Review

Does smoking increase risk of ovarian cancer? A systematic review

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Abstract

Objectives. Although early reports suggested that smoking was not associated with ovarian cancer risk, recent studies have reported positive associations for cancers of the mucinous subtype. We sought to clarify the relationship between smoking and ovarian cancer by histological subtype.

Methods. We conducted a systematic literature review and meta-analysis of studies investigating the association between smoking and risk of the different histological subtypes of epithelial ovarian cancer. Eight population-based case–control studies, one pooled analysis of case–control studies, and one cohort study met the inclusion criteria. Summary relative risks (RR), 95% confidence intervals (CI), and tests for heterogeneity were generated from random effects models.

Results. Combined, these studies included a total of 910 women with mucinous and 5564 with non-mucinous ovarian cancers. There was a significant doubling of risk of mucinous ovarian cancer in current smokers compared to never smokers (summary RR 2.1, 95%CI 1.7–2.7), but no increased risk of serous (1.0, 95%CI 0.8–1.2) or endometrioid (0.8, 95%CI 0.6–1.1) cancers and a significant risk reduction for clear cell cancers (0.6, 95%CI 0.3–0.9). The risk of mucinous cancer increased with increasing amount smoked but returned to that of never smokers within 20–30 years of stopping smoking.

Conclusions. Meta-analysis suggests that current smoking doubles a woman’s risk of developing mucinous ovarian cancer. Stopping smoking returns the risk to normal in the long term. Smoking may thus be one of the few modifiable factors offering potential for primary prevention of mucinous ovarian cancer.

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Keywords: Ovarian cancer; Histological subtype; Smoking; Meta-analysis; Risk factor

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Introduction

Epithelial ovarian cancer is a major cause of cancer death among women [1] and although important risk factors for the disease have been identified, few are readily modifiable [2]. Tobacco smoking is a modifiable cause of many types of cancer, but whether it influences a woman’s risk of ovarian cancer is not clear. Earlier reports mostly suggested that smoking was not associated with an increased risk of ovarian cancer [3–5]. There are, however, several different histological subtypes of ovarian cancer and evidence is accumulating to suggest that these subtypes, particularly the mucinous tumours, may arise via different causal pathways [2,6,7]. Recent studies investigating the relation between smoking and ovarian cancer have evaluated the different histological subtypes separately, reporting positive associations for mucinous tumours but not the other subtypes [8,9]. Results from a recently published pooled analysis of 10 case–control studies also suggest a specific relationship between smoking and invasive mucinous ovarian cancers [10]. This latter analysis was limited however, being restricted to US-based studies conducted mostly in the 1970s and 1980s and evaluating neither the effects of the amount of smoking nor time since stopping smoking. In addition, the relationship between smoking and borderline (low malignant potential) mucinous cancers was not assessed, and the results of a number of more recent population-based studies conducted outside the US were not included.

Smoking rates among women, particularly girls and young women, are increasing in most developed and developing regions [11,12] thus clarification of the relationship between smoking and mucinous ovarian cancers and the effects of smoking cessation is timely. Hence, we have conducted a systematic literature review and meta-analysis of the association between tobacco smoking and risk of epithelial ovarian cancer. Our aims were firstly to quantify the association separately for the different histological subtypes of ovarian cancer and invasive versus borderline tumours and, secondly, to evaluate the effects of amount and duration of smoking and, for past smokers, time since quitting smoking.

Materials and methods

We undertook a Medline® (1966–March 2005) search using the search terms “ovary or ovarian”, “cancer or neoplasm or carcinoma,” and “smoking or tobacco” and the search strategy developed by Haynes and colleagues [13] to identify etiologic studies. We identified additional studies by searching the reference lists of identified papers. Studies were considered eligible if they presented data pertaining to the relationship between smoking and epithelial ovarian cancer separately for the different histological subtypes of ovarian cancer and included adjustment for major ovarian cancer risk factors including age and parity and/or oral contraceptive use. The following information was extracted for all eligible studies: year of publication; country in which the study was conducted; type of study (cohort or case–control); the sampling frame for controls (population-based or hospital-based/other); numbers of cases and controls (or cohort size); and whether the study included invasive and/or borderline tumours. For the present review, we excluded hospital-based case–control studies a priori, because it is widely considered that smoking habits among hospitalised women do not reflect those of women in general and could thus lead to biased estimates of risk [14].

From the eligible studies that met the inclusion criteria, we extracted relative risks and confidence intervals for the association between smoking and ovarian cancer and recorded the factors adjusted for in the analyses. Where available in the published report, data were extracted relating to smoking status (never, ever, current or past), number of cigarettes smoked per day, duration of smoking in years, pack-years of smoking (where one pack-year is equivalent to smoking 20 cigarettes per day for one year) and time since quitting smoking. For accuracy, the extracted data were checked independently by two authors (SJ and PW).

Statistical analysis

We grouped the results from each study according to smoking status (never, past, current smoker) and number of pack-years smoked as these measures were most frequently reported. Some overlapping of the categories of number of pack-years smoked across studies was required to accommodate the different cut-points set by each study. The lowest category included women who had fewer than ten pack-years of smoking. Women in the medium category had between five and 24 pack-years of smoking, while those in the high category had 20–30 pack-years of smoking. The very high category included women who reported 30 or more pack-years of smoking. For our primary analyses, we included all ovarian tumours, both borderline and invasive, because several of the studies did not distinguish the two tumour types [8,9,15]. We then conducted secondary analyses examining borderline and invasive tumours separately, restricted to those studies which presented suitable data [16–21].

We estimated summary relative risks (RR) and 95% confidence intervals (CI) for the association between smoking and ovarian cancer from random effects models which were also used to test for heterogeneity of effect across studies. When the outcome is rare, as for ovarian cancer, the odds ratio in a case–control study is a good approximation of the rate ratio from a cohort study. We thus combined the odds ratios from the case–control studies with the rate ratio from the single cohort study. The results are also presented graphically using forest plots where each square and line represents the relative risk and confidence interval from a single study. The size of the square is inversely proportional to the variance of the logarithm of the RR, thus studies contributing more information are represented by larger squares. The diamond at the bottom of each plot represents the summary RR and CI for the studies combined. All analyses were conducted using the STATA statistical package [22].

Results

Overall we identified 33 reports from 30 individual studies that evaluated the association between smoking and ovarian cancer [3–5,8,9,15–21,23–42], 10 of which had considered the different histological subtypes separately [8,9,15–21,41]. One of these studies had used hospitalised patients as controls [41] and was excluded from the present analyses leaving eight reports from seven population-based case–control studies [8,9,15–20] and one prospective cohort study [21]. Results for invasive and borderline tumours were published separately for one of the case–control studies [17,20] thus for the purposes of clarity the two reports will be considered as separate studies. In addition, we identified a pooled analysis that combined the raw data from 10 US-based case–control studies [10] including one of the population-based studies above [8] and another nine studies that had not previously reported sub-type specific results. As 80% of the control subjects included in the pooled analysis were recruited from the general population and only 20% were hospital-based, we have, where possible, included the pooled data in our analysis in place of the single report by Marchbanks et al. [8]. To ensure that inclusion of this minority of hospital controls did not unduly affect our results, we also repeated the analyses excluding the pooled data and have
presented those results in the text. The included studies were thus undertaken in the USA (3940 cases), Canada (896 cases), Australia (794 cases) and Sweden (844 cases).

Collectively, the eligible case–control studies and the pooled analysis included data from 6020 women with incident epithelial ovarian cancer (including 878 with mucinous tumours) and 16,863 control women (Table 1). Five included women with either borderline or invasive tumours [8,9,15,18,19], two additional studies and the pooled analysis included only women with invasive cancer [16,20], while one was restricted to women with borderline tumours [17]. The cohort study included 454 women diagnosed with invasive epithelial ovarian cancer (including 32 mucinous cases) in a cohort of 89,835 women [21].

Seven percent of the case women in the cohort study had mucinous tumours while the corresponding percentages in the case–control studies were somewhat higher (due to the inclusion of borderline tumours), ranging between 9% and 20% (excluding the study of borderline tumours in which 42% were mucinous). Smokers were defined variously by the different studies as those who had smoked daily for a period of six or more months [9,19], those who had smoked daily for 12 or more months [18], or those who had smoked more than 100 cigarettes in their lives [8,15,16]. Current smokers were generally defined as women who had been smoking within 6 to 12 months of diagnosis (cases) or interview (controls). Two reports divided current smokers into those who smoked 10 or fewer cigarettes per day and those who smoked more than 10 per day [17,20], so we included the results for those who smoked more than 10 per day in our analyses of current smokers. In the one cohort study, the smoking data relate to status at the time of recruitment into the cohort [21]. Among the control women, the proportion of ever-smokers ranged from 38% to 55%, while 13% to 40% were current smokers. Five of the case–control studies reported data for amount of smoking measured variously as pack-years (4

<table>
<thead>
<tr>
<th>Study, country</th>
<th>Design</th>
<th>Cases/ Controls</th>
<th>Years of diagnosis</th>
<th>Invasiveness</th>
<th>Histological subtypes</th>
<th>Proportion of smokers among controls (person-years)</th>
<th>Adjusting factors*</th>
</tr>
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<tbody>
<tr>
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<td>1/2/3/4/5</td>
<td></td>
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<tr>
<td>Kuper 2000, USA [15]</td>
<td>Case–control</td>
<td>549/516</td>
<td>1992–1997</td>
<td>Invasive and borderline</td>
<td>M 14% S 56% O 30%</td>
<td>48% Not given</td>
<td>Yes Yes Yes Yes Yes</td>
</tr>
<tr>
<td>Marchbanks 2000, USA [8]</td>
<td>Case–control</td>
<td>447/3868</td>
<td>1980–1982</td>
<td>Invasive and borderline</td>
<td>M 18% S 52% E 19% O 11%</td>
<td>44% 36%</td>
<td>Yes Yes No No No</td>
</tr>
<tr>
<td>Green 2001, Australia [18]</td>
<td>Case–control</td>
<td>794/855</td>
<td>1990–1993</td>
<td>Invasive and borderline</td>
<td>M 14% S 57% O 1%</td>
<td>62% 16%</td>
<td>No Yes No Yes Yes</td>
</tr>
<tr>
<td>Riman 2001, Sweden [17]</td>
<td>Case–control</td>
<td>193/3899</td>
<td>1993–1995</td>
<td>Borderline only</td>
<td>M 15% NM 85%</td>
<td>51% 28%</td>
<td>Yes Yes No No No</td>
</tr>
<tr>
<td>Modugno 2002, USA [9]</td>
<td>Case–control</td>
<td>767/1367</td>
<td>1994–1998</td>
<td>Invasive and borderline</td>
<td>M 20% NM 80%</td>
<td>46% 23%</td>
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</tr>
<tr>
<td>Goodman 2003, USA (Hawaii and Los Angeles) [19]</td>
<td>Case–control</td>
<td>558/607</td>
<td>1993–1999</td>
<td>Invasive and borderline</td>
<td>M 7% S 38%</td>
<td>60% 13%</td>
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</tr>
<tr>
<td>Terry 2003, Canada [21]</td>
<td>Cohort</td>
<td>454/89,835</td>
<td>1980–2000</td>
<td>Invasive</td>
<td>M 12% S 52% E 27% O 18%</td>
<td>51% 22%</td>
<td>Yes Yes No No Yes</td>
</tr>
<tr>
<td>Pan 2004, Canada [16]</td>
<td>Case–control</td>
<td>442/2135</td>
<td>1994–1997</td>
<td>Invasive</td>
<td>M 16% NM 84%</td>
<td>51% 20%</td>
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</tr>
<tr>
<td>Riman 2004, Sweden [20]</td>
<td>Case–control</td>
<td>651/3873</td>
<td>1993–1995</td>
<td>Invasive</td>
<td>M 9% S 51% E 27% O 12%</td>
<td>57% 22%</td>
<td>Yes Yes No No No</td>
</tr>
<tr>
<td>Kurian 2005, USA [10]</td>
<td>Pooled analysis of case–control studies</td>
<td>2066/7484</td>
<td>1973–2001</td>
<td>Invasive</td>
<td>M 12% S 52% E 18% O 18%</td>
<td>46% 32%</td>
<td>Yes Yes No No No</td>
</tr>
</tbody>
</table>

Abbreviations: E, endometrioid; M, mucinous; NM, non-mucinous; O, other; S, serous.

* Adjusting factors: all studies adjusted for age with additional adjustment for (1) parity; (2) oral contraceptive use; (3) family history; (4) tubal ligation; (5) education; as noted. When adjustment was not made for listed confounders this was generally because inclusion of these factors did not substantially change the point estimates.

b Includes the data for invasive cancer from Marchbanks et al., 2000. Analyses include either the pooled analysis (where possible) or Marchbanks et al.
studies), cigarettes per day (3 studies), and/or duration of smoking (2 studies). The variable pack-years was thus used in this review to evaluate the association with amount of smoking.

*Serous cancers*

Three studies and the pooled analysis presented results for serous cancers separately. For a further four studies, we included the published risk estimates for non-mucinous tumours in this analysis because serous cancers account for a high proportion of such cancers. The results for current and past smokers compared to never smokers are shown in Figs. 1(a) and (b), respectively. Five of the studies, including the pooled analysis, found no association between smoking and risk of serous ovarian cancer while one found a significant 60% increased risk of serous cancer for current smokers[18] and another reported a marginally significant 28% increase in risk associated with past but not current smoking[16]. One study reported significant reductions in risk of serous invasive cancers among both former and current smokers[20].

There was no significant heterogeneity between the reported relative risks for serous tumours in past smokers (heterogeneity $\chi^2 = 10.7$ on 7 degrees of freedom[43], $p = 0.2$), but there was some heterogeneity among the results for current smokers ($\chi^2 = 14.7, df = 7, p = 0.04$). Overall, compared to never smokers, the summary relative risk of serous tumours was 1.0 (95%CI 0.8–1.2) for current smokers and 1.0 (95%CI 0.9–1.2) for past smokers. We repeated the meta-analysis excluding the data from the pooled analysis[10] and obtained identical results with a summary OR of 1.0 (95%CI 0.8–1.2) for current smokers and 1.0 (95%CI 0.9–1.2) for past smokers.

Of the four case–control studies that evaluated the relation with pack-years, three reported no association[8,9,16] while one found a significant 60% increased risk of serous tumours among women with more than 30 pack-years of smoking (data not shown)[18]. One of the remaining case–control studies reported a significant increase in risk of invasive serous cancers with years of tobacco use ($p$ for trend = 0.05), but not for number of cigarettes smoked per day[15], while the single cohort study also reported an increased risk of serous cancers but only among women who had smoked for more than 40 years[21]. In contrast, one study reported a significant reduction in risk of invasive serous ovarian cancer with increasing number of cigarettes smoked per day[20].

*Mucinous cancers*

The results of the studies that presented relative risks of mucinous cancers for current and past smokers compared to never smokers are shown in Figs. 1(c) and (d), respectively. One
of the studies [19] found no significant association between smoking and risk of mucinous ovarian cancer and a second study found no significant association for invasive mucinous cancers [20] although in both cases the point estimate was greater than one. The other studies all reported statistically significant two to three-fold increases in risk of mucinous ovarian cancer with current smoking. There was no significant heterogeneity between the results of the different studies (current smokers $\chi^2 = 6.5$, $df = 7$, $p = 0.5$; past smokers: heterogeneity $\chi^2 = 7.5$ on $df = 7$, $p = 0.4$). Women who were current smokers had a significant 2.1-fold increased risk of mucinous cancers compared to never smokers (95%CI 1.7–2.7), while the summary relative risk for past smoking versus never smoking was 1.1 (95%CI 0.9–1.4). When the data from the previous pooled analysis were excluded and the analysis repeated, almost identical results were seen with a summary OR of 2.1 (95%CI 1.6–2.8) for current smokers and 1.2 (95%CI 0.9–1.5) for past smokers. Although they did not present relative risks, Kuper et al. also reported a ‘doubling in risk’ of mucinous cancer for women who smoked more than an average of 40 cigarettes per day [15].

There was also a suggestion that the relative risk associated with smoking was somewhat higher for borderline than invasive mucinous tumours. The summary of relative risk for borderline mucinous tumours derived from the three studies that evaluated this was 2.4 (95%CI 1.4–4.1) [17–19] while a fourth study reported a 2.5-fold increase in risk for ever-smoking for borderline tumours [8]. In comparison, the estimate for invasive mucinous cancer derived from the same three studies was 1.4 (95%CI 0.8–2.4) while combining the data from all six studies that had presented relevant data [10,16,18–21] gave an OR of 2.0 (95%CI 1.5–2.7).

All four studies that presented results by pack-years smoked reported a significant increase in risk of mucinous ovarian cancer with increasing pack-years (Fig. 2) [8,9,16,18]. Compared to women who had never smoked, the summary relative risk for women in the group reporting the lowest number of pack-years smoked was 1.5 (95%CI 1.0–2.4); in the medium group it was 2.4 (95%CI 1.8–3.2); in the high group it was 2.9 (95%CI 2.0–4.1); and in the very high group it was 2.5 (95%CI 1.5–4.2). The same four studies also examined risk of mucinous ovarian cancer with time since quitting smoking. All four found the risk decreased with increasing time since stopping smoking and approached that in never smokers by the longest category studied (Fig. 3).
mucinous cancer among current smokers with two others reporting a non-significant 20% increase in risk [19,20] that, in one study, was restricted to women smoking more than 10 cigarettes per day [20]. The final study reported a ‘doubling in risk’ of mucinous cancer among heavy smokers [15]. Combining the results of the studies that presented subtype-specific relative risks suggests that current smokers have around a two-fold increased risk of developing mucinous ovarian cancer. This risk increases with increasing amounts of smoking but returns to baseline risk within 20–30 years of stopping smoking. Only one study reported a significant increase in risk of non-mucinous cancer among smokers [18] with two others reporting increases that were restricted to borderline serous tumours [19] or women who had smoked for more than 40 years [21]. One study found a significant reduction in risk of invasive serous cancer among smokers [20]. Although few studies reported results separately for endometrioid and clear cell cancers [10,19,21], current smokers may be at somewhat reduced risk of developing these types of tumours. Overall, therefore, smoking does not appear to increase risk of the non-mucinous types of epithelial ovarian cancer although an increase in risk of serous cancer associated with very long-term smoking cannot be ruled out.

While systematic reviews and meta-analyses can provide a better assessment of the relationship between specific factors and outcomes by increasing the power to investigate rare disease and allowing examination of the relationship across varying study settings, they cannot eliminate potential sources of error inherent in the included studies. All except one of the studies included in the current review used case–control data thus the potential for both selection and recall bias must be considered. It is possible that controls who agreed to take part in the studies may have had a lower prevalence of smoking than the general population. Controls may also have under-estimated their level of smoking. Such bias could lead to falsely elevated odds ratios in these studies, but would be expected to affect the results for all tumour types equally and so cannot explain the strikingly different patterns seen for mucinous and non-mucinous cancers, or the apparent inverse association with clear cell and possibly endometrioid tumours. Of note, the one hospital-based case–control study that considered this relation by histological subtype also reported increased risks for mucinous but not serous or endometrioid cancers among smokers [41]. Because our meta-analysis was based on published data, we were unable to independently investigate the effects of confounding or interaction. All of the included studies had, however, either adjusted for the major confounders or noted that adjustment did not affect the results thus it is unlikely that the results are due to confounding. The consistency between the findings for mucinous cancer from the pooled analysis, based on US women mostly diagnosed in the 1970s and 80s (OR 2.4, 95%CI 1.5–3.8) [10], and the results of the current meta-analysis excluding the pooled analysis (OR 2.1, 95%CI 1.6–2.8), based on women from the US and elsewhere who were diagnosed mostly in the 1990s, further supports the validity of the results.

In addition, use of the published data has required that we make decisions such as that to over-lap categories of pack-years of smoking in order to accommodate the different cut-points set by each study. Decisions of this type have to be made in all meta-analyses of observational studies when different investigators have used different cut-points. In practice, any misclassification as a result of the overlapped categories is only likely to have attenuated the true association.

Could the results be due to publication bias with authors only submitting results for publication or editors only accepting papers if they found some association with smoking? The pooled analysis [10] included previously unpublished subtype-specific results from nine studies of ovarian cancer. We repeated our meta-analysis including and excluding these data and our findings did not substantially change suggesting that publication bias does not explain the results. Although there are almost certainly further unpublished results, it is unlikely that these would have such strong inverse effects for smoking and mucinous cancer that they would negate the strong positive association observed among the published data.

The diagnosis of mucinous ovarian cancer is, however, complicated by the fact that mucinous tumours from the colon, appendix and pancreas, and occasionally the stomach and cervix, may present clinically as primary ovarian cancer [44]. This problem has only been appreciated relatively recently thus it is likely that, in older studies in particular, a proportion of tumours classified as invasive mucinous ovarian primaries were really gastrointestinal or possibly cervical cancers. Could the observed association between smoking and mucinous ovarian cancer simply represent an association between smoking and metastatic intestinal cancer? In two of the studies included in this review [8,18], a group of three pathologists reviewed all of the cases centrally to classify the histological subtype of each cancer. It is likely that the histological classification is most reliable in these studies and both reported strong associations between smoking and mucinous ovarian cancer, although the possibility of misclassification remains. In addition, the effects appear to be somewhat stronger for borderline tumours, which are much less likely to be misclassified [44].

There was no evidence of statistical heterogeneity between the results for mucinous cancer in the different studies. Only two studies reported no association between smoking and risk of mucinous ovarian cancer; however, the confidence limits around their estimates (95%CI 0.66–2.26 [19] and 0.50–2.79 among women who smoked more than 10 cigarettes per day [20]) are compatible with a two-fold increase in risk of mucinous ovarian cancer among current smokers. The main difference between the first of these studies and the others is the high proportion (41%) of Asian women, although the authors reported that their results did not differ appreciably between Asian and White women. That study also had the lowest proportion of current smokers at 13% and the highest proportion of mucinous tumours (20%). The second study included few women with invasive mucinous cancer thus the confidence limits around the estimates were very wide [20].
Among premenopausal women, smoking is associated with lower levels of circulating oestrogen, delayed conception, and early menopause while postmenopausal smokers have elevated levels of androgens [45,46]. Cigarette smoke also contains numerous carcinogenic chemicals, including benzo[a]pyrene which has been shown to initiate ovarian tumours in mice [47] and smoking-related DNA adducts have been detected in granulosa-lutein cells from women exposed to cigarette smoke [48]. An association between smoking and risk of ovarian cancer is therefore biologically plausible [8,18].

Histologically, mucinous ovarian tumours resemble cervical adenocarcinomas or intestinal epithelium. Although there is no relation between smoking and adenocarcinoma of the cervix [49], cigarette smoking has consistently been associated with mucinous cancers of the gastrointestinal tract. Gastric and pancreatic cancers are both classed as smoking-related diseases and, although the relation with colon cancer is less clear, smoking is strongly associated with development of adenomatous colorectal polyps, a pre-cursor of colon cancer [50]. It is thus plausible that a positive association between smoking and ovarian cancer could be specific for the mucinous subtype. In contrast, endometrioid and clear cell ovarian cancers are histologically similar to their endometrial counterparts and smoking has been associated with a reduced risk of endometrial cancer, presumably because of its anti-oestrogenic effects [50]. Non-mucinous ovarian cancers are more strongly related to hormonal and reproductive factors than mucinous cancers [6]. Thus the anti-oestrogenic effects of smoking might counteract the carcinogenic effects for these subtypes, as for endometrial cancer.

The finding is also in keeping with results of other studies suggesting that mucinous tumours are etiologically distinct from the other subtypes. In particular, women with mucinous tumours are less likely to have a family history of breast or ovarian cancer [7,10,51] and are very unlikely to have BRCA mutations [52]. In addition, some have found that the effects of reproductive risk factors are less pronounced for mucinous cancers [6,7,53] although other studies have not supported this [10,54].

In conclusion, our systematic review incorporating data from 910 women with mucinous ovarian cancer suggests that smoking approximately doubles a woman’s risk of developing mucinous ovarian cancer and that this risk increases with increasing amounts of smoking. It also suggests that this effect is reversible and that within 20–30 years of stopping smoking, a woman’s risk of mucinous ovarian cancer will return to that of a never smoker. Tobacco is thus one of the few known modifiable factors that offer some potential for primary prevention of ovarian cancer.

Acknowledgments

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The authors have no conflicts of interest to declare. Susan Jordan (corresponding author) had full access to all of the data and had the final responsibility for submitting the manuscript for publication.

The study was conceived by P Webb, D Whiteman and D Purdie and designed by S Jordan, P Webb, D Whiteman, and A Green. S Jordan conducted the literature searches and S Jordan and P Webb reviewed the studies and extracted the data. All authors contributed to drafting the manuscript.

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