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Cigarette smoking and the association with serous ovarian cancer in African American women: African American Cancer Epidemiology Study (AACES)

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Abstract

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Conflict of interest

None.

Background—Smoking is a risk factor for mucinous ovarian cancer (OvCa) in Caucasians. Whether a similar association exists in African Americans (AA) is unknown.

Methods—We conducted a population-based case-control study of incident OvCa in AA women across 11 geographic locations in the US. A structured telephone interview asked about smoking, demographic, health and lifestyle factors. Odds ratios and 95% confidence intervals (OR, 95% CI) were estimated from 613 cases and 752 controls using unconditional logistic regression in multivariable adjusted models.

Results—Associations were greater in magnitude for serous OvCa than for all OvCa combined. Compared to never smokers, increased risk for serous OvCa was observed for lifetime ever smokers (1.46, 1.11–1.92), former smokers who quit within 0–2 years of diagnosis (5.48, 3.04–9.86) and for total pack-years smoked among lifetime ever smokers (0–5 pack-years: 1.79, 1.23–2.59; >5–20 pack-years: 1.52, 1.05–2.18; >20 pack-years: 0.98, 0.61–1.56); however, we observed no dose response relationship with increasing duration or consumption and no significant associations among current smokers. Smoking was not significantly associated with mucinous OvCa. Associations for all OvCa combined were consistently elevated among former smokers. The proportion of ever smokers who quit within 0–2 years was greater among cases (23%) than controls (7%).

Conclusions—Cigarette smoking may be associated with serous OvCa among AA, which differs from associations reported among Caucasians. Exposure misclassification or reverse causality may partially explain the absence of increased risk among current smokers and lack of dose-response associations. Better characterization of smoking patterns is needed in this understudied population.

Keywords

cigarette smoking; racial-ethnic differences; gynecology; ovarian neoplasms; passive smoking; reverse causality

Introduction

Cigarette smoking and exposure to tobacco products is the single largest preventable cause of death and disease in the US (1). Smoking is causally linked to at least 13 cancers, including cancers of the oropharynx, larynx, esophagus, lung, upper (stomach, liver, pancreas, kidney, ureter) and lower (bladder, colorectum) gastro-intestinal organs, cervix and acute myeloid leukemia (2). Among ovarian cancers, which rank fifth in cancer deaths among women and accounts for more deaths than any other cancer of the female reproductive system (3), the adverse effect of smoking was reported most consistently with a significant increase in risk of mucinous compared to non-mucinous ovarian cancers in four large investigations (4–7). These reports echo earlier studies that found current or recent smoking, along with a higher number of total pack-years of smoking, was associated with approximately a two-fold increase in risk of mucinous ovarian cancer compared to no or weak associations for non-mucinous ovarian cancers (8–11). In addition, studies examining the association between second-hand smoke exposure and risk of ovarian cancer are sparse, and reported a significant increased risk among never smokers for borderline tumors only (12), a significant decreased risk among never smokers (13) or no association of gestational

or childhood environmental tobacco smoke exposure with the risk of invasive or borderline tumors among never smokers (14).

Studies of smoking and the association with ovarian cancer were conducted primarily among Caucasian women. The smoking prevalence among AA women is slightly lower than among Caucasian women and was estimated to be ~37% and 39%, respectively, in community settings in the southeastern US between 2002 and 2009 (15) and 15% and 18%, respectively, in the US generally in 2013 (1). Although the incidence of ovarian cancer in the US is lower among African American (AA) women than in Caucasian women (9.8 vs. 13.0 cases/100,000, respectively), 5-year relative survival is worse for AA women than Caucasian women across all ages (36% vs 44%, respectively) (16). A better understanding of the factors associated with ovarian cancer incidence could improve primary prevention strategies among AA women to reduce mortality in this population. The strength and magnitude of association between smoking and risk of ovarian cancer and specific tumor histotypes among AA women is unknown. Given reports of differences in distributions of ovarian cancer risk and protective factors among AA compared to Caucasian women (17, 18), we evaluated associations of cigarette smoking and second-hand smoke using data from the largest study of ovarian cancer in AA women, the African American Cancer Epidemiology Study (AACES).

Materials and Methods

Study Design and Participants

The study design of AACES was outlined in detail previously (19). Briefly, AACES is a population-based case-control study of incident primary ovarian cancer in women of self-identified African descent from 11 geographic locations in the US with a relatively high density of AAs in the population including Alabama, Georgia, Illinois, Louisiana, Michigan, North Carolina, New Jersey, Ohio, South Carolina, Tennessee and Texas.

Eligibility criteria for cases were that they self-identified as being of African descent (full or mixed race) and were between 20 to 79 years of age with histologically confirmed invasive epithelial ovarian cancer that was newly diagnosed between December 2010 and January 2016. Cases were identified from state cancer registries, SEER (Surveillance, Epidemiology and End Results) registries or individual hospital systems and enrolled through rapid case ascertainment. Controls were identified using list-assisted random-digit dialing from both landline and cellular telephone exchanges. Eligibility criteria for controls were that they self-identified as being of African descent (full or mixed race), had no previous history of ovarian cancer and had at least one ovary in tact. Controls were frequency matched to cases within 5-year age categories and by state of residence.

Of 3,210 participants contacted (1,680 cases and 1,530 controls), we excluded participants that were deceased (231 cases and 3 controls) or otherwise ineligible (171 cases and 80 controls), physician refusals (17 cases), participant refusals (351 cases and 350 controls) and those pending interviews (64 cases). We included for analysis 1,365 (613 cases and 752 controls) who completed a baseline questionnaire by January 2016; of these, 72 participants (58 cases and 14 controls) completed a shorter version of the baseline questionnaire. The

questionnaire was administered through a structured telephone interview coordinated by Duke University, NC and included questions on socio-demographic, health and lifestyle factors. In addition, alcohol and coffee consumption was obtained with a mailed, self-administered Block 2005 food frequency questionnaire (FFQ) for 110 food and beverages consumed in the one year before diagnosis for cases or in the year prior to the telephone interview for controls, following a protocol described previously (19, 20). Each participant provided verbal informed consent at the time of the telephone interview. The institutional review board at each site approved the study.

Smoking Exposure Assessment

We defined an ever smoker as a woman who had smoked at least 100 cigarettes in their lifetime. For each participant, we also asked if smoking continued at the reference date (date of diagnosis for cases or date of telephone interview for controls), the age at smoking initiation, the duration of smoking in years, the usual amount smoked on a daily basis and the age smoking stopped for former smokers. We compared age at smoking cessation, if applicable, to age at the reference date and categorized former smokers into those that quit within 2 years (including 46 cases and 6 controls who reported they stopped smoking in the year of their reference date), 3–20 years and > 20 years from diagnosis/reference date. Pack-years of smoking were calculated as number of cigarettes smoked per day divided by 20 and multiplied by the number of years smoked. Women who completed the longer baseline questionnaire also reported if they lived with a smoker either before or after 18 years of age, if they were exposed to maternal smoking before the age of 10 years or exposed to workplace smoking as an adult.

Statistical Analysis

Primary analyses evaluated associations between lifetime ever smoking (never, ever) or smoking categories (never, current, former that quit 0–2 years, 3–20 years and > 20 years from reference date) and risk of ovarian cancer using unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI). We estimated the degree of statistical heterogeneity in ORs across geographic locations using the likelihood ratio test comparing age- and study location- adjusted models with and without an interaction term between smoking categories and geographic location. Data were combined into a single dataset for pooled analyses following confirmation of no statistical heterogeneity (for lifetime ever smoker: $P_{\text{heterogeneity}}=0.45$ and for smoking status categories: $P_{\text{heterogeneity}}=0.22$). Multivariable models were adjusted for known or potential confounders and variables were retained if their removal resulted in a 10% or greater change in the effect estimate of smoking categories on the logarithmic scale with risk of ovarian cancer overall (21). The variables evaluated included age in years (continuous), geographic location (11 sites), body mass index (BMI) in kg/m^2 (continuous on the natural logarithmic scale), parity (nulliparous, 1, 2, 3 births), infertility defined as not able to become pregnant after trying for 2 years (no, yes), personal history of endometriosis (no, yes, missing), hysterectomy (no, yes), oral contraceptive hormone use (never, ever), menopausal status (pre- or peri-, post-) or any formulation of menopausal hormone use (no, yes) by menopausal status, personal history of tubal ligation (no, yes), education (high school or less, some post-high school training, college or graduate degree), alcohol (0, up to 1, > 1 drink per day, missing),

coffee (0, up to 1, > 1 cup per day, missing) and family history of breast or ovarian cancer in first degree relatives (no, yes, missing). Oral contraceptive use, menopausal hormone use by menopausal status, hysterectomy, endometriosis and family history were not confounders and were excluded from statistical models, but were evaluated as effect modifiers (see below). Missing values, where present, were included as a category level for each variable. For the 11 geographic locations combined, ORs were derived simultaneously for four different histotypes (serous, mucinous, endometrioid and clear cell) compared to all controls using polytomous logistic regression. Statistical heterogeneity of the ORs between smoking and each histotype was tested using the type 3 analysis of effects (22).

Additional analyses examined associations with daily cigarette consumption, duration of smoking and pack-years of smoking. To evaluate dose-response associations, a continuous form of smoking was included in models in increments of 5 cigarettes smoked per day, 5 pack-years smoked or 5 years of smoking using the median value for each increment. These increments were chosen to facilitate comparing our results directly with those of Faber et al (4) in a large study of Caucasian women. The association between smoking status and ovarian cancer was stratified by available variables to assess potential effect modification. Statistical heterogeneity in ORs across potential effect modifiers was evaluated using the likelihood ratio test comparing models with and without an interaction term between smoking categories and the variable of interest. Lastly, among 555 cases and 738 controls who completed the longer baseline questionnaire, we evaluated associations between second-hand smoking exposure and risk of ovarian cancer with and without stratification by smoking status at the reference date. We ran all analyses again after excluding 131 women who reported a prior cancer diagnosis speculating that changes in smoking behavior might occur, but found no substantial differences and report associations including these women.

Statistical tests were two-sided and implemented with SAS version 9 (SAS Institute, NC).

Results

The distribution of characteristics by cases and controls is shown in Table 1. Among AA, clear cell tumors were 5-fold less common than endometrioid tumors compared to Caucasians in whom the prevalence of these histotypes is similar (23). Although the proportion of self-reported lifetime ever smoking was similar among cases (44%) and controls (42%), the percentage of current smokers was 23% of cases and 47% of controls, whereas the percentage of former smokers was 76% of cases and 53% of controls. Notably, 23% of cases compared to 7% of controls reported quitting within 2 years of the reference date. Cases tended to have the expected risk factors for ovarian cancer including older age (greater than 60 years), nulliparity, never use of oral contraceptive hormones, infertility, personal history of endometriosis and a family history of breast or ovarian cancer.

Compared to never smokers, lifetime ever smokers had a nonsignificant 28% (95% CI= 1.00–1.63) increased risk of ovarian cancer (Table 2). This association was greater among former smokers who quit within 0–2 years of diagnosis (OR=4.24, 95% CI=2.44–7.36) with attenuation of the association observed with longer time since smoking cessation. Current smoking was associated with a non-significant decreased risk (OR=0.72, 95% CI=0.50–

1.04). We performed separate analyses that re-categorized as current smokers the 46 cases and 6 controls that reported quitting smoking in the year of the reference date, but the association with current smokers remained nonsignificant (OR=1.16, 95% CI=0.84–1.61) (data not shown). Additional analyses evaluated the number of cigarettes smoked daily and in pack-years and the number of years of smoking among all participants, among participants that excluded former smokers and among participants that excluded current smokers. Among all participants, the lowest level of daily cigarettes (OR=1.43, 95% CI=1.10–1.87) and pack-year cigarettes (OR=1.52, 95% CI=1.09–2.13) smoked was associated with the greatest risk of ovarian cancer with weaker associations observed at higher consumption. A non-linear association was seen with smoking duration, with the greatest risk observed between 11 and 20 years (OR=1.70; 95% CI=1.14–2.55). When analyses excluded former smokers, all ORs for current smokers were less than 1.0 and none of the associations were statistically significant. Results did not show a dose-response trend for any of the associations among all participants or among current smokers. When analyses excluded current smokers, increased risk associations became more apparent among former smokers with greater number of pack-years of cigarettes smoked up to, but not more than, 20 pack-years (OR=1.93, 95% CI=1.29–2.89) and for smoking duration over 20 years (OR=1.87, 95% CI=1.28–2.75). Only smoking duration showed a significant dose-response association (per 5 years: OR=1.02; 95% CI=1.01–1.03).

The pattern of associations with serous ovarian cancer was similar to those observed for all ovarian cancers combined, although the magnitude of the ORs was generally greater (Table 3). The strongest associations were observed among former compared to never smokers, particularly for longer duration (>20 years) of smoking (OR=2.19, 95% CI=1.45–3.31) and in a dose-response pattern (per 5 years: OR=1.03; 95% CI=1.01–1.04). Smoking was not associated with mucinous ovarian cancer (current smoking: OR=0.79, 95% CI=0.26–2.40 and former smoking: OR=0.71, 95% CI=0.23–2.25) nor with the other histotypes although the sample sizes were small (Supplementary Table 1, $P_{\text{tumor heterogeneity}}=0.0002$). Analyses that re-categorized as current smokers women who reported quitting smoking in the year of their reference date showed an elevated but nonsignificant risk for serous ovarian cancer (OR=1.32, 95% CI=0.92–1.90) but not mucinous ovarian cancer (OR=0.72, 95% CI=0.24–2.14) (data not shown).

There did not appear to be noticeable patterns in the characteristics of participants when evaluated by their smoking status other than what would be expected (e.g., a greater proportion of long-time quitters were older (>60 years), post-menopausal and obese) (Supplementary Table 2). These distributions generally did not translate into statistically significant differences in effect modification and ORs were consistently elevated among former smokers who quit within 0–2 years of their reference date, with the exception of BMI ($P_{\text{interaction}}=0.01$) and endometriosis history ($P_{\text{interaction}}=0.01$) (Supplementary Table 3). Compared to never smokers, current smokers seemed to have lower risk of ovarian cancer if overweight (BMI of 25–29.9 kg/m²) and among those with endometriosis; however, some associations could not be estimated. Lastly, there was no apparent modification of risk of ovarian cancer when smoking status was stratified by second hand smoke exposure (Supplementary Table 4). Instead, former smoking status was consistently associated with

risk of all ovarian cancers combined. Further, the main effect of second hand smoke exposure was not associated with ovarian cancer (Supplementary Table 5).

Discussion

In the current study, the general pattern of association from cigarette smoking suggested an increased risk of serous ovarian cancer among AA women in the US that was most consistently and significantly observed among women who stopped smoking within 2 years of their reference date. The increased risk appeared to be from moderate cigarette/pack-year consumption for a longer duration of time. However, we observed no increased risk among current smokers and no evidence for a dose-response relationship with increasing cigarette consumption or duration of use among current smokers.

There are two important observations in the present study that influence the interpretation of our results. First is the high proportion (14%) of deceased non-responders among the cases that was explained, in part, by advanced stage at diagnosis (19). Associations with a variable that influence survival or probability of study enrolment might be subject to a selection bias. Thus, it is possible that ovarian cancer patients who were current smokers were underrepresented in our study, thereby attenuating the association with current smoking that we observed.

The second observation is the consistent and significant increased risk observed among former smokers who reported quitting smoking within 2 years of their reference date compared to the nonsignificant association observed among current smokers. Among current smokers, the risk increased nonsignificantly when we included women who quit smoking in the year of their reference date, suggesting misreporting bias. In support of this, studies found 30% of self-reported nonsmoking newly diagnosed cancer patients with both tobacco related (24, 25) and traditionally non-tobacco related (25) cancers had measured cotinine in body fluids at levels identifying them as smokers. Misreporting bias was highest (35.4%) among patients who self-reported quitting smoking within the past year (25). Our data showed that cases were 3-fold more likely than controls to report stopping smoking within 2 years of the reference date and 52 women (46 cases and 6 controls) reported quitting in the diagnosis/reference year itself. It is also likely that, in the years preceding diagnosis, some cases experienced symptoms related to a nascent tumor that motivated smoking cessation leading to a statistical association that is interpreted incorrectly as an increased risk among former smokers. Consequently, our results are consistent with the occurrence of reverse causality as a plausible explanation for our findings (26). We do not believe this observation negates our conclusion that smoking is associated with an increased risk of ovarian cancer among AA in this study given the consistent and significant associations observed among former smokers. Instead, we have carefully parsed the analyses to identify important sources of potential bias that likely resulted in a shift of the observed associations away from current smokers. Nevertheless, our findings require validation.

Despite the above observations, a key finding in this study is that the pattern of association between cigarette smoking and ovarian cancer among AA women differed from that observed among Caucasian women. In four large investigations comprising a Caucasian

majority (4–7), smoking was most consistently associated with a significant increased risk of mucinous ovarian tumors. In the two studies with information on tumor behavior (4, 5), the risk was higher for borderline (OR 1.83 to 2.25) compared to invasive (OR 1.31 to 1.49) mucinous tumors. There was no consistent association with invasive serous ovarian cancer in these studies. In contrast, among AA in the present study, smoking cessation within 2 years of diagnosis was associated with over 5-fold risk of invasive serous ovarian cancer. Associations with the other histotypes were not statistically significant but were based on a small number of cases. In the present study, mucinous cancers represented 4% to 5% of all invasive ovarian cancers, which is the expected proportion (27), and it is unlikely that these tumors were underrepresented due to a selection or survival bias since there is no evidence to suggest this proportion differs between AA and Caucasian women (16). Even still, their under-representation would not explain the significant association observed with serous cancer.

Another key difference in smoking patterns between AA in this study and Caucasians is in the levels of daily cigarette consumption despite similar duration of smoking. For example, among ever smokers, 73% of AA ovarian cancer cases smoked fewer than 10 cigarettes per day and 27% smoked more than that, whereas among predominantly Caucasian cases (4), 42% smoked fewer than 10 cigarettes per day but 58% smoked more than that. Similar proportions of AA and Caucasians (4) smoked for less than 20 years (47% to 43%, respectively) and for longer than 20 years (53% and 57%, respectively). Others also reported higher mean levels of cigarette consumption among Caucasians compared to AA (28–30). Despite this, studies found higher levels of serum cotinine, a metabolite of nicotine, among AA than Caucasians for the same number of cigarettes smoked (28, 31, 32). These apparently contradictory observations have been attributable to a combination of genetically-determined (33) slower clearance of cotinine among AA smokers compared to Caucasian smokers and a 30% higher intake of nicotine per cigarette in AA than Caucasians (34). Although nicotine is not carcinogenic, it is highly correlated with tobacco carcinogens (34), suggesting AA may also have higher or prolonged exposure to tobacco-specific carcinogens for the same level of cigarette consumption compared to Caucasian smokers. Racial differences could also be influenced by mentholated cigarettes, which are twice as commonly smoked among AA than Caucasians (35). Mentholated cigarette smoking significantly inhibits metabolism of nicotine to cotinine compared to smoking non-mentholated cigarettes (36) and may explain the higher intake of nicotine per cigarette observed in AA than Caucasians (34). The present study did not assess consumption of mentholated cigarettes. Thus, the complex relationship between number of cigarettes smoked and cotinine levels suggests that daily cigarette consumption may not be a useful assessment of biological exposure in AA, and this could also explain the absence of a clear dose-response relationship between smoking and ovarian cancer risk in the present study.

Last, the association between former smokers and increased risk of ovarian cancer was consistently observed across strata of other variables with significant effect modification observed by BMI and endometriosis history. Current smoking is inversely associated with BMI (37) and increased BMI is associated with ovarian cancer (38, 39). Smoking is also widely reported to have anti-estrogenic effects (40) and both endometriosis and ovarian cancer are hormonally related events. These findings require cautious interpretation because

of the number of comparisons and the inability to estimate ORs for certain strata. Our results also suggested little modification by environmental smoking exposures. Other investigations of second-hand smoking either found a decreased risk of ovarian cancer among never smokers exposed to secondary smoke at home, work or other places in a hospital-based case-control study (13), an increased risk of borderline but not invasive tumors from secondary smoke exposures in childhood or adulthood among nonsmokers in a prospective cohort study (12) or no association between intrauterine or childhood exposure to environmental tobacco smoke with adult ovarian cancer risk among never smokers in a population-based case-control study (14). Thus, our results and those of two other population-based studies (12, 14) suggested no association with invasive ovarian cancer among never smokers from environmental smoking exposures during various life periods.

The strengths of this investigation are the large sample of AA women with ovarian cancer and detailed epidemiologic data collected across 11 geographic locations using a standardized protocol. Although selection bias and misreporting bias are important limitations in this study, exposure misclassification is common to all studies of self-reported smoking behavior and may not negate our observations of increased risk with ovarian cancer among AA in the current study. Using biomarkers such as serum cotinine could minimize the occurrence of exposure misclassification in future studies.

In conclusion, the pattern of association from cigarette smoking appears to suggest an increased risk of invasive serous ovarian cancer among AA women that differs from the association with mucinous ovarian cancer reported among Caucasians. The associations observed among recent quitters seem to be consistent with misreporting bias and reverse causality but requires validation. The absence of increased risk among current smokers and weak evidence for a dose-response with increasing cigarette consumption or duration of use requires better characterization of smoking patterns with risk of ovarian cancer in this understudied population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of 613 cases and 752 controls in AACES

Characteristic	Cases N (%)	Controls N (%)
Tumor histology		
Serous	409 (67)	-
Mucinous	28 (5)	-
Endometrioid	70 (11)	-
Clear cell	13 (2)	-
Other	93 (15)	-
Lifetime smoking status		
Never	340 (55)	437 (58)
Ever	273 (44)	315 (42)
Smoking categories at reference date		
Never	340 (55)	437 (58)
Current ^a	64 (23)	149 (47)
Former, time since quitting ^a		
> 0–2 yrs ^b	63 (23)	21 (7)
3–20 yrs	67 (24)	67 (21)
> 20 yrs	79 (29)	78 (25)
Age, years		
< 50	137 (22)	201 (27)
50 – 59	208 (34)	281 (37)
60	268 (44)	270 (36)
BMI (kg/m ²)		
< 25	83 (15)	141 (19)
25–29.9	146 (26)	198 (26)
30	328 (59)	412 (55)
Parity		
0	112 (18)	96 (13)
1	114 (19)	142 (19)
2	146 (24)	200 (27)
3	239 (39)	312 (42)
Infertility		
No	577 (94)	737 (98)
Yes	36 (6)	14 (2)
Endometriosis		
No	544 (89)	717 (95)
Yes	65 (11)	35 (5)
Hysterectomy		
No	471 (77)	583 (77)
Yes	142 (23)	752 (22)
Tubal ligation		

Characteristic	Cases N (%)	Controls N (%)
No	402 (66)	449 (60)
Yes	209 (34)	302 (40)
Oral contraceptive hormone use		
Never	180 (29)	151 (20)
Ever	433 (71)	601 (80)
Menopausal status		
Pre-/peri-menopausal	169 (28)	226 (30)
Post-menopausal	443 (72)	526 (70)
Menopausal status/MH use ^c		
Pre-/peri-menopausal/No	157 (26)	215 (29)
Pre-/peri-menopausal/Yes	15 (2)	12 (2)
Postmenopausal/No	331 (54)	410 (54)
Postmenopausal/Yes	110 (18)	115 (15)
Education		
High school or less	273 (44)	280 (37)
Some post-high school training	150 (24)	211 (28)
College or graduate degree	190 (31)	260 (35)
Alcohol drinks (per day)		
None	192 (31)	207 (27)
Up to 1	282 (46)	385 (51)
> 1	31 (5)	78 (10)
Missing ^d	108 (18)	82 (11)
Coffee cups (per day)		
None	137 (22)	181 (24)
Up to 1	284 (46)	348 (46)
> 1	84 (14)	141 (19)
Missing ^c	108 (18)	82 (11)
Family history		
No	444 (72)	594 (79)
Yes	156 (25)	134 (18)
Missing	13 (2)	24 (3)

^aCurrent and former smokers as a percentage of ever smokers

^bIncludes 46 cases and 6 controls who stopped smoking in year of the reference date

^cAny formulation of menopausal hormone (MH) use

^dNot all participants completed the food frequency questionnaire

Table 2

Associations between smoking and risk of ovarian cancer in AACES, 613 cases and 752 controls

Characteristic	Cases/Controls N	OR (95% CI)
Lifetime smoking status		
Never	340/437	1.0 (Ref)
Ever	273/315	1.28 (1.00–1.63)
Smoking categories at reference date		
Never	340/437	1.0 (Ref)
Current	64/149	0.72 (0.50–1.04)
Former, time since quitting		
> 0–2 yrs ^a	63/21	4.24 (2.44–7.36)
3–20 yrs	67/67	1.38 (0.92–2.06)
> 20 yrs	79/78	1.27 (0.86–1.87)
> 2 yrs	146/145	1.32 (0.97–1.79)
Cigarette consumption (per day)		
0 (Never)	340/437	1.0 (Ref)
1 – 10	200/209	1.43 (1.10–1.87)
11	73/106	0.96 (0.66–1.38)
Per 5 cigarettes per day	613/752	1.00 (0.98–1.02)
Cigarette consumption (pack-years)		
0	340/437	1.0 (Ref)
> 0–5	106/104	1.52 (1.09–2.13)
> 5–20	105/127	1.28 (0.93–1.78)
> 20	62/82	0.99 (0.66–1.48)
Per 5 pack-years	613/750	1.00 (0.99–1.01)
Duration of smoking (years)		
0 (Never)	340/437	1.0 (Ref)
1–10	57/78	1.09 (0.73–1.64)
11–20	71/60	1.70 (1.14–2.55)
> 20	144/176	1.20 (0.89–1.62)
Per 5 years smoking	612/751	1.01 (1.00–1.01)
<u>Associations excluding former smokers only</u>		
Cigarette consumption (per day)		
0 (Never)	340/437	1.0 (Ref)
1 – 10	50/114	0.74 (0.49–1.12)
11	13/34	0.55 (0.27–1.12)
Per 5 cigarettes per day	403/585	0.97 (0.94–1.00)
Cigarette consumption (pack-years)		
0	340/437	1.0 (Ref)
> 0–20	39/100	0.68 (0.44–1.06)
> 20	24/48	0.78 (0.44–1.38)
Per 5 pack-years	403/585	0.99 (0.98–1.01)

Characteristic	Cases/Controls N	OR (95% CI)
Duration of smoking (years)		
0 (Never)	340/437	1.0 (Ref)
1–20	16/39	0.72 (0.37–1.39)
> 20	47/109	0.71 (0.46–1.08)
Per 5 years smoking	403/585	0.99 (0.98–1.00)
<u>Associations excluding current smokers only</u>		
Cigarette consumption (per day)		
0 (Never)	340/437	1.0 (Ref)
1 – 10	160/112	1.97 (1.45–2.68)
11	49/54	1.12 (0.71–1.78)
Per 5 cigarettes per day	549/603	1.01 (0.99–1.03)
Cigarette consumption (pack-years)		
0	340/437	1.0 (Ref)
> 0–5	94/73	1.78 (1.23–2.58)
> 5–20	78/58	1.93 (1.29–2.89)
> 20	37/34	1.23 (0.72–2.10)
Per 5 pack-years	549/603	1.01 (1.00–1.02)
Duration of smoking (years)		
0 (Never)	340/437	1.0 (Ref)
1–20	53/63	1.57 (1.12–2.20)
> 20	155/103	1.87 (1.28–2.75)
Per 5 years smoking	549/603	1.02 (1.01–1.03)

Associations are adjusted for age (continuous), geographic location, parity (0, 1, 2, 3), infertility (no, yes), menopausal status (pre/peri-, post-), BMI (continuous on logarithmic scale), education (high school or less, some post-high school training, college or graduate degree), alcohol (0, up to 1, > 1 drink per day, missing) and coffee (0, up to 1, > 1 cup per day, missing)

^aIncludes 46 cases and 6 controls who stopped smoking in year of the reference date

Table 3

Associations between smoking and risk of serous ovarian cancer in AACES, 409 cases and 752 controls

Characteristic	Cases/Controls N	OR (95% CI)
Lifetime smoking status		
Never	216/437	1.0 (Ref)
Ever	193/315	1.46 (1.11–1.92)
Smoking categories at reference date		
Never	216/437	1.0 (Ref)
Current	39/149	0.74 (0.48–1.14)
Former, time since quitting		
> 0–2 yrs ^a	47/21	5.48 (3.04–9.86)
3–20 yrs	44/67	1.34 (0.86–2.11)
> 20 yrs	63/78	1.61 (1.06–2.45)
> 2 yrs	107/145	1.48 (1.03–2.06)
Cigarette consumption (per day)		
0 (Never)	216/437	1.0 (Ref)
1 – 10	148/209	1.69 (1.26–2.28)
11	45/106	0.97 (0.63–1.48)
Per 5 cigarettes per day	409/752	1.00 (0.98–1.02)
Cigarette consumption (pack-years)		
0	216/437	1.0 (Ref)
> 0–5	76/104	1.79 (1.23–2.59)
> 5–20	80/127	1.52 (1.05–2.18)
> 20	37/82	0.98 (0.61–1.56)
Per 5 pack-years	409/752	1.00 (0.99–1.01)
Duration of smoking (years)		
0 (Never)	216/437	1.0 (Ref)
1–10	37/78	1.17 (0.73–1.86)
11–20	51/60	2.08 (1.33–3.24)
> 20	105/176	1.37 (0.98–1.92)
Per 5 years smoking	409/752	1.01 (1.00–1.02)
<u>Associations excluding former smokers only</u>		
Cigarette consumption (per day)		
0 (Never)	216/437	1.0 (Ref)
1 - 10	31/114	0.76 (0.47–1.23)
11	7/34	0.55 (0.23–1.31)
Per 5 cigarettes per day	254/585	0.97 (0.93–1.01)
Cigarette consumption (pack-years)		
0	216/437	1.0 (Ref)
> 0–20	25/100	0.71 (0.43–1.19)
> 20	14/48	0.79 (0.40–1.57)
Per 5 pack-years	255/585	0.99 (0.97–1.01)

Characteristic	Cases/Controls N	OR (95% CI)
Duration of smoking (years)		
0 (Never)	216/437	1.0 (Ref)
1–20	9/39	0.72 (0.32–1.60)
> 20	30/109	0.75 (0.46–1.23)
Per 5 years smoking	255/585	0.99 (0.98–1.01)
<u>Associations excluding current smokers only</u>		
Cigarette consumption (per day)		
0 (Never)	216/437	1.0 (Ref)
1 – 10	122/112	2.39 (1.71–3.35)
11	32/54	1.15 (0.69–1.94)
Per 5 cigarettes per day	370/603	1.01 (0.99–1.03)
Cigarette consumption (pack-years)		
0	216/438	1.0 (Ref)
> 0–5	70/73	2.18 (1.46–3.25)
> 5–20	61/58	2.33 (1.50–3.63)
> 20	23/34	1.19 (0.65–2.19)
Per 5 pack-years	370/603	1.01 (1.00–1.03)
Duration of smoking (years)		
0 (Never)	216/437	1.0 (Ref)
1–20	37/63	1.86 (1.28–2.69)
> 20	117/103	2.19 (1.45–3.31)
Per 5 years smoking	370/603	1.03 (1.01–1.04)

Associations are adjusted for age (continuous), geographic location, parity (0, 1, 2, 3), infertility (no, yes), menopausal status (pre/peri-, post-), BMI (continuous on logarithmic scale), education (high school or less, some post-high school training, college or graduate degree), alcohol (0, up to 1, > 1 drink per day, missing) and coffee (0, up to 1, > 1 cup per day, missing)

^aIncludes 35 cases and 6 controls who stopped smoking in year of the reference date