown menopausal status, those who died of cancer without a specific cancer diagnosis or were lost to follow-up were excluded; a total of 70,259 women were included in our analysis.	Cox proportional hazards regression was used to derive hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between ovarian cancer risk and contraceptive methods. Contraceptive methods evaluated in this study included IUD, OC, TL and contraceptive shots; ever use was compared with never use. Durations of exposure time were calculated as the interval between start and end of use, except for TL and IUD, where removal had not occurred by baseline interview. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), and a two-sided probability with a significance level of 0.05 was used.	Ever use of any contraception was associated with a nonsignificant reduction in ovarian cancer risk (HR: 0.86, 95% CI: 0.60-1.24). Longer duration of IUD use was associated with lower ovarian cancer risk (p-value for trend 5 0.04). Compared with never users, women with durations of IUD use longer than the median (20 years) were 38% less likely to develop ovarian cancer (HR: 0.62, 95% CI: 0.40-0.97).	9/9

Appendix B – Literature review of other forms of hormonal contraceptives

APPENDIX C

Source	Selection				Comparability	Outcome			Overall Score
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present t the start of study	Comparability of cohorts on the basis of design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Kolomeyevskaya, N. V. et al. (2015). Oral Contraceptive Use and Reproductive Characteristics Affect Survival in Patients with Epithelial Ovarian Cancer: A Cohort Study. <i>International Journal of Gynecological Cancer</i> . 25 (9): 1587-1592. DOI: 10.1097/IGC.0000000000000540.	Somewhat represnetative of the average ovarian cancer cases in the community	drawn from the same community as the exposed cohort	written self report	Yes	Study cotrols for presence or absence of specific medical comorbidities, as well as reproductive factors including the use of hormonal medications. Individual subject information on treatment and survival, tumor stage, grade, and histologic type.	Record linkage	Yes	Complete follow up	9/9
Tsilidis, K. K. and Allen N. E et al. (2011). Oral Contraceptive Use and Reproductive Factors and risk of ovarian cancer in the European Perspective Inesvtigation into Cancer and Nutrition. <i>British Journal of Cancer</i> . 105 (9): 1436-42. DOI: 10.1038/bjc.2011.371.	Somewhat represnetative of the average ovarian cancer cases in the community	Drawn from the same community as the exposed cohort	Written self report	Yes	Study controls for oral contraceptive use as well as information on age at menarche and menopause, numbers of full-term pregnancies, incomplete pregnancies and age at first full-term pregnancy.	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias, >80% follow up	9/9
Fortner, R. T. and Ose, J. et al. (2015). Reproductive and hormone-related risk factors for epithelial ovarian cancer by histologic pathways, invasiveness and histologic subtypes: Results from the EPIC cohort. <i>International Journal of Cancer</i> . 137: 1196 - 1208. DOI: 10.1002/ijc.29471.	Somewhat represnetative of the average ovarian cancer cases in the community	Drawn from the same community as the exposed cohort	Written self report	Yes	Study controls for age at menarche, age at menopause, parity and number of full-term pregnancies, breast feeding, menstrual cycle regularity, OC use and duration, menopausal hormone replacement therapy (MHT) use, and hysterectomy	Record linkage	Yes	No statement	8/9
Bešević, J., Gunter, M. J., Fortner, R. T., Tsilidis, K. K., Weiderpass, E., Onland-Moret, N. C., ... Merritt, M. A. (2015). Reproductive factors and epithelial ovarian cancer survival in the EPIC cohort study. <i>British journal of cancer</i> , 113 (11), 1622–1631. doi:10.1038/bjc.2015.377	Somewhat represnetative of the average ovarian cancer cases in the community	Drawn from the same community as the exposed cohort	Written self report	Yes	Study controls for reproductive history, diet and lifestyle.	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias, >80% follow up	9/9

Appendix C – Quality assessment of cohort studies

Source	Selection				Comparability	Outcome			Overall Score
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present t the start of study	Comparability of cohorts on the basis of design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Huang, Z. and Gao, Y et al. (2014). Contraceptive methods and ovarian cancer risk among Chinese women: A report from the Shanghai Women's Health Study. International Journal of Cancer. 137 (3): 607-14. DOI: 10.1002/ijc.29412.	Somewhat represnetative of the average ovarian cancer cases in the community	Drawn from the same community as the exposed cohort	Structured interviews	Yes	study controls for contraceptive use and the duration of use, menopausal status, age at recruitment, education, years of ovulation, irregular ovulatory cycles (yes/no), first-degree family history of cancer (yes/no), body mass index (BMI), regular physical activity within 5 years (yes/no) and other contraceptive methods (never/ever).	Record linkage	Yes	Subjects lost to follow up unlikely to introduce bias, >80% follow up	9/9

Appendix C – Quality assessment of cohort studies

APPENDIX D

Source	Selection				Comparability	Exposure			Overall Score
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	
Cook, L. S. and Pestak, C. R. et al. (2017). Combined Oral Contraceptives Use Before the First Birth and Epithelial Ovarian Cancer Risk. <i>British Journal of Cancer</i> . 116: 265-269. DOI: 10.1038/bjc.2016.400.	Yes, with independent validation	Consecutive or obviously representative series of cases	Community controls	No history of disease	Study controls for outcome diagnosis date and reference data as well as demographic, lifestyle, and medical/reproductive factors, women provided information on COC use, including dates or ages of use	Written self report	Yes	Rate different and no designation (60% for cases and 53% for controls)	7/9
Chen, Y., Tan, X., Ding, Y., Mai, B., Huang, X., Hu, G., & Luo, X. (2016). WWOX CNV-67048 Functions as a Risk Factor for Epithelial Ovarian Cancer in Chinese Women by Negatively Interacting with Oral Contraceptive Use. <i>BioMed research international</i> , 2016, 6594039. doi:10.1155/2016/6594039	Yes, with independent validation	Consecutive or obviously representative series of cases	Community controls	No history of disease	Study controls for outcome and information on sociodemographic, smoking status, alcohol consumption, menstrual and reproductive histories, and contraceptive use	Written self report	Yes	No designation	7/9
Clendenen, T. V. and Arslan, A. A. et al. (2013). Circulating prolactin levels and risk of epithelial ovarian cancer. <i>Cancer Causes & Control</i> . 24:741-8. DOI: 10.1007/s10552-013-0156-6.	Yes, with independent validation	consecutive or obviously representative series of cases	Community controls	No history of disease	Study controls for age, menopausal status, and date of blood sampling	Structured interview where blind to case/control status	Yes	Non respondent described	8/9
Sieh, W. and Salvador, S. et al. (2013). Tubal ligation and risk of ovarian cancer subtypes: a pooled analysis of case-control studies. <i>International journal of Epidemiology</i> . 42(2): 578-89. DOI: 10.1093/ije/dyt042.	Yes, with independent validation	Consecutive or obviously representative series of cases	Community controls	No history of disease	Study controls for outcome and geographical region and age in all sites, and when warranted on race/ethnicity	Written self report	Yes	No designation	7/9
Wilailak, S. and Vipupinyo, C. et al. (2012). Depot medroxyprogesterone acetate and epithelial ovarian cancer: a multicentre case-control study. <i>BJOG</i> . 119 (6):672-677. DOI: 10.1111/j.1471-0528.2012.03298.x.	Yes, with independent validation	Consecutive or obviously representative series of cases	Community controls	No history of disease	Study controls for EOC diagnosis and sociodemographic factors, personal history, current disease, family history, reproductive history, contraceptive history and use of female hormones	Structured interview where blind to case/control status	Yes	No designation	8/9

Appendix D – Quality assessment of cross-sectional studies and derivatives

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