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A Prospective Study of Cigarette Smoking and the Risk of Inflammatory Bowel Disease in Women

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Abstract

Background & Aims—Long-term data on the influence of cigarette smoking, especially cessation, on the risk of Crohn's disease (CD) and ulcerative colitis (UC) are limited.

Methods—We conducted a prospective study of 229,111 women in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II). Biennially, we collected updated data on cigarette smoking, other risk factors, and diagnoses of CD or UC confirmed by medical record review.

Results—Over 32 years in NHS and 18 years in NHS II, we documented 336 incident cases of CD and 400 incident cases of UC. Compared to never smokers, the multivariate hazard ratio (HR) of CD was 1.90 (95% confidence interval [CI], 1.42–2.53) among current smokers and 1.35 (95% CI, 1.05–1.73) among former smokers. Increasing pack-years was associated with increasing risk

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Hamed Khalili- acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; study supervision; approval of final draft submitted.

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of CD (Ptrend< 0.0001) whereas smoking cessation was associated with an attenuation of risk. In contrast, the multivariate HRs of UC was 0.86 (95% CI, 0.61–1.20) among current smokers and 1.56 (95% CI, 1.26–1.93) among former smokers. The risk of UC was significantly increased within 2 to 5 years of smoking cessation (HR, 3.06; 95% CI, 2.00–4.67) and remained persistently elevated over 20 years.

Conclusions—Current smoking is associated with an increased risk of CD, but not UC. In contrast, former smoking is associated with an increased risk of UC, with risk persisting over two decades after cessation.

Keywords

smoking cessation; CD; UC

INTRODUCTION

The etiologies of Crohn's disease (CD) and ulcerative colitis (UC), the two main forms of inflammatory bowel disease (IBD), remain unknown, but are thought to be multifactorial, with both genetic and environmental influences.^{1, 2} Multiple studies have reported significant associations between cigarette smoking and the risk of IBD, although the effect of smoking appears to differ between CD and UC.^{3, 4} In prior analyses, current smoking has been associated with a higher risk of CD but a lower risk of UC. Moreover, smoking cessation may increase UC risk.^{3–11} Nonetheless, the majority of previous studies that assessed the relationship between smoking and IBD were retrospective, case-control studies limited by recall and selection biases.^{5–10} The few prospective cohort studies that have examined smoking included only a small number of cases and did not collect updated smoking status exposure data over long-term follow-up.^{12, 13}

We therefore performed a post-hoc analysis of smoking information, obtained prior to diagnosis, on the risk of IBD among 229,111 women enrolled in two large ongoing, prospective cohort studies. Over 32 years of follow-up, we documented 736 incident cases of CD and UC. Moreover, in both cohorts, smoking data was updated biennially, thereby minimizing misclassification of smoking exposure and allowing a detailed assessment of the influence of smoking cessation on the risk of incident CD and UC.

METHODS

Study Cohorts

The Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) are two large prospective cohort studies. NHS was initiated in 1976, when 121,701 U.S. female registered nurses, 30 through 55 years of age, completed a mailed questionnaire, including a detailed assessment of past and current smoking history.^{14–16} NHS II was established in 1989 with a parallel cohort of 116,671 U.S. female registered nurses, 25 through 42 years of age.^{17, 18} Every two years, participants in both cohorts have been followed with similar biennial questionnaires. In both cohorts, follow-up has remained greater than 90%. All aspects of this study were approved by the Partners' HealthCare Institutional Review Board and Children's Hospital Boston Institutional Review Board.

Assessment of smoking exposure

On the 1976 baseline NHS questionnaire and the 1989 baseline NHS II questionnaire, past and current smokers were asked to indicate the average number of cigarettes they smoked per day, the age at which they began smoking, and, among past smokers, the age at which they stopped smoking. Biennially, participants have provided updated data on their smoking

status and the number of cigarettes smoked in categories (1 to 4, 5 to 14, 15 to 24, 25 to 34, 35 to 44, or 45 or more cigarettes per a day). We assessed cumulative exposure to cigarette smoking according to pack-years, defined as having smoked one pack or 20 cigarettes/day over an entire year. The number of pack years was calculated by multiplying the number of packs smoked per day by the number of years during which that amount was smoked. For example, if one smoked 2 packs/day for 6 months, this would equal 1 pack year. All categories were created before data analysis (a priori).

Assessment of other exposures

Beginning with the 1976 questionnaire for NHS and the 1989 questionnaire for NHS II, women provided information for height, weight, oral contraceptive use, and post-menopausal hormone use that was updated with each biennial questionnaire. In a prior validation study, 184 women were weighed by technicians 6–12 months after completion of mailed questionnaire and reported weights were highly correlated with measured weights ($r=0.96$).¹⁹ Body-mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters.

Identification of CD and UC

We previously have detailed our methods for confirming self-reported cases of CD and UC.²⁰ Since 1976 in NHS I and 1989 in NHS II, participants have reported diagnoses of UC or CD through an open-ended response on biennial questionnaires. In NHS I, we specifically have queried participants about diagnoses of UC since 1982 and CD since 1992. In NHS II, we specifically have queried participants about diagnoses of both UC and CD since 1993. Participants were asked to indicate the time period in which they were diagnosed. When a diagnosis of CD or UC was reported on any biennial questionnaire, we mailed the participant a supplemental IBD survey, which included a more detailed description of CD and UC, as well as a questionnaire requesting detailed information regarding symptoms, diagnostic testing, and treatments, and permission to examine related medical records. If permission was granted, medical records were independently reviewed by two gastroenterologists, blinded to all exposure data. Reviewers extracted data regarding clinical presentation and endoscopic, histopathologic, radiologic and surgical specimen findings. Cases of CD and UC with date of diagnosis (date of initial endoscopic, histopathologic, radiologic, or surgical specimen evidence of CD or UC) were confirmed according to strict diagnostic criteria for CD and UC (See Supplementary Material online).^{21–25} Disagreements were resolved through consensus. We have previously confirmed that the baseline characteristics (smoking status, BMI, oral contraceptive use, post-menopausal hormone use) of participants for whom we were able to obtain complete medical records were similar to those of participants for whom we were unable to obtain sufficient records.²⁰ Participants for whom we did not confirm CD and UC were included in the analyses as non-cases.

Population for analysis

We excluded participants who did not provide smoking information on the baseline questionnaires in 1976 for NHS and in 1989 for NHS II. We also excluded women who reported a history of inflammatory bowel disease or cancer (except non-melanoma skin cancer) prior to study baseline and those who did not provide information on the baseline questionnaires for height, oral contraceptive use, or postmenopausal hormone use. After these exclusions, 115,290 women in NHS and 113,821 women in NHS II were eligible for analysis.

Statistical analyses

In the primary analysis, we calculated incidence rates of CD or UC for participants in each category of biennially updated smoking status by dividing the number of incident cases by the number of person-years of follow-up. Participants accrued follow-up time beginning on the date of the return of the baseline questionnaire and ending on the date of diagnosis of CD or UC, date of death, or at the end of the follow-up period, June 30, 2008 for NHS and June 30, 2007 for NHS II, whichever came first. We calculated hazard ratios by dividing the incidence rate in each exposure category by the incidence rate in the reference category. For smoking status, analyses compared current smokers and past smokers to the reference group, never smokers. We used Cox proportional hazards modeling to determine hazard ratios (HR) and 95% confidence intervals (CIs) and to simultaneously adjust for other potential risk factors to estimate hazard ratios and 95% confidence intervals. In our multivariate models, we adjusted for baseline body-mass index and biennially updated oral contraceptive use and postmenopausal hormone-replacement therapy, to account for changes in the use of these agents over follow-up. In secondary analyses, using a priori defined categories, we assessed the influence of smoking dose among current smokers, cumulative exposure to smoking cigarettes (pack years), and smoking cessation among past smokers. We performed a 2-year lagged analysis for the examination of smoking cessation and UC. Linear tests for trend were calculated for cumulative exposure to smoking and smoking cessation models. We performed tests of heterogeneity for the associations in both NHS and NHS II using the Q statistic and observed no significant heterogeneity (Q probability > 0.29). Thus, for all analyses, we combined data from both cohorts.²⁶ We evaluated the proportional hazards assumption by likelihood ratio tests comparing models with and without time-dependent variable-by-variable interaction terms. Statistical models satisfied the proportionality of hazards assumption. We used SAS software (version 9.1) for all analyses. We considered 2-sided P values less than 0.05 to be statistically significant. Adjustments for multiple comparisons were not performed since our smoking exposure variables were selected on the basis of a priori hypotheses and consistent with prior analyses of smoking in the cohorts.^{15, 16, 18}

RESULTS

Table 1 presents baseline characteristics of the eligible women at enrollment in NHS in 1976 and NHS II in 1989. In NHS, 33% of the nurses were current smokers, 23% were past smokers, and 44% never smoked. In NHS II, 14% of the nurses were current smokers, 21% were past smokers and 65% never smoked. For both cohorts, smoking status was updated biennially. During the 5,428,403 person-years of follow-up, we identified and confirmed 336 incident cases of CD and 400 incident cases of UC through 2008 in NHS and 2007 in NHS II.

Smoking status and risk of CD and UC

We observed a significantly higher risk of CD among the current and past cigarette smokers compared to never smokers (Table 2). Current smoking was associated with a multivariate hazard ratio (HR) of CD of 1.90 (95% confidence interval [CI], 1.42–2.53), whereas former smokers experienced a HR of 1.35 (95% CI, 1.05–1.73), after adjustment for other covariates. In contrast, current smoking was not significantly associated with the risk of UC (HR, 0.86; 95% CI, 0.61–1.20), but former smokers experienced a significant elevation in risk (HR, 1.56; 95% CI, 1.26–1.93). Of note, among current smokers, we did not observe an association between number of cigarettes per day and the risk of either CD or UC.

Cumulative smoking dose and risk of CD and UC

We further examined the influence of cumulative smoking dose, measured by pack-years on the risk of CD and UC. Increasing pack-years was associated with an increasing risk of CD among all participants ($P_{\text{trend}} < 0.0001$), and this association remained significant when we limited analyses to either current smokers ($P_{\text{trend}} < 0.0001$) or past smokers ($P_{\text{trend}} = 0.0002$) (Table 3). Given the heterogeneity in the effects of current and past smoking on the risk of UC, we examined cumulative pack-years among either current or past smokers (Table 4). While there was no effect of cumulative pack-years on UC risk among current smokers, increasing pack-years conferred a significant increase in risk among former smokers ($P_{\text{trend}} < 0.0001$).

Smoking cessation and risk of CD and UC

We examined the impact of cigarette smoking cessation on the risk of CD and UC. Compared to current smokers, smoking cessation appeared to attenuate the risk of CD over 20 years of follow-up ($P_{\text{trend}} = 0.03$) (Table 5). In contrast, there was an increase in risk of UC within 2 to 5 years of smoking cessation (HR, 3.06; 95% CI, 2.00–4.67), which remained significantly elevated even after increasing duration of smoking cessation (HR, 1.64; 95% CI, 1.02–2.64 for >20 years of smoking cessation). We considered the possibility that the association between smoking cessation and UC reflected cessation among affected, symptomatic subjects who had not yet received a physician-defined diagnosis. We therefore repeated the analysis in which we excluded cases documented within the first two years of each updated assessment of smoking status. Nonetheless, the results were not materially changed. Compared to current smokers, the multivariate HR for UC was 1.13 (95% CI, 0.74–1.70) for 2 years, 2.12 (95% CI, 1.37–3.25) for 2.1 to 5 years, and 2.10 (95% CI, 1.33–3.33) for 5.1 to 10 years after smoking cessation.

DISCUSSION

We performed a post-hoc analysis of two large, prospective cohort studies of women in which smoking information was obtained prior to the diagnoses of CD and UC. We found that both current and former cigarette smoking was associated with a significant increased risk of CD. Moreover, compared to never smokers, increasing pack-years among both current and past smokers conferred a significant increase in the risk of CD. In contrast, current smoking was not associated with risk of UC, but cessation of cigarette smoking significantly increased risk of UC within two to five years of smoking cessation, with this effect persisting more than 20 years after cessation.

Our findings for CD are consistent with observations from previous studies.^{3, 4, 6–10} One meta-analysis of seven retrospective case-control studies of smoking and CD reported a pooled OR of 2.0 (95% CI, 1.65–2.47) among current smokers and 1.80 (95% CI, 1.33–2.51) among past smokers, when compared to never smokers.³ A separate meta-analysis observed slightly lower risks of CD with an overall OR of 1.76 (95% CI, 1.40–2.22) among current smokers and OR of 1.30 (95% CI, 0.97–1.76) among past smokers, when compared to never smokers.

The apparent increased risk of UC among past smokers in the current study is consistent with findings in most previous analyses,^{3–8} though not all.^{9, 10, 27} Two prior meta-analyses reported a pooled OR of 1.64 (95% CI, 1.36–1.98)³ and 1.79 (95% CI, 1.37–2.34)⁴ for risk of UC among past smokers compared to never smokers. Of note, in the current study, increasing pack-years conferred a significant increase in the risk of UC only among former smokers. Although some studies have found a decreased risk of UC among current smokers,^{3–7, 9, 10, 28} other studies observed no statistically significant difference in risk

among current smokers compared to never smokers,^{8, 12, 13, 27, 29} consistent with our findings. Our finding of a relatively rapid increase in the risk of UC after smoking cessation was also observed in prior studies.^{5, 6, 11} Although this association could be secondary to smoking cessation related to subclinical UC, the persistent elevation in risk beyond 20 years of cessation, strong dose-response (in pack-years) on risk among former smokers, and similar findings when we excluded cases diagnosed within 2 years of smoking assessment support an association between smoking cessation and development of UC.

The distinctly different relationship between cigarette smoking and CD from that of smoking and UC underscores the complexity of the pathogenesis of these diseases.^{30, 31} Whereas cigarette smoking consistently heralds an elevated risk of CD, one might speculate that it may suppress risk of UC in a genetically predisposed individual until smoking cessation, at which time the withdrawal of a potential protective effect of smoking may precipitate the onset of UC or unmask its symptoms.³² Others have hypothesized that in a genetically susceptible individual, smoking status might influence disease phenotype, resulting clinically in the development of either CD or UC.³³

Although nicotine has been considered a potential putative agent influencing CD and UC risk, cigarettes also are associated with the generation of free radicals and carbon monoxide which may play a mechanistic role.³⁰ Smoking may also affect the colonic mucus layer, modify cytokine production, modulate humoral and cellular immunity (innate and adaptive responses), reduce smooth muscle tone and activity, change gut permeability, and affect the microvasculature.^{30, 31, 34, 35}

Our study has several strengths. The data collected prior to diagnosis avoids the potential recall and selection biases of previous retrospective, case-control studies. Our assessment of cigarette smoking and other risk factors were updated biennially, thus avoiding misclassification during follow-up and permitting a detailed examination of the influence of smoking cessation which is not feasible in cohort studies with only baseline smoking information.^{12, 13} The large number of participants and long-term follow-up facilitated ascertainment of a sufficient number of incident cases of CD and UC for robust associations. Lastly, the confirmation of cases of CD and UC by extensive medical record review by two blinded expert gastroenterologists and long-term follow-up over 32 years minimized misclassification of outcomes based upon self-report discharge coding.

We acknowledge some limitations of our study. Our cohort is composed entirely of female health professionals and may not represent the overall US population. However, as shown in our previous analyses, our age-specific incidence of CD and UC were largely similar to rates from other U.S. populations.²⁰ In addition, previous studies have shown that risk factors including smoking, body-mass index, and dietary intake among the participants in NHS and NHS II are consistent with those of the broader population of U.S. women.^{36–39} Despite these findings, we recognize that there may be potential unmeasured factors, uniquely associated with our cohort that may limit the generalizability of our findings. Our study was also limited to a population between age 25 and 55 at baseline enrollment. Thus, our findings may not be generalizable to CD and UC among younger age groups.

To our knowledge, our study represents the largest cohort study with prospectively collected and updated smoking information, examining the associations between smoking and inflammatory bowel disease. In summary, current and former cigarette smoking is associated with an increased risk of CD. In contrast, although current smoking was not associated with risk of UC, a history of former smoking, which persisted for several decades of cessation, was associated with an increased risk of UC. Further studies may clarify the

mechanisms by which smoking and smoking cessation influence the risk of inflammatory bowel disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NHS	Nurses' Health Study
NHS II	Nurses' Health Study II
HR	hazard ratio
CI	confidence interval

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Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- Cigarette smoking is associated with an increased risk of CD.
- Most, but not all, studies have shown that current smoking is associated with a decreased risk of UC, but past smoking is associated with an increased risk of UC.

2. WHAT IS NEW HERE

- The increased risk of UC following smoking cessation persists even after two decades of cessation, suggesting that the increased incidence associated with cessation does not significantly diminish with extended time.
- Smoking cessation attenuated the increased risk for CD, during two decades of follow-up.

Table 1a

Baseline Characteristics of the Nurses' Health Study (NHS) Study Cohort in 1976.

Total N= 115,290			
Characteristic	Never smokers N= 50,285	Past smokers N= 26,760	Current smokers N= 38,245
Mean age (years)	43	43	43
Body mass index [†]	24.1	24.0	23.2
Oral contraceptive use (%)			
Never use (%)	54	50	51
Past use (%)	40	44	42
Current use (%)	6	6	7
Postmenopausal women (%) ^{††}			
Never use of hormones (%)	29	28	32
Past use of hormones (%)	56	52	54
Current use of hormones (%)	18	19	20
Current use of hormones (%)	26	29	26

[†] The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

^{††} The percentages of those postmenopausal women with never use, past use, and current use of hormones after menopause.

Table 1b

Baseline Characteristics of the Nurses' Health Study II (NHS II) Study Cohort in 1989.

Total N= 113,821			
Characteristic	Never smokers N= 74,173	Past smokers N= 24,367	Current smokers N= 15,281
Mean age (years)	34	36	35
Body mass index [†]	24.1	24.1	24.1
Oral contraceptive use (%)			
Never use (%)	20	11	11
Past use (%)	67	77	76
Current use (%)	13	12	13
Postmenopausal women (%) ^{††}	3	3	4
Never use of hormones (%)	16	15	15
Past use of hormones (%)	12	13	15
Current use of hormones (%)	72	72	70

[†] The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

^{††} The percentages of those postmenopausal women with never use, past use, and current use of hormones after menopause.

Table 2

Risk of Crohn's Disease and Ulcerative Colitis According to Smoking Status.

Disease	Smoking Status		
	Never smokers	Past smokers	Current smokers
Crohn's disease			
No. of cases	144	117	75
No. of person years	2,785,355	1,719,199	923,849
Age-adjusted hazard ratio (95% CI)	1.00	1.37 (1.07–1.76)	1.88 (1.41–2.51)
Multivariate hazard ratio (95% CI) [†]	1.00	1.35 (1.05–1.73)	1.90 (1.42–2.53)
Ulcerative colitis			
No. of cases	190	167	43
No. of person years	2,785,355	1,719,199	923,849
Age-adjusted hazard ratio (95% CI)	1.00	1.59 (1.28–1.96)	0.86 (0.61–1.20)
Multivariate hazard ratio (95% CI)	1.00	1.56 (1.26–1.93)	0.86 (0.61–1.20)

[†] Multivariate hazard ratios were adjusted for age, body-mass index (<22, 22–24.9, 25–29.9, or ≥30), oral contraceptive use (never use, past use, current use), and postmenopausal hormone-replacement therapy (premenopausal women and postmenopausal women with never use, past use, or current use of hormone-replacement therapy).

Table 3

Risk of Crohn's Disease According to Pack-Years of Smoking.

Population	Never	5	5.1–10	10.1–25	> 25	P-Trend ^{††}
Past smokers						
No. of cases	144	16	19	49	32	
No. of person-years	2,793,567	526,847	321,237	501,579	326,928	
Age-adjusted hazard ratio (95% CI)	1.00	0.62 (0.37–1.04)	1.20 (0.74–1.94)	2.03 (1.46–2.84)	2.13 (1.41–3.22)	
Multivariate hazard ratio (95% CI) [†]	1.00	0.61 (0.36–1.02)	1.19 (0.73–1.92)	1.99 (1.42–2.78)	2.12 (1.40–3.21)	0.0002
Current smokers						
No. of cases	144	6	5	15	47	
No. of person-years	2,788,193	57,250	75,227	300,287	479,605	
Age-adjusted hazard ratio (95% CI)	1.00	2.23 (0.98–5.11)	1.36 (0.55–3.35)	1.17 (0.68–2.00)	2.56 (1.79–3.65)	
Multivariate hazard ratio (95% CI)	1.00	2.29 (1.00–5.23)	1.37 (0.56–3.38)	1.19 (0.69–2.04)	2.65 (1.86–3.79)	<0.0001
Past and current smokers						
No. of cases	144	22	24	64	79	
No. of person-years	2,796,590	584,138	396,497	801,929	806,592	
Age-adjusted hazard ratio (95% CI)	1.00	0.78 (0.50–1.22)	1.23 (0.80–1.90)	1.73 (1.28–2.33)	2.33 (1.73–3.14)	
Multivariate hazard ratio (95% CI)	1.00	0.77 (0.49–1.20)	1.22 (0.79–1.88)	1.70 (1.26–2.30)	2.34 (1.73–3.15)	<0.0001

[†] Multivariate hazard ratios were adjusted for age, body-mass index (<22, 22–24.9, 25–29.9, or ≥30), oral contraceptive use (never use, past use, current use), and postmenopausal hormone-replacement therapy (premenopausal women and postmenopausal women with never use, past use, or current use of hormone-replacement therapy).

^{††} P trend is for test for linear trend for pack years, reference group is never smokers.

Table 4

Risk of Ulcerative Colitis According to Pack-Years of Smoking.

Population	Pack-years of Smoking					P-Trend ^{††}
	Never	5	5.1–10	10.1–25	> 25	
Past smokers						
No. of cases	191	34	37	51	42	
No. of person-years	2,793,567	526,847	321,237	501,579	326,928	
Age-adjusted hazard ratio (95% CI)	1.00	1.03 (0.71–1.48)	1.82 (1.27–2.59)	1.65 (1.21–2.27)	2.40 (1.67–3.44)	
Multivariate hazard ratio (95% CI) [†]	1.00	1.01 (0.70–1.46)	1.78 (1.25–2.54)	1.62 (1.18–2.21)	2.35 (1.64–3.38)	<0.0001
Current smokers						
No. of cases	190	4	5	14	20	
No. of person-years	2,788,193	57,250	75,227	300,287	479,605	
Age-adjusted hazard ratio (95% CI)	1.00	1.28 (0.47–3.46)	1.11 (0.45–2.73)	0.84 (0.48–1.45)	0.86 (0.53–1.40)	
Multivariate hazard ratio (95% CI)	1.00	1.27 (0.47–3.45)	1.13 (0.46–2.78)	0.85 (0.49–1.47)	0.87 (0.54–1.41)	0.78

[†] Multivariate hazard ratios were adjusted for age, body-mass index (<22, 22–24.9, 25–29.9, or ≥30), oral contraceptive use (never use, past use, current use), and postmenopausal hormone-replacement therapy (premenopausal women and postmenopausal women with never use, past use, or current use of hormone-replacement therapy).

^{††} P trend is for test for linear trend for pack years, reference group is never smokers.

Table 5
Risk of Crohn's Disease and Ulcerative Colitis According to Years Since Quitting Smoking.

Disease	Current smokers	2	Years since quitting smoking				P-Trend ^{††}
			2.1–5	5.1–10	10.1–20	> 20	
Crohn's Disease							
No. of cases	73	11	11	15	47	32	
No. of person-years	915,207	118,136	162,897	231,418	511,679	622,449	
Age-adjusted hazard ratio (95% CI)	1.00	0.54 (0.41–0.72)	0.87 (0.54–1.40)	0.74 (0.42–1.29)	1.01 (0.70–1.46)	0.53 (0.34–0.81)	
Multivariate hazard ratio (95% CI) [†]	1.00	0.79 (0.53–1.17)	0.92 (0.57–1.49)	0.82 (0.47–1.45)	1.20 (0.81–1.78)	0.69 (0.43–1.12)	0.03
Ulcerative Colitis							
No. of cases	43	16	29	24	49	47	
No. of person-years	915,207	118,136	162,897	231,418	511,679	622,449	
Age-adjusted hazard ratio (95% CI)	1.00	1.15 (0.82–1.61)	2.97 (1.95–4.52)	1.91 (1.15–3.16)	1.73 (1.14–2.61)	1.44 (0.94–2.20)	
Multivariate hazard ratio (95% CI)	1.00	1.40 (0.91–2.14)	3.06 (2.00–4.67)	2.00 (1.20–3.34)	1.87 (1.21–2.88)	1.64 (1.02–2.64)	0.42

[†] Multivariate hazard ratios were adjusted for cumulative pack years, age, body-mass index (<22, 22–24.9, 25–29.9, or ≥30), oral contraceptive use (never use, past use, current use), and postmenopausal hormone-replacement therapy (premenopausal women and postmenopausal women with never use, past use, or current use of hormone-replacement therapy).

^{††} P trend is for test for linear trend for years since quitting; reference group is current smokers.