Cigarette Smoking and Risk of Epithelial Ovarian Cancer

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Abstract

Background: An increased risk of mucinous ovarian tumors among cigarette smokers has been observed in multiple studies. The association of smoking with other histologic types of ovarian cancer is less clear, but potentially holds greater importance for prevention of disease incidence and mortality.

Methods: In a population-based study of 812 women with ovarian cancer diagnosed in western Washington State from 2002-2005 and 1,313 controls, we assessed the risk associated with cigarette smoking, with a particular focus on tumor subgroups jointly classified according to the degree of invasiveness and histology. Information was collected through in-person interviews, and logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: The incidence of both borderline and invasive mucinous ovarian tumors was increased among women with a history of cigarette smoking (ORs and 95% CIs= 1.8, 1.2-2.9, and 1.8, 0.8-4.3, respectively). Increases in risk of these tumor types were most evident among women with greater smoking duration and pack-years of exposure, and among those who had smoked within the prior 15 years. We noted no clear patterns of risk of serous tumors with duration or pack-years of smoking; however, risk of these tumor types was somewhat elevated among women who had smoked within the previous 15 years (for borderline serous tumors, OR and 95% CI= 1.5, 0.9-2.3; for invasive serous tumors, OR and 95% CI= 1.4, 1.1-1.9). The risk of endometrioid, clear cell, and the remaining histologic types of invasive ovarian cancer was not increased among smokers.

Conclusion: In the aggregate, evidence is insufficient to determine whether smoking is linked with risk of serous or other nonmucinous histologic types of ovarian cancer. Studies that employ

additional histopathologic and molecular techniques to more accurately delineate subsets of tumors may improve our understanding of the impact of smoking on ovarian cancer risk.

Studies that have evaluated the relation of cigarette smoking with risk of specific histologies of epithelial ovarian cancer have consistently observed an increased risk of mucinous tumors (1). Whether the risk of other subtypes of ovarian cancer might also be influenced by cigarette smoking is less certain, as prior studies have not been uniform in their findings (2-14). Differences between studies may be attributable to several factors capable of influencing the composition of ovarian cancer subgroups, including: inaccurate designation of histologic subtypes; dissimilarities among studies in the definition of tumor subgroups; as-yet uncharacterized differences between borderline and invasive, and/or high grade and low grade, subsets of histologic types; and differences in the degree of study participation related to both smoking and histologic type.

In a population-based, case-control study of epithelial ovarian cancer, we assessed the risk associated with cigarette smoking, with a particular focus on characterizing risk among tumor subgroups jointly classified according to the degree of invasiveness and histology.

Methods

The population and methods used in this study have been described previously (15). Female residents of a thirteen-county area of western Washington State, 35-74 years of age, diagnosed with a primary invasive or borderline epithelial ovarian tumor during 2002-2005 were identified through a population-based registry that is part of the Surveillance, Epidemiology, and End Results program of the US National Cancer Institute. Of 1,058 eligible women identified, 812 (77%) were interviewed; of the interviewed cases, 595 had invasive disease. Reasons for not obtaining an interview included: physician refusal (n=23); inability to locate the patient (n=10); patient refusal (n=110) and death (n=103).

Tumors were coded by registry staff according to the third edition of the International Classification of Diseases for Oncology (ICD-O) (15, 16), and these codes were grouped according to guidelines of the World Health Organization (17) into the following histologic subgroups: serous (n=452); mucinous (n=112); endometrioid (n=104); clear cell (n=35); and other epithelial tumors (n=109). Of the mucinous tumors, 20.5% were invasive, while the corresponding percentages were 74.1, 94.2, 100.0, and 95.4 of serous, endometrioid, clear cell, and other epithelial tumors, respectively.

Controls were selected by random digit dialing (18) using stratified sampling in five-year age categories, one-year calendar intervals and two county strata in a 2:1 ratio to women with invasive epithelial ovarian cancer. For 14,561 (82.0%) of the 17,768 telephone numbers belonging to a residence, we determined whether an eligible (i.e., age- and county-eligible and, if so, with at least one ovary and no prior history of ovarian cancer) woman resided there. Of the 1,561 eligible women identified, 1,313 were interviewed (84.1%).

The study was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center, and all women provided signed informed consent before participating. In-person interviews pertained to the period of time before diagnosis (for cases) or before an assigned, comparable reference date (for controls), and included demographic and lifestyle characteristics, family history of cancer, and reproductive history. To collect smoking history, women were first asked if they had smoked in total 100 or more cigarettes. Women who responded in the affirmative were then asked their age at starting to smoke, and, if not smoking at the reference date, their age at stopping. In addition, they reported the total number of years smoked (accounting for time periods of nonsmoking of at least one year's duration) as well as the typical number of cigarettes per day.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression. The analyses shown are adjusted for the matching variables of age (5-year intervals), county of residence (two strata), and year of diagnosis/reference date as well as number of full-term births, duration of hormonal contraception, and education. However, because the number of invasive mucinous tumors was small, fully adjusted estimates proved unstable, resulting in notably wider confidence intervals and increased OR estimates (in contrast to the slightly reduced ORs observed in all other fully adjusted models). Thus, the results shown for invasive mucinous tumors are adjusted only for age (continuous), county of residence and year of diagnosis/reference date (2-year groups). We also assessed the potential confounding influence of other characteristics including race/ethnicity, history of tubal ligation and/or hysterectomy, family history of ovarian and/or breast cancer, personal history of cancer (breast cancer only, or any cancer other than nonmelanoma skin cancer), body mass index (assessed at age 30 and five years before the reference date), and use of hormone replacement therapy (estrogen-only, estrogen/progestogen combined, and other regimens of use); none of these produced a 10% or greater change in odds ratio estimates. We used polytomous logistic regression for analyses that separated case women according to the degree of invasiveness and/or histologic type of the tumor. Tests for linear trend were done using the maximum likelihood test with the categorical variable of interest entered as a continuous term. STATA was used for analysis (version 9.2; STATA Corporation, College Station, TX).

Results

The large majority of cases and controls were non-Hispanic whites. Cases were less likely than controls to have given birth, to have used hormonal contraception, and to have had a

tubal ligation (Table 1). Also, cases were less likely to have completed college. Family history of ovarian cancer was more commonly reported among cases.

Slightly more than half of controls (53.2%) and less than half of cases (47.2%) had smoked fewer than 100 cigarettes in their lifetimes, and comprised the never-smokers in our analyses. Overall, smoking was associated with a 30% increase in risk of epithelial ovarian cancer (Table 2). The strength of association was greater for borderline than for invasive tumors (ORs and 95% CIs for ever smoking= 1.5, 1.1-2.1, and 1.2, 1.0-1.4, respectively). For borderline tumors, risk increased with increasing number of years smoked and total pack-years of smoking; also, an increased risk was more evident among women who had smoked within the last 15 years than among women who had quit in the more distant past.

Because a greater proportion of borderline than invasive tumors are of mucinous histology, differences in risk between borderline and invasive tumors may reflect histologic differences in risk. Thus, we separately examined risk of serous and mucinous types of borderline and invasive tumors (Table 3). Among mucinous tumors, the strength of association for borderline and invasive types was similar (ORs and 95% CIs for ever smoking= 1.8, 1.2-2.9, and 1.8, 0.8-4.3, respectively), although small numbers of tumors limited the precision of risk estimates. Also, for mucinous tumors, increases in risk were most evident among women with greater smoking duration and pack-years of exposure, and among those who had smoked within 15 years before the diagnosis or reference date. Generally, the strength of association of smoking with risk of serous borderline and invasive tumors was similar (ORs and 95% CIs for ever smoking= 1.4, 0.9-2.0, and 1.3, 1.0-1.7, respectively), and was not as great as that for mucinous tumors. We noted no clear patterns of risk of serous tumors with increasing duration or pack-years of smoking (Table 3) and no particularly large increase in risk among very long-term (>30 years) smokers (results not shown). Risks were somewhat greater among women who

had smoked within the 15 years before the reference date (for borderline serous tumors, OR and 95% CI= 1.5, 0.9-2.3; for invasive serous tumors, OR and 95% CI= 1.4, 1.1-1.9).

Endometrioid, clear cell, and other histologic subgroups were predominantly or entirely invasive, precluding separate assessment of borderline tumors of histologies other than serous or mucinous. In analyses restricted to invasive cancers, we observed no increased risk of endometrioid, clear cell, or the remaining histologies among smokers, either when these were combined (Table 3) or considered as three separate subgroups (Table 4).

Because it has been hypothesized that low grade invasive serous tumors may share a common carcinogenic pathway with borderline serous tumors that is distinct from high grade serous tumors (19,20), we repeated our analysis after excluding, first, the 14 women with well-differentiated, and second, the 53 additional women with moderately differentiated serous invasive tumors, and observed no appreciable change in our results. Also, because some literature suggests that advanced stage invasive mucinous ovarian tumors may represent metastases from other intra-abdominal sites (19), we repeated our analysis after excluding the four women with such tumors in our case group; the association of ever-smoking with risk of invasive mucinous cancer was reduced (OR=1.3, 95% CI 0.5-3.3), but increases in risk remained evident among women who had smoked within the last 15 years or who had smoked for > 20 years.

Discussion

Several potential sources of bias should be considered in the interpretation of our results. It is possible that women who agreed to take part may have had a prevalence of smoking not representative of the source population of our study. To influence our findings, such selective participation would have had to occur to a different extent among controls than cases. We have

no information regarding the smoking behavior of selected cases or controls who refused to participate. However, some research on control participants in epidemiologic research (21) suggests that current smokers, in particular, may be more difficult to recruit. In the current study, participation was encouraged through multiple attempts to recontact and enroll potential controls selected during telephone screening (using the protocol described by Voigt (21), together with comparable procedures for recontacting cases); this may have allowed recruitment of an adequately representative group of participants. Given the observed differences in smoking-associated risks among women with different tumor histologies, it is unlikely that a selectively low degree of participation of potential controls who were current smokers is the sole explanation for our findings; however, such a bias could serve to falsely increase the strength of the observed associations.

Differing response proportions across histologic types of tumors could also influence our results if smoking behavior was linked to inability to interview cases. Overall, we enrolled a somewhat larger proportion of women with borderline (80.6%) than invasive (75.4%) tumors. We enrolled similar proportions of women with borderline serous and borderline mucinous tumors (82 and 80%, respectively). For invasive tumors, response proportions were: serous, 82%; mucinous, 77%; endometrioid, 88%; clear cell, 83%; and other epithelial, 53%. Tumors in the latter group were typically less well-differentiated and of an advanced stage, and nearly two-thirds of the non-interviewed women with such tumors died before they could be interviewed. If smoking is associated with the development of more aggressive or rapidly fatal tumors and women with such tumors are less likely to be interviewed, the strength of association with smoking we observed could be falsely low, particularly among histologic groups with low response proportions. Smoking as of the date of diagnosis has been associated with reduced survival in two recent studies. In the first, a study of 295 Danish women with stage III epithelial

ovarian cancer (80% of whom had serous cancers), the adjusted relative risk (RR) of ovarian cancer death among smokers was 1.65 (95% CI 1.22-2.24) (22). Risk of death was also increased among current smokers (within one year before diagnosis) in a study of 676 Australian women with invasive epithelial ovarian cancer (RR=1.36, 95% CI 1.01-1.84) (23).

Most studies of smoking and ovarian cancer risk that assessed associations with histologic subtypes were included in a meta-analysis of 9 population-based case-control studies and one cohort study, the majority of which included both borderline and invasive tumors (1). Among the combined studies, risk of mucinous ovarian cancer was doubled among current smokers and returned to that of never smokers within 20-30 years of stopping. The meta-analysis reported no association of current smoking with risk of serous tumors (summary RR=1.0, 95% CI 0.8-1.2, based on 8 reports) and point estimates of reduced risk of endometrioid (RR=0.8, CI 0.6-1.1, based on 4 reports) and clear cell cancers (RR=0.6, CI 0.3-0.9, based on 3 reports). For the analysis of "serous" tumors, significant heterogeneity across studies for the relation with current smoking was observed (p=0.04), and, for four of the eight studies included, risk estimates were based on all nonmucinous tumors combined because estimates restricted to serous tumors were not available. An additional study that assessed risk of serous tumors was not included in the meta-analysis because no data were available regarding smoking recency; in that study, a trend of increase in risk of invasive serous cancer with years of tobacco use was observed (3).

The single cohort study included in the meta-analysis, with 454 invasive ovarian cancers diagnosed between 1980 and 2000, reported an overall increased risk among women who had smoked for 40 or more years (RR=2.50, 95% CI 1.37-4.56); this finding was attributable exclusively to non-mucinous cancers, as none of the tumors occurring in the highest category of smoking duration was mucinous (8). In contrast, current smoking (assessed at entry into the

cohort) was only associated with an increased risk of mucinous tumors, leading these investigators to hypothesize that the length of time and recency of smoking required to influence risk may vary between histologic types of ovarian cancer.

In subsequent population-based reports, increased risks of mucinous, but not serous, borderline (12) and invasive (13) ovarian tumors were observed among current smokers in two Danish case-control studies. Risk of invasive serous disease was elevated by 30% among women who had smoked more than 15 years, relative to women who had smoked for a shorter duration (no comparison was provided to women who had never smoked) (13). In a cohort of over 100,000 women in Norway and Sweden (14), both former and current smokers had a greater than two-fold increase in risk of developing a borderline ovarian tumor, while the risk of invasive disease was not increased. When these results were further examined by histologic subtype, ever smokers had increased risks of serous borderline (RR=2.5, 95% CI 1.3-4.5) and mucinous borderline (RR=1.6, 95% CI=0.7-3.4) tumors; RRs of serous and mucinous invasive tumors were 1.0 (0.7-1.5) and 1.2 (0.5-2.9), respectively.

As noted above for the current study, findings of prior studies may also, to varying extents, have been influenced by differential loss of smoking cases or controls. Bias resulting from low case response proportions as a consequence of disease severity may be a particular concern for assessing risk across disease subsets when some subsets are associated with higher morbidity and mortality. Response proportions within histologic subgroups of ovarian tumors have seldom been reported. For all studies, inaccurate designation of histologic types, or failure to jointly consider both histology and degree of invasiveness, may further influence results.

One model of ovarian carcinogenesis proposes that invasive mucinous primary ovarian cancers may result as a progression of their borderline and benign counterparts, suggesting that these tumors may share at least some risk factors. This hypothesis is supported by the frequently

noted presence of a borderline component in mucinous invasive tumors and the common occurrence of KRAS mutations in both borderline and invasive mucinous tumors. In contrast, only the relatively uncommon low grade serous ovarian carcinoma are theorized to arise from borderline or benign serous tumors (19,20), while high grade serous cancers are thought to develop *de novo* from the ovarian surface epithelium, epithelial inclusion cysts, or possibly from exfoliated epithelial cells of the fallopian tube (24). While mutations of KRAS and its effector BRAF are rarely observed in high-grade serous invasive ovarian tumors, they are more often found in borderline and low-grade serous carcinomas, and low-grade serous tumors may also be accompanied by borderline disease (25). Kurian (11) suggested that smoking may induce mutations in KRAS, or exert a stronger carcinogenic effect in ovarian epithelial cells without a functional KRAS gene, noting that smoking has been linked with KRAS mutation in cancers of other sites; if so, such an effect might be expected to influence risk of both mucinous and serous ovarian tumors with such mutations. Although we noted no change in our results regarding risk of invasive serous ovarian cancer in a subanalysis that excluded well- or moderately-differentiated tumors, a more precise characterization of invasive serous tumors-- e.g., according to the presence of a borderline component or the presence of specific molecular features such as mutation of KRAS or other genes involved in its signaling pathway-- might allow the identification of differences in the relation of smoking with risk in subsets of this histologic type.

In the current study, risk of mucinous tumors was increased among women who had smoked cigarettes, and the increased risk was similar for borderline and invasive subtypes. The relation of cigarette smoking with risk of other histologic types of epithelial ovarian cancer was more difficult to characterize; we observed small increases in risk of borderline and invasive serous tumors, and no clear evidence of increased or decreased risk of other histologic types of invasive disease. Invasive serous tumors constitute the most common histologic group of

ovarian cancers, and are associated with poor survival; thus, even a relatively small increase in risk of this tumor type attributable to smoking could have substantial implications for prevention of ovarian cancer incidence and mortality. In the aggregate, available evidence is insufficient to determine whether smoking is linked with risk of serous and/or other nonmucinous ovarian cancers or, for serous cancers, whether this association differs between borderline and invasive types. Studies that minimize possible sources of bias and employ additional histologic and molecular techniques to more accurately delineate subsets of tumors may improve our understanding of the impact of smoking on ovarian cancer risk.

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Table 1. Characteristics of epithelial ovarian cancer cases and controls

Characteristic	Cases (*n*=812)	Controls (*n*=1,313)
	No. (%)	No. (%)
Age (years)		
35-44	122 (15.0)	155 (11.8)
45-54	278 (34.2)	378 (28.8)
55-64	251 (30.9)	449 (34.2)
65-74	161 (19.8)	331 (25.2)
No. of full-term pregnancies[a]		
Nulliparous	201 (24.8)	190 (14.5)
1	128 (15.8)	175 (13.3)
2	217 (26.8)	424 (32.3)
3+	265 (32.7)	524 (39.9)
Hormonal contraception (years)		
Never	235 (28.9)	255 (19.4)
<½	79 (9.7)	92 (7.0)
½-<5	256 (31.5)	481 (36.6)
5-<10	140 (17.2)	263 (20.0)
10+	102 (12.6)	222 (16.9)
BMI at age 30 (kg/m^2)[b]		
<25	639 (79.5)	1081 (83.2)
25-<30	100 (12.4)	147 (11.3)
30+	65 (8.1)	72 (5.5)
Family history of breast and ovarian cancer[b]		
No known history	465 (57.8)	792 (60.9)
Breast cancer only	242 (30.1)	418 (32.2)
Ovarian cancer only	60 (7.5)	53 (4.1)
Breast and ovarian cancer	37 (4.6)	37 (2.8)
Tubal ligation		
No	670 (82.5)	1018 (77.5)
Yes	142 (17.5)	295 (22.5)
Education[c]		
High school or less	232 (28.6)	309 (23.6)
Some college	303 (37.4)	480 (36.6)
College graduate	170 (21.0)	307 (23.4)
Post-college	105 (13.0)	215 (16.4)

[a]Data missing for 1 case.
[b]Data missing for 8 cases and 13 controls.
[c] Data missing for 2 cases and 2 controls.

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Table 2. Risk of epithelial ovarian cancer in relation to cigarette smoking overall and among women with borderline and invasive tumors

	Controls	Borderline tumors		Invasive tumors		All tumors	
	(*n*=1313)[a]	Cases (*n*=217)[a]	OR[b] (95% CI)	Cases (*n*=595)[a]	OR[b] (95% CI)	Cases (*n*=812)[a]	OR[b] (95% CI)
Never	698	91	1.0 (ref.)	292	1.0 (ref.)	383	1.0 (ref.)
Ever	614	126	1.5 (1.1-2.1)	303	1.2 (1.0-1.4)	429	1.3 (1.0-1.5)
Years since last smoked							
Current (≤ one year)	184	57	2.0 (1.3-3.0)	96	1.2 (0.9-1.6)	153	1.4 (1.1-1.8)
2-5	37	9	1.6 (0.7-3.7)	26	1.5 (0.9-2.6)	35	1.6 (1.0-2.6)
6-15	122	30	1.8 (1.1-2.9)	63	1.2 (0.9-1.7)	93	1.3 (1.0-1.8)
16-25	138	15	0.9 (0.5-1.6)	62	1.1 (0.8-1.5)	77	1.0 (0.8-1.4)
>25	133	15	1.2 (0.7-2.3)	56	1.1 (0.8-1.6)	71	1.1 (0.8-1.6)
Age first smoked (years)							
<15	114	29	1.6 (1.0-2.5)	50	1.0 (0.7-1.5)	79	1.2 (0.8-1.6)
15-19	335	73	1.7 (1.2-2.4)	174	1.2 (1.0-1.6)	247	1.3 (1.1-1.7)
20+	165	23	1.2 (0.7-2.0)	79	1.1 (0.8-1.5)	102	1.1 (0.9-1.5)
Age last smoked (includes current smokers)							
≤30	149	24	1.1 (0.6-1.8)	57	1.0 (0.7-1.4)	81	1.0 (0.7-1.3)
31-40	121	32	1.5 (0.9-2.5)	57	1.1 (0.8-1.6)	89	1.2 (0.9-1.7)
41-50	143	41	1.9 (1.2-2.9)	80	1.2 (0.9-1.7)	121	1.4 (1.0-1.9)
51+	201	29	1.8 (1.1-3.0)	109	1.3 (1.0-1.7)	138	1.4 (1.1-1.8)
Years smoked							
≤10	150	25	1.1 (0.7-1.8)	55	0.9 (0.7-1.3)	80	1.0 (0.7-1.3)
11-20	124	31	1.6 (1.0-2.5)	73	1.4 (1.0-2.0)	104	1.5 (1.1-2.0)
21-30	145	39	1.8 (1.2-2.8)	78	1.2 (0.9-1.7)	117	1.4 (1.0-1.8)
>30	191	30	1.8 (1.1-3.0)	97	1.2 (0.9-1.6)	127	1.3 (1.0-1.7)
p trend			*0.003*		*0.12*		*0.008*
Pack-years smoked							
≤80	151	31	1.3 (0.8-2.1)	75	1.3 (0.9-1.7)	106	1.3 (0.9-1.7)
81-310	155	33	1.5 (0.9-2.4)	70	1.1 (0.8-1.5)	103	1.2 (0.9-1.6)
311-630	155	30	1.4 (0.9-2.2)	74	1.1 (0.8-1.6)	104	1.2 (0.9-1.6)
631+	148	31	2.3 (1.4-3.8)	84	1.3 (0.9-1.7)	115	1.5 (1.1-2.0)
p trend			*0.003*		*0.19*		*.01*

[a] Numbers in column may not sum to total due to missing values.
[b] Adjusted for age, calendar year of diagnosis/reference date, county of residence, number of full term births, duration of hormonal contraception, and education.

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Table 3. Risk of borderline and invasive types of mucinous and serous tumors and of other invasive tumors in relation to cigarette smoking

	Mucinous tumors				Serous tumors				Other invasive tumors	
	Borderline		Invasive		Borderline		Invasive			
	Cases[a] (*n*=89)	OR[b] (95% CI)	Cases[a] (*n*=23)	OR[c] (95% CI)	Cases[a] (*n*=117)	OR[b] (95% CI)	Cases[a] (*n*=335)	OR[b] (95% CI)	Cases[a] (*n*=237)	OR[b] (95% CI)
Never	34	1.0 (ref.)	9	1.0 (ref.)	52	1.0 (ref.)	152	1.0 (ref.)	131	1.0 (ref.)
Ever	55	1.8 (1.2-2.9)	14	1.8 (0.8-4.3)	65	1.4 (0.9-2.0)	183	1.3 (1.0-1.7)	106	0.9 (0.7-1.2)
Years since last smoked										
≤ 15	47	2.6 (1.6-4.2)	12	2.7 (1.1-6.5)	45	1.5 (0.9-2.3)	110	1.4 (1.1-1.9)	63	0.9 (0.6-1.2)
>15	8	0.7 (0.3-1.6)	2	0.6 (0.1-2.9)	20	1.2 (0.7-2.1)	73	1.2 (0.9-1.6)	43	1.0 (0.6-1.4)
Age first smoked (years)										
<15	17	2.5 (1.3-4.8)	2	1.3 (0.3-6.1)	12	1.1 (0.6-2.2)	25	1.0 (0.6-1.6)	23	1.0 (0.6-1.6)
15-19	27	1.7 (1.0-3.0)	8	1.9 (0.7-5.0)	41	1.6 (1.0-2.5)	105	1.4 (1.1-1.9)	61	1.0 (0.7-1.4)
20+	10	1.3 (0.6-2.8)	4	2.1 (0.6-6.9)	12	1.1 (0.5-2.1)	53	1.4 (1.0-2.0)	22	0.7 (0.4-1.2)
Age last smoked (includes current smokers)										
≤40	19	1.1 (0.6-2.1)	2	0.5 (0.1-2.5)	33	1.3 (0.8-2.1)	63	1.1 (0.8-1.6)	49	0.9 (0.7-1.4)
>40	36	2.7 (1.6-4.6)	12	3.1 (1.3-7.6)	32	1.4 (0.9-2.3)	120	1.5 (1.1-2.0)	57	0.9 (0.6-1.2)
Years smoked										
≤ 20	17	1.1 (0.6-2.0)	2	0.5 (0.1-2.5)	36	1.5 (0.9-2.3)	73	1.3 (0.9-1.8)	53	1.0 (0.7-1.5)
>20	37	2.7 (1.6-4.5)	12	3.2 (1.3-7.7)	29	1.2 (0.8-2.1)	110	1.4 (1.0-1.8)	53	0.8 (0.6-1.2)
p trend		*<0.001*		*0.02*		*0.31*		*0.03*		*0.26*
Pack-years smoked										
≤ 310	21	1.2 (0.7-2.2)	5	1.2 (0.4-3.7)	41	1.5 (1.0-2.4)	83	1.3 (0.9-1.8)	57	1.0 (0.7-1.4)
>310	33	2.7 (1.6-4.6)	9	2.5 (1.0-6.6)	24	1.1 (0.7-1.9)	100	1.4 (1.0-1.9)	49	0.8 (0.6-1.2)
p trend		*0.001*		*0.06*		*0.47*		*0.04*		*0.33*

[a]Numbers in column may not sum to total due to missing values.
[b]Adjusted for age, county of residence, year of diagnosis/reference date, number of full term births, duration of hormonal contraception, and education.
[c]Adjusted for age, county of residence, year of diagnosis/reference date.

table
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Table 4. Risk of invasive epithelial ovarian tumors other than serous and mucinous subtypes in relation to cigarette smoking

	Endometrioid		Clear Cell		Other	
	Cases[a] (n= 98)	**OR[b] (95% CI)**	**Cases[a] (n= 35)**	**OR[b] (95% CI)**	**Cases[a] (n=104)**	**OR[b] (95% CI)**
Never	57	1.0 (ref)	21	1.0 (ref)	53	1.0 (ref)
Ever	41	0.9 (0.5-1.3)	14	0.7 (0.4-1.5)	51	1.0 (0.7-1.5)
Years since last smoked						
≤ 15	23	0.7 (0.4-1.3)	11	1.0 (0.5-2.2)	29	0.9 (0.6-1.5)
> 15	18	1.1 (0.6-1.9)	3	0.4 (0.1-1.4)	22	1.1 (0.7-1.9)
Age first smoked (years)						
<15	10	1.1 (0.5-2.3)	6	1.6 (0.6-4.3)	7	0.7 (0.3-1.6)
15-19	23	0.9 (0.5-1.5)	5	0.5 (0.2-1.4)	33	1.2 (0.7-1.9)
20+	8	0.6 (0.3-1.4)	3	0.6 (0.2-2.1)	11	0.9 (0.4-1.7)
Age last smoked (includes current smokers)						
≤40	25	1.2 (0.7-1.9)	4	0.5 (0.2-1.4)	20	1.0 (0.6-1.7)
>40	16	0.6 (0.3-1.1)	10	1.0 (0.4-2.2)	31	1.0 (0.6-1.7)
Years smoked						
≤20	26	1.2 (0.7-2.0)	4	0.5 (0.2-1.4)	23	1.1 (0.7-1.9)
>20	15	0.5 (0.3-1.0)	10	1.0 (0.4-2.3)	28	0.9 (0.6-1.5)
p trend		*0.10*		*0.55*		*0.76*
Pack-years smoked						
≤310	26	1.0 (0.6-1.7)	4	0.4 (0.1-1.2)	27	1.2 (0.7-1.9)
>310	15	0.7 (0.3-1.2)	10	1.2 (0.5-2.7)	24	0.9 (0.5-1.5)
p trend		*0.20*		*0.66*		*0.64*

[a]Numbers in column may not sum to total due to missing values.
[b]Adjusted for age, county of residence, year of diagnosis/reference date, number of full term births, duration of hormonal contraception, and education.