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Pelvic inflammatory disease and the risk of ovarian cancer: a meta-analysis

Zhiyi Zhou^{1,2,#}, Fangfang Zeng^{3,#}, Jianhui Yuan², Jinling Tang^{1,4}, Graham A. Colditz⁵, Shelley S. Tworoger^{6,7}, Britton Trabert^{8,*}, and Xuefen Su^{1,4,*}

¹School of public Health and Primary Care, Faculty of Medicine, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong, China

²Shenzhen Center for Disease Control and Prevention, Shenzhen, China

³Guangdong Provincial Key Laboratory of Food, Nutrition and Health, School of Public Health, Sun Yat-sen University, Guangzhou, 510080, China

⁴The Chinese University of Hong Kong Shenzhen Research Institute, Shenzhen, 518057, China

⁵Alvin J. Siteman Cancer Center and Department of Surgery, Washington University School of Medicine, 660 S Euclid Ave, St Louis, Missouri, 63110, USA

⁶Channing Division of Network Medicine, Harvard Medical School and the Brigham and Women's Hospital, 181 Longwood Ave., 3rd Fl., Boston, MA, 02115, USA

⁷Department of Epidemiology, Harvard T. H. Chan School of Public Health, 677 Huntington Avenue, Boston, MA 02115, USA

⁸Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, 9609 Medical Center Drive, MSC 9774, Bethesda, MD 20892, USA

Abstract

Purpose—Previous studies on pelvic inflammatory disease (PID) and the risk of ovarian cancer have found inconsistent results. We performed an updated meta-analysis to summarize the evidence of this association.

Methods—PubMed, Embase, and ISI web of science databases were searched through October 2016 for studies that investigated the PID and ovarian cancer association. Summary risk estimates were calculated using random-effects meta-analysis.

Result—Thirteen studies were eligible for analysis, which included six cohort studies and seven case-control studies. PID was associated with an increased risk of ovarian cancer overall [relative

Corresponding author contact information: Xuefen Su, ScD, MPH, Assistant Professor, School of Public Health and Primary Care, Faculty of Medicine, The Chinese University of Hong Kong, Room 508, 5/F, School of Public Health, Prince of Wales Hospital, Shatin, N.T., Hong Kong, Phone: 852-2252-8740, Fax: 852-2645-3098, xuefensu@cuhk.edu.hk. Britton Trabert, PhD, MS, Earl Stadtman Investigator, National Cancer Institute, Division of Cancer Epidemiology and Genetics, NCI Shady Grove, 9609 Medical Center Drive, MSC 9774, Bethesda, Maryland 20892-9774, Phone: (1-240)-276-7331, britton.trabert@nih.gov.

#Zhiyi Zhou and Fangfang Zeng contributed equally to this work and should be considered as co-first authors.

*Xuefen Su and Britton Trabert were equally responsible for conception and design, and manuscript writing, and should be considered as co-senior authors.

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risk (RR) 1.24, 95% CI 1.06–1.44; $I^2=58.8\%$]. In analyses stratified by race, a significant positive association was observed in studies conducted among Asian women (RR 1.69, 95% CI 1.22–2.34; $I^2=0\%$), but marginally significant among Caucasians (RR 1.18, 95% CI 1.00–1.39; $I^2=60.7\%$). Risk estimates were elevated in both cohort (RR 1.32; 95% CI 1.05–1.66; $I^2=64.7\%$) and case-control studies (RR 1.17; 95% CI 0.93–1.49; $I^2=57.6\%$), albeit not statistically significant in case-control studies.

Conclusions—Our results suggested that PID might be a potential risk factor of ovarian cancer, with pronounced associations among Asian women. Large and well-designed studies with objective assessment methods, such as hospital records, are needed to confirm the findings of this meta-analysis.

Keywords

Pelvic inflammatory disease; Inflammation; Ovarian cancer; Meta-analysis

Introduction

Ovarian cancer is a gynecologic malignancy with a high mortality rate affecting many women worldwide. The World Health Organization (WHO) estimated that the number of ovarian cancer deaths worldwide in 2015 was 162,129 [1]. In 2017, the expected numbers of new cancer cases and deaths in the United States are 22,440 and 14,080 respectively, and the number of deaths ranks the 5th of all fatal cancers in women [2]. Epithelial ovarian cancer makes up 90% of all histologic types [3]. Borderline ovarian tumors, or tumors with low malignant potential (LMP), are considered as clinical-pathologic features intermediate between benign and malignant with no stromal invasion and account for approximately 10–30% of non-benign ovarian tumors (NBOT) [4]. Ovarian carcinogenesis is not well understood [5], and chronic inflammation has been hypothesized as a potential mechanism [6–8]. The ‘inflammation’ hypothesis arises because ovarian cancer has been linked to events and conditions which are related to inflammation and repair (e.g., ovulation, endometriosis) [6]; while reduced risks have been observed for agents associated with direct anti-inflammatory actions (e.g., aspirin) [9]. Tubal ligation and hysterectomy are also associated with a reduced risk of ovarian cancer, likely because the direct route of exposure of initially transformed cells to the ovaries are blocked [6]. The factors released during inflammation and the repeated involvement of the affected ovarian epithelium both play critical roles in the pathological process of ovarian carcinogenesis [10]. Although historically viewed as arising from ovarian surface epithelium, recent data suggest that many of these tumors, specifically serous tumors, develop from the fimbria of the fallopian tube; specifically, that early carcinomas develop in the tube but grow robustly on the ovary [11, 12].

Several previous studies indicated that pelvic inflammatory disease (PID) might be a risk factor of ovarian cancer [7, 13–15]. PID is caused by sexually transmitted infections that ascend from the lower genital tract to produce infections at various sites in the upper genital tract, which include endometritis, salpingitis, pelvic peritonitis, and tubo-ovarian abscess [16]. Inflammatory stimuli by PID could influence ovarian cancer via a number of possible mechanisms. Chronic inflammation might directly influence the ovarian surface via

malignant transformation of epithelial cells, or may facilitate the conversion of premalignant lesions in the fallopian tubes to malignant lesions [8]. A small meta-analysis of PID and ovarian cancer was conducted in 2011 and included four studies in total [14]. Among the seven studies published in or before 2011, three of them [14, 17, 18] were not included in the prior meta-analysis [14]. Since 2011, six additional studies [15, 19–23] have been published. Furthermore, due to the limited number of studies/participants included in the previous meta-analysis [14], the potential sources of heterogeneity were not explored. Therefore, we undertook an updated meta-analysis to quantitatively assess the association between PID and ovarian cancer and to explore potential sources of heterogeneity.

Methods

Search strategy

We performed a systematic literature search of the PubMed (from 1966 to October 2016), Web of science (up to October 2016) and Embase (from 1980 to September 2016) electronic databases. To ensure that the meta-analysis was based on up-to-date results, we updated the literature search in PubMed on January 12, 2017. The following search terms and/or medical subject headings (MESH) were used: (“pelvic inflammatory” or “pelvic disease” or “adnexitis” or “ovary inflammation” or “oophoritis” or “parametritis” or “salpingitis” or “endometritis” or “inflammatory pelvic” or (“Pelvic inflammatory disease”[mesh])) and (((ovary or ovarian) and (cancer or cancers or carcinoma* or neoplasm* or malignan* ortumour or tumor)) or (“Ovarian Neoplasms”[MESH])). We also reviewed the reference lists of identified original and review articles to search for additional relevant studies. Only those articles published as full-text research papers in English were included.

Selection of studies

For inclusion, studies had to fulfill the following criteria: (1) the study was a case-control study (including a nested case-control study) or a cohort study; (2) the exposure was PID (including endometritis, salpingitis, pelvic peritonitis, and tubo-ovarian abscess); (3) the outcome was ovarian cancer, including invasive ovarian cancer and/or borderline ovarian tumors; and (4) the study reported odds ratios (OR), relative risks (RR), or hazard ratios (HR), and their corresponding 95% CIs. If multiple reports were published from the same study population, we included the most recent publication. Other pelvic diseases (e.g. endometriosis) were excluded, as they were not the focus of the current meta-analysis.

A total of 2,521 articles including potential duplicates across data sources were retrieved via literature search of the PubMed, Web of Science, and Embase databases (Figure 1). After title and abstract scanning, 2,461 articles were excluded (meta-analysis and editorial: N = 289; and irrelevant studies, such as animal studies, in vivo studies, or clinical trials: N = 2,172). We reviewed the full texts of the remaining 60 articles. Among them, 48 articles were excluded, as they did not report risk estimates or 95% CIs (N = 43), or were duplicates (N = 5). Thirty-three additional articles were identified with the updated literature search on January 12, 2017, and one new eligible study was included [22]. A total of 13 studies were included in this meta-analysis, including six cohort studies [14, 15, 19, 20, 22, 23] and seven case-control studies [7, 13, 17, 18, 21, 24, 25]. Three studies included only invasive ovarian

cancer [19, 20, 24], one study included only borderline ovarian tumors [23], and nine studies included both invasive ovarian cancer and borderline ovarian tumors [7, 13–15, 17, 18, 21, 22, 25]. Of these nine studies, seven reported combined results only [13–15, 17, 18, 22, 25], one reported results of combined, invasive, and borderline tumors [7], and one reported results of invasive cancer and borderline tumors separately, but not combined results [21].

Data extraction and quality assessment

Data were extracted independently by two investigators (ZZ and ZF) and differences were resolved by discussion with a third investigator (SX). Extracted data included the first author's name, year of publication, country of origin of the studies as a proxy for race, number of participants, mean or median age, duration of follow-up (for cohort studies), ascertainment and category of PID, outcome assessment (diagnosis), ORs or HRs of the outcome and the corresponding 95% CIs for each category of PID, and the covariates adjusted. The quality of each study was assessed by the Newcastle-Ottawa quality assessment scale (NOS) [26]. This instrument assesses the quality of studies in three aspects 'selection of cohorts or cases and controls (4 stars)', 'comparability of cohorts or cases and controls (2 stars)', and 'assessments of outcome (cohort studies) or ascertainment of exposure (case-control studies) (3 stars)'. The quality scores of the included studies ranged from 0 to 9, with 7 to 9 points indicating a high-quality study and 0 to 6 points indicating low-quality.

Statistical analysis

Because ovarian cancer is a rare outcome, ORs were considered acceptable approximations of RR and combined with RRs, resulting in a common estimate of RR [27]. Summary RR was calculated to quantify the association between PID and ovarian cancer. We transformed the RRs or ORs in each study by using their natural logarithms, and the standard errors (SEs) were calculated from the logarithmic-transformed values and their corresponding 95% CIs. The pooled RR with 95% CI was calculated based on the DerSimonian and Laird method [28]. Heterogeneity across studies was assessed using I^2 [29], and high heterogeneity is defined as an I^2 value of greater than 50% [30]. In the absence of significant heterogeneity, the fixed-effects model was used, and in its presence, the random-effects model was used to estimate the summary RR.

Because high heterogeneity was observed in the overall analyses, subgroup analyses were further conducted to explore the potential sources of heterogeneity selected *a priori*, including race, study design, tumor invasiveness, and adjustment for parity, family history of ovarian cancer, or oral contraceptive use. For the subgroup analysis by tumor invasiveness, five studies were included for invasive ovarian cancer only [7, 19–21, 24], three were included for borderline ovarian tumors only [7, 21, 23], and seven studies were included for combined invasive ovarian cancer and borderline ovarian tumors [13–15, 17, 18, 22, 25]. Although the Risch study [7] reported results for invasive ovarian cancer, borderline ovarian tumors, and combined, only the results of borderline tumor and invasive cancer were used to calculate the subgroup risk estimates. Publication bias was assessed by visual inspection of funnel plot, and Egger's linear regression asymmetry test was used to measure the degree of asymmetry of the funnel plot [31, 32]. Influence analyses were performed to evaluate the

influence of a single study on the overall estimate by excluding one study at a time. Statistical analyses were performed using STATA 12.1 software (College Station, TX, USA).

Results

Table 1 summarizes the characteristics of the meta-analyzed studies. Ten were conducted among primarily Caucasian populations and three among Asian populations. Because age was the most important confounder, all studies were adjusted for age. Additional adjustment for family history of ovarian cancer [13, 19, 21, 25], use of oral contraceptives [7, 13, 17, 18, 21, 25], education [13, 17, 18, 24], and menopausal status [13, 18] was made in some studies. Except the Lin et al. study, which had a maximum follow-up of 3 years [14], the mean/median follow-up period was 8.84 years [22], 17 years [19], 20.3 years in the inflammation cohort and 18.4 years in the control cohort [15], and 35 years [20, 23] years, respectively, in the six cohort studies. All cohort studies used hospital records, whereas all case-control studies used self-reported PID history collected via interviews or questionnaires (Table 1). The median quality score of the 13 publications was 7, with a range of 6–8 (Table 2).

Overall, PID was associated with an increased risk of ovarian cancer (RR 1.24, 95% CI 1.06–1.44), with high between-study heterogeneity ($I^2 = 58.8\%$, p for heterogeneity = 0.003) (Table 3 and Figure 2). No evidence of publication bias was observed in the funnel plot or Egger's linear regression asymmetry test ($p = 0.743$) (Figure 3).

Subgroup analyses were performed to explore *a priori* defined potential source of heterogeneity (Table 3). PID was significantly associated with ovarian cancer among Asians (RR 1.69, 95% CI 1.22, 2.34; $I^2 = 0\%$, p for heterogeneity = 0.504) [14, 22, 24]. A lower and marginally significant increased risk was observed in predominantly Caucasian studies (RR 1.18, 95% CI 1.00–1.39; $I^2 = 60.7\%$, p for heterogeneity = 0.005) [7, 13, 15, 17–21, 23, 25]. A significant heterogeneity was observed between Asian and Caucasian populations (p for between-group heterogeneity = 0.054). In the analysis stratified by study design, no a significant difference in risk estimates between cohort and case-control studies was observed (p for between-group heterogeneity = 0.472). PID was associated with an increased risk of ovarian cancer in both cohort studies (RR 1.32, 95% CI 1.05–1.66; $I^2 = 64.7\%$, p for heterogeneity = 0.015) [14, 15, 19, 20, 22, 23] and case-control studies (RR 1.17; 95% CI 0.93–1.49; $I^2 = 57.6\%$, p for heterogeneity = 0.021) [7, 13, 17, 18, 21, 24, 25], albeit the association was not statistically significant in case-control studies. PID history was associated with an increased risk of borderline ovarian tumors (RR 1.42, 95% CI 1.25–1.63; $I^2 = 0\%$, p for heterogeneity = 0.756) [7, 21, 23], whereas the association was not significant for invasive ovarian cancer (RR 1.06, 95% CI 0.85–1.32; $I^2 = 50\%$, p for heterogeneity = 0.092) [19–21, 24]; while the association for combined ovarian cancer and borderline ovarian tumors was elevated, although only marginally statistically significant (RR 1.30, 95% CI 0.99–1.70; $I^2 = 38.9\%$, p for heterogeneity = 0.132) [13–15, 17, 18, 22, 25] (p for between-group heterogeneity = 0.083). In addition, a significant positive association between PID and ovarian cancer was observed in studies not adjusted for oral contraceptive use (RR 1.33, 95% CI 1.06–1.67; $I^2 = 59.3\%$, p for heterogeneity = 0.022) [14, 15, 19, 20, 22–24] (p for between-group heterogeneity = 0.421). Influence analyses showed that the minimal RR was 1.19 (1.02–1.39) after excluding the Lin

study [14] and the maximal RR was 1.27 (1.07–1.52) after excluding the Rasmussen 2016 invasive ovarian cancer study [20] (Table 3).

Discussion

The current meta-analysis quantitatively assessed the association between PID and ovarian cancer. The summary RR supports an association between prior PID diagnosis and increased ovarian cancer risk. Stratified analyses indicated that PID was significantly associated with ovarian cancer risk among Asian women [14, 22, 24], but the risk was lower among Caucasian women [7, 13, 15, 17–21, 23, 25]. A significant positive association was observed in cohort but not case-control studies. In addition, PID was significantly associated with an increased risk of borderline ovarian tumors, and marginally associated with invasive ovarian cancer and borderline ovarian tumors combined, but not with invasive ovarian cancer alone. However, this classification was limited and results should be interpreted with caution, given that studies did not systematically report results for each subgroup.

In 2011, Lin et al. [14] conducted a meta-analysis including four case-control studies and found no association between PID and ovarian cancer risk [8]. In the current meta-analysis, with a total of 13 studies we observed that PID was associated with a 24% increased risk of ovarian cancer. High heterogeneity was found in our meta-analyses. With an additional nine studies, we were able to perform subgroup and influence analyses to further explore the potential sources of heterogeneity. We found that associations varied by race. Further, after excluding the large medical record linkage study by Lin et al. [14], the risk estimate was attenuated to 1.19 (1.02, 1.39) but still significant in leave-one-out analyses. A recently published large pooled analysis of 13 case-control studies found that PID was associated with an increased risk of borderline ovarian tumors but not ovarian cancer [33]. Including both cohort and case-control studies in the current meta-analysis, our results are largely consistent with the findings of the pooled analysis, in that we also observed a positive PID-borderline ovarian tumor association, but no association for invasive ovarian cancer only. In addition, we observed an increased risk of combined ovarian cancer and borderline ovarian tumors, which was not examined in the pooled analysis.

The increased risk of ovarian cancer associated with PID is biologically and pathologically plausible. In-vitro studies have shown that the cytokines and chemokines released during chronic inflammation can lead to malignant transformation [34]. In addition, some genes encoding coagulation factors and proteins involved in the inflammatory responses may exhibit tumorigenic functions, thus transforming the affected fallopian tube or ovarian epithelium into malignant cancer [35]. Pelvic inflammation can, therefore, inactivate cell differentiation and accelerate the development of ovarian tumors.

The different risk estimates observed between Caucasian and Asian women may be due to the medical record classification of PID in the study by Lin et al. [14]. Alternatively, it might be due to the differences in genetics and lifestyle factors, for instance, use of oral contraceptives [36, 37] and/or menopausal hormone therapy [38], between these racial groups. After immigration to the United States, the ovarian cancer risk among Asian women tends to approach that of Caucasian women [39], suggesting the potentially important roles

of lifestyles and environment in ovarian cancer risk. For instance, oral contraceptive pills are protective against ovarian cancer [40]. Oral contraceptive use in Asian populations might differ notably from that in other, such as Caucasian populations [14]. In addition, we found that PID was significantly associated with ovarian cancer risk in studies not adjusted for oral contraceptive use. The different mutation rates of genes in these racial groups might also account for the different results [41], as genes play important roles in the malignant transformation of ovarian epithelium during inflammation. In addition, screening and early treatment of sexually transmitted disease may also reduce severity of PID in the United States and other Western countries. For instance, in the U.S. and European countries, screening for chlamydia is nationwide, and it is considered a reportable disease and is rapidly treated, whereas chlamydia screening is not readily in place at a national level in Asian countries.

The increased risk observed among Asian women is based on three studies conducted in Asian populations. In the Shu et al. study [24], the risk estimate was based on 8 exposed cases and 1 exposed control, resulting in very wide confidence intervals (OR 3.0, 95% CI 0.3–30). The cohort study by Lin et al. [14] included lower genital tract infections in their definition of PID (ICD-9 code 616). More importantly, they assessed PID exposure during 2004–2005, and in this period women had to have 2 episodes of PID to be counted as exposed, and women were followed until the end of 2006, resulting in a maximum of 3 years of follow-up. This makes a causal association between PID and ovarian cancer less likely. The Shen et al. [22] study used the same data base as the Lin study, with the particular aim at exploring whether the findings from the Lin study could be reproduced with a longer follow-up [22]. A lower HR (1.33 95% CI 0.78–2.27) was observed with up to 10 years of follow-up. Although both studies used the same database (Longitudinal Health Insurance Database 2005, LHID2005), because PID cases were diagnosed in different periods (January 1st, 2004 and December 31st, 2005 in the Lin study, and January 1st, 2000 and December 31st, 2002 in the Shen study), we included both studies in the meta-analysis and observed a significant positive association among Asian women. However, given the limitations of these studies, the association between PID and ovarian cancer among Asian women should be interpreted with caution, and evaluated in future studies.

In the analysis stratified by study design, a significantly elevated risk was observed in cohort studies [14, 15, 19, 20, 22, 23], but not in case-control studies [7, 13, 17, 18, 21, 24, 25]. It should be noted that all cohort studies used hospital records, whereas all case-control studies used interviews or questionnaires for PID assessment. In the cohort studies using hospital records, the PID status was ascertained and confirmed by diagnosis and generally speaking was more objective and accurate than the self-reported assessment methods.

Misclassification of PID diagnosis is not entirely avoidable in observational studies, as the diagnostic criteria may have changed over time. In addition, a possibly more important reason for misclassification of PID status is that PID is an extremely difficult exposure to assess, with a suspected large proportion of cases being subclinical and therefore not captured by neither medical records nor self-reported history. However, differential recall between cases and non-cases may be less likely in investigations assessing the PID ovarian cancer association even in case-control studies, as the public awareness of PID and its potential association with ovarian cancer risk may not be high. Thus, the non-differential

recall may have attenuated the association further towards the null in case-control studies. Additional large studies should be conducted in the future to further elucidate this association. In the circumstances that a case-control study is the only feasible study design, hospital records should be used for objective and accurate PID assessment method.

A significant positive association was observed in the studies which were not adjusted for parity and in those studies which were not adjusted for family history of ovarian cancer. Confounding by parity and/or family history of ovarian cancer needs to be considered carefully in analyses of PID and ovarian cancer risk. Parity does not likely cause PID, but PID can influence subfertility and it is well documented that severe PID can affect tubal patency. Thus, parity is on the causal pathway between PID and ovarian cancer and can only serve as a potential mediator of the PID-ovarian cancer association. It is unlikely that family history of ovarian cancer predisposes women to PID; therefore it also does not satisfy the traditional definition of a potential confounding factor, so adjustment should be interpreted with caution. The meta-analysis results presented in the current manuscript suggest that inappropriate adjustment for these factors may attenuate or even change the direction of the association. The more appropriate estimates of the true association between PID and ovarian cancer are likely the studies not adjusting for these factors.

The current meta-analysis has several potential limitations. First, PID is a broad category which includes different types of inflammatory diseases (endometritis, salpingitis, pelvic peritonitis, and tuba-ovarian abscess). These diseases may play different roles in ovarian carcinogenesis and correspond to different levels of ovarian tumor risk. Unfortunately, with the exception of one study which specifically focused on salpingitis as the PID exposure [13], the other studies grouped the different types of diseases in the broad category of PID or pelvic inflammation, limiting our ability to assess the associations between different types of PID and ovarian cancer risk. Further, the cause of PID (e.g. type of sexually transmitted infection) and details of PID exposure, for instance, number of PID episodes, age at first PID, or time since first PID, were not available in most studies. In addition, we were not able to perform an analysis stratified by histologic subtype of ovarian cancer, as only three studies reported histotype-specific associations (one on combined invasive cancer and borderline ovarian tumors [17], one on invasive ovarian cancer [20], and one on borderline ovarian tumors [23]), although ovarian cancer is a heterogeneous disease with different risk factor profiles[20]. Second, of the total 13 studies included, the six (less than half of the total studies included) cohort studies [14, 15, 19, 20, 22, 23] assessed PID status based on documented medical records, whereas all the seven case-control studies [7, 13, 17, 18, 21, 24, 25] used self-reported PID history. We did observe a statistically significant and higher risk in cohort studies than in case-control studies. Considering the concern of recall bias in case-control studies, additional large cohort studies with long follow-up and objective and accurate PID assessment methods and adequate adjustment of important confounders should be conducted to provide valid estimates to better quantify the magnitude of the PID-ovarian cancer association.

In conclusion, this meta-analysis supports a positive association between PID and increased risk of ovarian cancer. The association was more pronounced among Asian than Caucasian women. Sexually transmitted infections need to be treated early to avoid potential adverse

sequelae of PID. The association also seemed to be most apparent in analyses of borderline ovarian tumors. However, given that the studies reporting combined results cannot be disentangled to determine the proportion related to borderline vs. invasive tumors, the results by tumor invasiveness should be interpreted with caution. Future large and well-designed cohort studies with objective and accurate PID assessment and adequate adjustment for important confounders need to be conducted to confirm the stronger association observed among Asian women and to determine if differential associations exist for borderline vs. invasive tumors.

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References

1. World Health Organization. Global Health Estimates 2015: Deaths by Cause, Age, Sex, by Country and by Region, 2000–2015. Geneva: 2016. http://www.who.int/healthinfo/global_burden_disease/GlobalCOD_method_2000_2015.pdf [Accessed 09 February 2017]
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. *CA Cancer J Clin*. 2017; 67:7–30. [PubMed: 28055103]
3. Schwartz PE. Diagnosis and treatment of epithelial ovarian cancer. *Minerva Ginecol*. 2003; 55:315–326. [PubMed: 14581856]
4. Trope CG, Kaern J, Davidson B. Borderline ovarian tumours. *Best Pract Res Clin Obstet Gynaecol*. 2012; 26(3):325–336. [PubMed: 22321906]
5. National Cancer Institute. [Accessed 09 September 2016] Ovarian epithelial, fallopian tube, and primary peritoneal cancer Treatment (PDQ(R)): Health Professional Version. 2016. <https://www.cancer.gov/types/ovarian/hp/ovarian-epithelial-treatment-pdq>
6. Ness RB, Cottreau C. Possible role of ovarian epithelial inflammation in ovarian cancer. *J Natl Cancer Inst*. 1999; 91:1459–1467. [PubMed: 10469746]
7. Risch HA, Howe GR. Pelvic inflammatory disease and the risk of epithelial ovarian cancer. *Cancer Epidemiol Biomarkers Prev*. 1995; 4:447–451. [PubMed: 7549798]
8. Kisielewski R, Tolwiska A, Mazurek A, Laudański P. Inflammation and ovarian cancer--current views. *Ginekol Pol*. 2013; 84:293–297. [PubMed: 23700863]
9. Trabert B, Ness RB, Lo-Ciganic WH, Murphy MA, Goode EL, Poole EM, Brinton LA, Webb PM, Nagle CM, Jordan SJ, Risch HA, Rossing MA, Doherty JA, Goodman MT, Lurie G, Kjær SK, Hogdall E, Jensen A, Cramer DW, Terry KL, Vitonis A, Bandera EV, Olson S, King MG, Chandran U, Anton-Culver H, Ziogas A, Menon U, Gayther SA, Ramus SJ, Gentry-Maharaj A, Wu AH, Pearce CL, Pike MC, Berchuck A, Schildkraut JM, Wentzensen N. Australian Ovarian Cancer Study Group Australian Cancer Study (Ovarian Cancer), Ovarian Cancer Association Consortium. Aspirin, nonaspirin nonsteroidal anti-inflammatory drug, and acetaminophen use and risk of invasive epithelial ovarian cancer: a pooled analysis in the Ovarian Cancer Association Consortium. *J Natl Cancer Inst*. 2014; 106:djt431. [PubMed: 24503200]
10. Macciò A, Madeddu C. Inflammation and ovarian cancer. *Cytokine*. 2012; 58:133–147. [PubMed: 22349527]
11. Kurman RJ, Shih IeM. Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer--shifting the paradigm. *Hum Pathol*. 2011; 42:918–931. [PubMed: 21683865]
12. Yates MS, Meyer LA, Deavers MT, Daniels MS, Keeler ER, Mok SC. Microscopic and early-stage ovarian cancers in BRCA1/2 mutation carriers: building a model for early BRCA-associated tumorigenesis. *Cancer Prev Res*. 2011; 4:463–470.

13. Parazzini F, La Vecchia C, Negri E, Moroni S, dal Pino D, Fedele L. Pelvic inflammatory disease and risk of ovarian cancer. *Cancer Epidemiol Biomarkers Prev.* 1996; 5:667–669. [PubMed: 8824371]
14. Lin HW, Tu YY, Lin SY, Su WJ, Lin WL, Lin WZ, Wu SC, Lai YL. Risk of ovarian cancer in women with pelvic inflammatory disease: a population-based study. *Lancet Oncol.* 2011; 12:900–904. [PubMed: 21835693]
15. McAlpine JN, Lisonkova S, Joseph KS, McComb PF. Pelvic inflammation and the pathogenesis of ovarian cancer: a cohort study. *Int J Gynecol Cancer.* 2014; 24:1406–1413. [PubMed: 25191876]
16. Lareau SM, Beigi RH. Pelvic inflammatory disease and tubo-ovarian abscess. *Infect Dis Clin N Am.* 2008; 22:693–708.
17. Merritt MA, Green AC, Nagle CM, Webb PM. Australian Cancer Study (Ovarian Cancer), Australian Ovarian Cancer Study Group. Talcum powder, chronic pelvic inflammation and NSAIDs in relation to risk of epithelial ovarian cancer. *Int J Cancer.* 2008; 122:170–176. [PubMed: 17721999]
18. Wu AH, Pearce CL, Tseng CC, Templeman C, Pike MC. Markers of inflammation and risk of ovarian cancer in Los Angeles County. *Int J Cancer.* 2009; 124:1409–1415. [PubMed: 19065661]
19. Stewart LM, Holman CD, Aboagye-Sarfo P, Finn JC, Preen DB, Hart R. In vitro fertilization, endometriosis, nulliparity and ovarian cancer risk. *Gynecol Oncol.* 2013; 128:260–264. [PubMed: 23116937]
20. Rasmussen CB, Jensen A, Albieri V, Andersen KK, Kjaer SK. Is pelvic inflammatory disease a risk factor for ovarian cancer? *Cancer Epidemiol Biomarkers Prev.* 2017; 26:104–109. [PubMed: 27672055]
21. Rasmussen CB, Faber MT, Jensen A, Hogdall E, Hogdall C, Blaakaer J, Kjaer SK. Pelvic inflammatory disease and risk of invasive ovarian cancer and ovarian borderline tumors. *Cancer Causes Control.* 2013; 24:1459–1464. [PubMed: 23615817]
22. Shen CC, Hu LY, Yang AC, Chiang YY, Hung JH, Tsai SJ. Risk of uterine, ovarian and breast cancer following pelvic inflammatory disease: a nationwide population-based retrospective cohort study. *BMC Cancer.* 2016; 16:839. [PubMed: 27809870]
23. Rasmussen CB, Jsensen A, Albieri V, Andersen KK, Kjaer SK. Increased risk of borderline ovarian tumors in women with a history of pelvic inflammatory disease: A nationwide population-based cohort study. *Gynecol Oncol.* 2016; 143:346–351. [PubMed: 27549433]
24. Shu XO, Brinton LA, Gao YT, Yuan JM. Population-based case-control study of ovarian cancer in Shanghai. *Cancer Res.* 1989; 49:3670–3674. [PubMed: 2731180]
25. Ness RB, Grisso JA, Cottreau C, Klapper J, Vergona R, Wheeler JE, Morgan M, Schlesselman JJ. Factors related to inflammation of the ovarian epithelium and risk of ovarian cancer. *Epidemiology.* 2000; 11:111–117. [PubMed: 11021606]
26. Wells, GA., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., Tugwell, P. [Accessed June 18 2016] The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. 2011. www.ohri.ca/programs/clinical_epidemiology/oxford.asp
27. Higgins, JPT., Green, S. [Accessed 08 August 2016] Cochrane handbook for systematic reviews of interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration. 2011. www.handbook.cochrane.org
28. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7:177–188. [PubMed: 3802833]
29. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002; 21:1539–1558. [PubMed: 12111919]
30. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; 327:557–560. [PubMed: 12958120]
31. Sterne JA, Egger M. Funnel plots for detecting bias in meta-analysis: guidelines on choice of axis. *J Clin Epidemiol.* 2001; 54:1046–1055.
32. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994; 50:1088–1101. [PubMed: 7786990]
33. Rasmussen CB, Kjaer SK, Albieri V, Bandera EV, Doherty JA, Høgdall E, Webb PM, Jordan SJ, Rossing MA, Wicklund KG, Goodman MT, Modugno F, Moysich KB, Ness RB, Edwards RP,

- Schildkraut JM, Berchuck A, Olson SH, Kiemeny LA, Massuger LF, Narod SA, Phelan CM, Anton-Culver H, Ziogas A, Wu AH, Pearce CL, Risch HA, Jensen A. on behalf of the Ovarian Cancer Association Consortium. Pelvic Inflammatory Disease and the Risk of Ovarian Cancer and Borderline Ovarian Tumors: A Pooled Analysis of 13 Case-Control Studies. *Am J Epidemiol*. 2016; 185:8–20. [PubMed: 27941069]
34. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. *Int J Cancer*. 2007; 121:2373–2380. [PubMed: 17893866]
35. Wang X, Wang E, Kavanagh JJ, Freedman RS. Ovarian cancer, the coagulation pathway, and inflammation. *J Transl Med*. 2005; 3:25. [PubMed: 15969748]
36. Whittemore AS, Harris R, Itnyre J. Characteristics relating to ovarian cancer risk: collaborative analysis of 12 US case-control studies. II. Invasive epithelial ovarian cancers in white women. Collaborative Ovarian Cancer Group. *Am J Epidemiol*. 1992; 136:1184–1203. [PubMed: 1476141]
37. Wang LY, OuYang L, Tong F, Zhang XJ, Li XD, Wang CC, Li X, Sun L, Sun YH. The effect of contraceptive methods on reproductive tract infections risk: a cross-sectional study having a sample of 52,481 women. *Arch Gynecol Obstet*. 2016; 294:1249–1256. [PubMed: 27538571]
38. Riman T, Nilsson S, Persson IR. Review of epidemiological evidence for reproductive and hormonal factors in relation to the risk of epithelial ovarian malignancies. *Acta Obstet Gynecol Scand*. 2004; 83:783–795. [PubMed: 15315588]
39. He J, Gao X, Ren Z. Global Incidence Patterns of Female Breast and Ovarian Cancers. *Chin Canc*. 2009; 18:169–172.
40. Beavis AL, Smith AJ, Fader AN. Lifestyle changes and the risk of developing endometrial and ovarian cancers: opportunities for prevention and management. *Int J Womens Health*. 2016; 8:151–167. [PubMed: 27284267]
41. Marshall M, Solomon S. Hereditary breast-ovarian cancer: clinical findings and medical management. *Plast Surg Nurs*. 2007; 27:124–127. [PubMed: 17901820]

Fig. 1.
Flow chart of study selection in the current meta-analysis

Fig. 2.

Forest plots of the association between pelvic inflammatory disease and ovarian cancer risk

Fig. 3.
Funnel plot of the association between pelvic inflammatory disease and ovarian cancer risk

Table 1

Characteristics of studies included in the meta-analysis

First author, year (Ref. no.)	Ethnicity	Study period	Cases	Controls/total sample size	Exposure & Exposure assessment	Outcome & Outcome assessment	Covariates
Case-control studies							
Shu, 1989 [24]	Asian	1984–1986	229	229 population-based	Pelvic infection: information was collected through direct interviews by trained interviewers.	Invasive ovarian cancer only (75.1% were epithelial, 7.4% were germ cell, 10.5% were sex cord, and 7.0% were other or undefined types), and borderline-type ovarian tumors were excluded. Cases were accrued from a population-based cancer register. 94.3% of the cases were histologically confirmed, with the remainder being diagnosed either through ultrasound (3.1%) or clinical examination (2.6%).	Education, number of live births, ovarian cyst, and age at menarche
Risch, 1995 [7]	Caucasian	1989–1992	450	564 population controls	History of PID (internal pelvic infection): assessed through in-person interviews. Vaginal infections or bladder infections were not included. The ages (or calendar years) for up to the first two episodes were recorded.	Histologically confirmed primary, malignant, or borderline malignant epithelial ovarian tumors, cancer registry; Regular review of all relevant hospital and laboratory pathology reports received in the province-wide operations of the Ontario Cancer Registry enabled ascertainment of the population-based sample.	Age (categorical and continuous), total years of oral contraceptive use, number of full-term pregnancies, total duration of breastfeeding, ever having a tubal ligation, a hysterectomy, and a mother or sister with ovarian or breast cancer
Parazzini, 1996 [13]	Caucasian	1983–1991	971	2,758 hospital-based	History of PID/salpingitis: assessed by trained interviewers and further checked with clinical records. Vaginal or bladder infections were NOT considered as an episode of PID.	Histologically confirmed epithelial ovarian cancer, hospital source; Data were collected from a network of hospitals, including the main teaching and general hospitals in the greater Milan area, Northern Italy.	Age, education, parity, family history of ovarian cancer, menopausal status, oral contraceptive use, and any pelvic surgery
Ness, 2000 [25]	Caucasian	1994–1998	766 ^a	1,362 ^a population-based	PID: assessed by standardized interviews conducted in the homes of participating women by trained interviewers...	Histologically confirmed 616 invasive epithelial ovarian cancer and 151 borderline epithelial ovarian tumors, hospital source; cases were ascertained from 39 hospitals around the Delaware Valley.	Age, number of pregnancies, family history of ovarian cancer, race, oral contraceptive use, tubal ligation, hysterectomy, and breast-feeding

First author, year (Ref. no.)	Ethnicity	Study period	Cases	Controls/total sample size	Exposure & Exposure assessment	Outcome & Outcome assessment	Covariates
Merritt, 2008 [17]	Caucasian	2002–2005	1,563	1,490 population-based	PID: Study participants filled in a comprehensive health and lifestyle questionnaire	Invasive and low malignant potential epithelial ovarian tumors, ascertained from hospitals and cancer registries Australia-wide; Histopathology abstraction and review confirmed the diagnosis.	Age, education, parity, and oral contraceptive pill use
Wu, 2009 [18]	Caucasian	1998–2002	604 ^a	679 ^a population-based neighborhood controls	Physician-diagnosed PID: assessed by in-person interviews (except 15 participants) using a comprehensive questionnaire. Age at first diagnosis and ever-treatment was also asked.	Histologically confirmed invasive (81%) or borderline (19%) epithelial ovarian tumors; The cases were identified by the Cancer Surveillance Program (CSP), part of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, covering all residents of Los Angeles County.	Race/ethnicity, age, education, tubal ligation, family history of breast/ovarian cancer, menopausal status, use of oral contraceptives and parity
Rasmussen, 2013 [21]	Caucasian	1995–1999	748 ^a	1,557 ^a population-based	History of physician-diagnosed PID (an infection in the uterus or fallopian tubes): assessed through in-person interviews by trained nurses.	Histologically verified epithelial ovarian tumors: 548 invasive ovarian cancer, and 200 ovarian borderline tumors ^a . Cases were recruited from 16 gynecological departments in Denmark and verified through linkage to the Danish Cancer Registry. Pathology reports were reviewed and histopathological review of the tissue specimens was performed in 30% of cases..	Age, pregnancy, oral contraceptive use, hormone replacement therapy use, and family history of ovarian and/or breast cancer
Cohort studies							
Lin, 2011[14]	Asian	Study period/mean duration of follow-up 2004–2006/3 yrs ^b	90 (42 in PID cohort; 48 in control cohort)	203,808 (67,936 women with PID; 135,872 controls)	PID diagnoses had been made on the basis of the patient's medical history, clinical features at presentation, and findings from bimanual palpation, ultrasonography, culture of vaginal samples, and laboratory data. PID was classified with the ICD codes 614, 615, and 616 (ninth revision, clinical modification). Patients with	A diagnosis of ovarian cancer was based on the presence of a pelvic mass on imaging (CT, MRI, and ultrasonography) recorded in the Longitudinal Health Insurance Database 2005 (LHID 2005).	Age, monthly income, degree of urbanisation, cardiovascular disease, diabetes mellitus, chronic liver disease, rheumatic disease, and endometriosis

First author, year (Ref. no.)	Ethnicity	Study period	Cases	Controls/total sample size	Exposure & Exposure assessment	Outcome & Outcome assessment	Covariates
Stewart, 2013 [19]	Caucasian	1982–2002/17 yrs	38	21,646	only one record of PID were excluded. Diagnoses of pelvic inflammatory disorders (PID) were collated from the Hospital Morbidity Data System from 1980 to 2010 (covering the recruitment period plus 2 years before and 8 years after). PID – ICD-9 codes 614.0–614.9; ICD-10 codes N70.1, N70.9, N73.0–N73.9. PID diagnoses recorded in hospital records at or prior to the start of follow-up (first infertility admission) were included.	Invasive epithelial ovarian cancer. Cases were identified from the Western Australia (WA) cancer registry; The study cohort and outcomes of interest were identified using the resources of the WA Data Linkage System	Age at the start of follow-up
McAlpine, 2014 [15]	Caucasian	1981–2012/20.3 yrs in the inflammation cohort; 18.4 yrs in the control cohort	7 (6 in the inflammation cohort; 1 in the control cohort)	1,440 (888 in the inflammation cohort; 552 in the control cohort)	Past pelvic inflammation (salpingo-oophoritis, repair of fimbrial phimosis, terminal salpingostomy, and tubo-cornual anastomosis) was assessed by a sole gynecologist trained in fertility surgery.	Epithelial ovarian cancer and borderline ovarian tumors. Cases were identified through linkage to the British Columbia Cancer Agency (BCCA) database and reviewed for clinicopathological parameters of interest.	Age, smoking, age at surgery, year of surgery, parity, gravidity, and history of oligo/amenorrhea and endometriosis
Rasmussen, 2016 invasive [20]	Caucasian	1978–2012/35.0 yrs	5,356 (246 in PID cohort, and 5,110 in non-PID cohort)	1,318,929 (81,281 women with PID, and 1,237,648 women with no PID)	The study cohort was linked to the Danish National Patient Registry to identify all women with a diagnosis of PID from January 1, 1978 to December 31, 2011. PID was defined as an upper genital tract infection, including endometritis, salpingitis, oophoritis, pelvic peritonitis, and tubo-ovarian abscess and coded according to ICD-8 during 1977–1993 and ICD-10 during 1994–2011.	Histologically verified invasive epithelial ovarian cancer (2784 serous, 651 mucinous, 738 endometrioid, 307 clear cell, and 876 other epithelial ovarian cancers). Cases were identified by linkage to the Danish Cancer Registry.	Parity, endometriosis, hysterectomy, and tubal ligation
Rasmussen, 2016 borderline [23]	Caucasian	1978–2012/35.0 yrs	2,736 (185 in PID cohort, and 2,551 in non-PID cohort)	1,318,925 (81,263 with PID, 1,237,662 with no PID)	The study cohort was linked to the Danish National Patient Registry to identify all women with a diagnosis of PID from January 1, 1978 to December 31, 2011. PID was defined as an upper genital tract	Epithelial borderline ovarian tumors (1290 serous, 1344 mucinous and 102 other). Cases were identified through linkage to the Pathology Data Bank, which holds information on all pathological	Adjusted for parity status

First author, year (Ref. no.)	Ethnicity	Study period	Cases	Controls/total sample size	Exposure & Exposure assessment	Outcome & Outcome assessment	Covariates
Shen, 2016 [22]	Asian	2000–2009/8.84 yrs for both PID and controls	58 (34 in PID cohort; 24 in control cohort)	64,536 (32,268 PID patients; and 32,268 controls without PID)	infection, including endometritis, salpingitis, oophoritis, pelvic peritonitis, and tubo-ovarian abscess. PID: Patients who were newly diagnosed with PID by an obstetrician- gynecologist between January 1st, 2000 and December 31st, 2002. Only patients who had at least two consensus PID diagnoses were included.	diagnoses from all Danish Pathology Departments. Histologically confirmed ovarian cancer cases reported in the Registry for Catastrophic Illness.	Age, hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, urbanization and income

CI, confidence interval; HR, hazard ratio; OR, odds ratios

^aThe case and control numbers were derived from tables which showed the numbers with PID and without PID and did not match with the total case and control numbers due to missing PID information.

^bmaximum 3 years of follow-up for the Lin study

Table 2

Quality assessment of included studies based on Newcastle–Ottawa scale

Author	year	Selection	Comparability	Exposure/Outcome	Total score
Case-control studies					
Shu [24]	1989	3	1	2	6
Risch [7]	1995	4	1	2	7
Parazzini [13]	1996	4	1	2	7
Ness [25]	2000	3	1	2	6
Merritt [17]	2008	4	1	2	7
Wu [18]	2009	3	1	2	6
Rasmussen [21]	2016	4	1	2	7
Cohort studies					
Lin [14]	2011	4	1	2	7
Stewart [19]	2013	3	2	3	8
McAlpine [15]	2014	3	1	3	7
Rasmussen invasive [20]	2016	4	1	3	8
Rasmussen borderline [23]	2016	4	1	3	8
Shen [22]	2016	4	1	3	8

Table 3
Total, stratified, and influence analyses of the associations between pelvic inflammatory disease and ovarian cancer

	No. of studies	Reference					<i>p</i> ^d
		RR ^a	RR (95% CIs) ^a	<i>p</i> ^b	<i>I</i> ²	<i>p</i> ^c	
Overall	13 ^e [7, 13–15, 17–25]	1.00	1.24 (1.06, 1.44)	0.007	58.8	0.003	
Stratified analyses							
Race							0.054
Asian	3 [14, 22, 24]	1.00	1.69 (1.22, 2.34)	0.002	0	0.504	
Caucasian	10 [7, 13, 15, 17–21, 23, 25]	1.00	1.18 (1.00, 1.39)	0.046	60.7	0.005	
Study design							0.472
Cohort studies	6 [14, 15, 19, 20, 22, 23]	1.00	1.32 (1.05, 1.66)	0.016	64.7	0.015	
Case-control studies	7 [7, 13, 17, 18, 21, 24, 25]	1.00	1.17 (0.93, 1.49)	0.186	57.6	0.021	
Tumor invasiveness^f							0.083
Invasive ovarian cancer only	5 [7, 19–21, 24]	1.00	1.06 (0.85, 1.32)	0.609	50.0	0.092	
Borderline ovarian tumors only	3 [7, 21, 23]	1.00	1.42 (1.25, 1.63)	<0.001	0	0.756	
Combined ovarian cancer and borderline ovarian tumors	7 [13–15, 17, 18, 22, 25]	1.00	1.30 (0.99, 1.70)	0.057	38.9	0.132	
Adjustment for parity							0.887
Not adjusted	7 [14, 17, 19, 21, 22, 24, 25]	1.00	1.26 (0.98, 1.61)	0.076	57.7	0.020	
Adjusted	6 [7, 13, 15, 18, 20, 23]	1.00	1.23 (0.99, 1.54)	0.063	66.3	0.011	
Adjustment for family history of ovarian cancer							0.166
Not adjusted	9 [7, 14, 15, 17, 18, 20, 22–24]	1.00	1.34 (1.13, 1.58)	0.001	52.1	0.033	
Adjusted	4 [13, 19, 21, 25]	1.00	1.03 (0.74, 1.44)	0.862	60.5	0.038	
Adjustment for oral contraceptive use							0.421
Not adjusted	7 [14, 15, 19, 20, 22–24]	1.00	1.33 (1.06, 1.67)	0.012	59.3	0.022	
Adjusted	6 [7, 13, 17, 18, 21, 25]	1.00	1.16 (0.91, 1.48)	0.221	62.1	0.015	
Influence analyses^g							
Minimal ^h	12	1.00	1.19 (1.02, 1.39)	0.023	54.4	0.01	
Maximal ⁱ	12	1.00	1.27 (1.07, 1.52)	0.007	54.4	0.01	

CI: confidence interval

^aRRs and 95% CIs were pooled by using the random effects model (the DerSimonian and Laird method)

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q p value of Z-test for significance of pooled RRs and 95% CIs
 c p value for between study heterogeneity test
 d p value for between-group heterogeneity test

e Rasmussen et al. 2013 [21] only reported results of invasive ovarian cancer and borderline ovarian tumors separately and contributed both invasive and borderline tumor data to the overall pooled estimates.
 f Both Risch et al. 1995 [7] and Rasmussen et al. 2013 [21] contributed data to both invasive cancer and borderline tumor subgroups. According to egger's test, $pr > |z| = 0.843$, hence no publication bias was found.

g Influence analysis was conducted by eliminating one study at a time.

h For minimal pooled RRs, the excluded study was the Lin et al. 2011 study [14].

i For maximal pooled RRs, the excluded study was the Rasmussen et al. 2016 invasive ovarian cancer study [20].