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Dose–response relationship between cigarette smoking and risk of ulcerative colitis: a nationwide population-based study

Seona Park[1] · Jaeyoung Chun[1,3] · Kyung-Do Han[2] · Hosim Soh[1] · Eun Ae Kang[1] · Hyun Jung Lee[1] · Jong Pil Im[1] · Joo Sung Kim[1]

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Abstract

Background Former cigarette smokers are at risk of developing ulcerative colitis (UC). However, the impact of smoking behavior on the occurrence of UC according to the amount smoked remains elusive. We aimed to determine the relationship between smoking behavior and the risk of UC development.

Methods We conducted a retrospective population-based cohort study using the National Health Insurance Service database in South Korea. From January 2009 to December 2012, 23,235,771 individuals over 18 years of age who underwent a national health examination were enrolled and followed until 2016. All study participants were divided into the following 3 groups: nonsmokers, former smokers, and current smokers. The primary endpoint was newly developed UC.

Results Compared with nonsmokers, the risk of UC development was significantly higher in former smokers [adjusted hazard ratio (aHR) 1.83; 95% confidence interval (CI) 1.73–1.95] but significantly lower in current smokers (aHR 0.92; 95% CI 0.87–0.98). Among current smokers, individuals who stopped smoking after the baseline evaluation had a significantly higher risk of UC development than those who continued to smoke (aHR 2.42; 95% CI 2.10–2.80). The risk of UC development among former smokers was significantly associated with smoking amount and duration. Among current smokers, however, the risk of UC development was not correlated with the cumulative lifetime smoking exposure. The preventive effect of current smoking on UC development was observed only in men (aHR 0.90; 95% CI 0.84–0.96).

Conclusions Compared with nonsmokers, former smokers have a significantly higher risk of UC development that may be proportional to the cumulative smoking exposure.

Keywords Claims data · Incidence · Smoking · Ulcerative colitis

Abbreviations

aHR	Adjusted hazard ratio
BMI	Body mass index
CI	Confidence interval
DM	Diabetes mellitus
HR	Hazard ratio
ICD-10	International Classification of Disease, Tenth Revision
NHIS	National Health Insurance Service
NHS I	Nurses' Health Study I
NHS II	Nurses' Health Study II
RID	Rare intractable disease
UC	Ulcerative colitis

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✉ Jaeyoung Chun
j40479@gmail.com

[1] Department of Internal Medicine, Liver Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Chongno-gu, Seoul 03080, South Korea

[2] Department of Biostatistics, College of Medicine, The Catholic University of Korea, Seoul, South Korea

[3] Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, 20, Eonju-ro 63-gil, Gangnam-gu, Seoul 06229, South Korea

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Introduction

Ulcerative colitis (UC) is a chronic and relapsing inflammatory disease localized in the colon and rectum [1]. The incidence and prevalence of UC is highest in North America and Europe but has also been increasing rapidly in Asia in recent years [2]. Accumulating evidence suggests that chronic intestinal inflammation is related to a combination of a dysregulated immune response with genetic and environmental factors and dysbiosis of intestinal microbes [1, 3]. The global phenomenon of an increasing trend in the prevalence of UC may be closely linked to environmental changes that promote the initiation and perpetuation of colonic inflammation.

As one of the possible environmental factors influencing the pathogenesis of UC, cigarette smoking has a unique association with the development of UC [4]. The causal relationship between UC and smoking behavior was first identified in 1982 by Harries et al. [5], who confirmed that the proportion of smokers was lower among patients with UC than among healthy controls. Since then, a number of clinical studies have reported that current smoking plays a protective role in the pathogenesis of UC, but that former smokers have an approximately 1.8-fold increased risk of the occurrence of UC versus nonsmokers [6–10]. However, it still remains unclear whether there is a dose–response relationship between the risk of UC development and cigarette smoking in the general population and which groups are at higher risk of UC development based on smoking behavior. Accordingly, the aims of this study were to determine if there is a dose–response relationship between cigarette smoking and the risk of UC development and to identify the individuals at high risk for UC based on smoking behavior.

Materials and methods

Data source and study population

This retrospective nationwide population-based study was performed using the database of the National Health Insurance Service (NHIS), which is a mandatory health insurance program for almost 97% of Koreans (approximately 51 million people) established by the Korean government [11]. The NHIS database contains information for each registrant on demographics, outpatient and inpatient medical use, and claims for medication prescribed and procedures performed. The NHIS recommends that all adult enrollees undergo a standardized national health examination at least every 2 years. Medical check-up items include physical measurements such as height, weight, body mass index (BMI), and blood pressure and laboratory tests such as serum total cholesterol and fasting glucose. Data on past medical, family, and social history including cigarette smoking, alcohol consumption, and physical activity were obtained from self-report questionnaires.

From the NHIS claim database, we evaluated 23,452,862 records for residents older than 18 years of age who had received at least 1 biennial medical check-up between January 2009 and December 2012. Among them, 195,100 people with missing values and 74,192 people who had been diagnosed with UC before the index date were excluded. Finally, a total of 23,183,570 individuals were analyzed and followed until December 2016.

Ethical considerations

This study performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. To protect personal information, all resident registration numbers were encrypted. For this reason, the study protocol was exempted from formal review by the Seoul National University Hospital Institutional Review Board (H-1703-107-840).

Definitions

Data on demographics (age, sex, and place of residence) and medical check-up items were evaluated. Smoking status was classified based on the self-report questionnaire records as follows: current smokers, defined as those who had smoked more than 5 packs (a total of 100 cigarettes) throughout their lifetime and continued to smoke; former smokers, defined as those who had smoked more than 5 packs (a total of 100 cigarettes) throughout their lifetime but had quit smoking; and nonsmokers, defined as those who had smoked 5 packs or fewer [12, 13]. Both former and current smokers recorded in the self-report questionnaire the total duration of smoking (years) and the average daily amount of cigarettes smoked (number of cigarettes per day). We reported the cumulative lifetime smoking exposure as the pack-year by multiplying the average cigarette consumption per day (pack) by the smoking period (years). Heavy drinkers were defined as individuals who consumed more than 30 g of alcohol per day on average. Regular exercise was defined as intense physical activity that made breathing faster than usual on more than 3 days a week for at least 20 min at a time or as moderate physical activity that made breathing slighter faster than usual on more than 5 days a week for at least 30 min at a time.

We also identified diabetes mellitus (DM), hypertension, and dyslipidemia as baseline comorbidities of the study population using International Classification of Disease, Tenth Revision (ICD-10) codes and additional information, as in previous work [14]. Participants were defined as having DM if they had a fasting blood glucose level of 126 mg/dL or more or were registered with ICD-10 codes E11–14 and had been prescribed medication for DM. Participants were defined as having hypertension if they had a systolic blood pressure of 140 mmHg or more, a diastolic blood pressure of 90 mmHg or more, or were registered with ICD-10 codes I10–13 and I15 and had been prescribed anti-hypertensive medications. Participants were defined as having dyslipidemia if they had a fasting serum total cholesterol of 240 mg/dL or more or were registered with the ICD-10 code E78 and had been prescribed lipid-lowering agents.

Study endpoints

The primary endpoint was newly diagnosed UC during the follow-up period. In 2006, the NHIS established a rare intractable disease (RID) registration program to reimburse 90% of the medical costs of patients with RIDs such as UC. To enroll in this program, patients with RIDs had to meet the diagnostic criteria for RIDs provided by the NHIS and be approved by qualified physicians [15]. When patients with UC are registered in the RID program, they are assigned a special code (V code; V131). We identified the incident patients with UC using both ICD-10 (K51) and V codes, as in a previous study [16]. Briefly, we retrospectively reviewed the medical records of all patients with UC at Seoul National University Hospital, a tertiary referral hospital in South Korea, to evaluate the accuracy of the above ICD-10 and V codes for UC diagnosis. The diagnostic sensitivity for the identification of UC patients was 96.4%.

Statistical analysis

Data are expressed as mean ± standard deviations for continuous variables and as proportions for categorical variables. Student's *t* test and analysis of variance were used to compare differences between continuous variables, and the chi-square test was used to compare differences between categorical variables. The incidence rates of UC were calculated and expressed as the number of events per 1000 person-years. The cumulative incidences of UC were compared between groups using the Kaplan–Meier method and the log-rank test. Cox proportional hazards models were used to analyze the adjusted risk of UC development based on smoking status and daily amount or duration of smoking, and the results are described as hazard ratios (HRs) with 95% confidence intervals (CIs). A p value less than 0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics of the study population

Among the 23,183,570 individuals analyzed, 14,355,062 (61.9%) were nonsmokers, 3,136,002 (13.5%) were former smokers, and 5,692,506 (24.6%) were current smokers. Former smokers and nonsmokers were significantly older than current smokers ($p < 0.001$). Male sex and heavy drinking were significantly associated with former or current smoking (both $p < 0.001$). Interestingly, study participants who exercised regularly were significantly less likely to be nonsmokers than former or current smokers ($p < 0.001$). The former smoker group had a significantly higher proportion of obese individuals compared with nonsmokers or current smokers ($p < 0.001$). Compared with nonsmokers and current smokers, former smokers also had significantly higher blood pressure, fasting blood glucose, and serum total cholesterol levels, as well as a higher prevalence of DM, hypertension, and dyslipidemia (all $p < 0.001$) (Table 1).

Incidence and risk of UC according to smoking status

After a median follow-up of 5.4 years, UC occurred in 5097 nonsmokers (0.06%), 2464 former smokers (0.08%), and 2321 current smokers (0.04%) (Table 2). The incidence rates of UC were 0.07, 0.15, and 0.08 per 1000 person-years in the nonsmoker, former, and current smoker groups, respectively. The cumulative incidence of UC in the former smokers had increased at a constant rate following the baseline, compared to the nonsmokers and current smokers (Supplementary Fig. 1a). After adjustment for age and sex, the risk of UC development was significantly higher in former smokers [adjusted HR (aHR) 1.74; 95% CI 1.64–1.85] and lower in current smokers (aHR 0.88; 95% CI 0.83–0.93) compared with nonsmokers (model 1 in Table 2). The risk of UC development after additional adjustment for income level, alcohol consumption, exercise, and BMI was also significantly higher in former smokers (aHR 1.83; 95% CI 1.73–1.95) but lower in current smokers (aHR 0.92; 95% CI 0.87–0.98) compared with nonsmokers (model 2 in Table 2). There was no

Table 1 Baseline characteristics of the study population

No. (%)	Nonsmokers n = 14,355,062	Former smokers n = 3,136,002	Current smokers n = 5,692,506	p value
Age, years[a]	48.9 ± 14.8	50.0 ± 13.4	43.4 ± 12.9	< 0.001
< 30	1,779,702 (12.4)	198,412 (6.3)	882,597 (15.5)	< 0.001
30–49	5,644,150 (39.3)	1,331,741 (42.5)	3,038,968 (53.4)	
≥ 50	6,931,210 (48.3)	1,605,849 (51.2)	1,770,941 (31.1)	
Male	3,615,395 (25.2)	2,904,324 (92.6)	5,228,024 (91.8)	< 0.001
Urban residence	7,751,729 (54.0)	1,648,527 (52.6)	3,143,446 (55.3)	< 0.001
Heavy drinker[b]	271,062 (1.9)	364,567 (11.6)	896,940 (15.8)	< 0.001
Regular exercise[c]	6,569,555 (45.8)	1,944,347 (62.0)	2,987,055 (52.5)	< 0.001
BMI, kg/m^{2}[a]	23.5 ± 3.3	24.4 ± 3.0	23.9 ± 3.3	< 0.001
< 18.5	677,437 (4.7)	61,008 (2.0)	197,420 (3.5)	< 0.001
18.5–22.9	6,131,916 (42.7)	956,065 (30.5)	2,125,395 (37.3)	
23.0–24.9	3,335,308 (23.2)	874,847 (27.9)	1,398,641 (24.6)	
25.0–29.9	3,700,320 (25.8)	1,131,990 (36.1)	1,732,770 (30.4)	
≥ 30	510,081 (3.6)	112,092 (3.6)	238,280 (4.2)	
Height, cm[a]	159.7 ± 8.4	168.7 ± 6.8	169.7 ± 7.2	< 0.001
Weight, kg[a]	60.0 ± 10.5	69.5 ± 10.5	69.1 ± 11.6	< 0.001
Systolic blood pressure, mmHg[a]	121.2 ± 15.6	125.2 ± 14.6	123.4 ± 14.2	< 0.001
Diastolic blood pressure, mmHg[a]	75.1 ± 10.1	78.1 ± 9.9	77.3 ± 9.9	< 0.001
Fasting glucose, mg/dL[a]	96.4 ± 21.9	101.0 ± 25.1	98.6 ± 25.8	< 0.001
Total cholesterol, mg/dL[a]	194.7 ± 37.0	195.5 ± 36.5	194.3 ± 36.8	< 0.001
Comorbidity				
Diabetes mellitus	1,224,257 (8.5)	389,343 (12.4)	535,852 (9.4)	< 0.001
Hypertension	3,761,287 (26.2)	1,050,574 (33.5)	1,291,264 (22.7)	< 0.001
Dyslipidemia	2,840,115 (19.8)	682,676 (21.8)	947,158 (16.6)	< 0.001

BMI body mass index, *No.* number

[a]Mean ± standard deviation

[b]Defined as a person who drinks more than 30 g of alcohol a day on average

[c]Defined as high-intensity exercise on more than 3 days a week for at least 20 min at a time or moderate-intensity exercise on more than 5 days a week for at least 30 min at a time

Table 2 Incidence and risk of ulcerative colitis according to smoking status

Smoking status	Total no. (n)	UC cases (n)	Person-years	UC incidence (per 1000 person-years)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Nonsmokers	14,355,062	5097	76,941,976	0.07	1 (reference)	1 (reference)
Former smokers	3,136,002	2464	16,942,813	0.15	1.74 (1.64–1.85)	1.83 (1.73–1.95)
Current smokers	5,692,506	2321	30,365,014	0.08	0.88 (0.83–0.93)	0.92 (0.87–0.98)

CI confidence interval, *HR* hazard ratio, *No.* number, *UC* ulcerative colitis

[a]Model 1: adjusted for age and sex

[b]Model 2: adjusted for model 1 + income level, alcohol consumption status, exercise level, and body mass index

statistically significant difference in baseline characteristics between individuals who experienced UC within and after 1 year from baseline among the former smokers, except diastolic blood pressure (Supplementary Table 1).

Risk of UC according to the amount of cigarettes smoked

We evaluated the risk of UC development according to the daily amount of cigarettes smoked in former and current

Table 3 Incidence and risk of ulcerative colitis according to daily smoking amount

Smoking status	No. of cigarettes smoked per day	Total no. (*n*)	UC cases (*n*)	Person-years	UC incidence (per 1000 person-years)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Nonsmokers	–	14,355,062	5097	76,941,976	0.07	1 (reference)	1 (reference)
Former smokers	< 10	565,358	377	3,052,252	0.12	1.53 (1.37–1.70)	1.57 (1.41–1.74)
	10–19	1,162,900	906	6,318,576	0.14	1.68 (1.56–1.82)	1.76 (1.63–1.90)
	≥ 20	1,407,744	1181	7,571,986	0.17	1.86 (1.73–2.00)	2.00 (1.85–2.15)
Current smokers	< 10	762,404	396	4,016,246	0.10	1.2 (1.08–1.33)	1.23 (1.11–1.37)
	10–19	2,380,565	1002	12,712,599	0.08	0.89 (0.83–0.96)	0.92 (0.85–1.00)
	≥ 20	2,549,537	923	13,636,169	0.07	0.77 (0.72–0.84)	0.82 (0.76–0.89)

CI confidence interval, *HR* hazard ratio, *No.* number, *UC* ulcerative colitis

[a]Model 1: adjusted for age and sex

[b]Model 2: adjusted for model 1 + income level, alcohol consumption status, exercise level, and body mass index

Table 4 Incidence and risk of ulcerative colitis according to smoking duration

Smoking status	Duration of smoking (years)	Total no. (*n*)	UC cases (*n*)	Person-years	UC incidence (per 1000 person-years)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Nonsmokers	–	14,355,062	5097	76,941,976	0.07	1 (reference)	1 (reference)
Former smokers	< 10	779,566	471	4,229,051	0.11	1.31 (1.18–1.44)	1.36 (1.23–1.50)
	10–19	1,806,290	1540	9,812,700	0.16	1.89 (1.77–2.02)	2.02 (1.89–2.16)
	≥ 20	550,146	453	2,901,061	0.16	2.12 (1.91–2.36)	2.17 (1.95–2.41)
Current smokers	< 10	949,178	343	5,008,058	0.07	0.75 (0.66–0.84)	0.78 (0.69–0.87)
	10–19	3,437,780	1422	18,504,606	0.08	0.86 (0.80–0.92)	0.92 (0.86–0.98)
	≥ 20	1,292,555	551	6,775,954	0.08	1.07 (0.97–1.18)	1.08 (0.98–1.19)

CI confidence interval, *HR* hazard ratio, *No.* number, *UC* ulcerative colitis

[a]Model 1: adjusted for age and sex

[b]Model 2: adjusted for model 1 + income level, alcohol consumption status, exercise level, and body mass index

smokers (Table 3). Compared with nonsmokers, the risk of UC development based on the average cigarette consumption per day, which was adjusted by age, sex, income, alcohol, exercise, and BMI, showed a dose–response relationship in former smokers (aHR, 1.57 in individuals who smoked less than 0.5 packs per day; aHR, 2.00 in individuals who smoked 1 or more pack per day) (model 2 in Table 3). In addition, current smokers who smoked less than 0.5 packs per day had a significantly higher risk of UC development than nonsmokers (aHR 1.23; 95% CI 1.11–1.37). However, current smokers who smoked 0.5 or more packs per day showed a tendency for a decreased risk of UC development according to the number of cigarettes smoked per day compared with nonsmokers (model 2 in Table 3).

There was also a significant dose–response relationship between the risk of UC development and the duration of smoking in former smokers (Table 4). Compared with nonsmokers, the aHRs of UC development among former smokers were 1.36, 2.02, and 2.17 in individuals who smoked cigarettes for less than 10, between 10 and 19, and 20 years or more, respectively (Model 2 in Table 4). Current smokers also showed a dose–response relationship between the duration of smoking and the adjusted risk of UC (aHRs, 0.78, 0.92, and 1.08 in the subgroups who smoked for less than 10, between 10 and 19, and 20 years, respectively; model 2 in Table 4). Based on the effect of the cumulative lifetime smoking exposure on UC development, former smokers showed a dose–response trend in the incidence of UC, except those who had smoked over 40 pack-years. In contrast, there was no significant difference in the risk of UC development among current smokers according to the cumulative smoking exposure (Fig. 1).

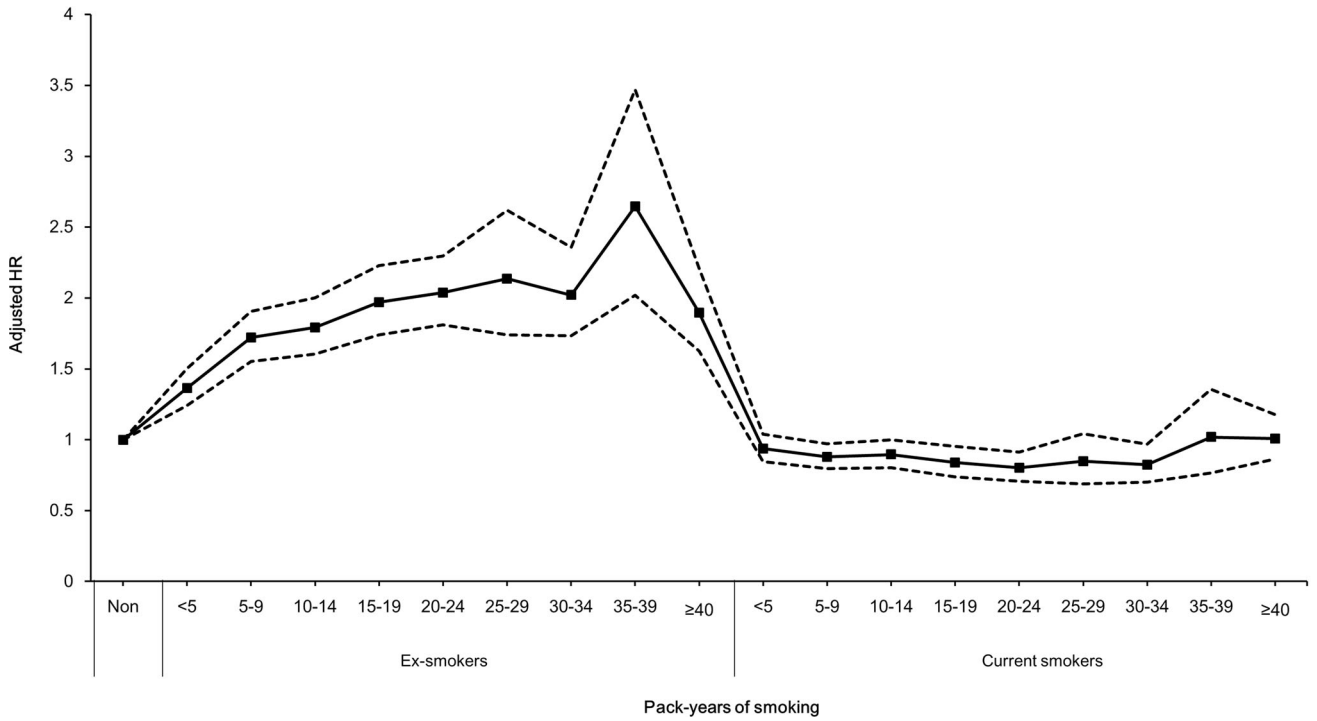

Fig. 1 Risk of ulcerative colitis development according to the cumulative amount of cigarettes smoked. Hazard ratios were adjusted for age and sex. Solid line indicates adjusted hazard ratios and dashed lines indicate 95% confidence interval, respectively

Effect of smoking cessation on the risk of UC

Of the 5,692,506 current smokers, 2,971,269 (52.2%) underwent a health check-up within 2 years after baseline (Table 5). Of them, 407,036 (13.7%) quit smoking before the follow-up check-up. Among current smokers at baseline, the incidence rates of UC were 0.18 in individuals who quit smoking and 0.08 in those who continued to smoke. Among current smokers at baseline, the risk of UC development was significantly higher in individuals who quit smoking than in those who continued to smoke (aHR 2.42; 95% CI 2.10–2.80) (model 2 in Table 5). The cumulative incidence of UC in individuals who quit smoking had increased at a constant rate since immediately after the follow-up health check-up, compared to those who continued to smoke (Supplementary Fig. 1b).

Subgroup analysis

Among former smokers, the risk of UC development was less pronounced in individuals younger than 30 years (aHR 1.43) than in those aged 30 years or older (aHR, 1.94 in those aged 30–49 years; aHR, 1.80 in those aged 50 years or more; interaction p value < 0.001). The preventive effect of current smoking on the development of UC decreased with age (aHR, 0.71 in individuals younger than 30 years; aHR, 0.91 in those aged 30–49 years; aHR, 1.05 in those aged 50 years or more; interaction P value < 0.001). In former smokers, the risk of UC development was not different between men and women (aHR 1.80 vs. 1.73). Among current smokers, however, the preventive effect of cigarette smoking on the development of UC was observed only in male individuals (aHR 0.90; 95% CI 0.84–0.96) (Fig. 2).

Table 5 Incidence and risk of ulcerative colitis according to changes in smoking status among current smokers

Current smoker's smoking status within 2 years	Total no. (n)	UC cases (n)	Person-years	UC incidence (per 1000 person-years)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
Quit smoking	407,036	265	1,452,735	0.18	2.37 (2.05–2.73)	2.42 (2.10–2.80)
Continued smoking	2,564,233	690	9,016,094	0.08	1 (reference)	1 (reference)

CI confidence interval, *HR* hazard ratio, *No.* number, *UC* ulcerative colitis

[a]Model 1: adjusted for age and sex

[b]Model 2: adjusted for model 1 + income level, alcohol consumption status, exercise level, and body mass index

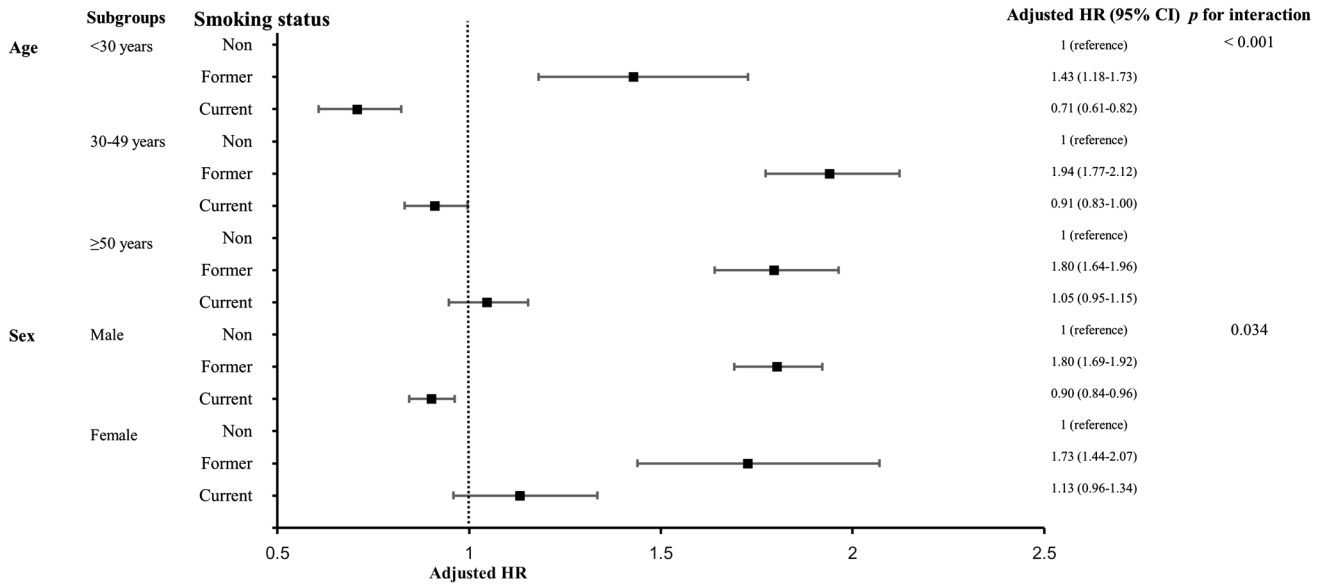

Fig. 2 Subgroup analysis regarding the risk of ulcerative colitis in terms of age and sex. Hazard ratios were adjusted for age, sex, alcohol consumption status, exercise level, and body mass index. *CI* confidence interval, *HR* hazard ratio

Discussion

This is the largest population-based epidemiological study to evaluate a possible dose–response relationship between smoking behavior and the risk of UC. This nationwide population-based cohort study of over 23,000,000 individuals from the general population found an UC incidence of 0.15 per 1000 person-years among former smokers, giving them a 1.8-fold risk of UC development versus nonsmokers. These findings are consistent with most previous studies reporting that the risk of UC development is significantly higher in former smokers than in nonsmokers [6, 7, 9, 17–23]. We also demonstrated that former smokers had 2.4 times the risk of UC occurrence compared with those who continued to smokes among current smokers at baseline. The cumulative incidence of UC in those who quit smoking has increased at a constant rate since immediately after the follow-up health check-up. In addition, there was a dose–response relationship between the risk of UC and previous exposure to cigarette smoking among former smokers, regardless of age and sex. In a recent prospective study of approximately 230,000 women from the United States, the risk of UC development had increased within 2–5 years and persisted for 20 years after smoking cessation [7]. Taken together, former smokers are at a higher risk of UC that begins early after smoking cessation and may last for several decades. Given the increased risk of the occurrence of UC in proportion to exposure to cigarette smoking, current smokers should quit smoking as soon as possible to reduce the subsequent risk of UC.

A meta-analysis published in 2006 reported that current smokers had an approximately 40% reduced risk of UC development compared with nonsmokers [9], although several studies included in the meta-analysis showed that current smoking did not significantly increase the risk of UC compared with never-smoking [19, 24, 25]. We found that current smokers had only an approximately 10% lower risk of UC development than nonsmokers. The cumulative lifetime amount of cigarette smoking did not affect the risk of UC among the current smokers because the daily amount of smoking was inversely associated with the risk of UC, but the duration of smoking was highly correlated with the risk of UC development. In addition, the preventive effect of cigarette smoking on the development of UC was only observed in males. These findings are consistent with the results of large-scale prospective cohort studies—the Nurses' Health Study (NHS I) and Nurses' Health Study II (NHS II)—showing that the risk of UC development was not significantly lower in current smokers compared with never-smokers and that cumulative exposure to cigarette smoking did not affect the incidence of UC among current female smokers [7]. A retrospective study demonstrated that current smoking delayed the mean age of UC onset by 9 years in men but had no effect in women [26]. Thus, the impact of cigarette smoking on the development of colitis may be critically modulated by sex. In addition, in this study, the ability of cigarette smoking to prevent the occurrence of UC tended to be lost with age. Considering the sex difference and tendency for a decreased effect of age on the preventive effects of

smoking on colitis among current smokers, cigarette smoking is hardly conducive to the prevention of UC.

It is still unclear why cigarette smoking seems to interfere with the development of UC and why smoking cessation induces the initiation of chronic relapsing intestinal inflammation. It has been hypothesized that nicotine, a major component of tobacco, might play a role in the preventive effects of cigarettes on the pathogenesis of UC [27]. As an anti-inflammatory alkaloid, nicotine acts on the α7 nicotinic acetylcholine receptor of immune cells to activate the cholinergic anti-inflammatory pathway [27, 28] and plays a role in decreasing intestinal permeability in UC, which is characterized by increased basal permeability through an impaired gut epithelial barrier [29].

However, nicotine may be just one of the complex pharmacodynamic effects of cigarette smoke. Indeed, cigarette smoke is a complex mixture of over 5000 chemicals, including components with immune-related or proinflammatory effects such as aniline, nickel, and copper [30]. These compounds modulate the composition of the gut microbiota, which possibly influences the pathogenesis of UC [31]. Decrease in gut microbial diversity and changes in gut microbial composition such as decrease in *Bacteroidetes* and *Firmicutes,* and increase in *Actinobacteria* and *Proteobacteria* are closely linked to UC [32–34]. Human studies have found that cigarette smoke depletes *Firmicutes* and *Actinobacteria* in the gut and increases *Clostridium,Bacteroidetes*, and *Proteobacteria* [31]. Smoking cessation increases microbial diversity as well as induces complex changes in the gut microbial composition such as increase in *Firmicutes* and *Actinobacteria*, and decrease in *Bacteroidetes andProteobacteria* [31, 35]. The dynamic impacts of changes in smoking behavior on the human gut microbiome might partially explain the role of environmental factors in the pathogenesis of UC, particularly because of the potential involvement of other confounding factors related to smoking behavior such as dietary changes, alcohol drinking, and increased body weight. A recent study demonstrated increased levels of *Firmicutes* and reduced levels of *Bacteroidetes* observed in obese men, which is similar to the gut microbial composition of former smokers [36]. Given the complex interactions among cigarette smoke, other environmental factors, the gut microbiota, and host susceptibility for colitis, further studies are needed to evaluate the direct effects of cigarette smoking on the pathogenesis of UC.

In terms of the sex difference in the effects of smoking on the development of UC, dysregulation of sex hormones related to cigarette smoking is a plausible explanation. Hsieh et al. [37] reported that serum testosterone levels were significantly lower in male current smokers than in healthy nonsmokers. A recent epidemiological study showed that androgen deprivation therapy was associated with a reduced risk of UC development in patients with prostate cancer [38]. In contrast, a nested case–control study from the NHS I and II demonstrated that serum testosterone levels were not related to the risk of UC in women [39]. Estrogen modifies colonic barrier function, enhances the humoral immune system, and contributes to thrombosis, which may lead to ischemic intestinal injury [40]. Smoking also reduces the serum concentration of estrogen in both men and women [41], but carbon monoxide, a byproduct of cigarette smoking, might be linked to the initiation of Th2-mediated mucosal inflammation in UC [42], together with a rebound increase in serum estrogen levels after smoking cessation in both men and women.

In this study, the risk of UC development in former smokers increased with a dose–response relationship up to 40 pack-years of cumulative smoking exposure, but decreased over 40 pack-years, which was comparable with those who had smoked from 15 to 35 pack-years. Most of the former smokers who had smoked over 40 pack-years were elderly. Therefore, aging might be a powerful confounder affecting the risk of UC developed by the cumulative smoking exposure in the subgroup, although the risk of UC was calculated after adjustment for age. The risk of developing UC in the former smokers may be proportional to the cumulative smoking exposure considering younger age at onset of UC.

The present study has some limitations due to its retrospective nature. First, the time-to-effect of smoking cessation on the risk of UC development among smokers could not be evaluated because we lacked data on the exact time of smoking cessation by the former smokers. However, former smokers may be exposed to the increased risk of UC within 2 years of smoking cessation, based on the results of the incidence of UC according to changes in smoking status among the current smokers. Second, because information regarding the disease activity and extent of the incident UC was not also available from the NHIS database, the effect of smoking behavior on the severity of colonic inflammation could also not be evaluated. Third, the effect of female sex on development of UC might be underestimated due to a small proportion of current smokers among women.

In conclusion, compared with nonsmokers, former smokers have an increased risk of UC development that may be proportional to the cumulative smoking exposure, especially up to 40 pack-years. In terms of sex, only male current smokers show higher risk of UC compared with nonsmokers. This risk does not show a dose–response relationship.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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