Cigarette smoking is associated with adverse survival among women with ovarian cancer: results from a pooled analysis of 19 studies

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Abbreviations: BMI: Body Mass Index; CI: confidence interval; FIGO: International Federation of Gynaecology and Obstetrics staging system; HR: hazard ratio; OCAC: Ovarian Cancer Association Consortium; pHR: pooled hazard ratio; SEER: Surveillance, Epidemiology, and End Results

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Novelty and impact: The association between cigarette smoking and ovarian cancer survival is unclear. In the largest study to date including 9,114 women diagnosed with ovarian cancer, we observed that smokers had worse survival compared with women who had never smoked.

The associations were most pronounced for mucinous and serous tumours, among women with localised disease and with longer follow-up since ovarian cancer diagnosis. Hence, this study identifies cigarette smoking as a modifiable factor associated with ovarian cancer survival.

ABSTRACT

Cigarette smoking is associated with an increased risk of developing mucinous ovarian tumours but whether it is associated with ovarian cancer survival overall or for the different histotypes is unestablished. Furthermore, it is unknown whether the association between cigarette smoking and survival differs according to strata of ovarian cancer stage at diagnosis. In a large pooled analysis, we evaluated the association between various measures of cigarette smoking and survival among women with epithelial ovarian cancer. We obtained data from 19 case-control studies in the Ovarian Cancer Association Consortium (OCAC), including 9,114 women diagnosed with ovarian cancer. Cox regression models were used to estimate adjusted study-specific hazard ratios (HRs), which were combined into pooled hazard ratios (pHR) with corresponding 95% confidence intervals (CIs) under random effects models. Overall, 5,149 (57%) women died during a median follow-up period of 7.0 years. Among women diagnosed with ovarian cancer, both current (pHR = 1.17, 95% CI: 1.08-1.28) and former smokers (pHR = 1.10, 95% CI: 1.02-1.18) had worse survival compared with never smoking women. In histotype-stratified analyses, associations were observed for mucinous (current smoking: pHR = 1.91, 95% CI: 1.01-3.65) and serous histotypes (current smoking: pHR = 1.11, 95% CI: 1.00-1.23; former smoking: pHR = 1.12, 95% CI: 1.04-1.20). Further, our results suggested that current smoking has a greater impact on survival among women with localised than disseminated disease. The identification of cigarette smoking as a modifiable factor associated with survival has potential clinical importance as a focus area to improve ovarian cancer prognosis.

INTRODUCTION

Ovarian cancer is the most deadly gynaecological disease in the Western World, causing more than 150,000 deaths worldwide in 2012.[1] Currently, no effective technique of routine population screening exists and, because ovarian cancer has non-specific symptoms,[2] up to 80% of all ovarian cancers are diagnosed at advanced stages.[3] As a consequence, women with ovarian cancer have a poor prognosis, with an overall 5-year survival of only around 40%.[3]

Factors known to play a role in ovarian cancer survival include age, stage and grade, but these are unmodifiable.[4,5] Thus, identification of modifiable factors that potentially improve prognosis for women diagnosed with ovarian cancer may have clinical and public health importance. However, little is known about modifiable lifestyle factors in ovarian cancer but in a recent paper, Nagle et al. found that higher BMI was associated with adverse survival among women with ovarian cancer.[6]

Even though the number of female smokers has declined in most parts of the Western world, cigarette smoking is still very common in many countries and it has been estimated that nearly 180 million adult women worldwide smoke cigarettes daily.[7] Cigarette smoking is known to affect the risk of developing epithelial ovarian cancer. The association differs by histotype, reflecting their different aetiologies, and the strongest association is observed for mucinous ovarian tumours.[8-11] Further, smoking has been found to correlate with survival for several malignancies including lung, breast and laryngeal cancer,[12-14] but only a few studies have investigated the association between cigarette smoking and epithelial ovarian cancer survival and the results have been inconclusive.[15-21] Four studies found that cigarette smoking was associated with worse survival,[15-18] whereas three studies found no association.[19-21] However, the results from most previous studies are based on small numbers of participants

(n = 61-1,997 women), only one of the studies performed separate analyses by histotype,[18] and only two of the studies investigated progression-free survival.[17,18]

By use of data from 19 case-control studies participating in the Ovarian Cancer Association Consortium (OCAC), the aim of this study was to investigate the prognostic impact of pre-diagnostic cigarette smoking on epithelial ovarian cancer survival, both overall and according to histotype. We furthermore investigated whether the association between smoking status and survival differed according to strata of stage of ovarian cancer at diagnosis (localised vs advanced stage).

MATERIALS AND METHODS

OCAC, which has been described in detail elsewhere,[22] is an international collaboration founded in 2005. For the present analyses, 19 case-control studies provided data on cigarette smoking, potential confounders and clinical follow-up information (Table 1).[23-41]

Using standardised formats, data from each OCAC study were centrally harmonised. All data were checked for internal consistency and, where necessary, clarification was provided by the original investigators. In the present study, women diagnosed with fallopian tube or peritoneal cancer as well as women diagnosed with borderline ovarian tumors were not considered for analyses. Consequently, the initial study population consisted of women diagnosed with epithelial ovarian cancers only (n = 14,150). From these, we excluded women with missing data on vital status or survival time (n = 1,364), smoking status (n = 1,973), age (n = 3), race/ethnicity (n = 20), tumour stage (n = 478) and grade (n = 1,198), leaving 9,114 women diagnosed with epithelial ovarian cancer eligible for analyses. Of these, there were 5,455

serous ovarian tumours (5,014 high-grade and 441 low-grade serous ovarian tumours), 611 mucinous, 1,473 endometrioid, 600 clear cell ovarian tumours, and 975 with other types of epithelial ovarian tumours. All individual studies included in OCAC had institutional review board and/or ethics committee approval and all study participants provided informed consent.

Assessment of cigarette smoking

Information on use of tobacco products other than cigarettes was limited to a few studies. Therefore, this study only addressed the prognostic impact of pre-diagnostic cigarette smoking on epithelial ovarian cancer survival. Information on cigarette smoking was obtained through self-administered questionnaires or in-person interviews and assessment of current and former smoking related either to date of diagnosis or interview, or one year prior to this depending on the study. We obtained information on smoking status prior to diagnosis (never, former or current), cigarette consumption (average number of cigarettes per day), total duration of smoking (years) and time since smoking cessation (years). Among the case-control studies included, various definitions were used to classify women who had smoked. Some studies used a definition of at least 100 cigarettes smoked during the lifetime (AUS,[28] CON,[40] DOV,[39] JPN,[26] MAY,[27] NCO,[30] NEC,[31] POL,[33] TBO,[41] and UCI[37]) whereas other studies used daily smoking for a period of 3, 6 or 12 months (GER,[29] HAW,[25] HOP,[38] NJO,[23] SEA,[35] STA,[34] UKO,[32] and USC[36]) or self-report of smoking without further specification (MAL[24]).

Covariate and clinical data

From all 19 studies included, we obtained information about the following covariates associated with smoking and/or survival: age at diagnosis, race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian or others, including unknown race), tumour grade (well,

moderately or poorly differentiated, or undifferentiated) and tumour stage at diagnosis. In the OCAC data, tumour stage was classified from a harmonised summary stage variable based on the International Federation of Gynaecology and Obstetrics (FIGO) staging system and the Surveillance, Epidemiology, and End Results (SEER) staging manuals and categorised as: localised, regional, distant or unknown. Information on FIGO and SEER stage was obtained by each OCAC study from a variety of sources including medical records, pathology reports, institutional databases, hospital tumour boards and cancer registries. Furthermore, 15 studies (all studies but SEA, STA, TBO and UKO) had information on recent BMI (one or five years prior to ovarian cancer, depending on the study) and 17 studies (all studies but JPN and TBO) provided information on level of education (≤high school vs >high school). Information on residual disease remaining after primary surgery was available from seven studies (AUS, HAW, JPN, MAL, MAY, NCO and NEC). In the common OCAC data set, residual disease was defined as the maximum dimension of disease remaining after primary surgery and categorised as: no macroscopic disease, macroscopic disease ≤1 cm, macroscopic disease >1 cm and ≤2 cm, macroscopic disease >2 cm, macroscopic disease (size unknown), tumour not resected or unknown. In the analysis, residual disease was categorised as a dichotomous variable (no macroscopic disease present vs macroscopic disease present).

Each study reported vital status and survival time and follow-up information was obtained from a variety of data sources including medical record review, patient contact, linkage with state cancer registries, use of the SEER registry and death-record databases. Overall survival time was calculated from date of diagnosis or date of study recruitment whichever came last, until date of death from any cause or, for living patients, date of last follow-up. Cause of death data was only available from seven studies (AUS, HAW, JPN, MAL, MAY, NCO and NEC) corresponding to 968 women of the 5,149 women who had died (19%). In the present

study, death due to an ovarian cancer diagnosis was defined as death due to progression of the disease. Among the women for whom cause of death data were available, the vast majority (94%) had died from ovarian cancer. Thus, all-cause mortality was used as the primary outcome in these analyses. Further, for the seven studies where data were available (AUS, HAW, JPN, MAL, MAY, NCO and NEC), progression-free survival time was calculated from date of diagnosis to date of documented clinical (e.g. ascites), biochemical (i.e., CA125) or radiological disease progression (CT scan), date of death or date of last follow-up for patients who had not progressed. For all 19 studies included, the time-period from date of diagnosis to date of study recruitment was available and left truncation at recruitment was used in all analyses to account for time elapsed between date of diagnosis and date of study recruitment, in order to reduce the likelihood of survivorship bias arising from the exclusion of eligible women who had died before recruitment.

Statistical analysis

Associations between the various variables of smoking and survival were analysed using a two-stage approach.[42] In stage one, adjusted study-specific hazard ratios (HRs) and corresponding standard errors were obtained from Cox regression models with time since diagnosis as the underlying time scale. Smoking status was included as a categorical variable (never, former or current), whereas "cigarette consumption", "duration of smoking" and "time since smoking cessation" were parameterised both as categorical and as continuous variables. Each categorical variable was categorised into ordinal groups with never smokers as the reference group. The associations between the continuous variables "cigarette consumption", "duration of smoking" and ovarian cancer survival were evaluated among ever smokers (former or current smokers), whereas the association between "time since smoking cessation" and survival was evaluated among former smokers only. All study-specific analyses were

adjusted for age (continuous, included as a linear variable), tumour stage (localised, regional or distant), tumour grade (well, moderately or poorly differentiated or undifferentiated) and race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian or other, including unknown race). Not all studies had data on BMI (continuous, per 5 kg/m^2), level of education (≤high school vs >high school) or residual disease (no macroscopic disease present vs macroscopic disease present) and these variables were therefore only included as adjustment factors in a subset of studies in additional statistical models.

In stage two, the study-specific estimates were combined by a random-effects inverse variance-weighted univariate meta-analysis into a pooled hazard ratio (pHR) with corresponding 95% CIs.[43] For all analyses, individual studies were included in the meta-analysis only if the following two requirements were met: 1) at least five observations with data on all covariates were available and 2) there were at least one observation with an event, i.e. death (or progression for the analyses on progression free survival). Statistical heterogeneity among studies was evaluated using the Cochran Q and I^2 statistics, but as only very little and non-consistent evidence of heterogeneity was observed in the analyses, potential sources of heterogeneity were not investigated further.

Analyses for the associations between smoking and overall survival were also conducted separately for the various standard histotypes of epithelial ovarian cancer (serous, mucinous, endometrioid and clear cell ovarian tumours). Additionally, serous ovarian tumours were categorised as either low- (grade 1) or high-grade (grade ≥2) serous tumours. A similar analytic approach was used to assess the association between cigarette smoking and progression-free survival. However, we only investigated the association between smoking status and progression-free survival for ovarian cancer overall and for serous ovarian tumours

because a limited number of cases impeded meaningful analyses for the remaining smoking variables and histotypes.

In a stratified analysis, we investigated whether the association between smoking status and overall survival differed according to strata of stage of ovarian cancer at diagnosis (localised vs advanced stage). For this analysis, pairwise comparisons were made using t-tests based on estimates and standard errors from the stratified analyses and p-values were adjusted for multiple testing by use of the Bonferroni procedure. Finally, sensitivity analyses for the association between cigarette smoking and overall survival were performed where follow-up was restricted at ≤5, >5 - ≤10 and >10 years after the diagnosis of epithelial ovarian cancer. These sensitivity analyses were only conducted for ovarian cancer overall and for serous ovarian tumours, as small numbers of cases prohibited these analyses for the other histotypes. All p-values presented are two-sided. We used the statistical package *meta* in R (version 3.1.0) for all analyses.

RESULTS

Detailed information on the 19 included case-control studies is shown in Table 1. Twelve studies were conducted in the United States, five in Europe and one each in Australia and Japan. The number of women diagnosed with epithelial ovarian cancer included in the studies varied from 33 (JPN) to 1,138 (USC). The age range at diagnosis varied from 19-93 years among women diagnosed between 1992 and 2012. Sixteen studies were population-based and three hospital-based (UKO, MAY and JPN). Eight studies (AUS, GER, JPN, MAY, SEA, TBO, UCI and UKO) involved information obtained from self-completed questionnaires, whereas 11 studies (CON, DOV, HAW, HOP, MAL, NCO, NEC, NJO, POL, STA and USC)

collected information by in-person interviews. Approximately 57% of the study women died during the follow-up period and 5-year survival was 48%. The median follow-up time was 7.0 years.

Among the 9,114 women with epithelial ovarian cancer, 54.5% were never smokers at diagnosis, 31.8% were former smokers, whereas current smokers constituted 13.7% of the study population (Table 2). Compared with never and former smokers, current smokers tended to be younger, were more often diagnosed with localised disease and with a mucinous or well-differentiated tumour. They were also more likely to be Black, were less obese, were less likely to have completed more than high school and more likely to have had residual disease compared with never and former smokers (all p-values <0.04).

Figure 1 shows the association between cigarette smoking status and overall survival following a diagnosis of epithelial ovarian cancer, by study site (HRs) and overall (pHRs). In Table 3, the adjusted pHRs for the associations between the various smoking variables and overall survival after a diagnosis of epithelial ovarian cancer and according to histotype are presented. For women with epithelial ovarian cancer, both current (pHR = 1.17, 95% CI: 1.08-1.28) (Table 3; Figure 1a) and former smokers (pHR = 1.10, 95% CI: 1.02-1.18) (Table 3; Figure 1b) had a worse overall survival compared with women who had never smoked. In addition, an increasing number of cigarettes smoked per day and duration of smoking tended to have a negative impact on overall survival whereas increasing time since smoking cessation tended to have a positive impact on overall survival of epithelial ovarian cancer.

Concerning the histotype-specific analyses, a number of associations are noteworthy. Both former (pHR = 1.12, 95% CI: 1.04-1.20) and current (pHR = 1.11, 95% CI: 1.00-1.23)

smokers diagnosed with serous ovarian tumours had a worse overall survival compared with never smokers (Table 3). Additional analyses stratified by grade revealed similar associations for women with high-grade (former smokers: pHR = 1.10, 95% CI: 1.02-1.18; current smokers: pHR = 1.11, 95% CI: 0.99-1.23) and low-grade serous ovarian tumours (former smokers: pHR = 1.43, 95% CI: 1.02-2.02; current smokers: pHR = 1.19, 95% CI: 0.80-1.78). The strongest associations were observed for mucinous ovarian tumours, where current smokers had a statistically significantly 91% worse survival (pHR = 1.91, 95% CI: 1.01-3.65) and former smokers a statistically non-significantly 43% worse survival (pHR = 1.43, 95% CI: 0.83-2.48) than never smokers. Also for this tumour type, an increasing number of cigarettes smoked per day tended to have a negative impact on survival (pHR = 1.10, 95% CI: 0.95-1.26 per each additional 5 cigarettes smoked per day). In addition, current smokers with endometrioid ovarian tumours tended to have a poorer survival (pHR = 1.27, 95% CI: 0.91-1.77), whereas no clear association between smoking status and overall survival was observed for clear cell tumours (Table 3).

Potential confounders in the association between smoking and overall survival of ovarian cancer include BMI and level of education. Additional adjustment for these two variables in a model restricted to studies where this information was available (n = 15, Supplementary Table 1) made virtually no changes to the estimated associations between smoking and overall survival, both when compared to results from the main statistical model (i.e., without adjustment for BMI and level of education) using data from these 15 studies only (Supplementary Table 2) and when compared with the results from the main statistical model using data from all 19 studies (Table 3). In addition, a statistical model including information on residual disease was also evaluated for the seven studies in which these data were available. In general, inclusion of this clinical variable did not result in any consistent changes

to the pooled estimates (Supplementary Table 3) when compared with results from the main statistical model including data from these seven studies only (Supplementary Table 4) and results from the main statistical model using data from all 19 studies (Table 3).

For epithelial ovarian cancer and for serous ovarian tumours, we investigated whether the association between smoking status and overall survival varied by tumour stage (Table 4). Compared with never smokers, current smokers (pHR = 1.63, 95% CI: 1.19-2.22) with all histotypes of ovarian cancer combined had worse overall survival among women with localised stage disease. A significantly weaker association was observed with current smoking among women with advanced stage disease (pHR = 1.16, 95% CI: 1.06-1.28) (p-value for pairwise comparison = 0.04). The same pattern was seen for former smoking but the pooled HRs for former smokers were not statistically significantly different across tumour stage strata (p-value = 0.21). Comparable, but slightly higher pHRs were observed for serous ovarian tumours as former (pHR = 1.46, 95% CI: 0.87-2.45) and current smokers (pHR = 1.67, 95% CI: 0.84-3.34) with localised disease had a poorer survival compared with never smokers. A less strong association was observed among women with advanced stage disease, but the pooled HRs for current and former smokers were not statistically significantly different across tumour stage strata (both p-values >0.05).

We also examined the association between smoking and overall survival for epithelial ovarian cancer and for serous ovarian tumours according to follow-up time since ovarian cancer diagnosis (Table 5). Where follow-up was censored at 5 years after diagnosis, both former (pHR = 1.10, 95% CI: 1.02-1.18) and current smokers with ovarian cancer overall (pHR = 1.17, 95% CI: 1.08-1.29) had a worse survival compared with never smokers. For the follow-up period from >5 to ≤10 years after ovarian cancer diagnosis, similar patterns of survival

were observed, although the pHRs did not reached statistical significance. Finally, for the follow-up period of >10 years after the ovarian cancer diagnosis, both former (pHR = 1.66, 95% CI: 1.14-2.42) and current smokers (pHR = 2.54, 95% CI: 1.27-5.09) had a poorer survival compared with never smokers. For all follow-up periods, virtually similar survival patterns applied to women with serous ovarian tumours. For both ovarian cancer overall and for serous ovarian tumours, an increasing number of cigarettes smoked per day tended to have a negative impact on survival in the follow-up period of >10 years after the ovarian cancer diagnosis, whereas no association between number of cigarettes smoked per day and survival was found in follow-up ≤10 years since diagnosis. Also, increasing time since smoking cessation tended to have a positive impact on survival only when the length of the follow-up period exceeded 10 years, whereas no consistent pattern between duration of smoking and survival was noted with increasing follow-up time since diagnosis.

Finally, we assessed the prognostic impact of smoking status on progression-free survival for ovarian cancer overall and for serous ovarian tumours in seven studies where this information was available. The pHRs resembled the results obtained for overall survival but the pHRs were not statistically significant, which may be explained by the relatively smaller numbers of women included for these analyses (data not shown).

DISCUSSION

To our knowledge, this is the largest study to date on cigarette smoking and epithelial ovarian cancer survival. We found that smoking status prior to diagnosis was associated with worse overall survival. Our results also showed that the association with smoking seemed to be different across histotypes of epithelial ovarian cancer being most pronounced for mucinous

tumours, where current smokers had an almost 2-fold worse survival compared with never smokers. Also, both former and current smoking was associated with worse survival following serous ovarian cancer (both for high-grade and low-grade serous tumours) and among current smokers with endometrioid ovarian tumours, whereas no appreciable relationships were observed for clear cell subtypes, though evaluation of this subtype was limited by small numbers. These associations remained virtually unchanged after additional adjustments for BMI, level of education and residual disease. Stratification by stage showed that smoking had a stronger association with overall survival among women with localised disease. Also, the magnitude of the association between smoking and overall survival appeared to increase with longer follow-up since ovarian cancer diagnosis. Finally, the results for progression-free survival resembled the results obtained for overall survival.

Only seven previous studies, including between 61 and 1,997 study subjects, have investigated the association between smoking and epithelial ovarian cancer survival.[15-21] However, one of the studies was based on data from a study site (MAL) that is included in the present analysis and consequently, results from this study will not be discussed further.[15] While three previous studies found no marked association,[19-21] the survival disadvantage associated with smoking observed in the present study is supported by the results from three other studies.[16-18] For example, in a study of 676 women with epithelial ovarian cancer, Nagle et al.[16] found that current smokers had 36% worse survival compared with non-smoking women and that worse survival was further increased with increasing number of pack-years and number of cigarettes smoked per day. Most recently, Kelemen et al.[18] studied 432 epithelial ovarian cancer patients receiving adjuvant chemotherapy from the Alberta Cancer Registry, Canada and while no association between smoking status and overall or progression-free survival among ovarian cancer overall was observed, histotype-specific

analyses showed that smoking women with mucinous ovarian tumours had worse overall and progression-free survival compared with non-smoking women.

The observed associations between smoking and overall as well as histotype-specific ovarian cancer survivals may be explained by a number of mechanisms. It has been suggested that carcinogens in tobacco smoke directly accelerate tumour growth resulting in earlier progression and death. It has also been suggested that smoking is associated with an increased risk of recurrence, postsurgical complications, a poorer response to treatment and an increased treatment-related toxicity.[44,45] Finally, smoking is known to be associated with an unhealthy lifestyle,[46] which may have a negative effect on survival.

We found that the association between smoking and survival observed for ovarian cancer overall was confined to the serous and especially mucinous histotypes of the disease and perhaps also to endometrioid tumours. Epidemiological studies have consistently found that the strongest association between smoking and risk of epithelial ovarian cancer appears to be with mucinous ovarian tumours,[8-11] and the present results add further knowledge about the relationship between smoking and epithelial ovarian cancer. However, biological explanations for histotype-specific survival differences with regard to smoking are not known and should be investigated further.

Our results suggested that current smoking may have a greater impact on survival among women with localised than disseminated disease. Further, we observed a tendency that smoking status was associated with an increasingly poorer survival with increasing follow-up. These results were observed both for ovarian cancer overall and for serous tumours, but evaluation of the other subtypes was hampered by small numbers. The results may reflect

differences in stage. Women who are diagnosed in an advanced stage disease are more likely to die shortly after diagnosis, whereas women who survive for a longer time period are more likely to have been diagnosed in a localised stage. Thus, our results suggest that smoking has the most substantial impact on long-term survival, which most often occur among women diagnosed in an early stage. Our findings are not surprising given the poor prognosis among women with advanced stage disease, which leaves little potential for other factors including smoking to have an impact on ovarian cancer survival.

A major strength of our study is the large sample size including more than 9,000 women with epithelial ovarian cancer, which allowed us to investigate associations between a number of variables of smoking and the various histotypes of epithelial ovarian cancer. For a subset of women, we also investigated progression-free survival and found no marked association, potentially due to insufficient power. We did not include ovarian cancer-specific survival analysis. However, among the limited cause of death data in our dataset, the vast majority died from ovarian cancer (94%) and we are thus confident that all-cause survival is a pertinent proxy for ovarian cancer survival. As the studies included in our pooled analysis were not selected from published studies, our analyses have not been affected by publication bias. Our analyses relied on individual data combined into a single dataset following careful central data harmonisation. By use of a two-stage approach, we were able to consider differences in study design and data collection across studies and to control for a number of potential confounders. Further, by utilising left truncated data, we decreased the likelihood of potential survivorship bias. Most importantly, adverse associations between smoking and survival were still observed after additional adjustment for BMI and level of education as well as the main clinical factors that affect survival: stage, grade and residual disease.

Women who smoke are known to have a higher degree of comorbidity compared with non-smokers[47] and comorbid conditions have a negative prognostic impact on survival from ovarian cancer.[48] Specifically, women with comorbidities may not tolerate standard treatments and are therefore more often offered less aggressive types of treatment compared with healthier women.[49] Unfortunately, we were not able to adjust for degree of comorbidity as this information was not available in our data at the time of analysis and we can therefore not rule out that our results may have been slightly affected by unmeasured confounding from comorbidity. However, as obesity and low socioeconomic status is highly associated with comorbidities,[50,51] our adjustment for BMI and level of education may have diminished potential confounding by comorbidity. Further limitations of this study include the fact that information on smoking habits was based on retrospective reports in all studies included in the present paper, which increases the risk of misclassification, and that these reports of smoking behaviours pertained to time periods prior to diagnosis rather than to during follow-up time. Newly diagnosed women with ovarian cancer could conceivably change their smoking behaviours and such information might not have been captured in the retrospective reporting. However, because the data on smoking were obtained independent of mortality events, any effects of possible misclassification are likely to be non-differential. In general, socially undesirable behaviours such as cigarette smoking may be prone to under-reporting, where current smokers may have categorised themselves as either never or former smokers and this may therefore have underestimated the true association between current smoking status and survival. In support of this idea, one study among others found that approximately one-third of newly diagnosed cancer patients who denied any current smoking had blood cotinine values at levels that supported active smoking.[52] Another possible limitation of the present work is that in some studies ovarian tumours may not have undergone systematic histopathological review. Hence, some extent of misclassification of the histotypes cannot be

excluded. Finally, our study design did not allow us to investigate how smoking cessation after a diagnosis of epithelial ovarian cancer could affect survival.

In conclusion, the results from this large pooled analysis indicate that cigarette smoking is associated with a worse survival in ovarian cancer patients; primarily among women diagnosed with serous and mucinous ovarian tumours. Furthermore, our results may also suggest that current smoking more strongly impairs survival among women with localised disease and that the effect of smoking on ovarian cancer prognosis increases with longer follow-up since ovarian cancer. Future studies are needed focusing on how smoking patterns after a diagnosis of ovarian cancer affect survival.

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Table 1. Characteristics of the 19 case-control studies included in the pooled analysis of cigarette smoking and survival following a diagnosis of ovarian cancer

Study[a]	Country	Study period	Cases (N)	Age range at diagnosis	Median follow-up time among living (years)	Number of women who died (%)	5-year survival (%)
AUS: Australian Ovarian Cancer Study & Australian Cancer Study[28]	Australia	2002-2006	1,007	20-80	7.1	629 (62.5)	482 (47.9)
JPN: Hospital-based Research Programme at Aichi Cancer Center[26]	Japan	2001-2005	33	32-72	5.0	12 (36.4)	10 (30.3)
GER: German Ovarian cancer study[29]	Germany	1993-1996	188	21-75	13.6	129 (68.6)	89 (47.3)
MAL: The Danish Malignant Ovarian Tumor Study[24]	Denmark	1994-1999	516	32-80	13.5	393 (76.2)	226 (43.8)
POL: Polish Ovarian Cancer Study[33]	Poland	2000-2003	171	32-74	5.2	90 (52.6)	55 (32.2)
SEA: Study of Epidemiology and Risk Factors in Cancer Heredity[35]	United Kingdom	1998- 2010	582	23-74	6.2	279 (47.9)	309 (53.1)
UKO: UK Ovarian Cancer Population Study[32]	United Kingdom	2006-2010	449	19-90	3.5	150 (33.4)	196 (43.7)
CON: Connecticut Ovary Cancer Study[40]	USA	1998-2003	301	36-81	7.6	177 (58.8)	174 (57.8)
DOV: Diseases of the Ovary and their Evaluation Study[39]	USA	2002-2005	462	35-74	6.4	256 (55.4)	251 (54.3)
HAW: Hawaii Ovarian Cancer Case-Control Study[25]	USA	1993-2008	388	24-87	6.6	200 (51.5)	190 (49.0)
HOP: Hormones and Ovarian Cancer Prediction Study[38]	USA	2003-2009	587	25-91	4.8	308 (52.5)	191 (32.5)
MAY: Mayo Clinic Ovarian Cancer Case-Control Study[27]	USA	2000-2009	481	21-91	4.7	277 (57.6)	144 (29.9)
NCO: North Carolina Ovarian Cancer study[30]	USA	1999-2008	833	22-74	6.9	496 (59.5)	354 (42.5)
NEC: New England Case-Control Study of Ovarian Cancer[31]	USA	1992-2003	826	21-77	12.3	476 (57.6)	486 (58.8)
NJO: New Jersey Ovarian Cancer Study[23]	USA	2002-2008	189	32-81	2.2	42 (22.2)	0 (0.0)[b]
STA: Family Registry for Ovarian Cancer and Genetic Epidemiology of Ovarian Cancer[34]	USA	1997-2001	427	21-64	10.1	248 (58.1)	224 (52.5)
TBO: Tampa Bay Ovarian Cancer Study[41]	USA	2000-2012	189	26-93	5.6	104 (55.0)	61 (32.3)
USC: Los Angeles County Case-Control Studies of Ovarian Cancer[38]	USA	1993-2005	1,138	20-84	11.4	721 (63.4)	646 (56.8)
UCI: University California, Irvine Ovarian Cancer Study[37]	USA	1993-2005	347	21-86	6.2	162 (46.7)	250 (72.0)
TOTAL		1992-2012	**9,114**	**19-93**	**7.0**	**5,149 (56.5)**	**4,338 (47.6)**

[a]All studies were population-based except for UKO, MAY and JPN that were all hospital-based.
[b]In the present study, no women included in NJO were followed for 5 years or more. Therefore, no women in NJO survived 5 years.

Table 2. Age distribution, covariate and clinical characteristics for the 9,114 women included in analysis, according to smoking status at diagnosis

	Smoking status					
Characteristics	**Never N (%)**		**Former N (%)**		**Current N (%)**	
Number of Women	**4,966 (54.5)**		**2,900 (31.8)**		**1,248 (13.7)**	
Age at diagnosis (years)[1]						
<40	328	(6.6)	114	(3.9)	119	(9.5)
40-49	953	(19.2)	463	(16.0)	326	(26.1)
50-59	1,528	(30.8)	965	(33.3)	408	(32.7)
60-69	1,356	(27.3)	913	(31.5)	279	(22.4)
≥70	801	(16.1)	445	(15.3)	116	(9.3)
Tumour stage[1]						
Localised	952	(19.2)	529	(18.2)	284	(22.8)
Regional	1,158	(23.3)	647	(22.3)	231	(18.5)
Distant	2,856	(57.5)	1,724	(59,4)	733	(58.7)
Histology[1]						
Serous	2,899	(58.3)	1,829	(63.1)	727	(58.3)
Serous low-grade	218	(4.4)	142	(4.9)	81	(6.5)
Serous high-grade	2,681	(54.0)	1,687	(58.2)	646	(51.8)
Mucinous	316	(6.4)	161	(5.6)	134	(10.7)
Endometrioid	839	(16.9)	460	(15.9)	174	(13.9)
Clear cell	374	(7.5)	150	(5.2)	76	(6.1)
Other	538	(10.8)	300	(10.3)	137	(11.0)
Grade[1]						
Well differentiated	634	(12.8)	357	(12.3)	214	(17.1)
Moderately differentiated	1,286	(25.9)	709	(24.4)	317	(25.4)
Poorly differentiated	2,739	(55.2)	1,657	(57.1)	669	(53.6)
Undifferentiated	307	(6.2)	177	(6.1)	48	(3.8)
Race/ethnicity[1]						
Non-Hispanic White	4,187	(84.3)	2,629	(90.7)	1,108	(88.8)
Hispanic White	150	(3.0)	73	(2.5)	25	(2.0)
Black	103	(2.1)	71	(2.4)	60	(4.8)
Asian	369	(7.4)	59	(2.0)	18	(1.4)
Other	156	(3.1)	67	(2.3)	34	(2.7)
BMI						
Median	24.19		24.33		23.43	
Interquartile range	21.48-28.34		21.64-28.59		20.90-27.48	
Missing	359	(7.2)	217	(7.5)	52	(4.2)
Level of education						
≤high school	2,168	(43.7)	1,275	(44.0)	771	(61.8)
>high school	2,621	(52.7)	1,516	(52.3)	438	(35.1)
Missing	177	(3.6)	109	(3.7)	39	(3.1)
Residual disease[2]						
No macroscopic disease present	539	(10.9)	255	(8.8)	128	(10.3)
Macroscopic disease present	714	(14.4)	420	(14.5)	214	(17.1)
Missing	3,713	(74.8)	2,225	(76.7)	906	(72.6)

[1]No missing data
[2]Only seven studies provided information on residual disease (AUS, HAW, JPN, MAL, MAY, NCO and NEC)

Table 3. Adjusted pooled hazard ratios (pHRs) and 95% confidence intervals (CIs) for the association between cigarette smoking and overall survival among 9,114 women from 19 studies with epithelial ovarian cancer, overall and by histotype

	Overall				Serous				Mucinous				Endometrioid				Clear cell			
	Cases	I^2 (%)	pHR[2]	95% CI	Cases	I^2 (%)	pHR[2]	95% CI	Cases	I^2 (%)	pHR[2]	95% CI	Cases	I^2 (%)	pHR[2]	95% CI	Cases	I^2 (%)	pHR[2]	95% CI
Smoking status[3]																				
Never smoker[4]	4,966	-	1.00	Ref.	2,899	-	1.00	Ref.	316	-	1.00	Ref.	835	-	1.00	Ref.	373	-	1.00	Ref.
Former smoker	2,900	17.6	1.10	(1.02-1.18)	1,829	0.0	1.12	(1.04-1.20)	161	43.5	1.43	(0.83-2.48)[1]	460	33.3	0.85	(0.63-1.15)	150	8.1	1.17	(0.74-1.85)
Current smoker	1,248	0.0	1.17	(1.08-1.28)	727	0.0	1.11	(1.00-1.23)	134	0.0	1.91	(1.01-3.65)	174	5.0	1.27	(0.91-1.77)	76	0.0	1.08	(0.67-1.75)
Cigarette consumption (per day)[5]																				
1-≤10	1,630	0.0	1.12	(1.04-1.21)	1,016	0.0	1.16	(1.06-1.27)	103	0.0	1.46	(0.74-2.88)	248	21.1	0.78	(0.55-1.10)	85	0.0	0.78	(0.45-1.33)
>10-≤20	1,535	0.0	1.12	(1.03-1.21)	922	0.0	1.08	(0.98-1.19)	124	16.5	1.69	(0.89-3.21)	227	58.9	1.17	(0.72-1.89)[1]	93	9.4	1.53	(0.93-2.51)
>20	615	10.9	1.24	(1.10-1.40)	383	0.0	1.26	(1.10-1.43)	45	52.4	2.59	(0.59-10.89)[1]	100	42.2	1.28	(0.74-2.21)	22	0.0	1.23	(0.53-2.86)
Per 5 cigarettes/day[6]		0.0	1.01	(0.99-1.03)		0.0	1.00	(0.98-1.02)		0.0	1.10	(0.95-1.26)		20.2	1.06	(0.98-1.14)		0.0	1.08	(0.94-1.24)
Duration of smoking before diagnosis[7]																				
1-≤10	923	8.5	1.07	(0.97-1.19)	565	0.0	1.10	(0.98-1.23)	53		NA[10]		156	34.4	0.96	(0.57-1.60)	48	0.0	1.80	(0.85-3.81)
>10-≤20	823	14.8	1.13	(1.00-1.26)	504	0.0	1.15	(1.02-1.29)	64	0.0	1.52	(0.60-3.82)	132	0.0	0.73	(0.49-1.08)	42	0.0	1.29	(0.67-2.46)
>20	2,267	24.6	1.16	(1.06-1.25)	1,411	0.0	1.14	(1.06-1.24)	159	45.6	1.90	(0.71-5.05)[1]	322	36.7	1.05	(0.75-1.46)	126	6.4	1.09	(0.70-1.69)
Per 5-year period[6]		50.1	1.02	(1.00-1.04)[1]		40.9	1.01	(0.99-1.04)[1]		22.4	0.95	(0.79-1.14)		27.3	1.05	(0.98-1.13)		9.4	1.04	(0.94-1.16)
Time from cessation to diagnosis (years)[8]																				
1-≤10	739	42.1	1.21	(1.04-1.40)[1]	424	32.7	1.24	(1.05-1.47)	55	0.0	1.93	(0.84-4.42)	126	21.3	1.15	(0.73-1.81)	32	0.0	0.93	(0.37-2.37)
>10-≤20	599	0.0	1.22	(1.09-1.37)	343	0.0	1.23	(1.07-1.41)	38	0.0	3.10	(0.99-9.72)	98	0.0	1.32	(0.86-2.03)	28	0.0	2.92	(1.13-7.54)
>20	1,086	0.0	1.08	(0.98-1.18)	668	0.0	1.15	(1.03-1.28)	51	0.0	1.53	(0.69-3.39)	172	0.0	0.79	(0.55-1.13)	60	9.0	1.35	(0.67-2.74)
Per 5-year period[9]		32.7	0.97	(0.95-1.00)		22.7	0.98	(0.95-1.01)		0.0	0.96	(0.82-1.12)		0.0	0.98	(0.90-1.06)		0.0	0.93	(0.77-1.12)

Numbers may not sum up to total because of missing data
[1]P-value for heterogeneity <0.05
[2]Adjusted for: age (continuous), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian or other), tumour stage (localised, regional or distant) and grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated)
[3]Number of studies included for analysis: overall = 19; serous = 19, mucinous = 15; endometrioid = 17; clear cell = 15
[4]Never smokers was used as the reference group for all categorical analyses
[5]Number of studies included for analysis: overall = 18; serous = 18, mucinous = 14; endometrioid = 16; clear cell = 14
[6]Among ever smokers
[7]Number of studies included for analysis: overall = 19; serous = 19, mucinous = 16; endometrioid = 17; clear cell = 15
[8]Number of studies included for analysis: overall = 18; serous = 17, mucinous = 12; endometrioid = 15; clear cell = 14
[9]Among former smokers only
[10]Not applicable due to unreliable model parameters (small numbers of events)

Table 4. Adjusted pooled hazard ratios (pHRs) and 95% confidence intervals (CIs) for the association between cigarette smoking status at diagnosis and overall survival among 9,114 women from 19 studies diagnosed with epithelial ovarian cancer, overall and for serous ovarian tumours, stratified by stage

	Overall							Serous						
	Localised stage			Advanced stage[1]				Localised stage			Advanced stage[1]			
	Cases	pHR[2]	95% CI	Cases	pHR[2]	95% CI	P-value	Cases	pHR[2]	95% CI	Cases	pHR[2]	95% CI	P-value
Smoking status														
Never	952	1.00	Ref.	4,014	1.00	Ref.		182	1.00	Ref.	2,705	1.00	Ref.	
Former	529	1.32	(0.96-1.82)	2,371	1.07	(1.00-1.15)	0.21	134	1.46	(0.87-2.45)	1,689	1.09	(1.01-1.17)	0.27
Current	284	1.63	(1.19-2.22)	964	1.16	(1.06-1.28)	0.04	56	1.67	(0.84-3.34)	665	1.09	(0.98-1.21)	0.23

[1] Advanced stage includes regional and distant stage
[2] Adjusted for age (continuous), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian or other) and grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated)

Table 5. Adjusted pooled hazard ratios (pHRs) and 95% confidence intervals (CIs) for the association between cigarette smoking and overall survival among 9,114 women from 19 studies diagnosed with epithelial ovarian cancer, overall and for serous ovarian tumours, according to length of follow-up since ovarian cancer diagnosis

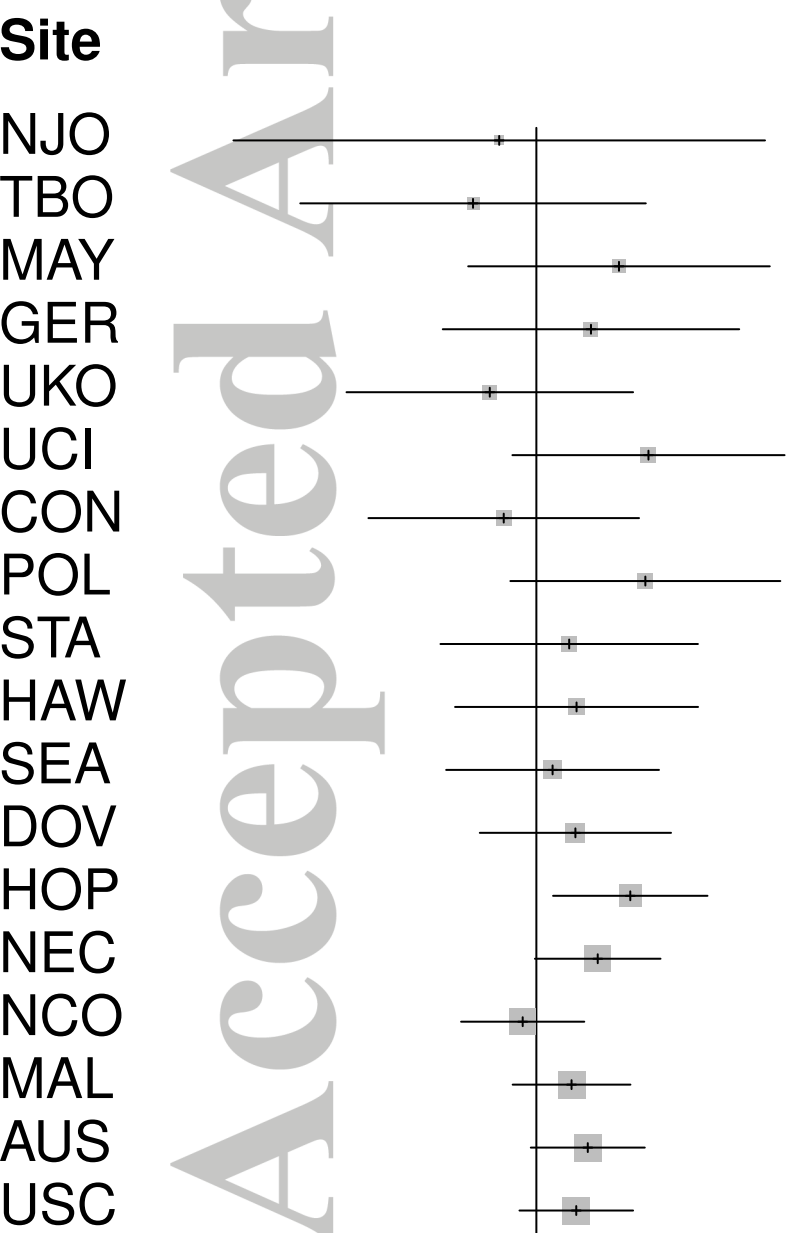
	Length of follow-up								
	≤5 years			>5 - ≤10 years			>10 years		
	Cases	pHR[1]	95% CI	Cases	pHR[1]	95% CI	Cases	pHR[1]	95% CI
Overall epithelial ovarian cancer									
Smoking status	9,114			4,308			1,419		
Never	4,966	1.00	Ref.	2,425	1.00	Ref.	775	1.00	Ref.
Former	2,900	1.10	(1.02-1.18)	1,303	1.09	(0.95-1.25)	425	1.66	(1.14-2.42)
Current	1,248	1.17	(1.08-1.29)	580	1.13	(0.90-1.41)	219	2.54	(1.27-5.09)
Cigarette consumption (per day)									
Per 5 cigarettes/day[2]		1.01	(0.99-1.03)		1.01	(0.96-1.05)		1.09	(0.95-1.25)
Duration of smoking before diagnosis (years)									
Per 5-year period[2]		1.02	(1.00-1.04)		1.00	(0.97-1.04)		1.03	(0.95-1.12)
Time from cessation to diagnosis (years)									
Per 5-year period[3]		0.97	(0.95-1.00)		0.97	(0.92-1.02)		0.90	(0.75-1.07)
Serous ovarian tumours									
Smoking status	5,455			2,117			583		
Never	2,899	1.00	Ref.	1,173	1.00	Ref.	310	1.00	Ref.
Former	1,829	1.12	(1.04-1.20)	662	1.09	(0.93-1.29)	183	1.93	(1.15-3.23)
Current	727	1.11	(1.00-1.23)	282	1.02	(0.80-1.31)	90	1.88	(0.90-3.93)
Cigarette consumption (per day)									
Per 5 cigarettes/day[2]		1.00	(0.98-1.02)		1.00	(0.94-1.05)		1.04	(0.91-1.19)
Duration of smoking before diagnosis (years)									
Per 5-year period[2]		1.01	(0.99-1.04)		1.00	(0.96-1.04)		0.99	(0.88-1.12)
Time from cessation to diagnosis (years)									
Per 5-year period[3]		0.98	(0.94-1.01)		1.00	(0.94-1.06)		0.87	(0.72-1.05)

[1]Adjusted for age (continuous), race/ethnicity (non-Hispanic White, Hispanic White, Black, Asian or other), tumour stage (localised, regional or distant) and grade (well differentiated, moderately differentiated, poorly differentiated or undifferentiated)
[2]Among ever smokers
[3]Among former smokers only

FIGURE LEGENDS

Figure 1. The association between cigarette smoking status at diagnosis and overall survival following a diagnosis of epithelial ovarian cancer, by study site and overall. Study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox regression models adjusted for age, race/ethnicity, stage and grade. The pooled hazard ratio (pHR) with corresponding 95% CI was estimated using a random effects model. a) Current versus never smokers; b) former versus never smokers.

Figure 1a



Site	HR	95% CI	Weight
NJO	0.86	(0.29 – 2.56)	0.62
TBO	0.77	(0.38 – 1.57)	1.48
MAY	1.41	(0.76 – 2.62)	1.94
GER	1.25	(0.68 – 2.31)	2.01
UKO	0.83	(0.46 – 1.49)	2.15
UCI	1.59	(0.91 – 2.78)	2.38
CON	0.87	(0.50 – 1.53)	2.41
POL	1.57	(0.90 – 2.73)	2.42
STA	1.14	(0.67 – 1.95)	2.66
HAW	1.18	(0.72 – 1.95)	2.99
SEA	1.07	(0.69 – 1.66)	3.90
DOV	1.17	(0.79 – 1.74)	4.83
HOP	1.47	(1.07 – 2.02)	7.40
NEC	1.29	(0.99 – 1.67)	11.19
NCO	0.95	(0.73 – 1.22)	11.63
MAL	1.16	(0.91 – 1.47)	12.72
AUS	1.24	(0.98 – 1.56)	13.58
USC	1.18	(0.93 – 1.49)	13.67
Pooled estimate	**1.17**	**(1.08 – 1.28)**	**100**

Heterogeneity: I^2=0%, p=0.7854

Figure 1b