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Cigarette smoking and the risk of invasive epithelial ovarian cancer in a prospective cohort study

P.D. Terry[a,*], A.B. Miller[b,c], J. G. Jones[d], T.E. Rohan[a]

[a]*Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Room 1301, Bronx, NY 10461, USA*

[b]*Department of Public Health Sciences, University of Toronto, Toronto, Canada*

[c]*Division of Clinical Epidemiology, Deutsches Krebsforschungszentrum, Heidelberg, Germany*

[d]*Department of Pathology, Montefiore Medical Center and Albert Einstein College of Medicine, Bronx, NY, USA*

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Abstract

Few cohort studies have examined the association between cigarette smoking and ovarian cancer risk, either overall, or by histological subtype. In relation to the latter, it has been suggested that mucinous ovarian tumours may be aetiologically unrelated to the other types of epithelial tumours and that their respective associations with cigarette smoking may differ. We examined the association between smoking and ovarian cancer risk using data from participants in a randomised controlled trial of screening for breast cancer involving 89,835 women aged 40–59 years at recruitment. Cox proportional hazards models were used to estimate rate ratios (RR) and 95% confidence intervals (CI). During an average of 16.5 years of follow-up, we observed 454 incident cases of ovarian cancer (184 serous, 67 endometrioid, 32 mucinous, 171 other or unknown). We found that women who had smoked for several decades had an approximately two-fold increased risk of epithelial ovarian cancer. Relative to never-smokers, women who had smoked for 40 years or more were at the highest risk (RR = 2.50, 95% CI = 1.37–4.56). The association with non-mucinous tumours was similar to that observed overall. For mucinous tumours, a two-fold increased risk was observed with smoking of shorter duration, although the number of mucinous tumours in our data-set was small. Long-term cigarette smoking may be associated with an increased risk of epithelial ovarian tumours.

Keywords: Ovarian neoplasms; Smoking; Menopause; Cohort studies

1. Introduction

Whether cigarette smoking is associated with altered ovarian cancer risk is unclear, although smoking-related B(a)P-DNA adducts found in ovarian follicular cells [1] support the biological plausibility of a positive association. The results of previous studies of ovarian cancer have been mixed, with most studies showing no association [2–10], and some showing positive associations [11–16]. Several explanations for the lack of consistency in previous studies have been suggested. First, differences in ovarian cancer risk factor profiles (particularly with respect to parity and oral contraceptive use) have been observed according to histological type, on the basis of which it has been suggested that mucinous and non-mucinous tumours are aetiologically distinct diseases [17]. Indeed, the few case-control studies conducted in the past 2 years support a positive association primarily between cigarette smoking and mucinous ovarian tumours [11–14]. The percentage of mucinous tumours in previous study populations has ranged from 9% [5] to 18% [12]. Thus, one can speculate that previous findings may have varied to some extent according to the percentage of mucinous ovarian tumours among the cases. Second, it is possible that mucinous and non-mucinous tumours are characterised by different lengths of time between the causal action of cigarette smoking and diagnosis, or that smoking acts at different stages in the development of the respective tumour types. For example, in a recent population-based, case-control

* Corresponding author. Tel.: +1-718-430-3038; fax: +1-718-430-8653.

E-mail address: pterry@aecom.yu.edu (P.D. Terry).

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study in the United States [13], smokers of high intensity (independent of duration) had a nearly two-fold increased risk of mucinous ovarian cancers, while smokers of long duration (independent of intensity) had a statistically significant increased risk of invasive serous (non-mucinous) tumours. Overall, however, relatively few studies have examined cigarette smoking in relation to ovarian cancer risk, and most have only examined qualitative smoking measures. Furthermore, few cohort studies have examined this association [10,15,16], and none has examined the association between cigarette smoking and ovarian cancer risk by histological type. Therefore, we examined the relationships between total cigarette smoking and ovarian cancer risk overall and by histological type in the largest prospective cohort study of this issue to date.

2. Patients and methods

2.1. Study population

The investigation was conducted using data from the Canadian National Breast Screening Study (NBSS). The NBSS is a multi-centre randomised controlled trial of mammography screening for breast cancer in 89,835 women aged 40–59 years at recruitment [18]. Participants were recruited between 1980 and 1985 by various means, including personal invitation by letter, group mailings to employees of large institutions and to members of professional associations, advertisements in newspapers, and public service announcements on the radio and television. Women who had experienced bilateral oopherectomy were excluded from the study.

2.2. Questionnaires

On enrolment in the NBSS, all participants completed a questionnaire that sought data on demographic characteristics, lifestyle (including cigarette smoking), menstrual and reproductive history, use of oral contraceptives and replacement oestrogens. Regarding smoking history, participants were first asked whether or not they had ever smoked. Women who had ever smoked were then asked how many cigarettes they smoked per day, for how many years they had smoked, and the year they had ceased smoking (former smokers only). Age at smoking commencement was calculated for each smoker by subtracting her total years of smoking (and the time since quitting for ex-smokers) from her age at recruitment.

2.3. Case definition and ascertainment

Outcome (incident epithelial ovarian cancer or death) was ascertained by means of computerised record linkages to the Canadian Cancer Database, and to the National Mortality Database, both of which are maintained by Statistics Canada, and to the Ontario Cancer Registry. During follow-up, we identified 454 incident invasive epithelial ovarian cancers, including 184 serous, 67 endometrioid, 32 mucinous, and 171 other or unspecified histological types. In the analyses, non-mucinous tumours were comprised of serous ($n = 184$) or endometrioid tumours ($n = 67$). There is good evidence from the NBSS and from other sources that the use of record linkage to ascertain incident cancer cases and deaths in Canada is both accurate and complete [20,21].

2.4. Statistical analysis

The linkages to the databases yielded data on mortality and cancer incidence to 31 December 2000 for women in Ontario, 31 December 1998 for women in Quebec, and 31 December 1999 for women in other regions in Canada. Cox proportional hazards models were used to estimate hazard rate ratios (RR) and 95% confidence intervals (CI) for the association between cigarette smoking and ovarian cancer risk. Multivariate models included terms for study centre, treatment allocation (intervention or control), age in 5-year age groups, Quetelet's index (wt(kg)/ht(m)^2), education level (less than high school, high school and university), vigorous physical activity (hours per day in tertiles, plus missing), menopausal status (pre-, peri- or post-menopausal), age at menarche (quartiles), oral contraceptive use (OC) and hormone replacement therapy (HRT) (never, plus quartiles of duration), and parity (nulliparous, plus tertiles of parity). For tests of trend in risk across successive levels of categorical variables, median values of each category were fitted in the risk models as successive integers [22]. Tests for interaction were based on likelihood ratio tests comparing models with and without product terms representing the variables of interest.

3. Results

During an average of 16.5 years of follow-up range (1–20 years) (1,329,853 person-years), 454 incident epithelial ovarian cancer cases were diagnosed (184 serous, 67 endometrioid, 32 mucinous, 171 other or unknown). Current smokers were slightly younger and slightly leaner than never or former smokers, and were less likely to have completed post-secondary education (Table 1). Current smokers were more likely to have ever used hormone replacement therapy than former or never smokers. Both current and former smokers were more likely to have ever used oral contraceptives and both had a higher alcohol intake than never smokers. On average, current smokers reported smoking 18.5 cigarettes per

Table 1
Baseline characteristics of the study cohort

Characteristics	Baseline smoking status[a]		
	Never (N = 40,776)	Former (N = 22,127)	Current (N = 17,794)
Person years	674,803	364,735	290,315
Age at baseline (mean, years)	48.6	48.1	47.8
Body mass index (median, kg/m^2)	24.2	24.1	23.7
Parity (mean number of children)	2.6	2.4	2.5
Age at menarche (mean, years)	12.8	12.8	12.8
Vigorous physical activity (%)	60.2	59.5	63.4
Education (% post-secondary)	27.7	33.1	22.5
Oral contraceptive use (%)	55.2	64.7	64.3
Hormone replacement therapy (%)	18.8	20.2	22.1
Menopausal status (% postmenopausal)	30.2	29.3	29.8
Alcohol consumption (median g/day)	1.2	3.8	3.6

[a] Comparisons of all of the characteristics shown in the table over strata of smoking status were statistically significant at $P < 0.05$, except age at menarche.

day (S.D. 10.3), while former smokers reported having smoked 15.4 cigarettes per day (S.D. 11.4).

Women who had ever smoked had a small, statistically non-significant increased risk of epithelial ovarian cancer compared with that of women who had never smoked (RR = 1.14, 95% CI = 0.95–1.38). The corresponding rate ratio for current smokers was 1.18 (95% CI = 0.93–1.50) and that for former smokers was 1.07 (95% CI = 0.86–1.34). Rate ratios for epithelial ovarian cancer in relation to quantitative measures of cigarette smoking are shown in Table 2. Risk was increased in women who were long-term smokers at recruitment. Specifically, women who had smoked for 40 years or longer had a risk that was more than two-fold that of never smokers. Similarly, women who had commenced smoking 40 years or more prior to recruitment (some of whom were no longer active smokers at that time) had a risk that was nearly two-fold that of never smokers. Women who currently, or had ever, smoked 40 cigarettes per day or more had a statistically non-significant 20% increased risk of ovarian cancer, and women who had consumed 40 pack-years of cigarettes or more had a statistically non-significant 29% increased risk. Commencement of smoking at an early age was not associated with an altered risk (Table 2). Among former smokers, there was no association between years since smoking ceased and ovarian cancer risk. The results described above were very similar in age-adjusted and multivariate-adjusted models. There was no evidence that risk in association with any of the smoking measures differed according to strata defined by menopausal status, physical activity, alcohol consumption, family history of ovarian cancer, relative body weight (BMI), HRT and OC use, parity, age at menarche or randomisation group (data not shown).

Table 2
Adjusted[a] rate ratios for epithelial ovarian cancer (all histological types combined) in relation to cigarette smoking

Smoking measure	Cases/person-years	RR (95% CI)
Cigarettes/day		
Never-smokers	218/674,737	1.0 (referent)
1–9	50/148,865	1.05 (0.77–1.43)
10–19	64/175,623	1.13 (0.85–1.50)
20–29	88/239,285	1.22 (0.95–1.57)
30–39	15/42,482	1.09 (0.63–1.87)
40+	12/33,346	1.20 (0.67–2.15)
P for trend[b]		0.14
Years smoked		
Never-smokers	218/674,737	1.0 (referent)
1–9	44/123,239	1.17 (0.84–1.62)
10–19	51/164,648	1.00 (0.73–1.37)
20–29	73/228,902	1.08 (0.82–1.41)
30–39	48/112,543	1.18 (0.85–1.63)
40+	12/12,047	2.50 (1.37–4.56)
P for trend[b]		0.09
Pack-years[c]		
Never-smokers	218/674,737	1.0 (referent)
1–9	75/228,233	1.07 (0.82–1.39)
10–19	47/143,735	1.05 (0.76–1.45)
20–29	35/109,973	1.02 (0.71–1.48)
30–39	38/83,451	1.46 (1.03–2.06)
40+	26/60,560	1.29 (0.86–1.95)
P for trend[b]		0.06
Years since smoking commenced		
Never-smokers	218/674,737	1.0 (referent)
1–9	7/24,539	1.04 (0.49–2.21)
10–19	25/93,067	0.90 (0.58–1.39)
20–29	97/306,567	1.11 (0.86–1.42)
30–39	81/192,026	1.16 (0.89–1.51)
40+	18/22,512	1.95 (1.18–3.24)
P for trend[b]		0.06
Age smoking commenced		
Never-smokers	218/674,737	1.0 (referent)
20+	126/379,879	1.03 (0.83–1.29)
16–19	93/221,662	1.37 (1.07–1.77)
<16	9/37,171	0.88 (0.45–1.73)
P for trend[b]		0.08
Years since cessation of smoking[d]		
Current smokers	104/290,303	1.0 (referent)
1–9	43/146,354	0.84 (0.59–1.20)
10–19	49/122,637	0.96 (0.68–1.37)
20+	30/72,093	0.99 (0.65–1.51)
P for trend[b]		0.97

RR, hazard rate ratio; 95% CI, 95% confidence interval.

[a] Multivariate models included age in 5-year age groups, treatment allocation (intervention, control), study centre, Quetelet's index (quartiles), education level (less than high school, high school and university), vigorous physical activity (hours per day in tertiles—with a separate category for missing), oral contraceptive use (never + 4 levels of duration), hormone replacement therapy (never + 4 levels of duration), parity (plus tertiles nulliparous), age of menarche (quartiles), and menopausal status (pre, peri, post).

[b] All P-values are from two-sided tests.

[c] Pack-years = (cigarettes smoked per day/20) multiplied by years smoked.

[d] Former and current smokers only, with additional adjustment for duration of smoking.

When the association between smoking status and epithelial ovarian cancer risk was examined by histological type (Table 3), current smokers, but not former smokers, had an approximately two-fold increased risk of mucinous tumours compared with that of never smokers. However, this finding was based on a small number of cases ($n = 32$). Since only one of the ovarian cancer cases in the highest categories of smoking intensity, latency and pack-years was of the mucinous type (and none of the cases in the highest category of smoking duration was mucinous), the findings for these smoking measures reported in Table 2 were not altered appreciably when mucinous tumours were removed from the analysis.

4. Discussion

The findings of this study suggest that smoking of long duration may be associated with an increased risk of ovarian cancer, especially among women who also smoked with high intensity. In particular, we found that women who had smoked for 40 years or more at recruitment, or who had commenced smoking 40 years or more prior to assessment, had a statistically significant two-fold increased risk of ovarian cancer. This finding related largely to the risk of non-mucinous ovarian tumours. Women in the highest categories of smoking intensity and pack-years had small, statistically non-significant, increased risks of non-mucinous ovarian tumours compared with that of women who had never smoked. We did not find a clear association between ovarian cancer risk and the age at which smoking commenced or, for ex-smokers, time since smoking cessation. Current smoking at baseline was associated with an increased risk of mucinous, but not of non-mucinous tumours.

There have been at least 11 previous studies of the association between cigarette smoking and ovarian cancer risk that have used quantitative measures of smoking related to intensity and duration (Table 4). Of these, nine were case-control studies [5,7–9,11–14,23] and two were prospective studies [15,16]. Four recent population-based case-control studies [11–14] have examined the association between smoking and ovarian cancer according to histological type [20–23]. In three of these studies [11,12,14], positive associations with smoking were stronger with, and in some cases limited to, tumours of the mucinous histological type. In the other recent study [13], smokers of high intensity had a nearly two-fold increased risk of mucinous ovarian cancers, while smokers of long duration had a statistically significant increased risk of invasive serous tumours only. One early case-control study [6], with 300 ovarian cancer cases that used both population and hospital controls, found no clear association with ever (compared with never) smoking, and reported that there were no differences in this association according to histological type. Five case-control studies in which all histological types of ovarian cancer were combined, of which one was population-based [7] and four were hospital-based [5,8,9,23], showed no clear association with cigarette smoking. Similarly, three other case-control studies in which all histological types of ovarian cancer were combined and which did not examine quantitative measures of cigarette smoking (and, therefore, are not shown in the table) found no association with ever having smoked cigarettes [2–4].

Of the two previous prospective cohort studies, both of which examined smoking intensity in relation to total ovarian cancer mortality, one found a statistically non-significant 70% increased risk for every additional 10 cigarettes smoked per day (modelled as a continuous variable) [16] and the other found a statistically significant positive trend with cigarettes smoked per day [15] (Table 4). The results of these cohort studies were based on a total of 40 and 24 deaths from ovarian cancer, respectively, and they both had relatively few cases among women who were in the highest smoking categories. Another cohort study compared the risk of ovarian cancer for ever versus never smokers [10], finding no association with this smoking measure (data not shown). None of the previous cohort studies examined the association between cigarette smoking and ovarian cancer risk by histological type.

Our findings raise the possibility that the association between cigarette smoking and ovarian cancers of the non-mucinous histological types are characterised by a long period of time between the causal action of cigarette smoking and cancer diagnosis, or that smoking acts

Table 3
Adjusted[a] rate ratios for epithelial ovarian cancer in relation to smoking status according to histological type

	Ovarian cancer by histological type				
Smoking status	Total epithelial ($n = 454$) RR (95% CI)	Serous ($n = 184$) RR (95% CI)	Endometrioid ($n = 67$) RR (95% CI)	Mucinous ($n = 32$) RR (95% CI)	Other ($n = 171$) RR (95% CI)
Never-smokers	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
Former-smokers	1.07 (0.86–1.34)	0.98 (0.69–1.40)	0.67 (0.37–1.22)	1.19 (0.48–2.93)	1.51 (1.06–2.15)
Current-smokers	1.18 (0.93–1.50)	1.04 (0.71–1.53)	0.81 (0.43–1.54)	2.29 (1.00–5.28)	1.40 (0.94–2.09)

[a] Adjusted for the same variables as in Table 2.

Table 4
Previous epidemiological studies of cigarette smoking and ovarian cancer risk that examined quantitative measures of exposure[a]

First author, study year (Ref.)	Study design	No. of cases/controls (or No. in cohort)	Age range (years)	Histological type	Smoking frequency (cigarettes/day)		Smoking duration or latency (years)		Pack years (packs/day×years)	
					Comparison	OR (95% CI)	Comparison	OR (95% CI)	Comparison	OR (95% CI)
Modugno, 2002 [14]	Population case-control	767/1,367	20–69	Mucinous			>14 vs. never	1.8 (1.2–2.7)[b]	25+ vs. never	2.7 (1.6–4.8)[b]
				Non-Mucinous			>14 vs. never	1.1 (0.9–1.3)	25+ vs. never	1.2 (0.9–1.6)
Kuper, 2000 [13]	Population case-control	549 / 516		Total ovarian	40+ vs. never	1.1 (0.6–1.9)	40+ vs. never	0.9 (0.6–1.5)	>30 vs. never	1.2 (0.8–1.8)
				Mucinous	> 40 vs. never	2.0 (No CI)				
				Invasive serous			Positive association	(No OR)[b]		
Green, 2001 [11]	Population case-control	794 / 855	18–79	Total ovarian	30+vs. never	1.8 (0.9–3.6)			30+vs. never	1.6 (1.1–2.3)[b]
				Mucinous	30+vs. never	3.8 (1.2–11.8)[b]			30+ vs. never	2.6 (1.2–5.5)[b]
				Non-mucinous	30+ vs. never	1.2 (0.5–2.6)			30+ vs. never	1.6 (1.0–2.1)[b]
Marchbanks, 2000 [12]	Population case-control	447/3,868	20–54	Serous			15+vs. never	1.0 (0.7–1.4)	25+vs. never	1.2 (0.8–1.8)
				Mucinous			15+vs. never	2.5 (1.5–4.5)	25+vs. never	3.1 (1.6–6.1)
				Endometiroid			15+ vs. never	0.8 (0.5–1.4)	25+ vs. never	0.9 (0.5–1.8)
				Other			15+vs. never	0.6 (0.3–1.2)	25+vs. never	1.0 (0.5–2.0)
Smith, 1984 [7]	Population case-control	58 / 612	20–54	Total ovarian					1.00 as a continuous variable	
Stockwell, 1987 [8]	Hospital case-control	889/3,921	–	Total ovarian	40+vs. never	1.1 (0.6–1.9)				
Tzonou, 1984 [23]	Hospital case-control	150 / 250	–	Total ovarian	11+ vs. non-smokers	0.8 (No CI)				
Hartge, 1989 [5]	Hospital case-control	296 / 343	20–79	Total ovarian			31+ vs. never	1.1 (0.7–1.8)		
Baron, 1986 [9]	Hospital case-control	296/2,118	40–89	Total ovarian					15+ vs. never	1.0 (0.7–1.5)
Tverdal, 1993 [16]	Prospective cohort	40/24,535	35–49	Ovarian mortality	10/day (continuous)	1.7 (0.7–4.3)				
Doll, 1980 [15]	Prospective cohort	24 / 6,194	20–85	Ovarian mortality	25+ vs. non-smokers[c]	1.3 (No CI)[b]				

OR, odds ratio.
[a] Five studies that examined qualitative smoking measures only are discussed in the text.
[b] Statistically significant test of trend reported ($P < 0.05$).
[c] The analysis was confined to current smokers and non-smokers.

at different stages in the development of the respective tumour types. It is important to note that only one of the previous studies [13] found a positive association between smoking duration and non-mucinous (invasive serous) ovarian tumours. However, that study is also the only one of the previous studies that examined smoking of 40 years' duration or longer. Our findings also suggest that the association between smoking and mucinous tumours is characterised by a relatively short period between the causal action of cigarette smoking and disease diagnosis, or that smoking may promote the growth of previously extant mucinous ovarian tumours. Consistent with this notion, Kuper and colleagues [13] found that current smoking was associated with increased risk of mucinous tumours, whereas invasive serous tumours (as mentioned above) were associated only with very long-term smoking. In the three other recent case-control studies that examined the association by histological type [11,12,14], smoking was associated with increased risk of mucinous tumours even after relatively short periods of smoking duration. For example, Green and colleagues [11] found similar, statistically significant increased risks of mucinous tumours among women in each category of smoking duration, latency and pack-years (including those with fewer than 5) compared with never smokers. In contrast, the risk of non-mucinous tumours in their data was increased most clearly among women with relatively long-term smoking. In the study by Marchbanks and colleagues [12], the relative risk of mucinous tumours among women with less than 5 years of smoking latency (RR = 7.2, 95% CI = 1.4–36.5) was higher than that for women with 15 years or more (RR = 2.5, 95% CI = 1.5–4.5), but no such differences were observed for non-mucinous tumours. Similarly, in the study by Modugno and colleagues [14], the relative risk of mucinous tumours among women with less than 5 years of smoking latency (RR = 6.2, 95% CI = 1.1–35.9) was higher than that for women with a latency of 15 years or more (RR = 2.5, 95% CI = 1.2–.2.7), but no such differences were observed for non-mucinous tumours.

In the previous studies that examined the association between cigarette smoking and ovarian cancer by histological type [11,12,14], there was a trend towards the null association between mucinous tumours and years since smoking ceased (most clearly in the study by Green and colleagues [11]). In contrast, we did not observe a clear trend for mucinous tumours, but the number of cases of these tumours in our data-set was low. If a carcinogen acts early in cancer development, its association with cancer risk will be characterised by a relatively long period of time between the causal action of cigarette smoking and diagnosis, or that smoking acts at different stages in the development of the respective tumour types [24,25]. In contrast, the association with risk of a carcinogen that acts late in cancer development would tend towards the null with increasing years since cessation of exposure to that carcinogen [24,25]. Thus, the findings of previous studies, in conjunction with those of our own study, suggest that cigarette smoking might increase the risk of mucinous and non-mucinous tumours, but that the respective associations may differ with respect to the length of time between the causal action of cigarette smoking and diagnosis, or that smoking acts at different stages in the development of the respective tumour types.

Differences between mucinous and non-mucinous tumours with respect to other risk factor associations have also been observed. Risch and colleagues [17], for example, confirmed prior observations that the inverse associations for serous and endometrioid tumours (both of which are non-mucinous) with respect to parity and OC use did not hold for the mucinous tumours. Based on these observations, it has been suggested that mucinous ovarian tumours might be aetiologically unrelated to the other types of epithelial tumours [17]. Whereas mucinous elements such as gastric or intestinal type glands may be seen in mature teratomas, a form of germ cell neoplasia, mucinous tumours are classified overall as surface epithelial tumours because transitions among the histological subtypes may be observed.

The major difference between mucinous and serous tumours is in their biological behaviour. Mucinous carcinomas of the ovary are slow-growing tumours that appear to develop from their benign counterparts. The fact that the transitions between the benign, borderline and malignant form of the disease can be seen in the same tumour suggests that over time there is a progression from benign to malignant [26]. K-ras mutational analysis, for example, demonstrates a higher prevalence of the mutation in carcinomas than in borderline or benign tumours, suggesting that in some cases acquisition of the K-ras mutation occurs in malignant transformation [27]. Serous carcinomas, on the other hand, seem to develop *de novo* rather than from a benign pre-existing lesion [28], although it is also possible that they progress rapidly and that the precursor lesion is obliterated prior to the detection of the tumour. Since the mucinous tumour is slow-growing, one might speculate that smoking contributes to the progression of the benign-malignant sequence, whereby the benign form of the tumour may have been present for some time, with smoking-induced changes leading to malignancy. Another possibility is that women who are actively smoking may come to medical attention more frequently than nonsmokers, thereby shortening the period between disease occurrence and detection among the smokers. Given that mucinous tumours, benign or malignant, tend to be quite large, they may then be detected more easily on routine physical exam or testing, so that any association that is observed with cigarette smoking might result from detection bias.

Among the strengths of our study was the large sample size of our cohort of women and the relatively long-term follow-up. The completeness of follow-up of the cohort [20,21] reduces the likelihood that our results reflect bias due to differential follow-up of long-term smokers compared with non-smokers. On the other hand, although we adjusted our estimates for a wide range of potentially confounding variables, we cannot exclude the possibility of residual confounding by other factors. In addition, the histological diagnoses of ovarian tumours were not subject to standardised review, but rather were reviewed by pathologists throughout the various provinces of Canada. If one histological type of ovarian tumour were associated more strongly with smoking than another, for example, misclassification by histological type would have tended to attenuate the stronger association [22,29]. The histological reviews were not standardised, which may have resulted in misclassification of outcome by histological type. In addition, we cannot rule out non-differential misclassification of the various measures of cigarette smoking. For example, we did not collect additional information on smoking during the follow-up period. It is likely that some women commenced smoking and others ceased during follow-up, and attenuation of the true rate ratios would be a likely consequence. Finally, although we note that some previous studies have examined tumours of the borderline type (particularly mucinous tumours), our study included data only on invasive ovarian cancers.

In conclusion, we found cigarette smoking of long duration was associated with an increased risk of epithelial ovarian cancer. The association with smoking duration was observed for non-mucinous tumours when examined separately from mucinous tumours. In contrast, we found an increased risk of mucinous ovarian tumours, but not non-mucinous tumours, among current smokers. These findings are consistent with those of previous studies that have shown smoking increased the risk of mucinous tumours shortly after smoking commencement, but with no clear monotonic trend with increasing duration or latency. The possibility that smoking acts at a later stage in mucinous ovarian tumour development compared with that of non-mucinous tumours, or that the association with mucinous tumours is characterised by a shorter length of time between cancer initiation and diagnosis, should be addressed in future studies. Clearly, there is a need for studies of ovarian cancer with larger numbers of each of the histological types of interest. Furthermore, studies conducted in populations screened for ovarian cancer would be particularly advantageous, since they would avoid the possibility that any associations that are observed are due to detection bias.

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