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Cigarette smoking and risk of ovarian cancer: a pooled analysis of 21 case–control studies

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Abstract

Purpose—The majority of previous studies have observed an increased risk of mucinous ovarian tumors associated with cigarette smoking, but the association with other histological types is unclear. In a large pooled analysis, we examined the risk of epithelial ovarian cancer associated with multiple measures of cigarette smoking with a focus on characterizing risks according to tumor behavior and histology.

Methods—We used data from 21 case–control studies of ovarian cancer (19,066 controls, 11,972 invasive and 2,752 borderline cases). Study-specific odds ratios (OR) and 95 % confidence intervals (CI) were obtained from logistic regression models and combined into a pooled odds ratio using a random effects model.

Results—Current cigarette smoking increased the risk of invasive mucinous (OR = 1.31; 95 % CI: 1.03–1.65) and borderline mucinous ovarian tumors (OR = 1.83; 95 % CI: 1.39–2.41), while former smoking increased the risk of borderline serous ovarian tumors (OR = 1.30; 95 % CI: 1.12–1.50). For these histological types, consistent dose–response associations were observed. No convincing associations between smoking and risk of invasive serous and endometrioid ovarian cancer were observed, while our results provided some evidence of a decreased risk of invasive clear cell ovarian cancer.

Conclusions—Our results revealed marked differences in the risk profiles of histological types of ovarian cancer with regard to cigarette smoking, although the magnitude of the observed associations was modest. Our findings, which may reflect different etiologies of the histological types, add to the fact that ovarian cancer is a heterogeneous disease.

Keywords

Case–control studies; Histological type; Ovarian neoplasms; Smoking

Introduction

Among women in the Western world, ovarian cancer is the sixth most common cancer diagnosed and the sixth leading cause of cancer death [1]. Ovarian cancer is the most lethal gynecologic cancer with an overall 5-year survival of 30–40 % [1,2]. Due to the poor prognosis, identification of potential factors for prevention of ovarian cancer may have important clinical and public health implications.

A growing body of studies has assessed cigarette smoking as a potential risk factor for ovarian cancer [3]. The strongest association appears to be with mucinous ovarian tumors [3–19], while the association with other histological types is less certain. A few studies have

observed increased risk of serous ovarian tumors associated with smoking [15, 19–21], but most studies found no association [3–6, 9, 11, 14, 16–18]. The associations between smoking and endometrioid and clear cell ovarian cancer risk are also of interest; some studies have found an inverse association [4, 5, 18, 20], but not all [6, 16]. Concerning tumor behavior, some studies have suggested that the association with smoking is stronger for borderline mucinous tumors compared with invasive mucinous cancers [3, 8, 19, 20], although not all [10, 15]. The inconsistent results reported from previous studies may be due to small numbers of study subjects, which reduces the precision of the risk estimates, particularly in analyses of multiple measures of smoking and analyses of tumor behavior and histology. Recently, however, a large meta-analysis conducted by the Collaborative Group on Epidemiological Studies of Ovarian Cancer found that current smoking increased the risk of invasive and borderline mucinous ovarian tumors. Furthermore, a decreased risk of endometrioid and clear cell ovarian tumors was observed, while no association was found for serous ovarian tumors [22]. However, this study did not include analyses on dose–response associations between various measures of cigarette smoking and ovarian cancer risk.

To further assess the association between cigarette smoking and ovarian cancer risk, we have used data from 21 recent case–control studies associated with the Ovarian Cancer Association Consortium (OCAC) [23]. In a pooled analysis, we examined the risk of ovarian cancer in relation to multiple measures of cigarette smoking including dose and duration of smoking with a particular focus on characterizing risks among tumor subgroups according to histology and degree of invasiveness.

Methods

The Ovarian Cancer Association Consortium (OCAC) is an international collaboration of ovarian cancer studies formed in 2005 to investigate associations between genetic polymorphisms and ovarian cancer risk and to identify epidemiological risk factors associated with development of ovarian cancer.

In the present study, we obtained data from 21 case–control studies: 19 OCAC case–control studies [24–43] and two case–control studies not included in OCAC (SON [44] and RPI [45]). Of these 21 studies, nine (AUS, GER, HAW, HOP, NEC, POL, RPI, SON, USC) [24, 27, 28, 32, 34, 40, 42–45] were also included in the recent metaanalysis performed by the Collaborative Group on Epidemiological Studies of Ovarian Cancer [22], whereas 12 studies (CON, DOV, MAL, MAY, NCO, NJO, NTH, SEA, STA, TBO, TOR, UKO) [25, 26, 29–31, 33, 35–39, 41] were only included in the present analysis. Characteristics of all 21 studies included in our study are presented in Table 1. All data were checked for internal consistency and clarifications were provided by the original investigators. Women with missing data on smoking status and those with non-epithelial tumors were excluded from analyses. In total, 14,724 women with epithelial ovarian cancer (11,972 invasive ovarian cancers and 2,752 borderline ovarian tumors) and 19,066 controls were included for analyses. In the majority (12) of the included studies (CON, HAW, HOP, MAY, NCO, NEC, NJO, POL, RPI, TBO, TOR, UKO) [25, 28, 30–34, 37–40, 45], a pathological review was performed for all eligible cases. In three studies (MAL, SEA, STA) [29, 35, 36], a pathological review was performed for a subset of cases, while in six studies (AUS, DOV, GER, NTH, SON, USC) [24, 26, 27, 41–44], there was no pathological review of cases. All analyses in the present paper were stratified by pathological review status, but the major results did not differ between the three groups and will not be presented further. All studies had institutional review board or ethics committee approvals.

Assessment of cigarette smoking

The present study addressed associations between cigarette smoking and risk of ovarian cancer, as data about use of other tobacco products were limited to a few studies. Data on cigarette smoking were collected either through self-administered questionnaires or in-person interviews (Table 1). We obtained information on the following variables: smoking status (current, former, or never smoker), cigarette consumption (average number of cigarettes/ day), total duration of smoking (years), age at smoking initiation, and time since smoking cessation (years). Ever smokers were defined differently by the participating studies either as those who had smoked at least 100 cigarettes in their lifetime (AUS, CON, DOV, MAY, NCO, NEC, TBO, and TOR), those who had smoked daily for a period of 3, 6, or 12 months (GER, HAW, HOP, NJO, POL, RPI, SEA, STA, UKO, and USC), or those who had ever smoked without any further specification (MAL, NTH, and SON). Current smokers were generally defined as women who were smoking within 12 months of the date of diagnosis (cases) or date of interview (controls). Information on smoking status and age at smoking initiation was available for all 21 studies. All studies but two (SEA and TBO) had information on average number of cigarettes smoked per day and duration of smoking. Information about time since smoking cessation was available from all but one study (TBO).

Statistical analysis

Associations between the various smoking exposures and risk of ovarian cancer were analyzed using a two-stage approach [46]. First, study-specific odds ratios (ORs) were obtained from logistic regression models adjusted for the selected confounding variables. The study-specific estimates were then combined into a pooled odds ratio (pOR) with corresponding 95 % confidence intervals (CIs). The pooled estimate was computed by weighting each estimate by the inverse of the sum of its variance and the across-studies variance using a random effects model [47]. Statistical heterogeneity among studies was evaluated using the Cochran Q test and I^2 statistics. Where heterogeneity was evident, we examined the data for potential sources of heterogeneity, including type of study (population-based vs. hospital-based case-control study) and method of data collection (self-administered questionnaire vs. in-person interview). For analyses, the variables 'cigarette consumption,' 'duration of smoking,' 'age at smoking initiation,' and 'time since smoking cessation' were parameterized both as categorical and continuous variables. Each categorical variable was categorized into ordinal groups with never smokers as the reference group. Dose-response associations between the continuous variables 'cigarette consumption,' 'duration of smoking,' and 'age at smoking initiation' and ovarian cancer were evaluated among ever smokers (current and former smokers combined) only, while the dose-response association between 'time since smoking cessation' and ovarian cancer was evaluated among former smokers only. In order to model these dose-response associations, smoking status was included as a categorical indicator variable together with the continuous variable for the smoking variable in question as suggested by Leffondré et al. [48].

We also examined the associations between cigarette consumption, duration of smoking, age at smoking initiation, and ovarian cancer among current smokers only. However, this did not alter the results substantially, and no changes in the direction of the associations were observed (data not shown). Therefore, all analyses for cigarette consumption, duration of smoking, and age at smoking initiation presented in the present paper are for former and current smokers combined. To consider the possibility that early cancer symptoms might have induced smoking cessation, we performed analyses using smoking status 1 year before diagnosis for cases and 1 year before interview for controls. However, as these analyses did not change the results substantially, we used smoking status within 12 months of the date of diagnosis/interview in our final analyses.

All models were adjusted for age, parity (ever/never having given birth and number of births as a continuous variable), oral contraceptive use (ever/never use and duration of use as a continuous variable), total months of breastfeeding (continuous variable), family history of breast or ovarian cancer in first-degree relatives (yes/no), and education (high school or less vs. more than high school). In studies that employed matching on age and/or race/ethnicity (Table 1), we adjusted for these variables by means of conditional logistic regression. For studies without matching (Table 1), we divided age into 5-year age groups and used unconditional logistic regression. Other potential confounding variables considered but not included in the final models were: age at first and last birth, hormone replacement therapy use, history of endometriosis, hysterectomy or tubal ligation, body mass index (BMI), menopausal status, and age at menarche. A covariate was included in the final models of all studies only if it altered the log of the pooled effect estimate for overall ovarian cancer risk by 10 % or more, that is, all studies were adjusted for the same confounders if information on the respective confounders was available.

Interactions between smoking status and menopausal status (pre-/perimenopausal vs. postmenopausal), parity (ever vs. never having given birth), oral contraceptive use (ever vs. never use), family history of breast or ovarian cancer in first-degree relatives (yes vs. no), and education (high school or less vs. more than high school), respectively, were tested. Linearity for all quantitative variables was tested by comparison with restricted cubic splines (5 knots placed at equidistant quintiles between 0.05 and 0.95), but no statistically significant deviations from linearity were observed. The significance of the interactions and nonlinear effects was computed by testing the inter-action/nonlinearity in each study separately by likelihood ratio tests and then comparing the distribution of these study-specific *p* values with a uniform distribution by a Kolmogorov–Smirnov test [49].

Subgroup analyses were conducted by tumor behavior (invasive or borderline) and histological type. For the most general variable ‘smoking status,’ heterogeneity across the different histological types was evaluated by pairwise comparisons of the risk estimates for each of the histological types. Invasive cancers were categorized as serous, mucinous, endometrioid, clear cell, or ‘other’ tumors (including mixed cell, undifferentiated tumors, and tumors with unknown histology). Invasive serous tumors were additionally categorized as low- (grade 1) or high- (grade 2+) grade [50]. Borderline ovarian tumors were categorized as either serous or mucinous. Borderline endometrioid and clear cell tumors are uncommon and therefore these tumor types were only included in the analyses for overall borderline ovarian tumors. All analyses were conducted using the statistical software package R, version 2.14.0 [51]. All *p* values were two-sided, and a significance level of 5 % was used.

Results

The distribution of histological types among invasive and borderline cases is presented in Table 2. Among the 11,972 women with invasive ovarian cancer, never smokers comprised 54.7 %, whereas former and current smokers constituted 31.8 and 13.6 %, respectively. For the 2,752 women with borderline ovarian tumors, 48.2 % were never smokers, 29.9 % were former, and 21.9 % current smokers. Among the 19,066 control women, 52.8 % were never smokers, 31.0 % were former, and 16.3 % current smokers.

Invasive ovarian cancer

Results of the pooled analysis for overall invasive ovarian cancer and stratified by histological type are presented in Table 3 and Fig. 1a – d. We found no association between cigarette smoking and overall invasive ovarian cancer risk, either for current (OR = 0.89; 95 % CI: 0.76, 1.04) or for former smokers (OR = 1.01; 95 % CI: 0.96, 1.07). No associations between the other smoking variables and risk of overall invasive ovarian cancer were

observed, except for duration of smoking where each extra 5 years of smoking among women who were ever smokers was associated with a 4 % increased risk (95 % CI: 1.02, 1.06).

The risk of serous ovarian cancer was not associated with any of the smoking variables, except for a tendency toward an increased risk associated with duration of smoking (OR = 1.03; 95 % CI: 1.00, 1.06, $p = 0.07$, per 5 years of smoking) and a statistically significantly increased risk among women who stopped smoking less than 10 years ago (OR = 1.21; 95 % CI: 1.05, 1.41) (Fig. 1a, b; Table 3). Additional analyses revealed no evidence of a statistically significant association between smoking and risk of low-grade (OR = 1.13; 95 % CI: 0.83, 1.53 for current smokers; OR = 1.08; 95 % CI: 0.84, 1.38 for former smokers) or high-grade (OR = 0.91; 95 % CI: 0.75, 1.10 for current smokers; OR = 1.05; 95 % CI: 0.96, 1.13 for former smokers) serous ovarian cancers (data not shown).

Women who currently smoked had a statistically significant increased risk of mucinous ovarian cancer of 1.31 (95 % CI: 1.03, 1.65, Fig. 1c; Table 3), whereas former smokers had no increased risk (Fig. 1d; Table 3). In addition, the risk of mucinous ovarian cancer increased with increasing numbers of cigarettes smoked per day and duration of smoking (OR = 1.12; 95 % CI: 1.05, 1.19, per 5 years of smoking). In contrast, age at smoking initiation and time since smoking cessation were not convincingly associated with mucinous ovarian cancer risk (Table 3).

We found no convincing association between smoking and risk of endometrioid ovarian cancer. In contrast, both former (OR = 0.77; 95 % CI: 0.66, 0.91) and current smokers (OR = 0.74; 95 % CI: 0.56, 0.98) had a statistically significant decreased risk of clear cell ovarian cancer. There was no dose–response association with duration of smoking or increasing number of cigarettes smoked per day, but clear cell ovarian cancer risk decreased slightly with increasing time since smoking cessation (OR = 0.96; 95 % CI: 0.92, 0.99) (Table 3). As BMI is a potential risk factor for endometrioid [52] and clear cell ovarian cancer, all analyses for these histological types were additionally adjusted for BMI. However, this did not change the risk estimates considerably (data not shown) and the final analysis did not include BMI as a confounder (Table 3).

Pairwise comparisons of the risk estimates for each of the histological types of ovarian cancer revealed that former smoking was associated with a reduced risk of clear cell invasive ovarian cancer that differed statistically significantly from the risk of both serous ($p < 0.001$), mucinous ($p < 0.05$), and endometrioid ($p < 0.05$) invasive ovarian cancer, while current smoking was associated with an increased risk of mucinous invasive ovarian cancer that differed statistically significantly from the risk of both serous ($p < 0.05$), endometrioid ($p < 0.01$), and clear cell ($p < 0.01$) invasive ovarian cancer (data not shown).

In a subanalysis, we analyzed the associations between smoking status and risk of invasive ovarian cancer (overall and according to histological type) among the 12 case–control studies included only in the present study and not in the previous meta-analysis from the Collaborative Group on Epidemiological Studies of Ovarian Cancer [22]. The results were virtually unchanged; the direction of the associations was not altered, but due to less statistical power the confidence intervals were wider and some estimates did not reach statistical significance (data not shown).

Lastly, for each histological type of invasive ovarian cancer, we also investigated interactions between smoking status and menopausal status, parity, oral contraceptive use, family history of breast or ovarian cancer, and education. Our results showed no interaction with any of these potential effect modifiers (all p values > 0.05) (data not shown).

Borderline ovarian tumors

Results of the pooled analysis for borderline ovarian tumors are based on data from 16 studies (Table 2). Both current (OR = 1.36; 95 % CI: 1.13, 1.64) and former smoking (OR = 1.18; 95 % CI: 1.01, 1.36) were associated with an increase in the risk of borderline ovarian tumors. Furthermore, we observed statistically significant increased risks for number of cigarettes per day and duration of smoking (Table 4).

For serous borderline ovarian tumors, risk was statistically significantly increased among former smokers (OR = 1.30; 95 % CI: 1.12, 1.50, Fig. 2b; Table 4), but not among current smokers (Fig. 2a; Table 4). There was also a statistically significant increased risk of serous borderline ovarian tumors associated with duration of smoking and a non-significant increased risk associated with number of cigarettes smoked per day (OR = 1.04; 95 % CI: 1.00, 1.08, $p = 0.07$, per 5 cigarettes per day). Furthermore, women who quit smoking less than 10 years ago had an increased risk of 1.52 (95 % CI: 1.20, 1.91). No statistically significant relationship was observed for age at smoking initiation and risk of serous borderline ovarian tumors (Table 4).

Current smoking increased the risk of mucinous borderline ovarian tumors (OR = 1.83; 95 % CI: 1.39, 2.41, Fig. 2c; Table 4), but we observed no increased risk among former smokers (Fig. 2d; Table 4). The risk of mucinous borderline ovarian tumors was also associated with all other smoking variables, except age at smoking initiation (Table 4).

Pairwise comparisons of the risk estimates for the histological types of borderline ovarian tumors revealed that current smoking was associated with an increased risk of mucinous borderline ovarian tumors that differed statistically significantly from the risk of serous borderline ovarian tumors ($p < 0.01$). In contrast, for former smoking, the different associations between smoking and risk of serous and mucinous borderline ovarian tumors did not reach statistical significance ($p = 0.07$) (data not shown).

When we analyzed the associations between smoking status and risk of borderline ovarian tumors (overall and according to histological type) among the 12 studies included only in the present study and not in the previous meta-analysis from the Collaborative Group on Epidemiological Studies of Ovarian Cancer [22], there was no change in the direction of the associations. However, due to less statistical power, the confidence intervals were wider and some estimates did not reach statistical significance (data not shown).

Finally, no effect modification between smoking status and any of the potential risk factors for serous or mucinous borderline ovarian tumors was observed (all p values > 0.05) (data not shown).

Analysis of heterogeneity across studies

For most analyses, no statistically significant heterogeneity across studies was observed. There were some exceptions, however, most notably for the analyses of smoking status associated with risk for overall and serous invasive ovarian cancer and for overall and mucinous borderline ovarian tumors. To examine whether study type or method of data collection could explain the observed heterogeneity, we conducted these analyses for population-based studies only and for studies that conducted in-person interviews only. However, these subanalyses did not show increased consistency among studies of the same type, as heterogeneity remained (data not shown).

Discussion

In this large pooled analysis, we examined the association between cigarette smoking and ovarian cancer risk according to tumor histology and behavior. Our results show that associations with cigarette smoking differ across histological types of ovarian cancer, although the strength of the associations observed was moderate. We found increased risks of both invasive and borderline mucinous tumors as well as of serous borderline ovarian tumors associated with cigarette smoking. For these histological types, consistent dose–response associations with multiple measures of smoking were observed, suggesting that the associations are likely to be causal. In contrast, no convincing associations between smoking and serous or endometrioid invasive ovarian cancer risk were observed. Lastly, we found some evidence of a decreased risk of clear cell invasive ovarian cancer associated with smoking. The present pooled analysis succeeds a meta-analysis on smoking and ovarian cancer risk from the Collaborative Group on Epidemiological Studies of Ovarian Cancer [22]. The majority of the case–control studies included in our paper (12 out of 21 studies) was not included in the previous meta-analysis. While the meta-analysis from the Collaborative Group on Epidemiological Studies of Ovarian Cancer focused on associations between overall smoking status (never, former, and current smoking) and ovarian cancer, our study also reported dose–response associations with ovarian cancer for different measures of cigarette smoking (cigarette consumption, duration of smoking, age at smoking initiation, and time since smoking cessation).

Our results showed a 31 % increased risk of invasive mucinous ovarian cancer and an 83 % increased risk of borderline mucinous ovarian tumors among current smokers. This is consistent with results from a recent meta-analysis from the Collaborative Group on Epidemiological Studies of Ovarian Cancer [22], where current smoking was associated with increased risks of mucinous invasive and borderline ovarian tumors of 49 % and 125 %, respectively. Furthermore, in line with other studies [5–8, 10–15, 19, 20], we found consistent dose–response associations between smoking duration and number of cigarettes smoked per day and risk of mucinous ovarian tumors, providing further evidence of the association.

As the number of female smokers is increasing globally [53] and invasive serous ovarian cancer constitutes the most common and lethal histological type of ovarian cancer, even a small increase in smoking-related risk of invasive serous ovarian cancer could have important implications for the worldwide incidence of ovarian cancer. However, in agreement with most previous studies [3–6, 9, 11, 14, 16–18, 22], but not all [45, 54], our results revealed no convincing evidence of an association between smoking and this histological type. Our study is the first to analyze the association between cigarette smoking and risk of low- and high-grade serous ovarian cancer separately, but our results did not reveal any significant risk differences for these subgroups. In contrast, we found evidence of a dose–response association between smoking and risk of serous borderline ovarian tumors, which is in line with a few previous studies [15, 19, 20], but not all [9, 14]. Our study showed a statistically significantly increased risk of serous borderline ovarian tumors among former but not current smokers. This finding may have been explained if former smokers were heavier smokers than current smokers, but this was not the case in our study material. Hence, this result is not easily explainable and may be a chance finding.

Some studies have suggested a protective effect of smoking against endometrioid ovarian cancer [4, 5, 18, 20, 22], while in agreement with our results others found no convincing association [3, 6, 16, 45, 54, 55]. In accordance with our results, two meta-analyses [3, 22] and one case–control study [55] found decreased risks for clear cell invasive ovarian cancer

associated with smoking, while four other studies reported inverse, but statistically nonsignificant, associations [18, 20, 45, 54].

Experimental studies support the potential for an increased risk of ovarian cancer associated with cigarette smoking. Cigarette smoke contains numerous carcinogenic chemicals, including benzo[a]pyrene, which has been shown to initiate development of ovarian tumors in mice [56]. Benzo[a]pyrene DNA adducts have also been found in ovarian follicular cells among women exposed to cigarette smoke and the presence of these adducts may increase the risk of DNA damage [57].

The observed risk differences between smoking and histological types of ovarian cancer may reflect their different etiologies [58]. Mucinous ovarian tumors are characterized by cells that resemble those of the cervix or intestines [59]. As cigarette smoking has been found to increase the risk of cervical and colon cancer [60, 61], it is reasonable to assume that smoking may also increase the risk of mucinous ovarian cancer. Smoking is known to reduce the risk of endometrial cancer [62], presumably because of its anti-estrogenic metabolic effects [62]. As clear cell ovarian tumors are histologically similar to those of the endometrium [59], the decreased risk of clear cell invasive ovarian cancer associated with smoking may reflect similar biological mechanisms. Furthermore, the differing risks of histological types of ovarian cancer associated with smoking may reflect that effects of smoking act on different stages in the development of the various histological ovarian tumors. Mucinous ovarian tumors seem to develop along a continuum of benign to borderline to invasive disease, whereas high-grade serous cancers appear to develop from microscopic precursors and evolve more rapidly [63]. It has been suggested that the major carcinogenic effect of smoking occurs in the early stages of a progression from benign to malignant disease [6, 8], which may explain why mucinous ovarian tumor cells are more vulnerable to cigarette smoking than serous ovarian tumor cells. Lastly, it is possible that genetic variation may explain some of the differences in the observed risk patterns. It has been proposed that smoking may induce mutations in the KRAS gene or exert a stronger carcinogenic effect on cells without a functional KRAS gene [18]. KRAS mutations are common in both invasive and borderline mucinous ovarian tumors, occur often in borderline and low-grade serous ovarian tumors, but are rarely observed in high-grade serous invasive ovarian cancer [63]. This difference in the distribution of KRAS mutations might partly explain the increased risk of borderline serous but not invasive serous ovarian tumors observed in our study. Consideration of gene-environment interactions in the future ovarian cancer studies may help to further clarify the association between cigarette smoking and different histological types of ovarian cancer.

The strengths of our work include the pooling of data from 21 individual studies, which increased the statistical power and enabled us to examine associations between multiple smoking variables, including dose and duration of smoking, and the major histological types of ovarian cancer. Moreover, the majority of the studies were population based with information about smoking from in-person interviews. In addition, the participating studies were not selected from published studies, that is, they were included even though separate analyses of individual studies did not demonstrate associations. Therefore, our analyses have not been affected by publication bias. The analyses relied on individual data combined into a single dataset following careful central data harmonization of smoking variables. Using a two-stage method, we were able to take into account differences in design and data collection across studies and to control for multiple confounders.

Our study also had some limitations. An important one is the possibility of recall bias, as all of the studies relied on retrospective reports of smoking behaviors. In addition, smokers may be more difficult to enroll, and therefore, controls who agreed to participate in the included

studies may have had a lower prevalence of smoking than the general population, which would have lead to an overestimation of the risk estimates. For example, a study by Pandeya et al. [64] found that non-participation of otherwise eligible controls falsely identified a significant association between smoking and serous ovarian cancer. However, if such response differences are present in our study, it is unlikely that they would entirely explain our findings of consistent and relatively strong associations between smoking and risk of mucinous tumors, but they may to some extent explain the weak associations observed between smoking and risk of serous tumors. In contrast, these potential response differences may have caused an underestimation of the inverse association between smoking and risk of clear cell tumors. Another potential limitation is that not all tumors from ovarian cancer cases have undergone a systematic histopathological review and thus some extent of misclassification of the histological types of ovarian cancer cannot be excluded. In particular, the diagnosis of mucinous ovarian cancer is complicated, and it is possible that a small proportion of tumors classified as invasive mucinous was really of gastrointestinal or cervical origin [59]. Moreover, some serous tumors may have been falsely identified as endometrioid tumors and vice versa [59]. However, all studies contributing to the analysis were conducted in the past two decades and histological misclassification is less likely to have been of concern in these studies compared with studies conducted in the more distant past. Lastly, heterogeneity was identified in some analyses. Restricting our analyses to population-based studies only or to in-person interview studies only did not eliminate this heterogeneity, and thus other unknown factors might be responsible. However, due to the large number of studies, the large number of statistical analyses performed, and study differences concerning factors that we were not able to address, it is unlikely that the homogeneity assumption would be satisfied in all analyses [65]. By using a random effects model, we accounted for heterogeneity, and for analyses with little or no heterogeneity, the random effects model is virtually identical to the fixed effects model.

In conclusion, in this large pooled analysis, we observed moderate increases in risk of invasive and borderline mucinous tumors and borderline serous tumors associated with cigarette smoking. For each of these histological types, the risk increased with increased daily cigarette consumption and duration of smoking. This dose–response relationship supports a causal association between smoking and ovarian cancer. In contrast, our results suggest that smoking is not likely to importantly increase the risk of invasive serous ovarian cancer. There was a decreased risk of invasive clear cell ovarian cancer in relation to smoking. Thus, our results indicate that differences in risk profiles with regard to cigarette smoking are not only present between mucinous and non-mucinous ovarian tumors but across the major histological types of invasive ovarian cancer. These findings further underscore the importance of histological subtype analyses in epidemiological, genetic, and clinical investigations of ovarian cancer, due to the vast heterogeneity in this disease.

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Fig. 1. Risk of invasive ovarian cancer associated with cigarette smoking status, by study site and overall. OR and 95 % CI were estimated using logistic regression models. **a** Serous ovarian cancer, current versus never smokers, **b** serous ovarian cancer, former versus never smokers, **c** mucinous ovarian cancer, current versus never smokers, and **d** mucinous ovarian cancer former versus never smokers. Each square and line in the figures represents the odds ratio and 95% confidence intervals from each study and the diamond at the bottom of the plot represents the pooled odds ratio. The size of the squares indicates the size of each study

Fig. 2. Risk of borderline ovarian tumors associated with cigarette smoking status, by study site and overall. OR and 95 % CI were estimated using logistic regression models. **a** Serous borderline ovarian tumors, current versus never smokers, **b** serous borderline ovarian tumors, former versus never smokers, **c** mucinous borderline ovarian tumors, current versus never smokers, and **d** mucinous borderline ovarian tumors, former versus never smokers. Each square and line in the figures represents the odds ratio and 95% confidence intervals from each study and the diamond at the bottom of the plot represents the pooled odds ratio. The size of the squares indicates the size of each study

Table 1
Characteristics of the case-control studies included in the pooled analysis of smoking and ovarian cancer

Region	Study	Site	Study period	Study type	Method of data collection	Age range	Matching
Australia	Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer)	AUS	2002–2006	Population-based	Self-completed questionnaire	18–80	Age (5-year groups)
Europe	German Ovarian Cancer Study	GER	1993–1996	Population-based	Self-completed questionnaire	21–75	Age (± 1 year)
	The Danish Malignant Ovarian Tumor Study	MAL	1995–1999	Population-based	in-person interview	31–80	Age (5-year groups)
	Nijmegen Ovarian Cancer Study	NTH	1989–2006	Hospital-based	Self-completed questionnaire	23–83	Age (5-year groups)
	Polish Ovarian Cancer Study	POL	2000–2004	Population-based	in-person interview	24–74	Age (5-year groups)
	Study of Epidemiology and Risk Factors in Cancer Heredity	SEA	1998-present	Population-based ^a	Self-completed questionnaire	19–77	No matching
North America	UK Ovarian Cancer Population Study	UKO	2006–2010	Hospital-based	Self-completed questionnaire	19–89	No matching
	Connecticut Ovary Study	CON	1998–2003	Population-based	in-person interview	35–79	Age (35–49, 50–64, 65–79)
	Diseases of the Ovary and their Evaluation Study	DOV	2002–2005	Population-based	in-person interview	35–74	Age (5-year groups)
	Hawaii Ovarian Cancer Study	HAW	1993–2008	Population-based	in-person interview	18–93	Age (± 2.5 year groups) and race/ethnicity
	Hormones and Ovarian Cancer Prediction	HOP	2003–2009	Population-based	in-person interview	24–93	Age (5-year groups)
	Mayo Clinic Ovarian Cancer Case Control Study	MAY	2000–2009	Hospital-based	Self-completed questionnaire	20–93	Age (5-year groups)
	North Carolina Ovarian Cancer Study	NCO	1999–2008	Population-based	Self-completed questionnaire	20–75	Age (5-year groups) and race/ethnicity
	New England-based Case-Control Study of Ovarian Cancer	NEC	1992–2003	Population-based	in-person interview	18–78	Age (5-year groups)
	New Jersey Ovarian Cancer Study	NJO	2002–2008	Population-based	in-person interview	23–88	No matching
	Roswell Park Ovarian Cancer Case-Control Study	RPI	1982–1998	Hospital-based	Self-completed questionnaire	14–96	Age (5-year groups)
	Southern Ontario Study	SON	1990–1993	Population-based	in-person interview	35–79	Age (35–49, 50–64, 65–79)
	Family Registry for Ovarian Cancer and Genetic Epidemiology of Ovarian Cancer	STA	1997–2002	Population-based	in-person interview	19–66	Age (5-year groups) and race/ethnicity
	Tampa Bay Ovarian Cancer Study	TBO	2000-present	Population-based	Self-completed questionnaire	26–93	Age (5-year groups)
	Familial Ovarian Tumor Study	TOR	1995–2003	Population-based ^a	in-person interview	21–99	Age (5-year groups)
	Los Angeles County Case-Control Studies of Ovarian Cancer	USC	1993–2005	Population-based	in-person interview	19–86	Age (5-year groups) and race/ethnicity

^aNon-population-based controls

Table 2

Number of observations among cases and controls by study site and histological type

Region	Study	Site	Controls	Invasive cases				Borderline cases					
				All	Serous (%) ^a	Mucinous (%) ^a	Endometrioid (%) ^a	Clear cell (%) ^a	Other (%) ^a	All	Serous (%) ^b	Mucinous (%) ^b	Other (%) ^{b, c}
Australia	Australian Ovarian Cancer Study and Australian Cancer Study (Ovarian Cancer)	AUS	1,448	1,035	635 (61.4)	39 (3.77)	126 (12.2)	79 (7.63)	156(15.1)	284	135 (47.5)	137 (48.2)	12 (4.23)
Europe	German Ovarian Cancer Study	GER	527	224	113(50.4)	25(11.2)	26(11.6)	6 (2.68)	54 (24.1)	28	16 (57.1)	9 (32.1)	3 (10.7)
	The Danish Malignant Ovarian Tumor Study	MAL	1,551	541	333 (61.6)	50 (9.24)	75 (13.9)	41 (7.58)	42 (7.76)	198	101 (51.0)	87 (43.9)	10 (5.05)
	Nijmegen Ovarian Cancer Study	NTH	567	206	92 (44.7)	29 (14.1)	49 (23.8)	14 (6.80)	22 (10.7)				
	Polish Ovarian Cancer Study	POL	516	209	94 (45.0)	15 (7.18)	29 (13.9)	7 (3.35)	64 (30.6)	20	16 (80.0)	3 (15.0)	1 (5.0)
	Study of Epidemiology and Risk Factors in Cancer Heredity	SEA	1,077	1,246	531 (42.6)	131 (10.5)	201 (16.1)	135 (10.8)	248 (19.9)	283	65 (23.0)	150 (53.0)	68 (24.0)
North America	UK Ovarian Cancer Population Study	UKO	800	467	246 (52.7)	44 (9.42)	75 (16.1)	43 (9.21)	59 (12.6)				
	Connecticut Ovary Study	CON	420	298	178 (59.7)	17 (5.70)	58 (19.5)	26 (8.72)	19 (6.38)	85	51 (60.0)	30 (35.3)	4 (4.71)
	Diseases of the Ovary and their Evaluation Study	DOV	1,309	593	335 (56.5)	23 (3.88)	97 (16.4)	35 (5.90)	103 (17.4)	217	117(53.9)	89 (41.0)	11 (5.07)
	Hawaii Ovarian Cancer Study	HAW	1,104	709	315 (44.4)	71 (10.0)	117 (16.5)	82(11.6)	124 (17.5)	187	89 (47.6)	91 (48.7)	7 (3.74)
	Hormones and Ovarian Cancer Prediction	HOP	1,802	677	366 (54.1)	36 (5.32)	97 (14.3)	52 (7.68)	126 (18.6)	97	58 (59.8)	29 (29.9)	10 (10.3)
	Mayo Clinic Ovarian Cancer Case Control Study	MAY	639	483	321 (66.5)	16 (3.31)	80 (16.6)	31 (6.42)	35 (7.25)	75	47 (62.7)	17 (22.7)	11 (14.7)
	North Carolina Ovarian Cancer Study	NCO	1,048	830	451 (54.3)	41 (4.94)	134(16.1)	88 (10.6)	116(14.0)	217	151 (69.6)	60 (27.6)	6 (2.76)
	New England-based Case-Control Study of Ovarian Cancer	NEC	1,242	829	460 (55.5)	55 (6.63)	167 (20.1)	112(13.5)	35 (4.22)	293	172 (58.7)	99 (33.8)	22 (7.51)
	New Jersey Ovarian Cancer Study	NJO	444	224	129 (57.6)	11 (4.91)	31 (13.8)	31 (13.8)	22 (9.82)				

Region	Study	Site	Controls	Invasive cases				Borderline cases					
				All	Serous (%) ^a	Mucinous (%) ^a	Endometrioid (%) ^a	Clear cell (%) ^a	Other (%) ^a	All	Serous (%) ^b	Mucinous (%) ^b	Other (%) ^{b, c}
	Roswell Park Ovarian Cancer Case-control Study	RPI	952	444	201 (45.3)	38 (8.56)	45 (10.1)	23 (5.18)	137 (30.9)				
	Southern Ontario Study	SON	551	363	212 (58.4)	39 (10.7)	69 (19.0)	29 (7.99)	14 (3.86)	84	42 (50.0)	40 (47.6)	2 (2.38)
	Family Registry for Ovarian Cancer and Genetic Epidemiology of Ovarian Cancer	STA	620	499	276 (55.3)	43 (8.62)	65 (13.0)	50 (10.0)	65 (13.0)	171	113(66.1)	46 (26.9)	12 (7.02)
	Tampa Bay Ovarian Cancer Study	TBO	96	184	117(63.6)	10 (5.43)	25 (13.6)	11 (5.98)	21 (11.4)				
	Familial Ovarian Tumor Study	TOR	542	590	385 (65.3)	54 (9.15)	112(19.0)	29 (4.92)	10 (1.69)	104	34 (32.7)	66 (63.5)	4 (3.85)
	Los Angeles County Case-Control Studies of Ovarian Cancer	USC	1,811	1,321	829 (62.8)	111 (8.40)	183 (13.9)	87 (6.59)	111 (8.40)	409	242 (59.2)	162 (39.6)	5 (1.22)
Total			19,066	11,972	6,619 (55.3)	898 (7.50)	1,861 (15.5)	1,011 (8.44)	1,583 (13.2)	2,752	1,449 (52.7)	1,115(40.5)	188 (6.83)

^aProportion of all invasive cases

^bProportion of all borderline cases

^cIncludes endometrioid, clear cell, and other histologies

Table 3
Adjusted pooled odds ratios and 95 % CI for the association between smoking and invasive ovarian cancer, overall and by histological type

	Studies (n)	Controls (n)	Overall ^a			Serous ^a			Mucinous ^a			Endometrioid ^a			Clear cell ^a		
			Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI
Smoking status	21																
Never smokers		10,060	6,544	1.00	Ref.	3,530	1.00	Ref.	452	1.00	Ref.	1,049	1.00	Ref.	605	1.00	Ref.
Former smokers		5,907	3,804	1.01	0.96, 1.07	2,195	1.05	0.97, 1.14	243	0.99	0.83, 1.17	578	0.98	0.86, 1.13	264	0.77	0.66, 0.91
Current smokers		3,099	1,624	0.89	0.76, 1.04 [*]	894	0.92	0.76, 1.10 [*]	182	1.31	1.03, 1.65	234	0.84	0.69, 1.02	104	0.74	0.56, 0.98
Cigarette consumption (per day)	19																
Never smokers		9,403	5,727	1.00	Ref.	3,151	1.00	Ref.	393	1.00	Ref.	915	1.00	Ref.	530	1.00	Ref.
>0– 10		3,533	1,979	0.98	0.92, 1.05	1,173	1.04	0.96, 1.13	131	0.99	0.80, 1.23	299	0.94	0.80, 1.11	123	0.72	0.58, 0.89
>10– 20		3,358	1,875	0.99	0.92, 1.07	1,080	1.02	0.92, 1.13	148	1.16	0.94, 1.44	268	0.92	0.76, 1.12	126	0.75	0.60, 0.93
>20		1,442	854	0.99	0.90, 1.09	511	1.05	0.94, 1.19	70	1.41	1.06, 1.89	130	0.99	0.80, 1.22	53	0.71	0.52, 0.97
Per 5 cigarettes/day ^c				1.00	0.99, 1.02		1.00	0.98, 1.02		1.04	0.99, 1.10		1.00	0.97, 1.04		0.99	0.94, 1.05
Duration of smoking (years)	19																
Never smokers		9,403	5,727	1.00	Ref.	3,151	1.00	Ref.	393	1.00	Ref.	915	1.00	Ref.	530	1.00	Ref.
>0– 10		2,047	1,034	0.91	0.83, 1.00	601	1.00	0.90, 1.12	68	0.82	0.61, 1.09	179	0.97	0.79, 1.19	66	0.71	0.54, 0.94
>10– 20		1,822	1,013	0.98	0.87, 1.10	592	1.05	0.91, 1.21	76	1.03	0.78, 1.36	156	0.90	0.69, 1.17 [*]	66	0.72	0.55, 0.96
>20– 30		1,794	1,049	1.03	0.94, 1.13	598	1.07	0.96, 1.20	80	1.28	0.98, 1.68	144	0.91	0.74, 1.13	70	0.78	0.59, 1.02
>30		2,617	1,611	1.03	0.93, 1.15 [*]	971	1.05	0.95, 1.16	124	1.62	1.22, 2.16	221	1.04	0.86, 1.26	100	0.76	0.58, 1.00
Per 5-year period ^c				1.04	1.02, 1.06		1.03	1.00, 1.06 [*]		1.12	1.05, 1.19		1.03	1.00, 1.07		1.04	0.99, 1.10
Age at smoking initiation (years)	21																
Never smokers		10,060	6,544	1.00	Ref.	3,530	1.00	Ref.	452	1.00	Ref.	1,049	1.00	Ref.	605	1.00	Ref.
<16		3,039	1,748	0.96	0.89, 1.04	1,005	1.03	0.94, 1.13	158	1.15	0.88, 1.51	242	0.83	0.68, 1.02	119	0.77	0.62, 0.97
16–19		3,099	1,808	0.96	0.89, 1.03	1,009	0.97	0.89, 1.07	137	1.10	0.89, 1.37	286	0.96	0.83, 1.12	133	0.79	0.64, 0.98
>19		2,763	1,781	1.02	0.94, 1.09	1,026	1.06	0.97, 1.15	126	1.17	0.94, 1.46	265	1.00	0.84, 1.18	112	0.73	0.58, 0.91
Per 1 year ^c				1.00	1.00, 1.01		1.00	0.99, 1.01		1.01	0.99, 1.03		1.00	0.99, 1.02		1.00	0.98, 1.03
Time since smoking cessation (years)	20																
Never smokers		10,011	6,446	1.00	Ref.	3,466	1.00	Ref.	452	1.00	Ref.	1,036	1.00	Ref.	605	1.00	Ref.
0– 10		1,660	1,118	1.16	1.05, 1.27	636	1.21	1.05, 1.41 [*]	86	1.20	0.93, 1.56	167	1.13	0.93–1.36	68	0.89	0.67, 1.18

	Studies (<i>n</i>)	Controls (<i>n</i>)	Overall ^a			Serous ^a			Mucinous ^d			Endometrioid ^a			Clear cell ^e		
			Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI
			1,555	0.96	0.86, 1.07	505	0.97	0.87, 1.09	66	1.19	0.89, 1.59	148	0.96	0.79–1.17	63	0.71	0.53, 0.95
>10– 20			2,444	0.95	0.84,1.07 [*]	888	1.00	0.88, 1.14 [*]	74	0.85	0.65, 1.12	225	0.99	0.79–1.24 [*]	113	0.80	0.64, 1.00
>20				0.99	0.97, 1.01 [*]		0.99	0.97, 1.01 [*]		0.98	0.94, 1.01		1.00	0.97–1.03 [*]		0.96	0.92, 0.99
Per 5-year period ^d																	

pOR pooled odds ratio, *CI*confidence interval

^{*}
p value for heterogeneity < 0.05

^aNumbers may not sum up to total because of missing data

^bAdjusted for parity (never/ever and continuous), breastfeeding (continuous), oral contraceptive use (yes/no and continuous), family history of breast and/or ovarian cancer (yes/no), and education (high school or less/more than high school)

^cAmong women who were ever smokers

^dAmong women who were former smokers

Table 4

Adjusted pooled odds ratios and 95 % CI for the association between smoking and borderline ovarian tumors, overall and by histological type

	Studies (n)	Controls (n)	Overall ^a			Serous ^a			Mucinous ^a		
			Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI
Smoking status	16										
Never smokers		8,610	1,327	1.00	Ref.	703	1.00	Ref.	521	1.00	Ref.
Former smokers		4,853	822	1.18	1.01, 1.36*	472	1.30	1.12, 1.50	286	1.03	0.85, 1.25
Current smokers		2,744	603	1.36	1.13, 1.64*	274	1.16	0.98, 1.37	296	1.83	1.39, 2.41*
Cigarette consumption (per day)	15										
Never smokers		8,002	1,174	1.00	Ref.	667	1.00	Ref.	446	1.00	Ref.
>0- 10		2,988	529	1.14	0.94, 1.39*	319	1.21	0.97, 1.51*	184	1.13	0.87, 1.47
>10- 20		2,835	496	1.27	1.07, 1.51*	256	1.16	0.98, 1.37	210	1.50	1.19, 1.89
>20		1,203	248	1.57	1.28, 1.92	132	1.51	1.22, 1.87	104	1.74	1.27, 2.39
Per 5 cigarettes/day ^c				1.04	1.01, 1.08		1.04	1.00, 1.08		1.05	1.01, 1.09
Duration of smoking (years)	15										
Never smokers		8,002	1,174	1.00	Ref.	667	1.00	Ref.	446	1.00	Ref.
>0- 10		1,737	324	1.03	0.83, 1.27*	210	1.17	0.88, 1.54*	97	0.87	0.67, 1.14
>10- 20		1,521	283	1.12	0.96, 1.31	165	1.15	0.95, 1.40	105	1.16	0.92, 1.48
>20- 30		1,505	344	1.59	1.32, 1.91	162	1.35	1.11, 1.64	162	2.05	1.54, 2.72
>30		2,196	323	1.54	1.26, 1.88	170	1.44	1.18, 1.75	134	1.72	1.22, 2.43*
Per 5-year period ^c				1.08	1.04, 1.11		1.06	1.02, 1.11		1.08	1.03, 1.13
Age at smoking initiation (years)	16										
Never smokers		8,610	1,327	1.00	Ref.	703	1.00	Ref.	521	1.00	Ref.
<16		2,537	584	1.31	1.10, 1.55*	304	1.26	1.08, 1.47	238	1.38	1.07, 1.80*
16-19		2,637	441	1.13	0.96, 1.33	236	1.17	0.98, 1.40	176	1.18	0.91, 1.53
>19		2,345	379	1.31	1.11, 1.54	195	1.31	1.08, 1.59	160	1.51	1.24, 1.85
Per 1 year ^c				1.00	0.98, 1.01		1.00	0.98, 1.02		1.00	0.98, 1.02
Time since smoking cessation (years)	16										
Never smokers		8,610	1,327	1.00	Ref.	703	1.00	Ref.	521	1.00	Ref.

Studies (n)	Controls (n)	Overall ^a			Serous ^d			Mucinous ^d		
		Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI	Cases	pOR ^b	95 % CI
0- 10	1,354	316	1.44	1.21, 1.70	190	1.52	1.20, 1.91	106	1.28	1.01, 1.62
>10- 20	1,320	202	1.03	0.82, 1.28	109	1.10	0.87, 1.38	82	1.17	0.90, 1.52
>20	2,031	243	1.01	0.84, 1.21	152	1.26	1.03, 1.54	67	0.77	0.58, 1.02
Per 5-year period ^d			0.99	0.96, 1.03		1.03	1.00, 1.06		0.95	0.90, 1.01

pOR pooled odds ratio, CI confidence interval

* p value for heterogeneity < 0.05

^aNumbers may not sum up to total because of missing data

^bAdjusted for parity (never/ever and continuous), breastfeeding (continuous), oral contraceptive use (yes/no and continuous), family history of breast and/or ovarian cancer (yes/no), and education (high school or less/more than high school)

^cAmong women who were ever smokers

^dAmong women who were former smokers