Cancer Causes & Control (2019) 30:1023–1032
https://doi.org/10.1007/s10552-019-01198-8

REVIEW ARTICLE

Dose–risk relationships between cigarette smoking and ovarian cancer histotypes: a comprehensive meta-analysis

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Received: 15 January 2019 / Accepted: 17 June 2019 / Published online: 24 June 2019

Abstract

Purpose Although smoking has not been associated with overall ovarian cancer risk, a different impact on various histotypes has been reported. Our aim is to provide an accurate, up-to-date estimate of the dose–risk relationships between cigarette smoking and epithelial ovarian cancer, overall and by histotypes.

Methods Using an innovative approach for the identification of original study publications, we conducted a systematic review and meta-analysis of epidemiological studies published on the topic until September 2018. Summary relative risks (RR) for cigarette smoking were estimated using random-effects models; dose–risk relationships were evaluated using one-stage random-effects models with restricted cubic splines.

Results Thirty-seven studies were considered in the meta-analysis. The summary RRs for current versus never smokers were 1.05 (95% confidence interval CI 0.95–1.16) for overall ovarian cancer, 1.78 (95% CI 1.52–2.07) for mucinous, 0.77 (95% CI 0.65–0.93) for clear cell, 0.81 (95% CI 0.73–0.91) for endometrioid, and 1.05 (95% CI 0.94; 1.17) for serous cancer. The risk of borderline mucinous (RR 2.09) and serous (RR 1.16) tumors was higher than for invasive cancers (RR 1.44 and 0.95, respectively). For mucinous cancer, risk was noticeably higher with smoking intensity and duration (RR 2.35 for 20 cigarettes/day, and 2.11 for 20 years of smoking). A non-significant linear relation was found with smoking intensity, duration, and time since quitting for overall ovarian cancer and other histotypes.

Conclusions This uniquely large and comprehensive meta-analysis confirms that although cigarette smoking does not appear to be a risk factor for ovarian cancer, and it is even slightly protective for some rare histotypes, there is a strong dose–risk relationship with mucinous ovarian cancer.

Keywords Dose–response relationship · Histotypes · Invasiveness · Meta-analysis · Ovarian cancer · Tobacco smoking

Introduction

Ovarian cancer is the eighth most common cancer and the eighth cause of death from cancer in women worldwide, with about 295,000 incident cases and 185,000 deaths each year [1]. Besides family history, and inherited mutations, major risk factors include hormonal and reproductive factors, with parity, use of combined oral contraceptives, tubal ligation, and hysterectomy protecting against ovarian cancer risk, and hormone replacement therapy increasing it [2–4]. However, the risk for the etiological factors has been reported to differ for various ovarian cancer histotypes.

Among environmental risk factors, epidemiological studies have investigated the role of tobacco (particularly cigarette) smoking on epithelial ovarian cancer and, in general, they did not find any strong association [2, 5–8]. A pooled

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10552-019-01198-8) contains supplementary material, which is available to authorized users.

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analysis of 51 epidemiological studies, and covering 28,000 ovarian cancer cases suggested a slight, though significant, increase in the risk of ovarian cancer among current cigarette smokers (summary relative risk, RR 1.07, 95% confidence interval CI 1.00–1.14) [6]. Another pooled analysis of 21 case–control studies on approximately 14,000 cases reported no association between current cigarette smoking and invasive ovarian cancer (summary RR 0.89, 95% CI 0.76–1.04), but found a higher risk for borderline ovarian tumor (summary RR 1.36, 95% CI 1.13–1.64) [7].

Many studies report a significantly higher risk of mucinous ovarian cancer among smokers, although the quantification of this risk is still unclear [2, 5–8]. The RR for mucinous ovarian cancer for current versus never smokers ranged between 1.30 and 2.30 in various studies, being 1.79 (95% CI 1.47–2.17) in the pooled analysis by Beral et al. [6] and 1.31 (95% CI 1.04–1.66) in the pooled analysis by Faber et al. [7]. It has also been suggested that the excess risk of borderline mucinous tumors is higher than that of invasive cancers, although previous studies were not sufficiently large to establish whether this difference was significant [6–9].

For other ovarian cancer histotypes, an inverse association has been reported for endometrioid and clear cell cancer [6, 7], but the magnitude of this association is still not clear. No significant association was reported for serous ovarian cancer [6, 7], although Faber and colleagues suggested a dose–response relationship between cigarette smoking intensity and duration and the risk of borderline serous cancer [7].

To provide an accurate and up-to-date quantification of the relation between cigarette smoking and ovarian cancer risk, also according to histotypes and invasiveness, and specify the functions that best describe the dose–risk relationships, we conducted a comprehensive review and meta-analysis of all the pertinent epidemiological studies available to date.

Methods

The present systematic review and meta-analysis were conducted using an innovative method for the identification of original publications, which combines an umbrella and traditional review. This methodology has been described in detail in a previous publication and has been summarized below [10]. The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42017063991).

Search strategy

In a first step, through a comprehensive literature search on various databases (PubMed/MEDLINE, Embase, Institute for Scientific Information Web of Science, and Cochrane Database of Systematic Reviews), we conducted an umbrella review to identify all meta-analyses, pooled analyses, and reviews on the relations between cigarette smoking and the risk of cancer at any site published up to 28 April 2017 [10]. Out of 888 publications, we identified two systematic reviews/meta-analyses [11, 12] and three pooled analyses [4, 6, 7] reporting data on ovarian cancer (Supplementary Fig. 1). We also examined two Monographs of the International Agency for Research on Cancer (IARC) on tobacco smoking [13, 14]. Meta-analyses and systematic reviews were used only to identify original study publications. Pooled analyses were considered also as original study publications, since the corresponding estimates are based on individual-level data. Screening the reference lists of the seven reports identified 49 non-duplicate original study publications providing information on the relation between tobacco smoking and ovarian cancer risk.

In a second step, we carried out an updated literature search (Supplementary Box 1) to identify studies on tobacco smoking and ovarian cancer risk published between 1 January 2008 (i.e., the year of the conduction of the last and most comprehensive review available on the topic [11]) and 28 September 2018. After the exclusion of ineligible or duplicate publications, and the inclusion of eight additional publications identified from other sources, this literature search resulted in 30 original study publications and pooled analyses on tobacco smoking and ovarian cancer risk (Supplementary Fig. 1).

Considering the non-duplicate publications identified through the umbrella review and those identified in the update, we obtained 74 original study publications or pooled analyses that were screened for eligibility. These were independently screened for eligibility by two reviewers (CSa and XL). Differences between the two were solved with the help of a third reviewer (AL).

Eligibility criteria

We included in the present review/meta-analysis all studies that satisfied the following eligibility criteria: (i) they were case–control studies (including nested case–control studies or pooled analyses of case–control studies) or cohort studies (including pooled analyses of cohort studies); (ii) they were published as original articles in English; (iii) they provided data on humans, in the general female population; (iv) they provided information on cigarette smoking; (v) they reported estimates of the RR—including odds ratios (OR), hazard ratios (HR), or mortality rate ratios—of epithelial ovarian cancer (overall and/or for specific histotypes) for at least one variable among smoking status (former, current, and/or ever) and dose–response variables (intensity, duration, and/or time since quitting), compared to never or current cigarette smokers, and reported the corresponding 95% CIs, or provided

sufficient information to compute them. We excluded publications reporting RR estimates for non-epithelial ovarian cancer or mixed/combined ovarian histotypes.

Out of the 74 original study publications/pooled analyses identified, 17 were excluded as ineligible (Supplementary Fig. 1).

When results from the same study were provided in more than one original publication/pooled analysis, we included in the meta-analysis only those reported in the most recent and/or complete publication.

Data extraction

For each eligible study, we collected general information on the publication (first author, year of publication, journal), study (country, study name, calendar period, study design, outcome, and sample size), the model used to compute the estimates (including adjustments), and the RR, with the corresponding 95% CIs, for various exposure categories and, when available, the number of cases and controls (or subjects at risk/person years for cohort studies).

When necessary, we used the method for pooling non-independent estimates described by Hamling et al. [15], in order to change the reference category or to collapse the RRs for two or more categories.

Statistical methods

We calculated summary RRs for epithelial ovarian cancer for current, former, and ever smokers versus never smokers, using random-effects models, to take into account the heterogeneity of risk estimates [16]. We calculated RRs separately for case–control and cohort studies, for specific histotypes (clear cell, endometrioid, mucinous, and serous ovarian cancer), and for invasive cancer or borderline tumor. Heterogeneity between studies was assessed using the χ^2 test, and inconsistency was measured using the I^2 statistic, which represents the proportion of total variation attributable to between-study variance [17]. We also conducted stratified analyses according to different study characteristics, including geographic area, type of controls (for case–control studies), endpoint (for cohort studies), and year of publication. To evaluate publication bias, we examined the funnel plots [18] and used Egger's test for funnel plot asymmetry [19].

We investigated both linear and non-linear relationships between smoking intensity (for current vs. never smokers), duration (for current vs. never smokers), and time since quitting (for former vs. current smokers), and the log-RR for overall ovarian cancer and major histotypes. For each dose–response variable, we tested the log-linearity using the Wald test; when the log-linearity was accepted, we modeled the association between exposure and the log-RR for ovarian cancer using linear regression; when the log-linearity was rejected, we evaluated the non-linear relationship using a one-stage random-effects dose–response model [20]. In the latter case, we modeled the dose–response variables using restricted cubic splines with three knots at fixed percentiles of their distributions (10, 50, and 90%) [21, 22]. For each category, the level of exposure was assigned as the midpoint between the upper and the lower bounds; for open-ended upper categories, the level of exposure was determined as 1.2 times the lower bound [22–24]. In a few studies, where the covariance among log-RRs was not computable because of missing information for the number of cases and/or controls, we redistributed cases and/or controls in various dose–response exposure categories on the basis of the distribution from all the other studies combined [25].

For all statistical analyses, we used the R-software version 3.4.1 (R Development Core Team, 2017), in particular, the "*meta*" and "*dosresmeta*" packages [10, 25].

The main findings of the present meta-analysis are also set out in a dedicated website (www.epideuro.eu/scp) that will be periodically updated. The website also provides data on companion meta-analyses on the association between cigarette smoking and other cancer types [22].

Results

Of the 57 eligible study publications/pooled analyses, 20 were not considered in the analyses, since the results were reported in other publications; thus, 37 original studies (including four pooled analyses) met the eligibility criteria and were included in the present meta-analysis. (Supplementary Table 1). Supplementary Table 2 lists the publications for which data were partially excluded from the meta-analysis, and the reasons for exclusion. Supplementary Tables 3 and 4 summarize, respectively, the main characteristics of the 20 case–control studies [6, 7, 26–43] and 17 cohort studies [2, 8, 9, 44–57] included. The original publications were published between 1986 and 2017 and were based on 70,646 ovarian cancer cases. Fourteen studies on overall ovarian cancer provided a measure of the association—or information to derive it—for current smokers, 14 for former smokers, and 21 for ever smokers, as compared to never smokers. There were 24 studies reporting RR estimates for smoking intensity (12 among current smokers), 20 for smoking duration (7 among current smokers), and 9 for time since quitting. Fourteen studies reported the RRs for at least one histotype.

Figure 1 shows the study-specific and summary RRs for ovarian cancer for current versus never cigarette smokers, overall and by study design. The summary RR was 1.05 (95% CI 0.95–1.16) for all studies combined; the corresponding estimates were 0.97 (95% CI 0.84–1.12) for case–control studies, and 1.15 (95% CI 0.99–1.33) for

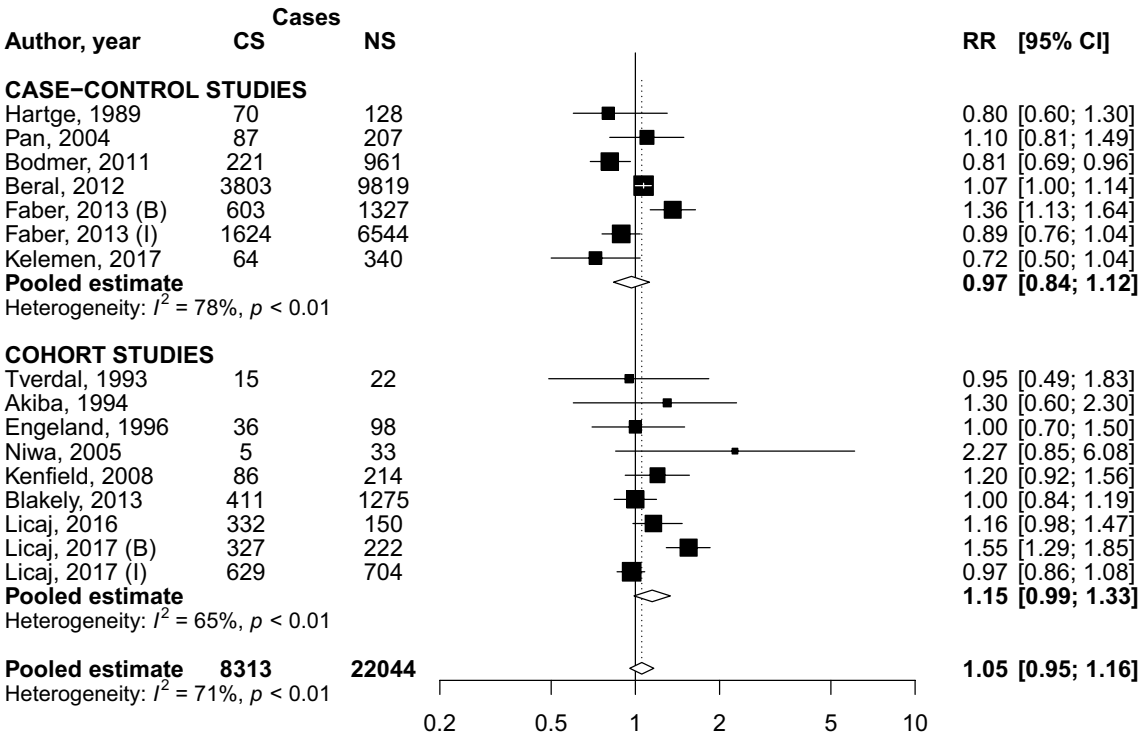

Fig. 1 Forest plot for study-specific and summary relative risk (RR) of ovarian cancer for current cigarette smokers (CS) versus never smokers (NS), overall and by study design. *B* borderline, *95% CI* 95% confidence interval, *I* invasive. For Akiba, 1994, numbers of CS and NS are not given since they were not provided in the published study

cohort studies. For all pooled estimates, there was significant between-studies heterogeneity. The summary RRs for ovarian cancer for former versus never cigarette smokers were 1.07 (95% CI 1.00–1.13) overall, 1.12 (95% CI 1.02–1.23) for case–control studies, and 1.00 (95% CI 0.93–1.07) for cohort studies (Supplementary Fig. 2). The corresponding figures for ever versus never cigarette smokers were 1.05 (95% CI 1.00–1.10) overall, 1.05 (95% CI 0.99–1.12) in case–control, and 1.05 (95% CI 0.97–1.14) in cohort studies (Supplementary Fig. 3). There were no significant differences in the RRs for ovarian cancer for current, former, and ever smokers across strata of geographic area, type of controls, endpoint, and year of publication (Supplementary Table 5).

No evidence of publication bias emerged from studies of ovarian cancer on current (Supplementary Fig. 4), former (Supplementary Fig. 5), and ever (Supplementary Fig. 6) smokers either on visual inspection of the funnel plots or by Egger's test (respectively, $p = 0.88$, $p = 0.43$, and $p = 0.47$ for current, former, and ever smokers).

Figure 2 shows the RRs for various histotypes of ovarian cancer among current versus never cigarette smokers. There was significantly lower risk of clear cell (RR 0.77; 95% CI 0.65–0.93) and endometrioid (RR 0.81; 95% CI 0.73–0.91) ovarian cancer, with a RR of 0.80 (95% CI 0.73–0.88) for both histotypes combined. A significantly higher risk was found for mucinous cancer (RR 1.78; 95% CI 1.52–2.07), but no significant association was found for serous ovarian cancer (RR 1.05; 95% CI 0.94–1.17). The RR estimates differ significantly between the four ovarian cancer histotypes (p for heterogeneity < 0.001), but heterogeneity between studies disappeared, except for serous cancer. The RRs for clear cell, endometrioid, mucinous, and serous ovarian cancers for former (Supplementary Fig. 7) and ever smokers (Supplementary Fig. 8) were consistent with those for current smokers, except for mucinous cancer in former smokers, where no significant association was observed.

We found no association between current smoking and invasive ovarian cancer (RR 0.96; 95% CI 0.88–1.03), while the RR was 1.48 (95% CI 1.31–1.67) for borderline ovarian tumor (p for heterogeneity across groups < 0.001; Fig. 3). The RR was 1.44 (95% CI 1.23–1.67) for invasive mucinous cancer and 2.09 (95% CI 1.78–2.46) for borderline mucinous tumor ($p = 0.039$). The RR was 0.95 (95% CI 0.88–1.02) for invasive serous cancer and 1.16 (95% CI 1.03–1.30) for borderline serous tumor ($p = 0.23$). No heterogeneity between studies was observed in any of the invasiveness/histotype strata. The results for former (Supplementary Fig. 9) and ever smokers (Supplementary Fig. 10) according to ovarian

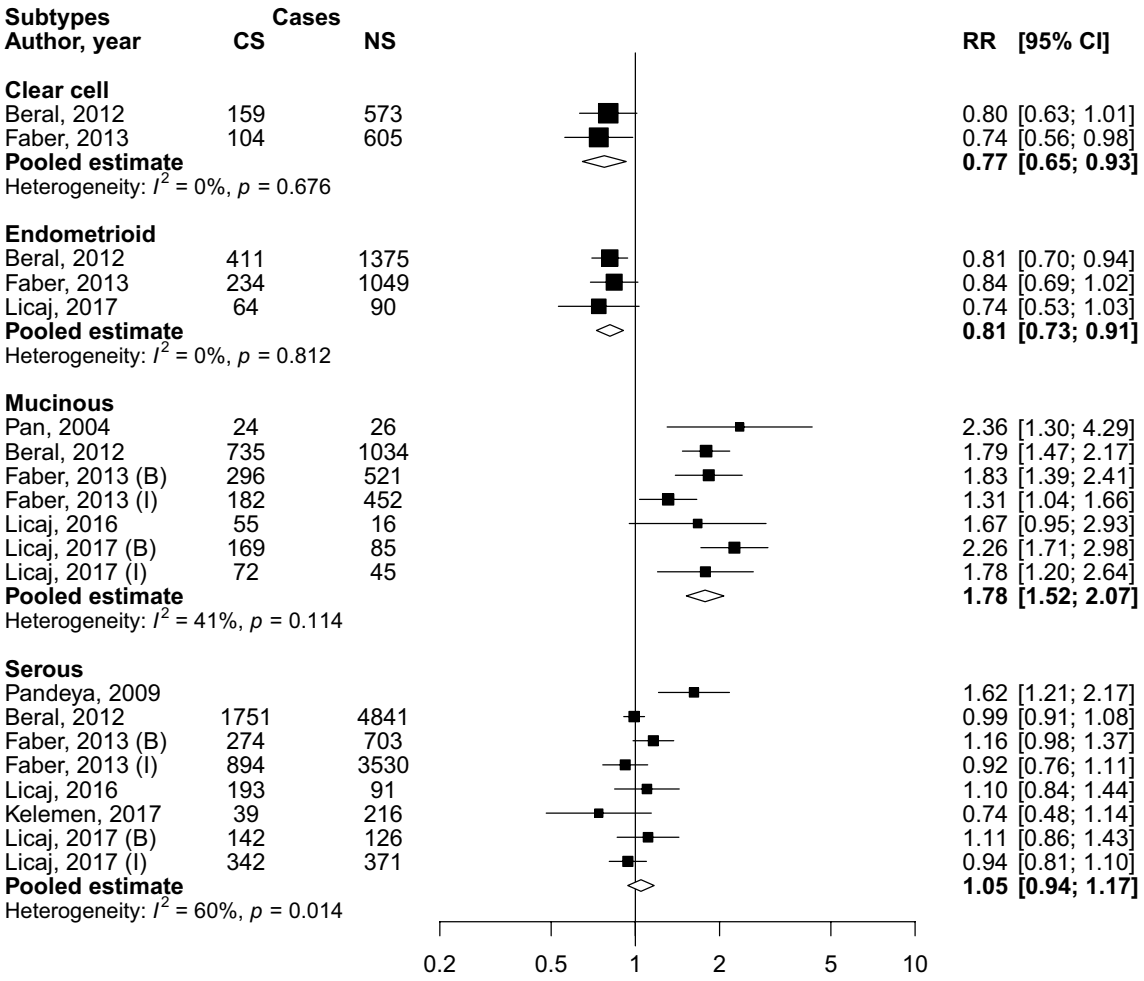

Fig. 2 Forest plot for study-specific and summary relative risk (RR) of ovarian cancer for current cigarette smokers (CS) versus never smokers (NS) according to major histotypes. *B* borderline; *95% CI* 95% confidence interval; *I* invasive. For Pandeya, 2009, numbers of CS and NS are not given since they were not provided in the published study

cancer invasiveness were consistent with those for current smokers.

Figure 4 shows the dose–response relationships between smoking intensity (panel A), duration (panel B), and time since quitting (panel C), and the risk of mucinous ovarian cancer. There was a sharp non-linear increase in risk with increasing smoking intensity: the RR for current versus never smokers was 2.00 (95% CI 1.62–2.47) for 10 cigarettes/day, and 2.35 (95% CI 1.70–3.26) for 20 cigarettes/day (Supplementary Box 2). The risk rose non-linearly with smoking duration up to 15 years, and declined slightly thereafter. The RRs were 2.06 (95% CI 1.43–2.97) for 10 years of smoking, 2.11 (95% CI 1.72–2.59) for 20 years, and 1.60 (95% CI 0.94–2.74) for 30 years. The risk decreased linearly with time since quitting smoking, with RR for former versus current smokers of 0.65 (95% CI 0.52–0.82) after 10 years since quitting, i.e., similar to the risk of never versus current smokers (RR 0.56; 95% CI 0.48–0.66; data not shown). No significant dose–response relationships were found for overall ovarian cancer (Supplementary Fig. 11), for endometrioid (Supplementary Fig. 12) or serous cancer (Supplementary Fig. 13).

Discussion

Our study integrates the results from three previous pooled analyses [2, 6, 7]. One was an investigation from a collaborative group including 51 cohort and case–control studies on ovarian cancer [6]. This study reported risk estimates according to histotypes and invasiveness, but did not include dose–response associations for different measures of cigarette smoking. The second pooled analysis, considering 21 studies, investigated dose–response relationships according to various measures of cigarette smoking, but included only case–control studies [7]. The third provided only estimates

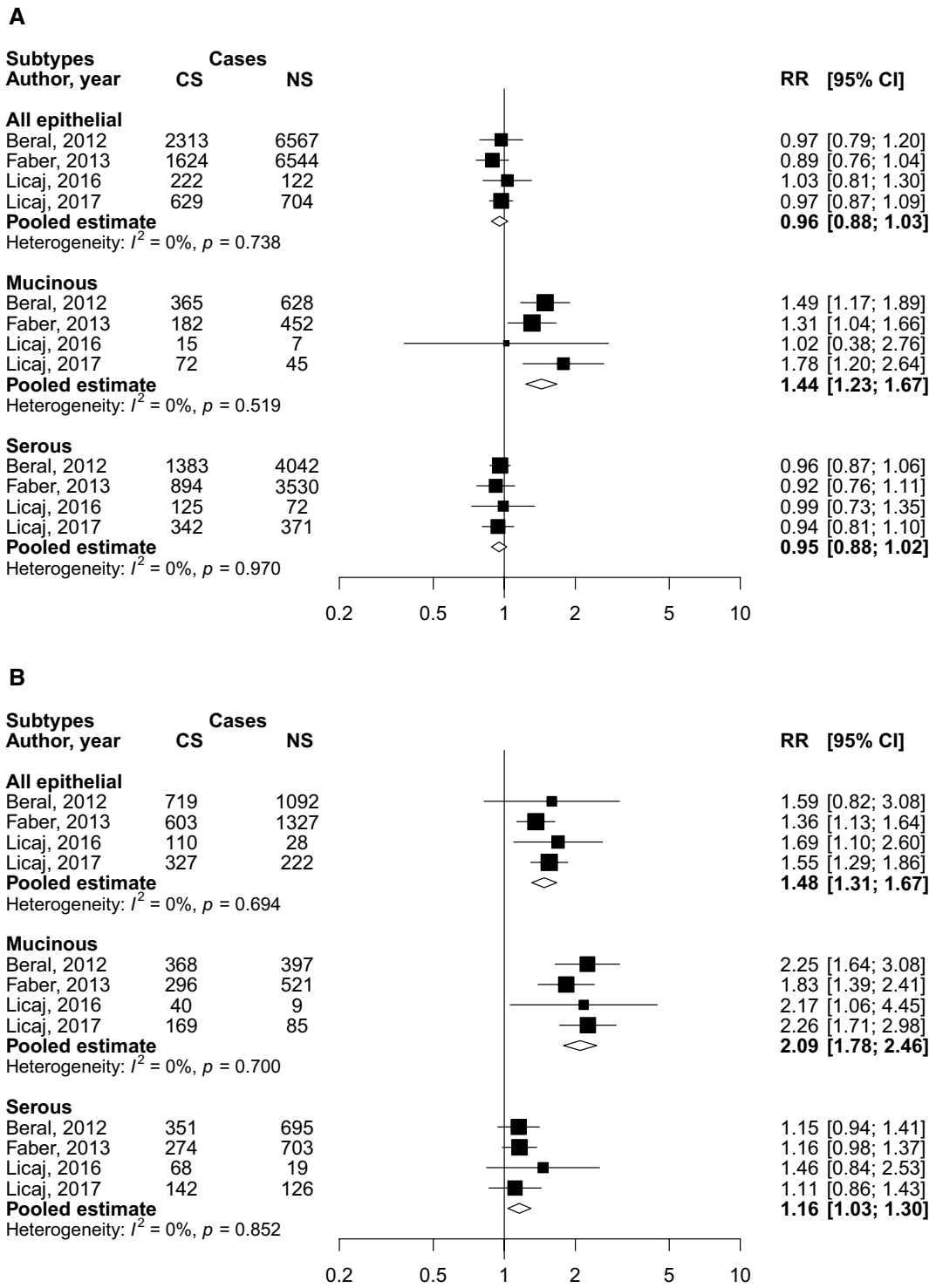

Fig. 3 Forest plot and summary relative risk (RR) of invasive ovarian cancer (**A**) and borderline ovarian tumors (**B**) (overall and by major histotypes) for current cigarette smokers (CS) versus never smokers (NS)

for ever smokers and pack-years of smoking among ever smokers [2]. Therefore, none of the previous pooled analyses adequately analyzed all the aspects considered in our meta-analysis.

Using all epidemiological data available to date on cigarette smoking and ovarian cancer risk, we confirmed the different roles of cigarette smoking on various histotypes [6–8]. In particular, we found a significant 80% excess risk

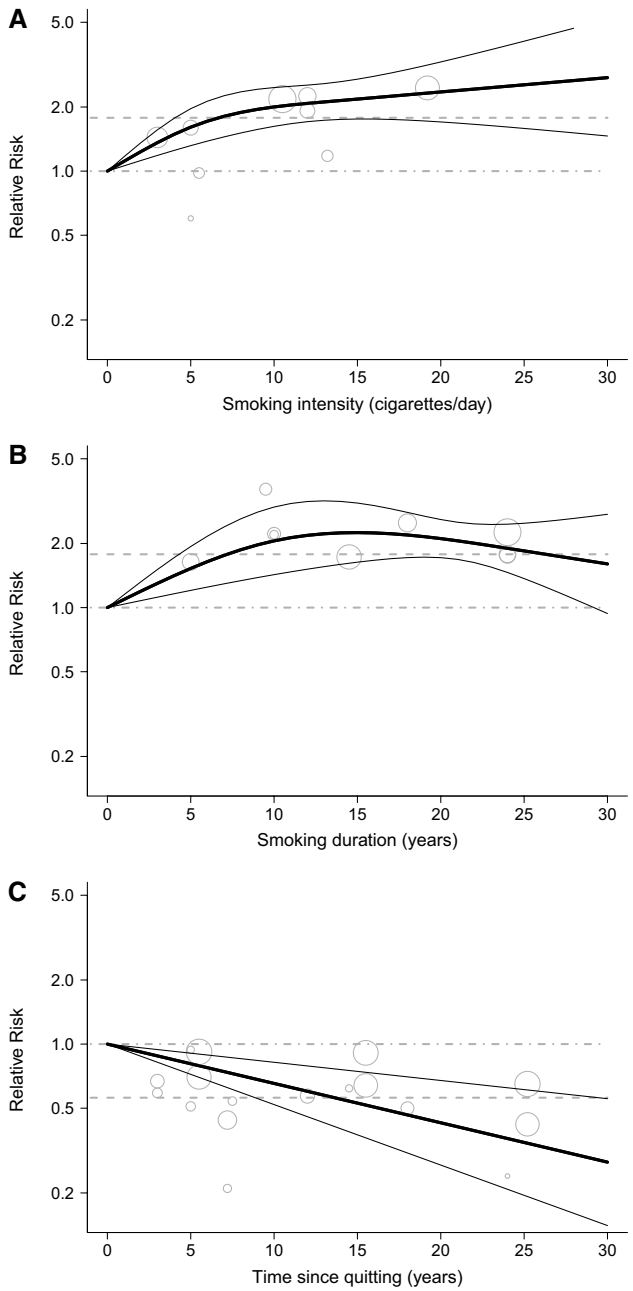

Fig. 4 Relative risk (RR) for the dose–response relationships between cigarette smoking intensity, duration, and time since quitting, and mucinous ovarian cancer. **A** Cigarette smoking intensity (based on four studies); **B** cigarette smoking duration (based on four studies); **C** time since quitting (based on six studies). ——— Restricted cubic spline from a random-effects dose–response model (**A**, **B**), or linear model (**C**). ——— 95% confidence interval of the spline (**A**, **B**) and linear (**C**) model; – – – – RR for current versus never cigarette smokers (**A**, **B**), or for never versus current cigarette smokers (**C**). – · – · – RR for the reference category (never smokers in **A**, **B**, current smokers in **C**). ◯ RR for various exposure categories in each study in the analysis, where the area of the circle is proportional to the precision (i.e., to the inverse variance) of the RR

of mucinous ovarian cancer in current smokers, and further quantified the significant protective effect on clear cell and endometrioid cancer.

When we examined ovarian cancer risk by tumor invasiveness, we found a significantly higher excess risk of borderline ovarian tumor than invasive cancer in current cigarette smokers. In agreement with two previous pooled analyses [6, 7], this was observed in particular for borderline mucinous tumor. However, we also found a significant, though small, higher risk of borderline serous tumor, as previously suggested in the pooled analysis by Faber et al. [7].

With reference to the dose–response relationships, we found a non-linear increase in the risk of mucinous cancer with increasing intensity and duration of smoking. Moreover, compared to current smokers, the risk of mucinous cancer among former smokers decreased with time since stopping smoking, reaching the level of never smokers 15 years after stopping. For overall epithelial ovarian cancers as for other histotypes, we did not see any meaningful dose–risk relationships.

From the perspective of biological mechanisms, the direct association between cigarette smoking and mucinous tumors can be explained by their similarity of this neoplasm with cervical adenocarcinoma and colorectal cancer [58], both of which have been directly associated with tobacco exposure [5]. Similarly, endometrioid and clear cell cancers share biological similarities with endometrial cancer [58], which has been inversely associated with tobacco smoking, due to the possible anti-estrogenic effect of smoking [5]. The effect of tobacco smoking may be stronger in the early stage of (ovarian) carcinogenesis. Therefore, the stronger tobacco-related risk for mucinous than for serous cancer can be explained by the fact that for the mucinous histotype there is a continuum from benign to borderline and invasive disease, while serous ovarian cancer, generally high grade, does not originate from borderline tumor [59]. Moreover, somatic KRAS gene mutations induced by cigarette smoking are more common in mucinous than serous borderline ovarian tumor [60], like in borderline tumors than invasive cancers [61].

Among the limitations of the present study are those inherent to meta-analyses of epidemiological studies. First, case–control and cohort studies are prone to various recall and selection bias, as well as to confounding. Hospital-based controls in particular may report higher frequency of tobacco smoking than population-based ones. However, the consistency of most findings across study design and sources of controls is a reassurance against any major role of such bias. In addition, most studies adjusted risk estimates for various major known confounding factors for ovarian cancer. Second, we pooled data from several epidemiological studies in various populations, including subjects with different characteristics (e.g., race) and background risk levels, using different methods, therefore giving heterogeneous estimates.

However, our analyses stratified by various study characteristics, indicated histology and invasiveness of ovarian cancer as the major sources of between-studies heterogeneity. Third, information on cigarette smoking was self-reported in most studies so some misclassification of information is possible. In this regard, the higher ovarian cancer risk in former than current tobacco smokers, particularly in case–control studies, may be due to biased self-reported information on smoking status in newly diagnosed cancer patients [62]. This may also be due to the fact that former smokers may have quitted because of health problems, thus the health status of former smokers may be generally worst as compared to that of current smokers [63]. The histotype classification can also suffer by some misclassification, although the substantial differences in the tobacco risk between histotypes indicate that any such misclassification is unlikely to have played a major role.

The present meta-analysis has several strengths. First, we tried to include as many epidemiologic studies as possible, including the three large pooled analyses [2, 6, 7]. To reach this scope, we used an original and innovative approach combining an umbrella review with a traditional systematic review [10], we also considered information from publications not indexed in PubMed, such as the IARC Monographs [13, 14]. Following this approach, we were able to identify more efficiently all original study publications, including several studies that were not captured in previous meta-analyses, although satisfying their inclusion criteria. Second, we carefully screened every single publication in order to avoid including results obtained from the same study. Third, we estimated the risk functions best describing the dose–risk relationships with smoking intensity, duration, and time since stopping smoking, which have been only the subject of a pooled analysis of case–control studies [7]. In addition, we provided the first evidence of a non-linear relation between smoking intensity and duration and mucinous ovarian cancer, suggesting a high excess risk even for a low number of cigarettes per day and a few years of smoking. Furthermore, our risk estimates were consistent across strata of most of the selected characteristics, i.e., geographic area, type of controls, endpoint evaluated, and year of publication. We also used random-effects estimates to take account of heterogeneity. The studies included in our meta-analyses may vary in quality; however, we did not assign quality scores and did not a priori exclude any study for design weakness or data quality. Finally, the figures given in the present study are important from a public health perspective. They will enable us to quantify the cancer burden attributable to cigarette smoking on both the individual and population levels, and provide essential information to guide policy decisions for the control of tobacco smoking and cancer prevention.

In conclusion, from this comprehensive review and meta-analysis based on an original search design, we can confirm that current cigarette smoking is not associated with overall and serous ovarian cancer and is only slightly inversely associated with clear cell and endometrioid cancer. However, it is associated with a significant 80% increased risk of mucinous cancer. This risk rises to over 2 for 20 cigarettes/day or 20 years of use, and is higher for borderline tumors than invasive cancers. Although mucinous cancer accounts for only 7–14% of all epithelial ovarian cancers [64], this excess risk should not be ignored as the prognosis for some forms of this histotype appears to be worse than for other histotypes [65]. It is therefore important to avoid starting smoking and to promote stopping it to protect women against (mucinous) ovarian cancer.

Acknowledgments The authors thank Dr. J.D. Baggott for language editing.

Author contributions SG and AL had the original study idea and designed the innovative methodology for the identification of original publications. AL, CSa, and XL identified the publications, extracted the data, and did the statistical analyses, with the help of GP. CSa, CB, SG, and AL wrote the manuscript. CB, VB, and CSp provided statistical and epidemiological supervision. All authors contributed to critically reviewing and revising the draft manuscript, and approval of its final version.

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