Smoking status before and after colorectal cancer diagnosis and mortality in Korean men: A population-based cohort study

남성 대장암 환자에서 진단 전과 후의
흡연 상태에 따른 사망률:
인구 기반 코호트 연구

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서울대학교 대학원

협동과정 종양생물학전공

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지도교수 신애선

이 논문을 장도은 석사 학위논문으로 제출함

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협동과정 종양생물학전공

장 도 은

장도은의 석사 학위논문을 인준함

2020년 7월

위 원 장 _____ (인)

부 위 원 장 _____ (인)

위   원 _____ (인)

Abstract

Smoking status before and after colorectal cancer diagnosis and mortality in Korean men: A population-based cohort study

Doeun Jang

Interdisciplinary Program in Cancer Biology

The Graduate School

Seoul National University

College of Medicine

Smoking is a well-known risk factor for colorectal cancer. However, the effects of smoking before and after cancer diagnosis on mortality have not been addressed thoroughly. Thus, our aim was to evaluate the associations between the prediagnosis and postdiagnosis smoking status and mortality among colorectal cancer patients who were diagnosed between 2003 and 2016.

The National Health Information Database (NHID), which covers approximately 97% of the Korean population, is used in this study. The data are composed of colorectal cancer patients who were newly diagnosed between 2002 and 2016 and were followed up from the date of diagnosis until death or July 13, 2017. A retrospective cohort

consisted of 37,079 male colorectal cancer patients. Smoking status was extracted from information collected within 2 years of a colorectal cancer diagnosis for prediagnosis and at least 1 year later for postdiagnosis. Prediagnosis or postdiagnosis smoking status was defined as nonsmoker or smoker. Prediagnosis and postdiagnosis smoking statuses were categorized into four groups (nonsmoker/nonsmoker, nonsmoker/smoker, smoker/nonsmoker, and smoker/smoker). The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazard model with "smoker" as a reference. Stratification analysis was conducted according to the subsite and treatment.

During a median of 6.3 years of follow−ups, 3,980 patients died. The median duration from the prediagnosis smoking status assessment to colorectal cancer diagnosis was 0.37 years and from cancer diagnosis to postdiagnosis smoking status assessment was 2.53 years. Significantly elevated mortality was observed in prediagnosis smokers regardless of the postdiagnosis smoking status (smoker/nonsmoker (HR, 1.25; 95% CI, 1.15 to 1.36) and in the smoker/smoker group (HR, 1.20; 95% CI, 1.08 to 1.33)). However, there was no association between prediagnosis and postdiagnosis smoking status and colorectal cancer−specific mortality. Among patients treated with surgical operations only, those who quit smoking after diagnosis showed lower mortality compared to

continual smokers (HR, 0.78; 95% CI, 0.66 to 0.94, smoker/smoker as reference).

Smoking status before colorectal cancer diagnosis has a strong impact on the prognosis of colorectal cancer patients, and postdiagnosis smoking status is also associated with elevated mortality among these patients. Smoking cessation may improve survival, especially among early−stage colorectal cancer patients.

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Introduction

Colorectal cancer epidemiology

According to GLOBOCAN 2018, colorectal cancer is the 3rd-most common cancer among both sexes and men, and 2nd among women (1). In the United States, the colorectal cancer incidence has decreased since 1998, and the incidence trends are similar among the sexes (2).

Colorectal cancer is the 2nd-leading cause of cancer deaths among both sexes, is 4th among men, and is 3rd among women globally (1). The mortality trend in colorectal cancer has declined since the mid-1940s in the United States (2).

In Korea, colorectal cancer was the 2nd-most commonly diagnosed cancer in general (with 28,111 new colorectal cancer cases) and the 3rd-most commonly diagnosed cancer among men (16,653 new colorectal cancer cases) and women (11,458 newly diagnosed colorectal cancer cases) in 2017 (3). The age-standardized colorectal cancer incidence has decreased since 2010 in Korea (3).

Colorectal cancer was the 3rd-leading cause of cancer deaths in general (8,691 colorectal cancer deaths), 4th among men (4,981

colorectal cancer deaths), and 2nd among women (3,710 colorectal cancer deaths) in 2017 (3). The age−standardized colorectal cancer mortality has decreased since 2005 in Korea (3).

Risk factors for colorectal cancer

There are some nonmodifiable risk factors related to colorectal cancer (4, 5). Age is closely related to colorectal cancer incidence. The incidence rates of colorectal cancer exponentially increase with aging, greatly rising after age 50 (2, 4). Men tend to have higher colorectal cancer incidence rates in most populations (1, 5, 6). Having a family history of colorectal cancer or adenomatous polyps is one of the risk factors (4, 7). For individuals with a family history, the relative risk of colorectal cancer incidence is increased, and the risk is highly increased if there are more than two first−degree relatives with this history (7). The inherited genetic factor is the established risk factor for colorectal cancer (4). Familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) increases the risk or colorectal cancer incidence (4, 8)

Inflammatory bowel disease, including ulcerative colitis and Crohn

disease, is known to be related to the colorectal cancer incidence (4, 9-11). Chronic diseases, including diabetes mellitus and hypertension, have been associated with the development of colorectal cancer (5).

Dietary factors are strongly associated with the risk of colorectal cancer (4, 12). High consumption of processed meat and alcoholic drinks is related to an increased risk of colorectal cancer; in addition, red meat consumption has a probable positive association with colorectal cancer development (4, 5, 12, 13). There is strong evidence that obesity is related to a higher risk of colorectal cancer (4, 5, 12, 14). Alcohol consumption and cigarette smoking are established risk factors for colorectal cancer (4, 5, 12, 13). Both smoking and regular alcohol consumption play a key role in colorectal cancer development (4, 5, 12, 13).

Colorectal cancer and cigarette smoking

Smoking is a well-established risk factor for colorectal cancer (15-17), and smoking was responsible for 27.6% of the cancer burden and was the leading cause of smoking-attributable disability-adjusted life-years (DALYs) in 2015 (18). Smoking leads to

increased mortality as well as to an increased risk of colorectal cancer incidence (15, 19). Smoking leads to poor prognosis when current smokers are compared with nonsmokers (20). People who are continual smokers after cancer diagnosis are at higher risk for future cancers and death (20). In the 2014 U.S. Surgeon General's Report, tobacco smoking was said to lead to premature death, and these results apply to cancer patients as well as survivors (20).

As cancer therapy has improved (21) and the 5-year survival rates for patients with colorectal cancer increased 18.8 percentage points from 1993 to 1995 and 2013 to 2017 (3), it has become important to estimate the association between lifestyle behavior and mortality among patients diagnosed colorectal cancer. After colorectal cancer diagnosis, patients may be recommended to make lifestyle changes to improve their prognosis. Previous studies reported that 24-44% of patients who smoked at cancer diagnosis succeeded in quitting smoking (22-24). However, it is unclear whether changes in smoking behavior affect mortality.

There have been some studies that assessed the association between smoking status before cancer diagnosis and mortality (15, 19, 25-32) and after cancer diagnosis and mortality (31, 33, 34), but

few studies have investigated changes in smoking status from prediagnosis to postdiagnosis (31, 35, 36). However, the time point of tobacco cessation is not clear among these studies.

According to a previous study, there are slight differences in the 5-year relative survival rate between colon and rectal cancers, and in treatment patterns by stages (21). Smoking is more strongly associated with risk of rectal cancer compared to colon cancer (27).

Table 1. Previous studies investigating the association between smoking status and mortality among cancer patients

Author (Year)	Study design	Number of subjects	Time of measurement	Outcome	Exposure	Results
Botteri E (2008) (15)	Meta-analysis	17 studies	Before colorectal cancer diagnosis	Colorectal cancer mortality	Ever vs Never Current vs Never Former vs Never	RR: 1.25 (1.14−1.37) RR: 1.28 (1.15−1.42) RR: 1.23 (1.14−1.32)
Liang PS (2009) (19)	Meta-analysis	36 studies	Before colorectal cancer diagnosis	Colorectal cancer mortality	Current vs Never Former vs Never	RR: 1.27 (1.05−1.53) RR: 1.20 (0.98−1.47)
Ordonez−Mena JM (2018) (25)	Cohort	12,414 cases	Before colorectal cancer diagnosis	All−cause mortality Colorectal cancer mortality	Current vs Never Former vs Never Current vs Never Former vs Never	HR: 1.29 (1.04−1.60) HR: 1.12 (1.04−1.20) HR: 1.15 (0.95−1.41) HR: 1.00 (0.91−1.09)
Chao A (2000) (26)	Cohort	781,351 cases	At colorectal cancer diagnosis	Colorectal cancer mortality	Current vs Never Former vs Never	RR: 1.22 (1.09−1.37) RR: 1.41 (1.26−1.58)
Tsoi KK (2009) (27)	Meta-analysis	2 studies	Before colorectal cancer diagnosis	Colorectal cancer mortality	Current vs Never	RR: 1.58 (1.09−2.29) (male) RR: 1.28 (1.10−1.48) (female)

Table 1. Continued

Author (Year)	Study design	Number of subjects	Time of measurement	Outcome	Exposure	Results
Jayasekara H (2018) (28)	Cohort	698 cases	Before colorectal cancer diagnosis	Colorectal cancer mortality	Ever vs Never	HR: 1.34 (0.96−1.86)
Walter V (2014) (29)	Meta−analysis	6 studies	Before or after cancer diagnosis	All−cause mortality	Current vs Never	HR: 1.26 (1.15−1.37)
Phipps AI (2011) (30)	Cohort	2,264 cases	Before colorectal cancer diagnosis	All−cause mortality	Current vs Never	HR: 1.51 (1.24−1.83)
					Former vs Never	HR: 1.26 (1.07−1.49)
					Ever vs Never	HR: 1.33 (1.14−1.55)
				Colorectal cancer mortality	Current vs Never	HR: 1.30 (1.09−1.74)
					Former vs Never	HR: 1.14 (0.93−1.38)
					Ever vs Never	HR: 1.21 (1.01−1.45)

Table 1. Continued

Author (Year)	Study design	Number of subjects	Time of measurement	Outcome	Exposure	Results
Yang B (2015) (31)	Cohort	2,548 cases	Before colorectal cancer diagnosis	All-cause mortality	Current vs Never Former vs Never	RR: 2.12 (1.65−2.74) RR: 1.18 (1.02−1.36)
				Colorectal cancer mortality	Current vs Never Former vs Never	RR: 2.14 (1.50−3.07) RR: 0.89 (0.72−1.10)
		2,256 cases	After colorectal cancer diagnosis	All-cause mortality	Current vs Never Former vs Never	RR: 2.22 (1.58−3.13) RR: 1.21 (1.03−1.42)
				Colorectal cancer mortality	Current vs Never Former vs Never	RR: 1.92 (1.15−3.21) RR: 0.91 (0.71−1.18)
Warren GW (2013) (32)	Cohort	5,185 cases	At cancer diagnosis	All-cause mortality	Current vs Recent quitted Current vs Former Current vs Never	HR: 1.17 (1.03−1.32) HR: 1.29 (1.17−1.42) HR: 1.38 (1.23−1.54)
Wang Y (2019) (33)	Cohort	35,093 cases	After cancer diagnosis	Colon cancer mortality	Current vs Never Former vs Never	HR: 1.41 (1.09−1.82) HR: 1.19 (1.02−1.39)
Tamakoshi A (2017) (34)	Cohort	5,864 cases	After colorectal cancer diagnosis	All-cause mortality	Current vs Never Former vs Never	HR: 1.38 (1.06−1.81) HR: 1.27 (1.02−1.59)

Table 1. Continued

Author (Year)	Study design	Number of subjects	Time of measurement	Outcome	Exposure	Results
Tao L (2013) (35)	Cohort	1,632 cases	At cancer diagnosis	All−cause mortality	Current vs Never	HR: 1.13 (0.91−1.41)
					Former vs Never	HR: 0.97 (0.70−1.12)
			After cancer diagnosis	All−cause mortality	Quitted vs Intermittent	HR: 0.89 (0.70−1.12)
					Quitted vs Continued	HR: 1.76 (1.37−2.27)
Walter V (2015) (36)	Cohort	3,130 cases	After colorectal cancer diagnosis	Colorectal cancer mortality	Continued vs Never	HR: 1.16 (0.91−1.48)
				All−cause mortality	Continued vs Never	HR: 1.17 (0.89−1.54)

Purpose of this study

We conducted this study to investigate how the smoking status before and after colorectal cancer diagnosis is associated with mortality among Korean men with colorectal cancer.

Methods

Data source

This study was conducted using the National Health Information Database (NHID) of the National Health Insurance Service, which is a retrospective cohort consisting of full claim data (37). The customized NHID is composed of information that is collected, managed, and maintained by the National Health Insurance Corporation and modified upon request by researchers. The data contain medical resource use information, medical prescriptions, demographic characteristics, and health examinations from 2002 to 2016.

Identification of study subjects

The colorectal cancer cases were defined based on the 10th International Classification of Diseases (ICD-10) diagnostic code corresponding to colorectal cancer (C18-20) and the claim code for its treatment between 2002 and 2016 (Table 2) (38).

Among colorectal cancer patients diagnosed from 2002 to 2016

(N=248,011), we excluded female patients (N=99,626) and individuals for whom the gender was not noted (N=730). Among the male colorectal cancer patients, we selected subjects who were diagnosed with colorectal cancer and who had undergone biannual health examinations (N=118,395). We excluded colorectal cancer patients who did not complete the smoking questionnaire at least once (N=464) and who were diagnosed before age 20 or had no age noted (N=12), did not have information on smoking at least within 2 years and after 1 year of diagnosis (N=80,302), had information missing on body mass index (BMI), physical activity, alcohol use, duration of smoking, and subsite (N=538). Finally, 37,079 participants were included in the final analysis (Figure 1).

Individuals who received any cancer treatment in a customized database from the national health insurance service from 2002 to 2016, N=248,011

1) Female colorectal cancer patients, N=99,626

2) Colorectal cancer patients with no gender indicated, N=730

Male colorectal cancer patients, N=147,655

Participants who did not have a health examination, N=29,260

Participants who had health examinations, N=118,395

Participants who did not complete the smoking questionnaire at least once, N=464

Participants who completed the smoking questionnaire at least once, N=117,931

1) Participants who were diagnosed before aged 20 or had no age noted, N=12

3) Participants who did not have information on smoking within 2 years and after 1 year, N=80,302

4) Participants who did not have information on their body mass index, frequency of physical activity, frequency of alcohol consumption, duration of smoking before diagnosis, and anatomical subsite, N=538

Final colorectal cancer patients for analysis, N=37,079

Figure 1. Selection of the study population.

Table 2. List of claim codes for colorectal cancer treatments in the National Health Insurance Service

Treatment	Claim codes
Operation	
Right. or Left. hemicolectomy	QA671, Q2671
Subtotal colectomy	Q1261, Q1262
Total colectomy	QA672, Q2672
Segmental resection	QA673, Q2673
Colectomy with proximal colostomy and distal stump	QA679, Q2679
Transanal rectal tumor resection	Q2891
Transsacral or parasacral rectal tumor resection	Q2890
Abdominal approach rectal tumor resection	Q2892
Transanal endoscopic microsurgery of rectal tumor resection	Q2893
Anterior resection	QA921, Q2921
Low anterior Resection	Q2927, QA922, Q2922
Abdominoperineal resection	QA923, A2923
Abdominal pull−through operation	QA924, A2924
Total coloprotectomy with ileostomy	QA925, A2925
Total coloprotectomy with ileal pouch−anal anastomosis	QA926, A2926

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Table 2. Continued

Treatment	Claim codes
Chemotherapy	
Capecitabine	122701ATB, 122702ATB
5–Fluorouracil	161430BIJ, 161431BIJ, 161432BIJ
Leucovorin	566132BIJ, 566134BIJ, 622630BIJ, 622631BIJ, 622632BIJ, 521001BIJ, 521002BIJ
Irinotecan	177430BIJ, 177431BIJ, 177432BIJ, 177433BIJ, 177434BIJ, 177435BIJ, 177436BIJ, 177437BIJ
Bevacizumab	554330BIJ, 554331BIJ
Cetuximab	556430BIJ
Oxaliplatin	205830BIJ, 205834BIJ, 205803BIJ, 205832BIJ
Radiotherapy	
HD051, HD054, HD052, HD055, HD053, HD056, HD057, HD058, HD059, HD061, HD071, HD072, HD073, HD080, HD081, HD082, HD083, HD084, HD085, HD086, HD087, HD088, HD089	

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Identification of smoking variables

Patient smoking status was extracted from self−reported questionnaires during the health examinations. Health examinations were used within 2 years before colorectal cancer diagnosis and 1 year after colorectal cancer diagnosis (Figure 2). According to a previous study, sixty percent of patients relapsed within 2 months after surgical treatment (39). Thus, the tobacco status 1 year after colorectal cancer diagnosis could reflect the maintenance of smoking cessation.

The prediagnosis smoking status was defined as smoker or nonsmoker. The postdiagnosis smoking status was defined as smoker or nonsmoker. Participants were grouped according to the prediagnosis and postdiagnosis smoking status into four groups (nonsmoker/ nonsmoker, nonsmoker/smoker, smoker/nonsmoker, and smoker/smoker). Data on the duration of smoking were collected during the prediagnosis health examination, and categorized into four groups (<10, 10−19, 20−29, and ≥30 years).
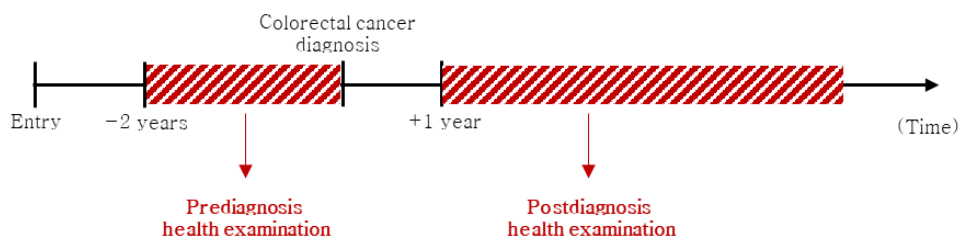
Figure 2. The time of the prediagnosis and postdiagnosis health examinations.

Identification of outcome

The death dates and causes of death data of the subjects were individually linked to each subject using Statistics Korea data. Colorectal cancer-specific deaths were identified using ICD-10 codes (C18-20). The participants were followed until death or July 13, 2017, whichever occurred first. In an analysis regarding the association between prediagnosis smoking status and mortality, the follow-up duration was calculated from the date of diagnosis to death or the end of the follow-up. When we performed analyses about the postdiagnosis smoking status or change of smoking status and mortality, the follow-up duration was calculated from the date of postdiagnosis health examination to death or the end of the follow-up.

Covariates

The covariates were selected from a review of previous studies (40-42), and the associations between candidate variables and smoking status or mortality were assessed. Data on the frequency of alcohol intake and frequency of physical activity

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were collected by self-reported questionnaires during the prediagnosis health examination. Anthropometric indices including height and weight were measured in health care centers during the prediagnosis health examinations. The body mass index (BMI) was calculated as the subject's weight (kg) divided by the square of the subject's height (m^2). The BMI was categorized into 4 groups ($<$18.5; 18.5$-$24.9; 25.0$-$29.9; and $\geq$30) based on the World Health Organization classification. Because we used claim data, we had limited information for assessing the tumor stage of the colorectal cancer patients. Therefore, we categorized the subjects into three groups by the treatment they had received, based on the idea that early$-$stage patients are likely to be treated only with surgery, while advanced$-$stage patients tend to be treated with chemotherapy or radiotherapy without surgery (43). For this study, we used the type of treatment to reflect the cancer stage of the patients (Figure 3). We used the claim data from within 1 year of colorectal cancer diagnosis when calculating the Charlson comorbidity index using Quan's coding algorithms (44).
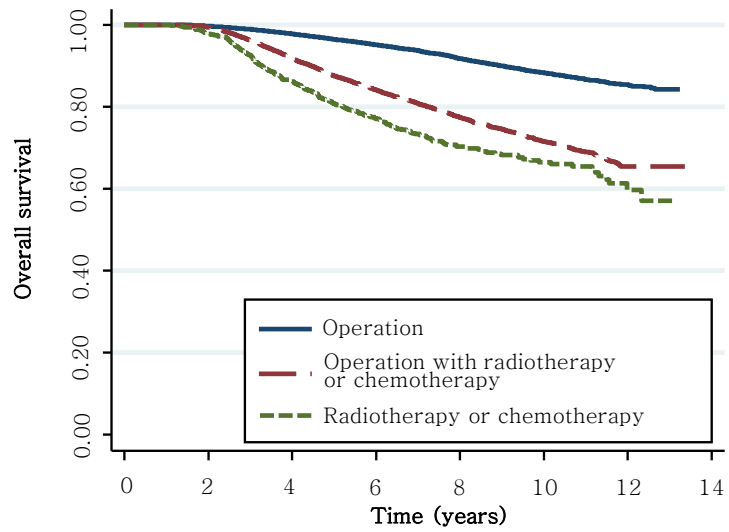
Treatment				Number at risk				
Operation	2511	2492	2058	1399	801	388	86	0
Operation with radiotherapy or chemotherapy	1060	1043	811	533	312	142	21	0
Radiotherapy or chemotherapy	135	130	95	61	32	15	37	0

Figure 3. Survival curve by treatment.

Statistical analysis

The characteristics of the participants were compared by conducting a chi-square test for categorical variables and a t-test or analysis of variance (ANOVA) for numerical variables. We used a Cox proportional hazards regression model to evaluate the association between the smoking status and all-cause and colorectal cancer-specific mortality among colorectal cancer patients by calculating the hazard ratios (HRs) and 95% confidence intervals (95% CIs).

The age at diagnosis with colorectal cancer, BMI, frequency of physical activity, frequency of alcohol intake, treatment, and Charlson comorbidity index were considered potential confounders; thus, they were included in the model for adjustment.

To confirm the differences by treatment, the analyses were stratified by treatment. Because a previous study reported that there was a different association between smoking and overall mortality by anatomic site (15, 28), we conducted stratified analyses by subsite, that is, colon (C18) versus rectum (C19-20). All the statistical analyses were conducted by using SAS software version 9.4 (SAS

Institute Inc., Cary, NC, USA), and the figures were generated by using STATA/ SE 14 (StataCorp, College Station, TX, USA).

Sensitivity analyses

The individuals included in the sensitivity analyses had health examination within two years of their colorectal cancer diagnosis.

Additional several sensitivity analyses were performed. First, we restricted the subjects who had health examinations within 1 year before their colorectal cancer diagnosis to reflect the smoking status shortly before their diagnosis (Figure 4A). Second, we used the health examination from between one and three years from the colorectal cancer diagnosis to collect the postdiagnosis smoking status (Figure 4B). Third, to investigate the association between the smoking status and long-term survival, we conducted a sensitivity analysis with patients who survived more than five years and had health examinations between one and three years from colorectal cancer diagnosis (Figure 4C). Finally, we repeated the analysis using a health examination conducted between three and five years from the colorectal cancer diagnosis among patients who survived for more than five years (Figure 4D).

Among patients in sensitivity analyses, about 5−7% of the subjects had missing values regarding the Charlson comorbidity index and subsite. Thus, we replaced these missing values with the mode values from others who had the same age at diagnosis.
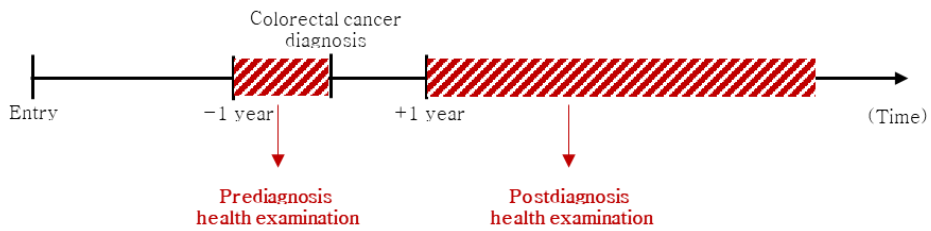
Figure 4A. Prediagnosis smoking status within 1 year before colorectal cancer diagnosis and postdiagnosis smoking status after 1 year.
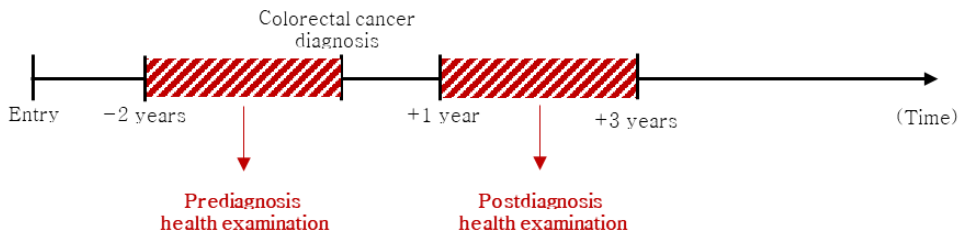
Figure 4B. Prediagnosis smoking status within 2 years before colorectal cancer diagnosis and postdiagnosis smoking status between 1 and 3 years after diagnosis.
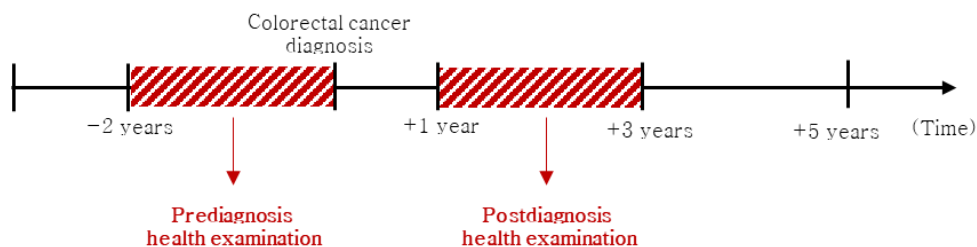
Figure 4C. Prediagnosis smoking status within 2 years before colorectal cancer diagnosis and postdiagnosis smoking status between 1 and 3 years after diagnosis among patients who survived for more than 5 years.
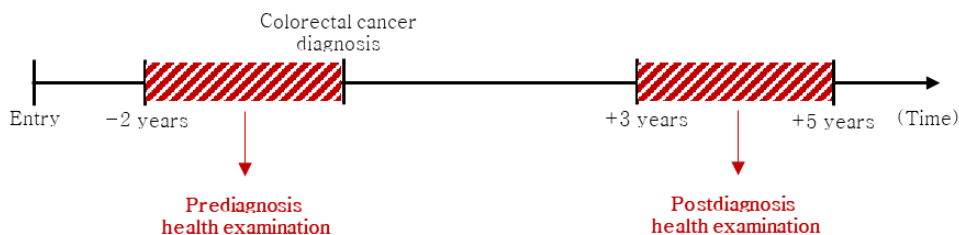
Figure 4D. Prediagnosis smoking status within 2 years before colorectal cancer diagnosis and postdiagnosis smoking status between 3 and 5 years after diagnosis among patients who survived for more than 5 years.

Results

Primary analysis

The patients included in this study were younger and received operations only for treatment. Their follow−up period was longer, and all−cause and colorectal cancer deaths were less frequently observed compared to the excluded subjects. (Table 3).

Compared to the patients who were nonsmokers before their colorectal cancer diagnosis, those who were smokers were younger, more likely to have a low BMI, low frequency of physical activity, drink alcohol frequently, high probability of being treated with radiotherapy or chemotherapy, relatively low Charlson comorbidity index, and the proportion of rectal cancer patients were higher (all p−values ＜0.01) (Table 4).

Similar to the prediagnosis smoker characteristics, the smokers after colorectal cancer diagnosis were younger, tended to have a low BMI, participated in physical activity before colorectal cancer diagnosis, consumed alcohol frequently, and had a relatively low Charlson comorbidity index. The postdiagnosis smokers were likely to be treated

by operation only compared to the nonsmokers (all p-values < 0.01) (Table 5).

The proportions of participants who continued to smoke after diagnosis and who quit after diagnosis among colorectal cancer patients were 10.1% and 16.7%, respectively. Compared to the nonsmoker/nonsmoker, the patients who had ever smoked were younger, tended to be underweight or had a normal BMI, less likely to perform physical activity, had a lower frequency of alcohol intake, were treated by radiotherapy or chemotherapy, had a higher Charlson comorbidity index, and frequently had colon cancer (Table 6).

We conducted univariate regression analyses of the subject characteristics and risk of death. Elevated risk of death were observed among patients who were older, were in an advanced stage as assumed because they underwent cancer treatment, were underweight, consumed alcohol for more than five days, and have more than three comorbidity index factors. However, there was no significant relation between the subsite and risk of death (Table 7).

During the median follow-up at 6.3 years (245,542 person-years), 3,980 deaths occured among the colorectal cancer patients. The median

duration from prediagnosis smoking status assessment to colorectal cancer diagnosis was 0.37 years, and from cancer diagnosis to postdiagnosis smoking status assessment, it was 2.53 years.

Compared to not smoking before colorectal cancer diagnosis, smoking before colorectal cancer diagnosis was associated with significantly increased mortality (HR, 1.23; 95% CI, 1.14 to 1.32). Subjects who had smoked 10−19 years before diagnosis showed the highest mortality among the smokers (1.48 [1.19 to 1.83]).

Significantly elevated mortality was found in the population of patients who smoked after colorectal cancer diagnosis compared to those who were not smokers after diagnosis (1.14 [1.04 to 1.25]).

When the prediagnosis/postdiagnosis smoking status was considered during the analysis, a marginal increase in mortality among participants who started smoking after colorectal cancer diagnosis compared to participants who had never smoked was observed (1.20 [1.00 to 1.45]). Additionally, patients who quit smoking after colorectal cancer diagnosis, namely smokers/nonsmokers in terms of the prediagnosis/postdiagnosis smoking status, showed significantly elevated mortality compared with those who did not quit smoking (1.25 [1.15 to 1.36]). Patients who were exposed to tobacco for 10−29 years before their colorectal cancer diagnosis had higher mortality (10−19

years: 1.48 [1.19 to 1.83]; and 20-29 years: 1.40 [1.20 to 1.63]).

Furthermore, the mortality was also elevated among patients who had

continually smoked before and after their colorectal cancer diagnosis

(1.20 [1.08 to 1.33]). Among the subjects who had smoked before

diagnosis and continued smoking after diagnosis, the patients who

smoked for 10-19 years showed the highest mortality, although the

differences between the groups were marginally significant (1.47 [1.00

to 2.17]) (Table 8).

There was no significant association between the prediagnosis or

postdiagnosis smoking status and the colorectal cancer-specific

mortality. Regarding the change in smoking status, the

smoker/nonsmoker group showed significantly elevated colorectal

cancer-specific mortality (1.17 [1.05 to 1.30]) (Table 9).

In the stratified analysis according to subsite, quitting smoking after

diagnosis was significantly associated with increased mortality among

colon cancer patients (1.27 [1.14 to 1.43]) and rectal cancer patients

(1.26 [1.11 to 1.43]). Continual smoking among colon cancer patients

was significantly associated with elevated mortality (1.23 [1.07-

1.42]), although there was marginally significantly increased mortality

among rectal cancer patients (1.18 [1.00-1.39]). For rectal cancer

patients, starting smoking after their cancer diagnosis was significantly related to increased mortality (1.45 [1.11 to 1.89]) (Table 10).

When we defined the smoker/smoker group as the reference, smoking cessation after diagnosis was associated with elevated mortality among both colon cancer patients (1.03 [0.88 to 1.22]) and rectal cancer patients (1.07 [0.89 to 1.28]), although the association was not statistically significant. Starting smoking after diagnosis was not significantly related to elevated mortality among rectal cancer patients (1.23 [0.91 to 1.66]) (Table 11)

For the stratified analysis according to cancer treatment, both prediagnosis and postdiagnosis smoking had significant relations to elevated mortality among colorectal cancer patients who had operations only (1.34 [1.03 to 1.74] for nonsmoker/smoker; 1.30 [1.13 to 1.49] for smoker/nonsmoker; and 1.66 [1.44 to 1.92] for smoker/smoker). Among colorectal cancer patients who had operations with radiotherapy or chemotherapy, however, smoking cessation after colorectal cancer diagnosis was only significantly associated with elevated mortality (1.25 [1.12 to 1.40]) (Table 12).

When we defined the smoker/smoker group as a reference, both prediagnosis nonsmoking and postdiagnosis nonsmoking was related to

decreased mortality among colorectal cancer patients who underwent surgery only (0.60 [0.52 to 0.70] for nonsmoker/nonsmoker; 0.81 [0.60 to 1.08] for nonsmoker/smoker; and 0.78 [0.66 to 0.94] for smoker/nonsmoker). However, associations between the prediagnosis/postdiagnosis smoking status and mortality among colorectal cancer patients who underwent surgery with radiotherapy or chemotherapy were different from those among colorectal cancer patients who underwent surgery only. In brief, quitting smoking after colorectal cancer diagnosis was significantly associated with increased mortality only among colorectal cancer patients who underwent surgery with radiotherapy or chemotherapy (1.38 [1.14 to 1.66]) (Table 13).

Table 3. Characteristics of colorectal cancer patients by study inclusion in men

	Included in study		Excluded from study		P−value
	(N=37,079)		(N=110,576)		
Age at colorectal cancer diagnosis					<0.001
Mean±SD	62.0	(10.3)	63.7	(11.7)	
Treatment					<0.001
Operation only	25,117	(67.7)	55,845	(50.5)	
Operation with radiotherapy or chemotherapy	10,606	(28.6)	39,855	(36.0)	
Radiotherapy or chemotherapy	1,356	(3.7)	14,876	(13.5)	
Follow−up period, years					<0.001
Mean±SD	6.6	(2.8)	4.6	(3.9)	
Deaths, n(%)	3,981	(10.7)	43,349	(39.2)	<0.001
Colorectal cancer deaths, n(%)	2,137	(5.8)	31,370	(28.4)	<0.001

Abbreviation: SD=Standard deviation.

Table 4. Characteristics according to smoking status before colorectal cancer diagnosis

Characteristics before diagnosis	Nonsmoker (N=25,979)		Smoker (N=11,100)		P-value
Age at diagnosis, years					<0.001
<50	2,319	(8.9)	1,912	(17.2)	
50−59	6,321	(24.3)	3,748	(33.8)	
60−69	9,563	(36.8)	3,680	(33.2)	
≥70	7,776	(29.9)	1,760	(15.9)	
BMI before diagnosis					<0.001
<18.5	456	(1.8)	376	(3.4)	
18.5−24.9	15,318	(59.0)	7,279	(65.6)	
25.0−29.9	9,511	(36.6)	3,209	(28.9)	
≥30.0	694	(2.7)	236	(2.1)	
Frequency of physical activity before diagnosis (per week)					<0.001
0	11,895	(45.8)	5,644	(50.9)	
1−2	6,187	(23.8)	2,897	(26.1)	
≥3	7,897	(30.4)	2,559	(23.1)	
Frequency of alcohol intake before diagnosis (per week)					<0.001
<1	13,099	(50.4)	3,491	(31.5)	
1−2	6,953	(26.8)	3,733	(33.6)	
3−4	3,324	(12.8)	2,204	(19.9)	
≥5	2,603	(10.0)	1,672	(15.1)	

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Table 4. Continued

Characteristics before diagnosis	Nonsmoker (N=25,979)		Smoker (N=11,100)		P-value
Treatment					<0.001
Operation	17,738	(68.3)	7,379	(66.5)	
Operation with radiotherapy or chemotherapy	7,377	(28.4)	3,229	(29.1)	
Radiotherapy and chemotherapy	864	(3.3)	492	(4.4)	
Charlson comorbidity index					<0.001
0	1,453	(5.6)	790	(7.1)	
1	3,228	(12.4)	1,512	(13.6)	
2	3,527	(13.6)	1,610	(14.5)	
≥3	17,771	(68.4)	7,188	(64.8)	
Subsites					<0.001
Colon	15,564	(59.9)	6,228	(56.1)	
Rectum	10,415	(40.1)	4,872	(43.9)	

Abbreviation: BMI=Body mass index.

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Table 5. Characteristics according to smoking status after colorectal cancer diagnosis

Characteristics after diagnosis	Nonsmoker (N=32,058)		Smoker (N=5,021)		P−value
Age at diagnosis, years					<0.001
<50	3,490	(10.9)	741	(14.8)	
50−59	8,417	(26.3)	1,652	(32.9)	
60−69	11,512	(35.9)	1,731	(34.5)	
≥70	8,639	(27.0)	897	(17.9)	
BMI before diagnosis					<0.001
<18.5	644	(2.0)	188	(3.7)	
18.5−24.9	19,276	(60.1)	3,321	(66.1)	
25.0−29.9	11,320	(35.3)	1,400	(27.9)	
≥30.0	818	(2.6)	112	(2.2)	
Frequency of physical activity before diagnosis (per week)					<0.001
0	14,797	(46.2)	2,742	(54.6)	
1−2	7,865	(24.5)	1,219	(24.3)	
≥3	9,396	(29.3)	1,060	(21.1)	
Frequency of alcohol intake before diagnosis (per week)					<0.001
<1	14,767	(46.1)	1,823	(36.3)	
1−2	9,272	(28.9)	1,414	(28.2)	
3−4	4,556	(14.2)	972	(19.4)	
≥5	3,463	(10.8)	812	(16.2)	

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Table 5. Continued

Characteristics after diagnosis	Nonsmoker (N=32,058)		Smoker (N=5,021)		P-value
Treatment					<0.001
Operation	21,456	(67.0)	3,652	(72.7)	
Operation with radiotherapy or chemotherapy	9,411	(29.4)	1,195	(23.8)	
Radiotherapy and chemotherapy	1,182	(3.7)	174	(3.5)	
Charlson comorbidity index					0.001
0	1,918	(6.0)	325	(6.5)	
1	4,080	(12.7)	660	(13.1)	
2	4,368	(13.6)	769	(15.3)	
≥3	21,692	(67.7)	3,267	(65.1)	
Subsites					0.196
Colon	18,883	(58.9)	2,909	(57.9)	
Rectum	13,175	(41.1)	2,112	(42.1)	

Abbreviation: BMI=Body mass index.

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Table 6. Characteristics according to smoking status before and after colorectal cancer diagnosis

Characteristics before and after diagnosis	Prediagnosis				P-value
	Nonsmoker		Smoker		
	Postdiagnosis				
	Nonsmoker	Smoker	Nonsmoker	Smoker	
	(N=25,134)	(N=729)	(N=6,177)	(N=3,762)	
Age at diagnosis, years					<0.001
<50	2,202 (8.8)	117 (13.9)	1,288 (18.6)	624 (14.9)	
50−59	6,090 (24.2)	231 (27.3)	2,327 (33.6)	1,421 (34.0)	
60−69	9,266 (36.9)	297 (35.2)	2,246 (32.4)	1,434 (34.3)	
≥70	7,576 (30.1)	200 (23.7)	1,063 (15.4)	697 (16.7)	
BMI before diagnosis					<0.001
<18.5	429 (1.7)	27 (3.2)	215 (3.1)	16,1 (3.9)	
18.5−24.9	14,782 (58.8)	536 (63.4)	4,494 (64.9)	2,785 (66.7)	
25.0−29.9	9,250 (36.8)	261 (30.9)	2,070 (29.9)	1,139 (27.3)	
≥30.0	673 (2.7)	21 (2.5)	145 (2.1)	91 (2.2)	
Frequency of physical activity before diagnosis (per week)					<0.001
0	11,383 (45.3)	512 (60.6)	3,414 (49.3)	2,230 (53.4)	
1−2	6,009 (23.9)	178 (21.1)	1,856 (26.8)	1,041 (24.9)	
≥3	7,742 (30.8)	155 (18.3)	1,654 (23.9)	905 (21.7)	

Table 6. Continued

	Prediagnosis				P-value
	Nonsmoker		Smoker		
	Postdiagnosis				
Characteristics before and after diagnosis	Nonsmoker (N=25,134)	Smoker (N=729)	Nonsmoker (N=6,177)	Smoker (N=3,762)	
Frequency of alcohol intake before diagnosis (per week)					<0.001
<1	12,584 (50.1)	515 (61.0)	2,183 (31.5)	1,308 (31.3)	
1–2	6,793 (27.0)	160 (18.9)	2,479 (35.8)	1,254 (30.0)	
3–4	3,224 (12.8)	100 (11.8)	1,332 (19.2)	872 (20.9)	
≥5	2,533 (10.1)	70 (8.3)	930 (13.4)	742 (17.8)	
Treatment					<0.001
Operation	17,139 (68.2)	599 (70.9)	4,326 (62.5)	3,053 (73.1)	
Operation with radiotherapy or chemotherapy	7,159 (28.5)	218 (25.8)	2,252 (32.5)	977 (23.4)	
Radiotherapy and chemotherapy	836 (3.3)	28 (3.3)	346 (5.0)	146 (3.5)	
Charlson comorbidity index					<0.001
0	1,421 (5.7)	32 (3.8)	497 (7.2)	293 (7.0)	
1	3,145 (12.5)	83 (9.8)	935 (13.5)	577 (13.8)	
2	3,407 (13.6)	120 (14.2)	961 (13.9)	649 (15.5)	
≥3	17,161 (68.3)	610 (72.2)	4,531 (65.4)	2,657 (63.6)	
Subsites					<0.001
Colon	15,075 (60.0)	489 (57.9)	3,808 (55.0)	2,420 (58.0)	
Rectum	10,059 (40.0)	356 (42.1)	3,116 (45.0)	1,756 (42.1)	

Abbreviation: BMI=Body mass index.

Table 7. Univariate regression analyses on basic characteristics and risk of death among the colorectal cancer patients included in this study

	Person-years	No. of deaths	HR	95% CI
Age at diagnosis, years				
<50	26,140.74	245	Ref.	
50–59	51,989.92	595	1.19	1.03–1.39
60–69	66,756.28	1,182	1.96	1.71–2.26
≥70	46,136.63	1,654	4.38	3.82–5.02
Subsite				
Colon	120,343.64	2,335	Ref.	
Rectum	70,679.93	1,341	0.96	0.93–1.06
Treatment				
Operation	134,459.57	1,542	Ref.	
Operation with radiotherapy or chemotherapy	50,300.93	1,792	3.00	2.81–3.20
Radiotherapy or chemotherapy	6,263.08	342	4.28	3.80–4.81
BMI before diagnosis				
<18.5	3,900.74	141	1.75	1.49–2.07
18.5–24.9	117,422.05	2,407	Ref.	
25.0–29.9	64,949.02	1,044	0.77	0.72–0.83
≥30	4,751.76	84	0.97	0.79–1.19
Frequency of physical activity before diagnosis				
0	88,430.40	1,974	Ref.	
1–2	49,520.59	790	0.68	0.62–0.73
≥3	53,072.59	912	0.75	0.70–0.81
Frequency of alcohol intake before diagnosis				
<1	89,941.44	1,891	Ref.	
1–2	53,607.06	794	0.74	0.68–0.80
3–4	26,977.03	504	0.91	0.83–1.00
≥5	20,498.04	487	1.15	1.05–1.27

Table 7. Continued

	Person-years	No. of deaths	HR	95% CI
Charlson comorbidity index				
0	9,008.84	26	Ref.	
1	20,515.52	73	1.05	0.69−1.60
2	23,826.73	107	1.46	0.98−2.16
≥3	137,672.48	3,470	7.42	5.18−10.63

Abbreviations: BMI=Body mass index, HR=Hazard ratio, CI=Confidence interval.

Table 8. Association between prediagnosis and postdiagnosis status for smoking and all-cause mortality in men

Smoking status	No. of patients (N=37,079)	No. of deaths (N=3,980)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Prediagnosis							
Nonsmoker	25,979	2,819	173,026.02	1.00		1.00	
Smoker	11,100	1,161	72,516.93	1.29	1.20−1.38	1.23	1.14−1.32
Duration of smoking, years*							
<10	5,180	437	27,081.25	1.27	1.15−1.41	1.25	1.12−1.38
10−19	1,209	88	8,552.68	1.44	1.16−1.79	1.48	1.19−1.83
20−29	2,536	195	16,833.66	1.41	1.22−1.64	1.40	1.20−1.63
≥30	2,175	441	20,049.34	1.24	1.12−1.38	1.12	1.01−1.24
Postdiagnosis							
Nonsmoker	32,058	3,450	212,111.50	1.00		1.00	
Smoker	5,021	530	33,431.44	1.14	1.04−1.25	1.14	1.04−1.25

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Table 8. Continued

Smoking status	No. of patients (N=37,079)	No. of deaths (N=3,980)	Person–years	Age–adjusted HR	95% CI	HR¶	95% CI
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	25,134	2,703	166,878.59	1.00		1.00	
Nonsmoker/smoker	845	116	6,147.44	1.26	1.04–1.51	1.20	1.00–1.45
Smoker/nonsmoker	6,924	747	45,232.92	1.37	1.26–1.48	1.25	1.15–1.36
Duration of smoking, years*							
<10	3,133	279	16,427.00	1.37	1.21–1.55	1.27	1.12–1.44
10–19	813	62	5,749.57	1.52	1.18–1.97	1.50	1.16–1.93
20–29	1,671	149	11,043.89	1.64	1.39–1.95	1.56	1.32–1.86
≥30	1,307	257	12,012.46	1.22	1.07–1.39	1.09	0.96–1.24
Smoker/smoker	4,176	414	27,284.01	1.20	1.08–1.34	1.20	1.08–1.33
Duration of smoking, years*							
<10	2,047	158	10,654.25	1.15	0.98–1.36	1.24	1.05–1.46
10–19	396	26	2,803.11	1.32	0.90–1.95	1.47	1.00–2.17
20–29	865	46	5,789.77	1.00	0.75–1.35	1.07	0.80–1.44
≥30	868	184	8,036.88	1.31	1.13–1.52	1.18	1.01–1.37

Abbreviations: HR=Hazard ratio, CI=Confidence interval.

¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

* Prediagnosis duration of smoking.

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Table 9. Association between prediagnosis and postdiagnosis status for smoking and colorectal cancer-specific mortality in men

Smoking status	No. of patients (N=37,079)	No. of colorectal cancer deaths (N=2,137)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Prediagnosis							
Nonsmoker	25,979	1,510	173,026.02	1.00		1.00	
Smoker	11,100	627	72,516.93	1.13	1.03−1.25	1.08	0.98−1.19
Duration of smoking, years*							
<10	5,180	240	27,081.25	1.07	0.93−1.22	1.06	0.92−1.22
10−19	1,209	61	8,552.68	1.29	0.99−1.68	1.32	1.02−1.72
20−29	2,536	143	16,833.66	1.39	1.16−1.66	1.33	1.11−1.60
≥30	2,175	183	20,049.34	1.05	0.90−1.23	0.93	0.79−1.08
Postdiagnosis							
Nonsmoker	32,058	1,919	212,111.50	1.00		1.00	
Smoker	5,021	218	33,431.44	0.78	0.67−0.89	0.83	0.72−0.96

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Table 9. Continued

Smoking status	No. of patients (N=37,079)	No. of colorectal cancer deaths (N=2,137)	Person-years	Age-adjusted HR	95% CI	HR[¶]	95% CI
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	25,134	1,468	166,878.59	1.00		1.00	
Nonsmoker/smoker	845	42	6,147.44	0.82	0.60−1.11	0.81	0.59−1.10
Smoker/nonsmoker	6,924	451	45,232.92	1.31	1.18−1.46	1.17	1.05−1.30
Duration of smoking, years*							
<10	3,133	165	16,427.00	1.21	1.03−1.43	1.10	0.94−1.30
10−19	813	47	5,749.57	1.47	1.09−1.98	1.38	1.03−1.86
20−29	1,671	113	11,043.89	1.65	1.36−2.01	1.48	1.22−1.81
≥30	1,307	126	12,012.46	1.20	1.00−1.45	1.02	0.85−1.23
Smoker/smoker	4,176	176	27,284.01	0.83	0.71−0.97	0.88	0.75−1.03
Duration of smoking, years*							
<10	2,047	75	10,654.25	0.83	0.66−1.05	0.95	0.76−1.21
10−19	396	14	2,803.11	0.90	0.53−1.52	1.13	0.66−1.92
20−29	865	30	5,789.77	0.84	0.59−1.22	0.94	0.65−1.35
≥30	868	57	8,036.88	0.81	0.62−1.06	0.75	0.57−0.98

Abbreviations: HR=Hazard ratio, CI=Confidence interval.

[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

* Prediagnosis duration of smoking.

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Table 10. Association between smoking status change and all-cause mortality in men by subsite

Prediagnosis/postdiagnosis smoking status	No. of patients (N=37,079)	No. of deaths (N=3,980)	Person-years	Age-adjusted HR	95% CI	HR[¶]	95% CI
Colon							
Nonsmoker/nonsmoker	15,075	1,621	99,154.05	1.00		1.00	
Nonsmoker/smoker	489	58	3,542.15	1.10	0.85−1.43	1.01	0.78−1.31
Smoker/nonsmoker	3,808	401	24,855.72	1.35	1.21−1.51	1.27	1.14−1.43
Smoker/smoker	2,420	236	15,592.13	1.21	1.05−1.39	1.23	1.07−1.42
Rectum							
Nonsmoker/nonsmoker	10,059	1,082	67,724.54	1.00		1.00	
Nonsmoker/smoker	356	58	2,605.29	1.47	1.13−1.92	1.45	1.11−1.89
Smoker/nonsmoker	3,116	346	20,377.20	1.38	1.22−1.56	1.26	1.11−1.43
Smoker/smoker	1,756	178	11,691.87	1.19	1.02−1.40	1.18	1.00−1.39

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

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Table 11. Association between smoking status change and all−cause mortality in men by subsite (reference change)

Prediagnosis/postdiagnosis smoking status	No. of patients (N=37,079)	No. of deaths (N=3,980)	Person− years	Age− adjusted HR	95% CI	HR[¶]	95% CI
Colon							
Nonsmoker/nonsmoker	15,075	1,621	99,154.05	0.83	0.72−0.95	0.81	0.71−0.93
Nonsmoker/smoker	489	58	3,542.15	0.91	0.68−1.21	0.82	0.61−1.10
Smoker/nonsmoker	3,808	401	24,855.72	1.12	0.95−1.31	1.03	0.88−1.22
Smoker/smoker	2,420	236	15,592.13	1.00		1.00	
Rectum							
Nonsmoker/nonsmoker	10,059	1,082	67,724.54	0.84	0.71−0.98	0.85	0.72−1.00
Nonsmoker/smoker	356	58	2,605.29	1.23	0.92−1.66	1.23	0.91−1.66
Smoker/nonsmoker	3,116	346	20,377.20	1.15	0.96−1.38	1.07	0.89−1.28
Smoker/smoker	1,756	178	11,691.87	1.00		1.00	

Abbreviations: HR=Hazard ratio, CI=Confidence interval.

[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

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Table 12. Association between smoking status change and all−cause mortality in men by treatment

Prediagnosis/postdiagnosis smoking status	No. of patients (N=37,079)	No. of deaths (N=3,980)	Person−years	Age−adjusted HR	95% CI	HR[¶]	95% CI
Operation							
Nonsmoker/nonsmoker	17,139	1,136	115,756.49	1.00		1.00	
Nonsmoker/smoker	599	59	4,384.03	1.53	1.18−1.99	1.34	1.03−1.74
Smoker/nonsmoker	4,326	256	29,233.82	1.39	1.21−1.59	1.30	1.13−1.49
Smoker/smoker	3,053	229	20,075.38	1.80	1.56−2.07	1.66	1.44−1.92
Operation with radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	7,159	1,343	46,148.75	1.00		1.00	
Nonsmoker/smoker	218	48	1,557.05	1.14	0.85−1.52	1.10	0.82−1.47
Smoker/nonsmoker	2,252	431	13,923.81	1.29	1.16−1.44	1.25	1.12−1.40
Smoker/smoker	977	149	6,279.01	0.93	0.79−1.10	0.91	0.77−1.08
Radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	836	224	4,973.35	1.00		1.00	
Nonsmoker/smoker	28	9	206.35	0.95	0.49−1.86	0.90	0.46−1.76
Smoker/nonsmoker	346	60	2,075.29	0.79	0.59−1.06	0.80	0.60−1.07
Smoker/smoker	146	36	929.62	1.00	0.70−1.42	0.99	0.69−1.42

Abbreviations: HR=Hazard ratio, CI=Confidence interval.

[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Table 13. Association between smoking status change and all-cause mortality in men by treatment (reference change)

Prediagnosis/postdiagnosis smoking status	No. of patients (N=37,079)	No. of deaths (N=3,980)	Person-years	Age-adjusted HR	95% CI	HR[¶]	95% CI
Operation							
Nonsmoker/nonsmoker	17,139	1,136	115,756.49	0.56	0.48−0.64	0.60	0.52−0.70
Nonsmoker/smoker	599	59	4,384.03	0.85	0.64−1.14	0.81	0.60−1.08
Smoker/nonsmoker	4,326	256	29,233.82	0.77	0.65−0.92	0.78	0.66−0.94
Smoker/smoker	3,053	229	20,075.38	1.00		1.00	
Operation with radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	7,159	1,343	46,148.75	1.08	0.91−1.27	1.10	0.92−1.30
Nonsmoker/smoker	218	48	1,557.05	1.23	0.88−1.70	1.21	0.87−1.67
Smoker/nonsmoker	2,252	431	13,923.81	1.39	1.15−1.67	1.38	1.14−1.66
Smoker/smoker	977	149	6,279.01	1.00		1.00	
Radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	836	224	4,973.35	1.00	0.70−1.43	1.01	0.70−1.45
Nonsmoker/smoker	28	9	206.35	0.96	0.46−1.99	0.91	0.44−1.90
Smoker/nonsmoker	346	60	2,075.29	0.80	0.53−1.21	0.80	0.53−1.22
Smoker/smoker	146	36	929.62	1.00		1.00	

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Sensitivity analyses

Subjects who had health examinations within 1 year before their colorectal cancer diagnosis were included from the sensitivity analysis. The characteristics of the subjects under sensitivity analysis were similar to those under the primary analysis (Table 14, Table 15, and Table 16).

Therefore, the results were analogous to the primary analysis results. Prediagnosis and postdiagnosis smoking was associated with elevated mortality. Significantly elevated mortality was observed among patients who quit smoking after their colorectal cancer diagnosis and in those who had continually smoked before and after diagnosis (Table 17). Similar to the primary result, there was no significant association between prediagnosis and postdiagnosis smoking status and colorectal cancer-specific mortality, although elevated colorectal cancer-specific mortality was observed among patients who quit smoking (Table 18).

Smoking cessation after colorectal cancer diagnosis was significantly associated with elevated mortality among colon and rectal cancer patients (Table 19). In a stratified analysis on cancer

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treatments, smoking before and after diagnosis was related to increased mortality among patients who underwent surgical treatment only (Table 20).

  When we extracted information on the postdiagnosis smoking status from one to three years after diagnosis, similar results were observed. The prediagnosis and postdiagnosis smoking status were related to an increased risk of death. The smoker/nonsmoker and smoker/smoker groups showed significantly elevated mortality (Table 21). Associations between the smoking status and risk of colorectal cancer deaths were similar to the results of the primary analysis (Table 22). Most of the results were analogous to the primary analysis as stratified by subsite and treatment (Table 23, Table 24).

  The short-term tobacco cessation rates were approximately 70% immediately after cancer diagnosis, although 60% of them relapsed after surgery (39). Thus, we performed sensitivity analyses on long-term surviving patients who survived for more than five years. A positive association between the prediagnosis and postdiagnosis

smoking status and all-cause mortality were consistent with the primary results (Table 25, Table 29). The relation between prediagnosis and postdiagnosis smoking status and colorectal cancer-specific mortality were consistent with the primary results, although the results were not significant among the smoker/nonsmoker group (Table 26, Table 30).

In the analyses stratified by subsite, the positive relations were consistent with the primary results, while the results were not significant among rectal cancer patients (Table 27, Table 31). When we performed the stratified analyses by treatment, most of the results were similar to the primary results, although the point estimates were increased among postdiagnosis smokers who underwent radiotherapy or chemotherapy, regardless of their smoking status before diagnosis (Table 28). In the sensitivity analysis that extracted the postdiagnosis smoking status between three and five years from diagnosis, the results were consistent with the primary results (Table 32).

Table 14. Characteristics according to smoking status before colorectal cancer diagnosis among subjects who have health examinations within 1 year before colorectal cancer diagnosis

Characteristics before diagnosis	Nonsmoker (N=20,161)		Smoker (N=8,702)		P-value
Age at diagnosis, years					<0.001
<50	1,851	(9.2)	1,518	(17.4)	
50–59	5,165	(25.6)	3,036	(34.9)	
60–69	7,412	(36.8)	2,863	(32.9)	
≥70	5,733	(28.4)	1,285	(14.8)	
BMI before diagnosis					<0.001
<18.5	358	(1.8)	299	(3.4)	
18.5–24.9	11,913	(59.1)	5,747	(66.0)	
25.0–29.9	7,356	(36.5)	2,473	(28.4)	
≥30.0	534	(2.7)	183	(2.1)	
Frequency of physical activity before diagnosis (per week)					<0.001
0	9,093	(45.1)	4,413	(50.7)	
1–2	4,859	(24.1)	2,264	(26.0)	
≥3	6,209	(30.8)	2,025	(23.3)	
Frequency of alcohol intake before diagnosis (per week)					<0.001
<1	10,018	(49.7)	2,698	(31.0)	
1–2	5,526	(27.4)	2,977	(34.2)	
3–4	2,606	(12.9)	1,736	(20.0)	
≥5	2,011	(10.0)	1,291	(14.8)	

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Table 14. Continued

Characteristics before diagnosis	Nonsmoker (N=20,161)		Smoker (N=8,702)		P−value
Treatment					<0.001
Operation	13,887	(68.9)	5,826	(67.0)	
Operation with radiotherapy or chemotherapy	5,643	(28.0)	2,494	(28.7)	
Radiotherapy and chemotherapy	631	(3.1)	382	(4.4)	
Charlson comorbidity index					<0.001
0	1,189	(5.9)	659	(7.6)	
1	2,617	(13.0)	1,229	(14.1)	
2	2,790	(13.8)	1,281	(14.7)	
≥3	13,565	(67.3)	5,533	(63.6)	
Subsites					<0.001
Colon	12,130	(60.2)	4,921	(56.6)	
Rectum	8,031	(39.8)	3,781	(43.5)	

Abbreviation: BMI=Body mass index.

Table 15. Characteristics according to smoking status after colorectal cancer diagnosis among subjects who have health examinations within 1 year before colorectal cancer diagnosis

Characteristics after diagnosis	Nonsmoker (N=24,921)		Smoker (N=3,942)		P−value
Age at diagnosis, years					<0.001
<50	2,795	(11.2)	574	(14.6)	
50−59	6,863	(27.5)	1,338	(33.9)	
60−69	8,911	(35.8)	1,364	(34.6)	
≥70	6,352	(25.5)	666	(16.9)	
BMI before diagnosis					<0.001
<18.5	504	(2.0)	153	(3.9)	
18.5−24.9	15,050	(60.4)	2,610	(66.2)	
25.0−29.9	8,735	(35.1)	1,094	(27.8)	
≥30.0	632	(2.5)	85	(2.2)	
Frequency of physical activity before diagnosis (per week)					<0.001
0	11,370	(45.6)	2,136	(54.2)	
1−2	6,180	(24.8)	943	(23.9)	
≥3	7,371	(29.6)	863	(21.9)	
Frequency of alcohol intake before diagnosis (per week)					<0.001
<1	11,318	(45.4)	1,398	(35.5)	
1−2	7,363	(29.6)	1,140	(28.9)	
3−4	3,575	(14.4)	767	(19.5)	
≥5	2,665	(10.7)	637	(16.2)	

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Table 15. Continued

Characteristics after diagnosis	Nonsmoker (N=24,921)		Smoker (N=3,942)		P–value
Treatment					<0.001
Operation	16,836	(67.6)	2,877	(73.0)	
Operation with radiotherapy or chemotherapy	7,204	(28.9)	933	(23.7)	
Radiotherapy and chemotherapy	881	(3.5)	132	(3.4)	
Charlson comorbidity index					0.004
0	1,579	(6.3)	269	(6.8)	
1	3,298	(13.2)	551	(14.0)	
2	3,460	(13.9)	611	(15.5)	
≥3	16,587	(66.6)	2,511	(63.7)	
Subsites					0.583
Colon	14,738	(59.1)	2,313	(58.7)	
Rectum	10,183	(40.9)	1,629	(41.3)	

Abbreviation: BMI=Body mass index.

Table 16. Characteristics according to smoking status before and after colorectal cancer diagnosis among subjects who have health examinations within 1 year before colorectal cancer diagnosis

Characteristics before and after diagnosis	Prediagnosis				P-value
	Nonsmoker		Smoker		
	Postdiagnosis				
	Nonsmoker (N=19,530)	Smoker (N=631)	Nonsmoker (N=5,391)	Smoker (N=3,311)	
Age at diagnosis, years					<0.001
<50	1,765 (9.0)	86 (13.6)	1,030 (19.1)	488 (14.7)	
50−59	4,983 (25.5)	182 (28.8)	1,880 (34.9)	1,156 (34.9)	
60−69	7,188 (36.8)	224 (35.5)	1,723 (32.0)	1,140 (34.4)	
≥70	5,594 (28.6)	139 (22.0)	758 (14.1)	527 (15.9)	
BMI before diagnosis					<0.001
<18.5	336 (1.7)	22 (3.5)	168 (3.1)	131 (4.0)	
18.5−24.9	11,515 (59.0)	398 (63.1)	3,535 (65.6)	2,212 (66.8)	
25.0−29.9	7,161 (36.7)	195 (30.9)	1,574 (29.2)	899 (27.2)	
≥30.0	518 (2.7)	16 (2.5)	114 (2.1)	69 (2.1)	
Frequency of physical activity before diagnosis (per week)					<0.001
0	8,715 (44.6)	378 (59.9)	2,655 (49.3)	1,758 (53.1)	
1−2	4,726 (24.2)	133 (21.1)	1,454 (27.0)	810 (24.5)	
≥3	6,089 (31.2)	120 (19.0)	1,282 (23.8)	743 (22.4)	

Table 16. Continued

Characteristics before and after diagnosis	Prediagnosis				P-value
	Nonsmoker		Smoker		
	Postdiagnosis		Postdiagnosis		
	Nonsmoker (N=19,530)	Smoker (N=631)	Nonsmoker (N=5,391)	Smoker (N=3,311)	
Frequency of alcohol intake before diagnosis (per week)					<0.001
<1	9,643 (49.4)	375 (59.4)	1,675 (31.1)	1,023 (30.9)	
1–2	5,402 (27.7)	124 (19.7)	1,961 (36.4)	1,016 (30.7)	
3–4	2,528 (12.9)	78 (12.4)	1,047 (19.4)	689 (20.8)	
≥5	1,957 (10.0)	54 (8.6)	708 (13.1)	583 (17.6)	
Treatment					<0.001
Operation	13,440 (68.8)	447 (70.8)	3,396 (63.0)	2,430 (73.4)	
Operation with radiotherapy or chemotherapy	5,480 (28.1)	163 (25.8)	1,724 (32.0)	770 (23.3)	
Radiotherapy and chemotherapy	610 (3.1)	21 (3.3)	271 (5.0)	111 (3.4)	
Charlson comorbidity index					<0.001
0	1,162 (6.0)	27 (4.3)	417 (7.7)	242 (7.3)	
1	2,546 (13.0)	71 (11.3)	749 (13.9)	480 (14.5)	
2	2,704 (13.9)	86 (13.6)	756 (14.0)	525 (15.9)	
≥3	13,118 (67.2)	447 (70.8)	3,469 (64.4)	2,064 (62.3)	
Subsites					<0.001
Colon	11,751 (60.2)	379 (60.1)	2,987 (55.4)	1,934 (58.4)	
Rectum	7,779 (39.8)	252 (39.9)	2,404 (44.6)	1,377 (41.6)	

Abbreviation: BMI=Body mass index.

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Table 17. Association between prediagnosis and postdiagnosis smoking status and all−cause mortality among subjects who had health examinations within 1 year before colorectal cancer diagnosis

Smoking status	No. of patients (N=28,863)	No. of deaths (N=2,930)	Person− years	Age− adjusted HR	95% CI	HR[¶]	95% CI
Prediagnosis							
Nonsmoker	20,161	2,052	133,253.76	1.00		1.00	
Smoker	8,702	878	56,374.58	1.32	1.21−1.43	1.23	1.13−1.34
Duration of smoking, years							
<10	4,215	352	22,274.94	1.29	1.15−1.45	1.24	1.10−1.39
10−19	945	66	6,552.79	1.43	1.11−1.84	1.46	1.14−1.88
20−29	2,042	158	13,360.58	1.46	1.24−1.73	1.42	1.20−1.68
≥30	1,500	302	14,186.26	1.27	1.12−1.43	1.12	0.99−1.27
Postdiagnosis							
Nonsmoker	24,921	2,530	163,596.63	1.00		1.00	
Smoker	3,942	400	26,031.72	1.15	1.03−1.27	1.15	1.03−1.28

Table 17. Continued

Smoking status	No. of patients (N=28,863)	No. of deaths (N=2,930)	Person-years	Age-adjusted HR	95% CI	HR[¶]	95% CI
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	19,530	1,972	128710.33	1.00		1.00	
Nonsmoker/smoker	631	80	4543.43	1.23	0.98−1.54	1.15	0.92−1.44
Smoker/nonsmoker	5,391	558	34886.30	1.39	1.27−1.53	1.24	1.13−1.37
Duration of smoking, years							
<10	2,528	224	13,388.50	1.40	1.22−1.61	1.25	1.09−1.44
10−19	642	47	4,446.84	1.50	1.12−2.02	1.49	1.11−2.01
20−29	1,342	119	8,758.72	1.68	1.39−2.03	1.55	1.28−1.88
≥30	879	168	8,292.24	1.22	1.04−1.43	1.05	0.90−1.23
Smoker/smoker	3,311	320	21,488.29	1.23	1.09−1.38	1.23	1.09−1.39
Duration of smoking, years							
<10	1,687	128	8,886.44	1.15	0.96−1.38	1.23	1.02−1.47
10−19	303	19	2,105.96	1.31	0.83−2.06	1.41	0.89−2.22
20−29	700	39	4,601.86	1.07	0.78−1.48	1.15	0.83−1.59
≥30	621	134	5,894.03	1.36	1.14−1.62	1.25	1.04−1.49

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.
[*] Prediagnosis duration of smoking.

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Table 18. Association between smoking status change and colorectal cancer–specific mortality among subjects who have health examinations within 1 year before colorectal cancer diagnosis

Smoking status	No. of patients (N=28,863)	No. of colorectal cancer deaths (N=1,604)	Person–years	Age–adjusted HR	95% CI	HR¶	95% CI
Prediagnosis							
Nonsmoker	20,161	1,121	133,253.76	1.00		1.00	
Smoker	8,702	483	56,374.58	1.15	1.03–1.28	1.08	0.97–1.21
Duration of smoking, years*							
<10	4,215	192	22,274.94	1.06		1.03	0.88–1.21
10–19	945	47	6,552.79	1.29	0.96–1.75	1.34	0.99–1.81
20–29	2,042	115	13,360.58	1.41	1.15–1.72	1.32	1.08–1.62
≥30	1,500	129	14,186.26	1.10	0.91–1.32		
Postdiagnosis							
Nonsmoker	24,921	1,433	163,596.63	1.00		1.00	
Smoker	3,942	171	26,031.72	0.80	0.68–0.93	0.86	0.73–1.01

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Table 18. Continued

Smoking status	No. of patients (N=28,863)	No. of colorectal cancer deaths (N=1,604)	Person-years	Age-adjusted HR	95% CI	HR[¶]	95% CI
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	19,530	1,094	128710.33	1.00		1.00	
Nonsmoker/smoker	631	27	4543.43	0.73	0.50−1.07	0.71	0.48−1.04
Smoker/nonsmoker	5,391	339	34886.30	1.31	1.16−1.49	1.14	1.00−1.29
Duration of smoking, years[*]							
<10	2,528	128	13,388.50	1.18	0.98−1.42	1.04	0.87−1.26
10−19	642	35	4,446.84	1.40	1.00−1.98	1.37	0.97−1.93
20−29	1,342	90	8,758.72	1.66	1.33−2.07	1.44	1.15−1.81
≥30	879	86	8,292.24	1.25	1.00−1.55	1.02	0.82−1.28
Smoker/smoker	3,311	144	21,488.29	0.88	0.73−1.04	0.93	0.78−1.12
Duration of smoking, years[*]							
<10	1,687	64	8,886.44	0.86	0.67−1.11	0.98	0.76−1.27
10−19	303	12	2,105.96	1.02	0.57−1.80	1.22	0.69−2.17
20−29	700	25	4,601.86	0.88	0.59−1.31	0.97	0.65−1.45
≥30	621	43	5,894.03	0.87	0.64−1.18	0.82	0.60−1.11

Abbreviations: HR=Hazard ratio, CI=Confidence interval.

[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

[*] Prediagnosis duration of smoking.

Table 19. Association between smoking status change and all-cause mortality in men by subsite among subjects who have health examinations within 1 year before colorectal cancer diagnosis

Prediagnosis/postdiagnosis smoking status	No. of patients (N=28,863)	No. of deaths (N=2,930)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Colon							
Nonsmoker/nonsmoker	11,751	1,185	76648.14	1.00		1.00	
Nonsmoker/smoker	379	42	2718.35	1.10	0.81−1.50	0.98	0.72−1.34
Smoker/nonsmoker	2,987	300	19262.89	1.38	1.22−1.57	1.28	1.12−1.46
Smoker/smoker	1,934	179	12418.72	1.20	1.02−1.40	1.24	1.05−1.46
Rectum							
Nonsmoker/nonsmoker	7,779	787	52062.19	1.00		1.00	
Nonsmoker/smoker	252	38	1825.08	1.43	1.03−1.97	1.37	0.99−1.90
Smoker/nonsmoker	2,404	258	15623.40	1.40	1.21−1.61	1.23	1.06−1.42
Smoker/smoker	1,377	141	9069.57	1.26	1.06−1.51	1.24	1.03−1.49

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

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Table 20. Association between smoking status change and all-cause mortality in men by treatment among subjects who have health examinations within 1 year before colorectal cancer diagnosis

Prediagnosis/postdiagnosis smoking status	No. of patients (N=28,863)	No. of deaths (N=2,930)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Operation							
Nonsmoker/nonsmoker	13,440	821	90186.39	1.00		1.00	
Nonsmoker/smoker	447	37	3246.56	1.47	1.06−2.04	1.28	0.92−1.78
Smoker/nonsmoker	3,396	194	22647.73	1.50	1.28−1.76	1.39	1.18−1.63
Smoker/smoker	2,430	176	15884.22	1.84	1.56−2.17	1.70	1.44−2.01
Operation with radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	5,480	990	34916.82	1.00		1.00	
Nonsmoker/smoker	163	37	1146.78	1.17	0.84−1.63	1.15	0.82−1.59
Smoker/nonsmoker	1,724	321	10574.25	1.27	1.11−1.44	1.22	1.07−1.39
Smoker/smoker	770	113	4892.36	0.92	0.76−1.12	0.90	0.74−1.10
Radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	610	161	3607.12	1.00		1.00	
Nonsmoker/smoker	21	6	150.09	0.78	0.34−1.76	0.79	0.35−1.79
Smoker/nonsmoker	271	43	1664.32	0.71	0.50−1.00	0.73	0.51−1.03
Smoker/smoker	111	31	711.71	1.11	0.76−1.64	1.16	0.78−1.73

Abbreviations: HR=Hazard ratio, CI=Confidence interval.

¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Table 21. Association between prediagnosis and postdiagnosis status of smoking and all-cause mortality in men who have health examinations between one and three years from colorectal cancer diagnosis

Smoking status	No. of patients (N=29,819)	No. of deaths (N=3,676)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Prediagnosis							
Nonsmoker	20,949	2,604	135,038.73	1.00		1.00	
Smoker	8,870	1,072	55,984.84	1.29	1.20−1.38	1.21	1.13−1.31
Postdiagnosis							
Nonsmoker	25,934	3,200	118,545.58	1.00		1.00	
Smoker	3,885	476	17,487.60	1.15	1.04−1.27	1.14	1.03−1.25
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	20,349	2,510	93,385.44	1.00		1.00	
Nonsmoker/smoker	600	94	2,993.34	1.27	1.04−1.57	1.21	0.99−1.49
Smoker/nonsmoker	5,585	690	25,160.15	1.35	1.24−1.47	1.25	1.14−1.36
Smoker/smoker	3,285	382	14,494.25	1.21	1.08−1.34	1.18	1.06−1.32

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

Table 22. Association between prediagnosis and postdiagnosis status for smoking and colorectal cancer−specific mortality in men who have health examinations between one and three years from colorectal cancer diagnosis

Smoking status	No. of patients (N=29,819)	No. of colorectal cancer deaths (N=2,050)	Person−years	Age−adjusted HR	95% CI	HR¶	95% CI
Prediagnosis							
Nonsmoker	20,949	1,448	135,038.73	1.00		1.00	
Smoker	8,870	602	55,984.84	1.14	1.03−1.26	1.08	0.98−1.20
Postdiagnosis							
Nonsmoker	25,934	1,837	118,545.58	1.00		1.00	
Smoker	3,885	213	17,487.60	0.83	0.72−0.95	0.87	0.75−1.01
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	20,349	1,410	93,385.44	1.00		1.00	
Nonsmoker/smoker	600	38	2,993.34	0.89	0.65−1.23	0.87	0.63−1.21
Smoker/nonsmoker	5,585	427	25,160.15	1.30	1.17−1.45	1.17	1.05−1.31
Smoker/smoker	3,285	175	14,494.25	0.88	0.75−1.03	0.91	0.78−1.07

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

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Table 23. Association between smoking status change and all-cause mortality in men who have health examinations between one and three years from colorectal cancer diagnosis by subsite

Prediagnosis/postdiagnosis smoking status	No. of patients (N=29,819)	No. of deaths (N=3,676)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Colon							
Nonsmoker/nonsmoker	12,761	1,638	60,079.23	1.00		1.00	
Nonsmoker/smoker	366	47	1,916.06	1.02	0.77−1.37	0.99	0.74−1.32
Smoker/nonsmoker	3,259	414	15,465.35	1.33	1.19−1.48	1.26	1.12−1.40
Smoker/smoker	1,990	236	9,029.45	1.19	1.04−1.37	1.19	1.04−1.37
Rectum							
Nonsmoker/nonsmoker	7,588	872	33,306.21	1.00		1.00	
Nonsmoker/smoker	234	47	1,077.28	1.74	1.30−2.33	1.62	1.21−2.18
Smoker/nonsmoker	2,326	276	9,694.80	1.39	1.22−1.60	1.26	1.10−1.45
Smoker/smoker	1,295	146	5,464.80	1.24	1.04−1.48	1.20	1.00−1.44

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Table 24. Association between status for smoking change and all-cause mortality in men who have health examinations between one and three years from colorectal cancer diagnosis by treatment

Prediagnosis/postdiagnosis smoking status	No. of patients (N=29,819)	No. of deaths (N=3,676)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Operation							
Nonsmoker/nonsmoker	13,993	1,039	66,826.01	1.00		1.00	
Nonsmoker/smoker	432	46	2,212.63	1.59	1.19−2.14	1.48	1.10−1.99
Smoker/nonsmoker	3,524	245	16,868.20	1.43	1.24−1.65	1.31	1.14−1.51
Smoker/smoker	2,407	212	10,835.59	1.85	1.60−2.15	1.70	1.46−1.97
Operation with radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	5,637	1,232	23,867.72	1.00		1.00	
Nonsmoker/smoker	150	41	694.29	1.22	0.90−1.67	1.16	0.85−1.58
Smoker/nonsmoker	1,797	391	7,275.10	1.27	1.13−1.43	1.23	1.09−1.39
Smoker/smoker	762	128	3,195.29	0.87	0.72−1.04	0.83	0.69−1.01
Radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	719	239	2,691.70	1.00		1.00	
Nonsmoker/smoker	18	7	86.42	0.88	0.41−1.86	0.76	0.36−1.61
Smoker/nonsmoker	264	54	1,016.85	0.76	0.56−1.03	0.80	0.59−1.09
Smoker/smoker	116	42	463.37	1.13	0.82−1.58	1.12	0.80−1.56

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Table 25. Association between prediagnosis and postdiagnosis status for smoking and all-cause mortality in men who survived for more than 5 years and have health examinations between one and three years from colorectal cancer diagnosis

Smoking status	No. of patients (N=18,780)	No. of deaths (N=1,463)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Prediagnosis							
Nonsmoker	13,282	1,029	109,951.66	1.00		1.00	
Smoker	5,498	434	45,556.25	1.38	1.23−1.55	1.34	1.19−1.50
Postdiagnosis							
Nonsmoker	16,139	1,228	71,172.90	1.00		1.00	
Smoker	2,641	235	11,679.87	1.41	1.22−1.62	1.40	1.21−1.61
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	12,804	979	56,261.10	1.00		1.00	
Nonsmoker/smoker	478	50	2298.10	1.41	1.06−1.87	1.46	1.09−1.94
Smoker/nonsmoker	3,335	249	14,911.80	1.34	1.16−1.54	1.29	1.12−1.49
Smoker/smoker	2,163	185	9,381.77	1.51	1.29−1.77	1.48	1.26−1.74

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

Table 26. Association between prediagnosis and postdiagnosis status for smoking and colorectal cancer−specific mortality in men who survived for more than 5 years and have health examinations between one and three years from colorectal cancer diagnosis

Smoking status	No. of patients (N=18,780)	No. of colorectal cancer deaths (N=505)	Person− years	Age− adjusted HR	95% CI	HR[¶]	95% CI
Prediagnosis							
Nonsmoker	13,282	358	109,951.66	1.00		1.00	
Smoker	5,498	147	45,556.25	1.14	0.94−1.38	1.07	0.87−1.31
Postdiagnosis							
Nonsmoker	16,139	446	71,172.90	1.00		1.00	
Smoker	2,641	59	11,679.87	0.87	0.66−1.14	0.93	0.71−1.22
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	12,804	347	56,261.10	1.00		1.00	
Nonsmoker/smoker	478	11	2298.10	0.82	0.45−1.49	0.94	0.51−1.72
Smoker/nonsmoker	3,335	99	14,911.80	1.26	1.00−1.58	1.14	0.91−1.44
Smoker/smoker	2,163	48	9,381.77	0.94	0.69−1.27	0.97	0.71−1.31

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

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Table 27. Association between smoking status change and all−cause mortality in men who survived for more than 5 years and have health examinations between one and three years from colorectal cancer diagnosis by subsite

Prediagnosis/postdiagnosis smoking status	No. of patients (N=18,780)	No. of deaths (N=1,463)	Person− years	Age− adjusted HR	95% CI	HR[¶]	95% CI
Colon							
Nonsmoker/nonsmoker	7,993	638	36,406.95	1.00		1.00	
Nonsmoker/smoker	313	32	1,537.06	1.41	0.99−2.02	1.39	0.97−1.98
Smoker/nonsmoker	1,994	164	9,498.18	1.40	1.17−1.66	1.36	1.14−1.63
Smoker/smoker	1,310	123	5,933.14	1.66	1.37−2.02	1.64	1.34−2.00
Rectum							
Nonsmoker/nonsmoker	4,811	341	19,854.16	1.00		1.00	
Nonsmoker/smoker	165	18	761.04	1.41	0.88−2.27	1.57	0.97−2.53
Smoker/nonsmoker	1,341	85	5,413.62	1.24	0.98−1.58	1.16	0.91−1.48
Smoker/smoker	853	62	3,448.63	1.28	0.97−1.68	1.27	0.96−1.68

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

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Table 28. Association between status of smoking change and all−cause mortality in men who survived for more than 5 years and have health examinations between one and three years from colorectal cancer diagnosis by treatment

Prediagnosis/postdiagnosis smoking status	No. of patients (N=18,780)	No. of deaths (N=1,463)	Person−years	Age−adjusted HR	95% CI	HR[¶]	95% CI
Operation							
Nonsmoker/nonsmoker	9,271	502	41,001.28	1.00		1.00	
Nonsmoker/smoker	366	32	1,794.58	1.76	1.23−2.52	1.64	1.14−2.35
Smoker/nonsmoker	2,237	109	10,218.75	1.30	1.06−1.60	1.23	0.99−1.52
Smoker/smoker	1,621	121	7,053.47	2.17	1.78−2.65	2.03	1.66−2.50
Operation with radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	3,182	421	13,731.79	1.00		1.00	
Nonsmoker/smoker	105	17	465.27	1.34	0.83−2.18	1.35	0.83−2.19
Smoker/nonsmoker	962	126	4,118.08	1.35	1.10−1.65	1.28	1.04−1.58
Smoker/smoker	479	53	2,047.77	0.99	0.74−1.31	0.96	0.72−1.28
Radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	351	56	1,528.04	1.00		1.00	
Nonsmoker/smoker	7	1	38.25	0.51	0.07−3.70	0.74	0.10−5.48
Smoker/nonsmoker	136	14	574.97	0.80	0.44−1.45	0.76	0.40−1.46
Smoker/smoker	63	11	280.53	1.16	0.61−2.23	1.10	0.56−2.14

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Table 29. Association between prediagnosis and postdiagnosis status for smoking and all-cause mortality in men who survived for more than 5 years and have health examinations between three and five years from colorectal cancer diagnosis

Smoking status	No. of patients (N=18,377)	No. of deaths (N=1,489)	Person-years	Age-adjusted HR	95% CI	HR¶	95% CI
Prediagnosis							
Nonsmoker	13,072	1,073	106,959.16	1.00		1.00	
Smoker	5,305	416	43,314.90	1.31	1.17−1.47	1.26	1.12−1.42
Postdiagnosis							
Nonsmoker	15,970	1,278	100,800.73	1.00		1.00	
Smoker	2,407	211	14,822.48	1.37	1.18−1.58	1.32	1.14−1.53
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	12,649	1,028	79,607.95	1.00		1.00	
Nonsmoker/smoker	423	45	2,695.60	1.45	1.07−1.95	1.38	1.02−1.86
Smoker/nonsmoker	3,321	250	21,192.77	1.28	1.11−1.47	1.22	1.06−1.41
Smoker/smoker	1,984	166	12,126.88	1.43	1.21−1.68	1.38	1.17−1.63

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

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Table 30. Association between prediagnosis and postdiagnosis status for smoking and colorectal cancer−specific mortality in men who survived for more than 5 years and have health examinations between three and five years from colorectal cancer diagnosis

Smoking status	No. of patients (N=18,377)	No. of colorectal cancer deaths (N=536)	Person− years	Age− adjusted HR	95% CI	HR[¶]	95% CI
Prediagnosis							
Nonsmoker	13,072	381	106,959.16	1.00		1.00	
Smoker	5,305	155	43,314.90	1.11	0.92−1.35	1.08	0.89−1.32
Postdiagnosis							
Nonsmoker	15,970	473	100,800.73	1.00		1.00	
Smoker	2,407	63	14,822.48	0.96	0.74−1.25	1.02	0.78−1.32
Prediagnosis/postdiagnosis							
Nonsmoker/nonsmoker	12,649	370	79,607.95	1.00		1.00	
Nonsmoker/smoker	423	11	2,695.60	0.88	0.49−1.61	0.89	0.49−1.62
Smoker/nonsmoker	3,321	103	21,192.77	1.16	0.93−1.45	1.09	0.87−1.37
Smoker/smoker	1,984	52	12,126.88	1.02	0.76−1.37	1.08	0.80−1.44

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
[¶] Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, physical activity, and treatment.

Table 31. Association between smoking status change and all-cause mortality in men who survived for more than 5 years and have health examinations between three and five years from colorectal cancer diagnosis by subsite

Prediagnosis/postdiagnosis smoking status	No. of patients (N=18,377)	No. of deaths (N=1,489)	Person-years	Age-adjusted HR	95% CI	HR[¶]	95% CI
Colon							
Nonsmoker/nonsmoker	7,944	677	51,358.83	1.00		1.00	
Nonsmoker/smoker	266	28	1,743.50	1.45	0.99−2.11	1.35	0.92−1.97
Smoker/nonsmoker	1,974	161	13,182.71	1.31	1.10−1.45	1.26	1.06−1.51
Smoker/smoker	1,212	108	7,596.11	1.48	1.21−1.81	1.45	1.18−1.78
Rectum							
Nonsmoker/nonsmoker	4,705	351	28,249.13	1.00		1.00	
Nonsmoker/smoker	157	17	952.11	1.48	0.91−2.41	1.48	0.91−2.42
Smoker/nonsmoker	1,347	89	8,010.06	1.21	0.95−1.53	1.16	0.91−1.47
Smoker/smoker	772	58	4530.77	1.33	1.00−1.76	1.28	0.96−1.70

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Table 32. Association between status of smoking change and all−cause mortality in men who survived for more than 5 years and have health examinations between three and five years from colorectal cancer diagnosis by treatment

Prediagnosis/postdiagnosis smoking status	No. of patients (N=18,377)	No. of deaths (N=1,489)	Person−years	Age−adjusted HR	95% CI	HR¶	95% CI
Operation							
Nonsmoker/nonsmoker	9,146	511	57,993.39	1.00		1.00	
Nonsmoker/smoker	311	24	2,004.53	1.69	1.12−2.54	1.58	1.04−2.38
Smoker/nonsmoker	2,258	117	14,572.47	1.42	1.16−1.74	1.31	1.07−1.61
Smoker/smoker	1,497	111	9,134.55	2.23	1.82−2.75	2.06	1.66−2.55
Operation with radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	3,148	456	19,494.85	1.00		1.00	
Nonsmoker/smoker	99	16	612.76	1.20	0.73−1.97	1.15	0.69−1.89
Smoker/nonsmoker	930	121	5,798.88	1.13	0.92−1.39	1.09	0.88−1.35
Smoker/smoker	426	41	2,610.78	0.78	0.56−1.07	0.75	0.54−1.04
Radiotherapy or chemotherapy							
Nonsmoker/nonsmoker	355	61	2,119.72	1.00		1.00	
Nonsmoker/smoker	13	5	78.32	2.04	0.82−5.10	1.53	0.60−3.90
Smoker/nonsmoker	133	12	821.42	0.64	0.34−1.21	0.65	0.34−1.26
Smoker/smoker	61	14	381.56	1.28	0.71−2.29	1.25	0.69−2.25

Abbreviations: HR=Hazard ratio, CI=Confidence interval.
¶ Adjusted for age at diagnosis, frequency of drinking, Charlson comorbidity index, body mass index, and physical activity.

Discussion

In this study, the patients who quit smoking after their colorectal cancer diagnosis were younger, overweight or obese, frequently engaged in physical activity, and less likely to consume alcohol compared to continual smoker. A study reported that in postdiagnosis former smokers, patients who quit smoking after their cancer diagnosis, were likely to be older, have higher BMI, have high physical activity, and be former drinkers (33). Patients who quit cigarette smoking tended to be treated with operations along with chemotherapy or radiotherapy, radiotherapy or chemotherapy, and have higher CCI compared to continual smokers, although they had lower CCI compared to the nonsmoker/nonsmoker or nonsmoker/smoker groups. We adjusted the CCI and performed stratified analyses by treatment to minimize the confounding effect.

A previous study showed that approximately 18% of cancer patients were current smokers, and 10% of those were recent quitters, while 35% of those were former smokers (32). Another study reported that 36% of smoker before diagnosis quitted smoking after diagnosis (45). In our study, approximately 11% of patients were smokers

before the colorectal cancer diagnosis and continued smoking afterwards, and approximately 19% of patients quit smoking after their colorectal cancer diagnosis.

In this study, the prediagnosis smoking status was associated with increased mortality among colorectal cancer patients. A cohort study in the CHANCES consortium showed significantly increased mortality among those patients who were former smokers and current smokers before their colorectal cancer diagnosis (25). A meta-analysis showed an increased all-cause mortality among current smokers from 5 to 51% compared to never smokers (29). Our results were similar to previous results showing that smoking status before colorectal cancer diagnosis was associated with elevated all-cause mortality (30, 34, 36).

Smoking status after colorectal cancer diagnosis was associated with elevated mortality. Our results were analogous with previous studies that reported the postdiagnosis smoking status was associated with a higher risk of mortality (31, 35).

Additionally, all-cause mortality among colorectal cancer patients who quit smoking after diagnosis was not significantly different from that in colorectal cancer patients who had continually smoked from the time point before the colorectal cancer diagnosis. Our results are inconsistent with a previous population-based cohort in the US that reported increased all-cause mortality among current smokers at the time of breast cancer diagnosis, and the continual smokers after diagnosis showed elevated all-cause mortality, although there was an attenuated risk of mortality among quitters after diagnosis (42). One possible explanation is that lifetime cumulative exposure to smoking plays a key role in mortality. Because our patients' diagnosis age was greater than 60 years old, cumulative exposure to smoking before diagnosis was likely to be from lifetime exposure and greater than that after diagnosis. Thus, the modification of the smoking status after colorectal cancer diagnosis may not substantially influence mortality among smokers at cancer diagnosis. Additionally, these results could have occured because some patients who quit smoking after diagnosis did so as a result of their poor health conditions (46).

In our results, there were no association between prediagnosis or postdiagnosis smoking status and colorectal cancer—specific mortality. Changes in smoking status after cancer diagnosis were not significantly associated with colorectal cancer—specific mortality. The association between smoking status and colorectal cancer—specific mortality may be attenuated since smokers tend to have comorbidities; however, we adjusted for the Charlson comorbidity index. A previous study indicated that patients who smoked before their cancer diagnosis were significantly associated with elevated colorectal cancer—specific mortality (30). However, one study showed that there was no association between prediagnosis smoking and colorectal cancer—specific mortality (32), and another study reported that increased colorectal cancer mortality was observed among current smokers before diagnosis, although not significantly (41). Postdiagnosis current smoking was associated with increased colorectal cancer—specific mortality compared to never smoking (31).

Former or current smokers with a gastrointestinal malignancy at the time of surgery tended to have poor postoperative outcomes,

including surgical infection, combined pulmonary complications, and secondary surgery (47–49). Smoking cessation after diagnosis was related to a lower risk of mortality than continual smoking among putative early–stage cancer patients who underwent surgery only. Previous studies regarding the association between postoperative outcomes and smoking have reported a significantly elevated risk of postoperative mortality among current smokers (23, 49, 50). Continued smoking after diagnosis may lead to surgery complications, toxicity, immune suppression, and recurrence (49, 51, 52). Our finding that those who quit smoking after their colorectal cancer diagnosis showed a lower risk of mortality than continual smokers was analogous to these studies.

 Although the claim data did not contain the colorectal cancer stage, patients who were treated with surgery only were likely to have early–stage disease (53, 54). Thus, the baseline hazard for mortality would be higher among colorectal cancer patients who underwent surgery with radiotherapy or chemotherapy and among those who were treated with radiotherapy or chemotherapy than among those who received surgery only. Hence, the impact of smoking cessation after diagnosis on the decrease in mortality would not be revealed

among colorectal cancer patients who underwent surgery with radiotherapy or chemotherapy due to the high baseline hazard.

Furthermore, smoking before colorectal cancer diagnosis had a greater impact on the increase in mortality than smoking after diagnosis in this study. Because smoking has been reported to affect the early stage of carcinogenesis (55−57), a greater impact of prediagnosis smoking than from postdiagnosis smoking on mortality seems to be biologically plausible. Moreover, there have been studies reporting that the treatment effect was not good in patients who were smokers before their cancer diagnosis. Thus, a decreased treatment effect due to smoking before diagnosis would worsen the prognosis of colorectal cancer patients.

In sensitivity analyses, subjects who quit tobacco smoking after diagnosis were likely to have better prognosis compared to continual smoking among patients who survived more than 5 years. It is possible that patients in poor health conditions may have died within 5 years from their diagnosis. Thus, actual changes in smoking behavior may influence the patients who survive more than 5 years.

Our study has several limitations. Since we used claim data, it was not possible to precisely identify all of the factors in the colorectal cancer patients. Thus, we used operational definitions with treatment codes and hospitalization notes on the colorectal cancer treatments (Table 1). These assumptions could diminish an overestimation of the colorectal cancer incidence. The claim data do not contain information on the stage of colorectal cancer, which is crucial when predicting the prognosis. Accordingly, we conducted stratified analyses by treatment (operation only, operation with radiotherapy or chemotherapy, and radiotherapy or chemotherapy) to reflect the cancer stage of colorectal cancer patients by regarding the cancer treatment as a proxy for the cancer stage. In our study, the survival analysis according to treatment reasonably predicted the prognosis (Figure 1). The accuracy of information on smoking may have been diminished because the questionnaire was self-reported. Previous studies indicated that smoking rates were underreported by patients compared to those based on cotinine levels in saliva or serum (39, 58).

Despite the limitations above, this study has meaning in that the prediagnosis and postdiagnosis smoking status were considered

simultaneously during the analysis to assess the association between smoking and mortality. Previous studies evaluated mortality among colorectal cancer patients in relation to changes in smoking status. However, detailed information on changes in smoking status before and after diagnosis has rarely been considered in previous studies.

Using data covering the overall colorectal cancer patients identified in Korea is one strength of this study. We used the operational definition for colorectal cancer, and thus, this work is unlikely to include individuals who were not colorectal cancer patients.

Conclusion

In conclusion, we suggest that the prediagnosis smoking status has a greater impact on all−cause mortality among colorectal cancer patients. The postdiagnosis smoking status is also associated with elevated mortality among colorectal cancer patients. Additionally, smoking cessation may help to improve survival after diagnosis among colorectal cancer patients who were treated by operation only. Since patients who undergo surgery only are more likely to survive long−term, smoking cessation is crucial in these patients.

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국문초록

흡연은 잘 알려진 대장암의 위험요인이며, 진단 전 흡연이 암 진단 후 예후에 부정적 영향을 끼친다고 알려져 있다. 하지만 대장암환자에서 진단 전과 후의 흡연이 사망률에 미치는 효과는 잘 알려져 있지 않다. 따라서, 본 연구의 목적은 대장암 환자에서 진단 전과 후의 흡연 상태와 사망률 간의 연관성을 평가하고자 함이다.

본 연구에서는 국민건강보험공단 데이터베이스에 등록된 자료를 이용하여 후향적 코호트 연구를 진행하였다. 2002년부터 2016년 사이에 새롭게 대장암으로 진단 받은 대상자에서 여성, 진단 시점 기준 최소 2년 이내 및 1년 이후의 검진 자료가 없는 대상자를 제외하였다. 연구 대상자는 대장암 진단일부터 사망 또는 2017년 7월 13일까지 추적 관찰하였다. 진단 전 흡연 상태는 대장암 진단일 기준 2년 이내의 검진 자료를 사용하였다. 진단 후 흡연 상태는 진단일 기준 1년 이후의 검진 자료를 사용하였다. 진단 전과 후의 흡연 상태는 비흡연자 또는 흡연자로 분류하였다. 또한 진단 전과 후의 흡연 상태 변화는 4개의 그룹으로 범주화 하였다 (비흡연자/비흡연자, 비흡연자/흡연자, 흡연자/비흡연자, 흡연자/흡연자). 위험 비와 95% 신뢰구간은 Cox 비례 위험 모형을 이용하여 추정하였다. 또한 세부 부위(대장, 직장)와 치료군에 따라 층화분석을 진행하였다.

총 37,079명의 대상자에서 3,980명이 사망하였으며, 추적 기간 중앙값은 6.3년이었다. 진단 후의 흡연 상태와 관계 없이 진단 전

흡연자에서 유의하게 증가된 사망률이 관찰되었다 (흡연자/비흡연자 [HR, 1.25; 95% CI, 1.15 to 1.36], 흡연자/흡연자 [HR, 1.20; 95% CI, 1.08 to 1.33]). 수술적 요법으로만 치료를 받은 환자에서 진단 후 금연한 대상자는 지속적으로 흡연을 한 대상자에 비하여 낮은 사망률을 보였다 (흡연자/비흡연자 [HR, 0.78; 95% CI, 0.66 to 0.94]).

대장암 진단 전 흡연 상태는 증가된 사망률과 연관성이 있었다. 진단 후 흡연 상태 역시 사망률 증가와 연관성이 있었다. 특히 조기 대장암 환자라고 생각되는 수술적 치료만 받은 대장암 환자에서 진단 전 흡연자가 진단 후 금연을 할 경우 생존을 향상시킬 수 있을 것으로 사려된다.