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Statin use and site-specific risk of colorectal cancer in individuals with hypercholesterolemia from the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS)

Jae-Woo Lee [a], Na-Young You [b], Yeseul Kim [a], Yonghwan Kim [c], Joungyoun Kim [b,**,1], Hee-Taik Kang [a,d,*,1]

[a] Department of Family Medicine, Chungbuk National University Hospital, Cheongju, Republic of Korea
[b] Department of Information & Statistics, Chungbuk National University, Cheongju, Republic of Korea
[c] Department of Family Medicine, Yonsei University College of medicine, Seoul, Republic of Korea
[d] Department of Family Medicine, Chungbuk National University College of Medicine, Cheongju, Chungbuk, Republic of Korea

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Abstract *Background and aims:* We investigated the association between statin use and site-specific risk of colorectal cancer in individuals with hypercholesterolemia.
Methods and results: This study is based on the National Health Insurance Service-National Health Screening Cohort, conducted during 2002–2015. Statin users were classified as high and low users according to medication possession ratio (MPR). Statin nonusers comprised participants who did not use statins during the entire follow-up period. In total, 17,737 statin users and 13,412 statin nonusers were included in the analysis, with a median follow-up period of 12.7 years. Cox proportional hazards regression models were adopted after stepwise adjustment for confounders to investigate prospective association between statin usage and colorectal cancer risk. In total, 378 (2.3%) of 16,588 male participants and 239 (1.6%) of 14,561 female participants had colorectal cancer during the follow-up period. Compared to nonusers, fully adjusted hazard ratios (HRs) (95% confidence intervals [95% CIs]) for colorectal cancer risk in high statin users were 0.56 (0.42–0.75) in men and 0.64 (0.46–0.90) in women. In men, the fully adjusted HRs for proximal and rectal cancer for high users were 0.29 (0.15–0.56) and 0.52 (0.35–0.78), respectively, compared to those for nonusers. In women, statistical significance was seen only in rectal cancer (HR 0.43 [0.25–0.72]) but not in proximal or distal colon cancer.
Conclusions: High statin users with hypercholesterolemia were associated with lower risk of overall colorectal cancer, especially proximal colon cancer in men and rectal cancer in both sexes.

* Corresponding author. Department of Family Medicine, Chungbuk National University Hospital, Chungbuk National University College of Medicine, 1 Chungdae-ro, Seowon-gu, Cheongju, Chungcheongbuk-do, 28644, Republic of Korea. Fax: +82 43 269 6675.
** Corresponding author. Department of Information & Statistics, Chungbuk National University, 1 Chungdae-ro, Seowon-gu, Cheongju, Chungbuk, 28644, Republic of Korea. Fax: +82 43 273 5928.
E-mail addresses: joungyoun@chungbuk.ac.kr (J. Kim), kanght0818@gmail.com (H.-T. Kang).
[1] These co-corresponding authors equally contributed to this work.

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Introduction

Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide [1]. Its incidence is increasing globally in both sexes [2]. In Korea, malignant neoplasm is the leading cause of death. More than 200,000 cancer cases were newly diagnosed in 2015 [3]. The age-standardized incidence and mortality of colorectal cancer in Korea were 30.4 and 8.5 per 100,000 persons, respectively, in 2015 [3].

The best way to reduce cancer mortality is prevention and early detection. Health authorities in Korea provide national cancer screening program for the five most common cancer types, namely, stomach, liver, colorectal, breast, and uterine cervical cancer. Early diagnosis of colorectal cancer may contribute to better survivor outcomes and quality of life. Beneficial effects of aspirin on the prevention of colorectal cancer and reduced mortality may contribute to future reduction of the burden of illness [4,5]. The USPSTF recommended low-dose aspirin use for primary prevention of cardiovascular disease and colorectal cancer in adults aged 50–59 years who have high cardiovascular risk [6].

Dyslipidemia results in atherosclerotic cardiocerebrovascular diseases (CCVDs). Statins, known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, which inhibit the rate-limiting enzyme of the mevalonate pathway, are commonly used for primary and secondary prevention of these CCVDs in individuals with dyslipidemia. Because HMG-CoA reductase is involved in cholesterol synthesis and cell growth regulation, statins can have chemopreventive activity against cancer development and progression [7]. In vitro studies have supported a potential role for statin use to prevent colorectal cancer. Overexpression of HMG-CoA reductase has been observed in colorectal cancer cells [8]. Statins were shown to induce apoptosis in cancer cell lines in vitro through inhibition of HMG-CoA reductase [9,10].

However, findings on the association between colorectal cancer risk and statin use are not consistent. Several studies have shown a negative association but some have not [11–16]. Thus, the association between colorectal cancer development and statin use should be investigated in a larger population and for a longer duration. The proximal and distal colon and rectum have different embryologic origins, metabolic enzyme activities, physiological functions, fecal composition, bile acid metabolism, and intestinal transit times [17]. Some studies showed a null association between colorectal cancer risk and statin usage [12,13]. The reason might be due to the ignorance of anatomical sites. Studies have also demonstrated that the risk factors for colorectal cancer in Koreans had different impacts on other anatomical sites [18]. After further classification of colorectal cancer according to anatomical sites of origin, examination of the association between statin use and colorectal cancer risk may be useful, especially in large-scale cohort studies.

The aim of this study was to investigate the association between statin use and incident malignant neoplasm of the colorectum using a Korean National Health Insurance Service (NHIS)-National Health Screening Cohort (NHIS-HEALS) after adjusting for age and other confounding factors including socioeconomic status, health behaviors, and laboratory data. We further examined the relationship of statin use and site-specific cancer incidence after stratification according to degree of statin usage and anatomical classification of colorectum.

Methods

Study participants

In this study, we analyzed data from the National Health Insurance Service-Health Screening (NHIS-HEALS) cohort, conducted by NHIS from 2002 to 2015. The NHIS-HEALS cohort enrolled 514,795 participants, a nationally representative randomly selected population from the health screening program in 2002 and 2003 who were aged between 40 and 79 years. It provided demographic information such as socioeconomic variables; medical variables such as diagnostic code, drug prescriptions, medical institution, and death; and health checkup data such as health questionnaire surveys, physical examinations, and biochemical test results. A detailed description of the study design and methods has been published previously [19].

The participants in this study numbered 76,372 with hypercholesterolemia as follows: (1) total cholesterol level $\geq$250 mg/dL at initial screening or (2) taking antidyslipidemic medication during 2002–2003.

Figure 1 shows the flowchart for inclusion and exclusion. We excluded individuals who had been diagnosed with malignant neoplasia (10th edition of the International Classification of Diseases [ICD-10] codes C00–C97 or D00-D09 between 2002 and 2004), who died from any cause between 2002 and 2004, who had been diagnosed with ischemic heart disease (ICD-10 codes I20–I25) or cerebrovascular disease (ICD-10 codes I60–I69) between 2002 and 2003, who or were aged 79 years or older at the time of the initial screening. After these exclusions, 63,641 individuals were included.

We classified participants into two groups according to statin usage (statin users and nonusers). Statin users were defined as participants who had used statins during 2002–2003, and statin nonusers comprised participants who did not use statins during 2002–2015 despite having hypercholesterolemia. In total, 30,436 individuals who had started using a statin since January 1, 2004, were excluded. Incomplete data of the variables for confounders ($n = 2056$) were also excluded.

In total, 31,149 participants (16,588 men and 14,561 women) were included in this study, and statin users numbered 17,737 individuals (8100 men and 9637 women) (Fig. 1). The Institutional Review Board of Chungbuk National University approved the present study

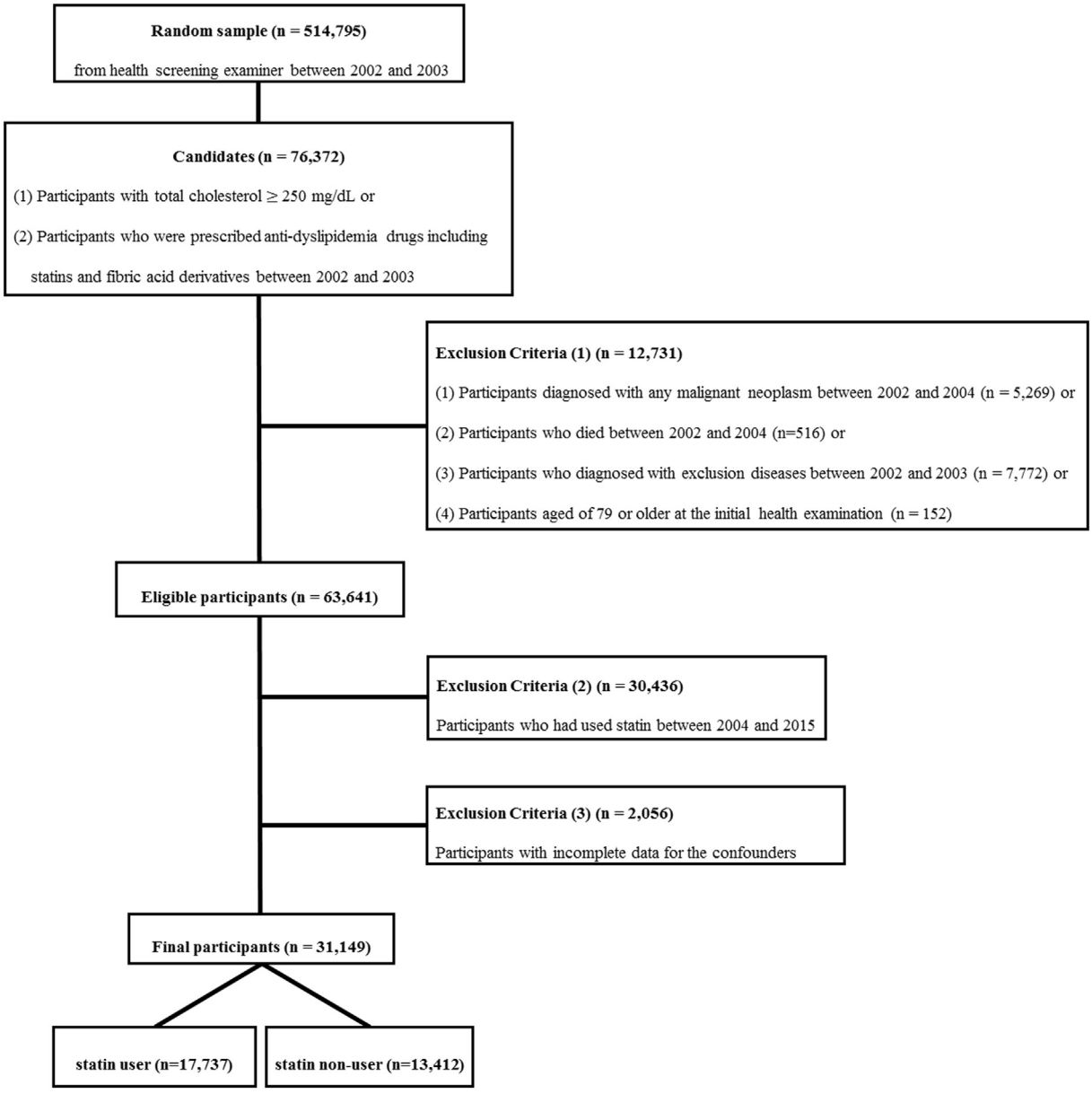

Figure 1 Flowchart of inclusion and exclusion.

(CBNU-201711-BMETC-564-01), which was conducted according to the guidelines of the Declaration of Helsinki (1975).

Variables

In this study, we included possible confounders of age, body mass index (BMI), blood pressure, blood glucose level, total cholesterol level, smoking status, alcohol consumption, physical activity, history of hypertension and diabetes, and income status at the time of screening during 2002−2003 Smoking status was categorized into ever smokers and never smokers. Alcohol consumption was divided into three groups − rare, less than twice per month; sometimes, twice per month to twice per week; and often, more than twice per week. Physical activity was categorized into three groups − rare, individuals who rarely incorporate exercise; sometimes, individuals who incorporate exercise between one and four days per week; and regular, individuals who incorporate exercise more than four days per week. History of hypertension and diabetes was defined using self-reported questionnaire. Income status was categorized into three groups − low, 0 to $\leq$30th percentile; middle, >30th to $\leq$70th percentile; and high, >70th to 100th percentile.

Assessment of statin usage

Statin users were defined as participants who used statin during 2002−2003, and statin nonusers comprised

participants who did not use statin during 2002–2015 despite hypercholesterolemia. The statins prescribed during the study period were pravastatin, simvastatin, atorvastatin, cerivastatin, lovastatin, fluvastatin, rosuvastatin, pitavastatin, and ezetimibe/simvastatin. Statin users were categorized into two groups (low and high users) according to the degree of statin usage based on Medication Possession Ratio (MPR). MPR was defined as the ratio of total prescription days of statin out of the total study period. In the statin user group, the study start date was defined as the first prescription date of statin. Otherwise, the study start date was differently defined as the first day of screening with total cholesterol level above 250 mg/dL or the first prescription date for other antidyslipidemic drug except statin in statin nonusers. For patients diagnosed with colorectal cancer during 2005–2015, the initial diagnosis date of colorectal cancer was the end date. If a patient was never diagnosed with colorectal cancer during the follow-up period, his/her study end date was the last screening date or the institution visiting date.

Operational definition of colorectal cancer

The definition of colorectal cancer was based on the main diagnosis with the ICD-10 code C18.0-C20.0 to reduce the possibility of false positives. To investigate the association between statin and anatomical site-specific risk of colorectal cancer, we discriminated malignant neoplasms of the proximal and distal colon and rectum using ICD-10 code of the main diagnosis, such as C18.0-C18.5, C18.6-C18.7, and C19–C20, respectively.

Statistical analysis

All data for continuous variables were presented as the mean ± standard error (SE). Data for categorical variables were presented as the percentage ± SE. To compare between groups, the chi-square test was performed for categorical variables and ANOVA for continuous variables. To assess the effect of statin usage, we compared the overall survival rates depending on statin usage. For this, we used the Kaplan-Meier estimates and log-rank test. We used the Cox proportional hazards model to estimate the hazard ratios for colorectal cancer risk and adjusted the effects of possible confounders for men and women separately. We performed two models of Cox proportional hazards analysis according to composition of confounders – (1) Model 1: age only, and (2) Model 2: all confounders under consideration (age, BMI, systolic blood pressure, glucose, total cholesterol, income status, smoking status, drinking status, physical activity, diabetes, and hypertension).

All statistical tests were two-tailed, and statistical significance was determined at $P < 0.05$. The statistical package SAS enterprise guide version 7.1 (SAS Inc., Cary, NC) and R studio version 3.3.3 were used to perform the analyses.

Results

In this study, 31,149 participants had a median follow-up of 12.7 years. Table 1 and Supplementary Table 1 show baseline characteristics according to statin use. Statin users were older than nonusers for both sexes. Statin users had higher BMI, systolic blood pressure, and glucose levels but lower total cholesterol level. Statin users likely had more diabetes mellitus and hypertension. In general, statin users had more regular physical activity and belonged to higher income groups.

Figure 2 demonstrates the significant difference in risk for overall and site-specific colorectal cancer incidence according to statin usage. For men, high statin users had the lowest incidence of overall colorectal, proximal colon, and rectal cancers (all p-values < 0.05). For women, the incidence of overall colorectal cancer (p-value $= 0.032$) and rectal cancer (p-value $= 0.002$) was significantly different among the three groups of statin usage.

The results from Cox proportional hazards regression models are provided in Tables 2 and 3. Compared to nonusers, estimates of HRs (95% CIs) for overall colorectal cancer in high statin users were 0.60 (0.46–0.79) in men and 0.64 (0.47–0.88) in women after adjusting for age only (Model 1). Fully adjusted HRs (95% CIs) of high users were 0.56 (0.42–0.75) and 0.64 (0.46–0.90) in men and women, respectively (Model 2). After stratifying colon into proximal colon, distal colon, and rectum according to anatomical site, the fully adjusted HRs for proximal colon cancer and rectal cancer in high users were 0.29 (0.15–0.56) and 0.52 (0.35–0.78) in men compared to those in nonusers, respectively. For women, adjusted HR for rectal cancer was 0.43 (0.25–0.72) and was not significant for proximal colon or distal colon.

For all subjects, the results of Cox proportional hazards regression analysis are shown in Supplementary Table 2. Compared to nonusers, fully adjusted HRs of high users for overall colorectal, proximal colon, and rectal cancer were 0.60 (0.45–0.80), 0.30 (0.16–0.57), and 0.57 (0.39–0.85), respectively. Supplementary Fig. 1 based on the Kaplan–Meier estimates shows that high users from all subjects had the lowest incidence of overall colorectal cancer and rectal cancer (all p-values < 0.01).

Discussion

The scientific debate continues regarding the association between statin use and risk of malignant neoplasm. In this study, we found that high statin users had lower risk of colorectal cancer incidence than nonusers with hypercholesterolemia. The findings were different according to sex and anatomical site of colorectum.

Statins inhibit HMG-CoA reductase in the mevalonate pathway. The mevalonate pathway produces mevalonic acids, which are precursors of cholesterol and some nonsterol isoprenoid derivatives. Isoprenoid derivatives play an important role in the regulation of various cellular functions including proliferation, differentiation, and

Table 1 Baseline characteristics.

Men	Non-users	Low-users	High-users	p-value
Number of subjects (%)	8488 (51.2)	4050 (24.4)	4050 (24.4)	
Age, years	51.2 ± 0.1	53.4 ± 0.1	54.5 ± 0.1	<0.001
BMI, kg/m^2	24.5 ± 0.0	25.0 ± 0.0	25.5 ± 0.0	<0.001
SBP, mmHg	129.6 ± 0.2	131.9 ± 0.3	135.0 ± 0.3	<0.001
Glucose	104.4 ± 0.6	107.8 ± 0.7	116.1 ± 0.8	<0.001
Total cholesterol	263.2 ± 0.5	226.6 ± 0.7	234.1 ± 0.8	<0.001
DM, %	2.9 ± 0.2	9.4 ± 0.5	16.3 ± 0.6	<0.001
Hypertension, %	5.0 ± 0.2	14.5 ± 0.6	23.6 ± 0.7	<0.001
Ever smokers, %	61.8 ± 0.5	55.8 ± 0.8	54.7 ± 0.8	<0.001
Drinking status, %				<0.001
Rare	32.9 ± 0.5	34.8 ± 0.7	36.7 ± 0.8	
Sometimes	46.7 ± 0.5	44.9 ± 0.8	45.2 ± 0.8	
Often	20.4 ± 0.4	20.3 ± 0.6	18.1 ± 0.6	
Physical activity, %				<0.001
Rare	48.5 ± 0.5	48.2 ± 0.8	43.2 ± 0.8	
Sometimes	43.0 ± 0.5	41.1 ± 0.8	43.3 ± 0.8	
Regular	8.4 ± 0.3	10.6 ± 0.5	13.5 ± 0.5	
Income status, %				<0.001
Low	20.6 ± 0.4	17.1 ± 0.6	15.8 ± 0.6	
Middle	32.2 ± 0.5	31.8 ± 0.7	28.8 ± 0.7	
High	47.2 ± 0.5	51.1 ± 0.8	55.4 ± 0.8	
Women				
Number of subjects (%)	4924 (33.8)	4818 (33.1)	4819 (33.1)	NA
Age, years	58.2 ± 0.1	58.7 ± 0.1	59.3 ± 0.1	<0.001
BMI, kg/m^2	24.3 ± 0.0	25.2 ± 0.0	25.4 ± 0.0	<0.001
SBP, mmHg	128.6 ± 0.3	131.1 ± 0.3	133.3 ± 0.3	<0.001
Glucose	103.7 ± 0.9	104.6 ± 0.6	108.8 ± 0.7	<0.001
Total cholesterol	266.9 ± 0.6	234.5 ± 0.7	239.2 ± 0.7	<0.001
DM, %	3.2 ± 0.3	10.1 ± 0.4	15.6 ± 0.5	<0.001
Hypertension, %	9.9 ± 0.4	20.5 ± 0.6	30.6 ± 0.7	<0.001
Ever smokers, %	4.7 ± 0.3	4.0 ± 0.3	3.9 ± 0.3	0.092
Drinking status, %				<0.001
Rare	83.5 ± 0.5	85.5 ± 0.5	88.4 ± 0.5	
Sometimes	14.4 ± 0.5	12.8 ± 0.5	10.4 ± 0.5	
Often	2.0 ± 0.2	1.7 ± 0.2	1.2 ± 0.2	
Physical activity, %				<0.001
Rare	70.3 ± 0.7	65.7 ± 0.7	59.3 ± 0.7	
Sometimes	20.4 ± 0.6	23.0 ± 0.6	27.6 ± 0.6	
Regular	9.3 ± 0.4	11.4 ± 0.5	13.2 ± 0.5	
Income status, %				<0.001
Low	31.6 ± 0.7	27.8 ± 0.6	23.1 ± 0.6	
Middle	31.8 ± 0.7	33.6 ± 0.7	32.0 ± 0.7	
High	36.6 ± 0.7	38.6 ± 0.7	44.9 ± 0.7	

Abbreviation: BMI, body mass index; SBP, systolic blood pressure; DM, diabetes mellitus.
Drinking status: Rare, less than twice per month; Sometimes, twice per month – twice per week; Often, more than twice per week.
Physical activity: Rare, less than once per week; Sometimes, 1–4 days per week; Regular, more than four days per week.
Income status: Low, 0 to ≤30th percentile of income; Middle, >30th to ≤70th percentile of income; High, >70th to 100th percentile of income.

survival [20,21]. Statins have been shown to arrest cell cycle progression [22], to induce apoptosis [23], to suppress angiogenesis [24], to inhibit low-grade chronic inflammation [25], and to alter adhesion and migration of tumor cells [26]. The anticancer effects of statins have been reported in colon cancer cells in vitro [27] and in rodent models [28]. A few studies have reported that statins are carcinogenic in animal models [29], but more evidence supports a chemopreventive role in cancers [21,30].

Colorectal cancer is the third incident malignant neoplasm and fourth cause of cancer death in Korea [3]. There is no doubt that the best option to alleviate the burden of cancer is prevention. Statins are the most prescribed medication to prevent CCVDs, which are the second and third cause of death, through pluripotent effects including lipid-lowering action. There have been several studies on the association between statin use and colorectal cancer risk. However, the results of these studies are inconsistent, with few studies reporting reduced risk. A previous meta-analysis conducted in 2007 by Bonovas et al. [12] did not support the inverse association between statin use and colorectal cancer risk using 18 studies published between 1995 and 2007. Nevertheless, another recent meta-analysis of 42 studies [14] suggested that statin use was associated with a modest risk reduction of colorectal cancer (RR = 0.90, 95% CI 0.86–0.95) and rectal cancer (RR = 0.81, 95% CI 0.66–0.99), consistent with the findings of present research.

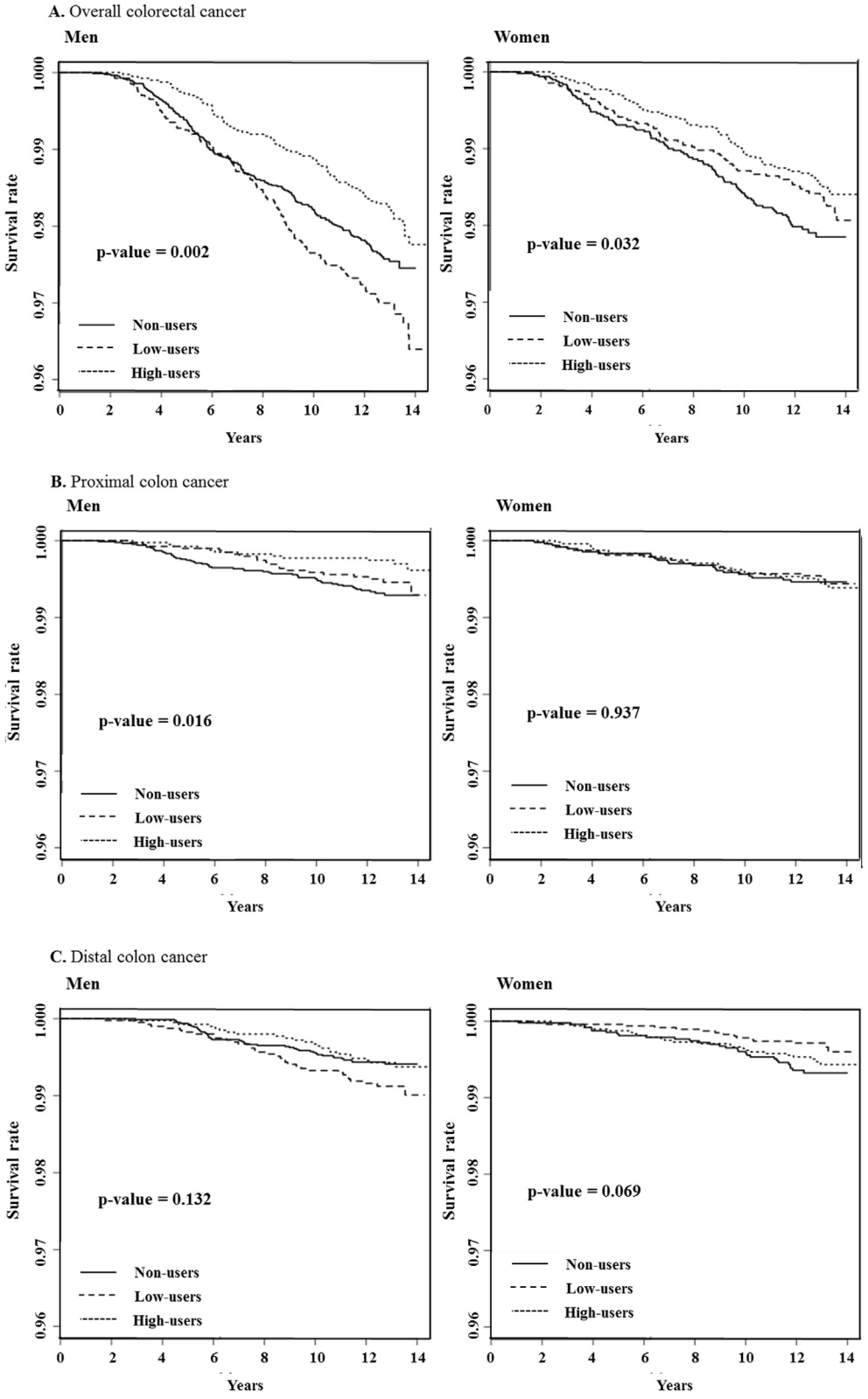

Figure 2 Kaplan-Meier estimates for overall and site-specific colorectal cancer risk according to statin usage. A. Overall colorectal cancer, B. Proximal colon cancer, C. Distal colon cancer, D. Rectal cancer. P-values were obtained from log-rank tests.

In our study, the risks of colorectal cancer were different according to anatomical site and sex. In men, the fully adjusted HRs for proximal and rectal cancer in high statin users were 0.29 (0.15–0.56) and 0.52 (0.35–0.78), respectively, compared to nonusers. In women, statistically significant risk reduction was observed only in rectal cancer (HR 0.43 [0.25–0.72]). In contrast, an association between statin usage and distal colon cancer development

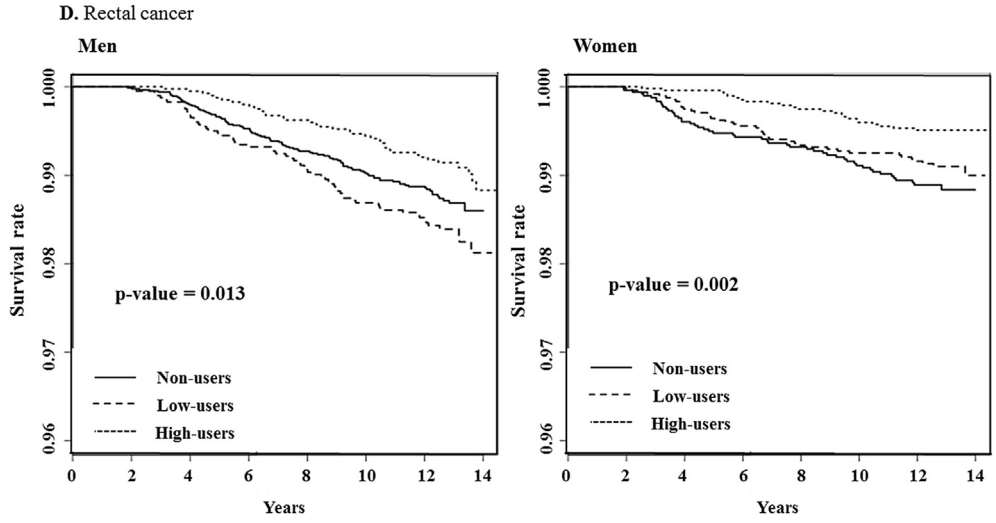

Figure 2 (*continued*).

Table 2 Crude and Adjusted association between Statin Use and risk of overall colorectal cancer.

Hazard ratios (95% confidence intervals)	Men		Women	
	Model 1	Model 2	Model 1	Model 2
Overall colorectal cancer				
Statin usage				
Low-users vs. nonusers	1.09 (0.86–1.37)	1.05 (0.82–1.35)	0.77 (0.57–1.04)	0.78 (0.57–1.07)
High-users vs. nonusers	0.60 (0.46–0.79)	0.56 (0.42–0.75)	0.64 (0.47–0.88)	0.64 (0.46–0.90)

Model 1: adjusted for age.
Model 2: adjusted for age, body mass index, systolic blood pressure, glucose, total cholesterol, income status (low, middle, and high), smoking status, alcohol consumption, physical activity, diabetes (yes or no), and hypertension (yes or no).

was not observed in either sex (Table 3). Statins also had different effects on colorectal cancer development depending on the combination of sex and statin usage. For example, in proximal colon cancer, the hazard difference between nonusers and high users depended on sex (p-value $\leq$ 0.015) (Supplementary Table 2).

This implies the possibility that the statins influenced the risks of proximal and distal colon and rectal cancers differently according to sex. According to previous studies, the sex differences in colorectal cancer are predominant in proximal colon cancer for women and distal colon cancer for men [31,32]. Both genetic and environmental factors

Table 3 Cox proportional hazards ratios for site-specific colorectal cancer according to statin use.

Hazard ratios (95% confidence intervals)	Men		Women	
	Model 1	Model 2	Model 1	Model 2
Proximal colon cancer				
Statin usage				
Low-users vs. nonusers	0.64 (0.38–1.06)	0.60 (0.35–1.03)	0.90 (0.51–1.60)	0.83 (0.46–1.52)
High-users vs. nonusers	0.32 (0.17–0.60)	0.29 (0.15–0.56)	0.96 (0.55–1.68)	0.87 (0.48–1.57)
Distal colon cancer				
Statin usage				
Low-users vs. nonusers	1.31 (0.84–2.05)	1.26 (0.78–2.04)	0.48 (0.26–0.90)	0.54 (0.28–1.03)
High-users vs. nonusers	0.80 (0.48–1.32)	0.73 (0.43–1.26)	0.76 (0.44–1.30)	0.88 (0.49–1.57)
Rectal cancer				
Statin usage				
Low-users vs. non-users	1.12 (0.82–1.54)	1.08 (0.77–1.52)	0.78 (0.52–1.17)	0.80 (0.52–1.23)
High-users vs. non-users	0.58 (0.39–0.85)	0.52 (0.35–0.78)	0.40 (0.25–0.66)	0.43 (0.25–0.72)

Model 1: adjusted for age.
Model 2: adjusted for age, body mass index, systolic blood pressure, glucose, total cholesterol, income status (low, middle, and high), smoking status, alcohol consumption, physical activity, diabetes (yes or no), and hypertension (yes or no).

can also affect sex differences in colorectal cancer development [32]. The proximal and distal colon and rectum have different embryological origins. These three parts of the colorectum have morphological, physiological, biochemical, and genetic differences. Site-specific cancers are sometimes thought to be distinct cancer types [33]. In addition, ethnic difference of colorectal cancer incidence was reported in the US [34]. Rectal cancer was most common for male Asian patients living in the US, whereas proximal colon cancer was most common for white and black patients among both men and women, as well as female Asian patients [34]. In addition, recent molecular studies [15,35] have suggested that proximal and distal colon and rectal cancer could have different molecular characteristics such as tumor methylation status, KRAS mutation, microsatellite instability, and CpG island methylator phenotype (CIMP) status. For example, high CIMP is mainly found in the proximal colon, whereas no-CIMP and microsatellite-stable tumors are mainly located in the distal colon [35]. Lee et al. [15] reported that statin usage reduced KRAS wild-type colorectal cancers (RR = 0.80, 95% CI = 0.60 to 1.06) and rectal cancer (RR = 0.59, 95% CI = 0.41 to 0.84). The above studies suggested that the risks of colorectal cancer could be different by anatomical site and molecular subtype.

This study has several limitations that should be considered for interpretation. First, although several potential confounding factors were adjusted for, some residual confounding factors could not be completely controlled in this study, including lifestyle factors and underlying genetic or familial conditions. We also could not include the nonstatin lipid-lowering agents as confounders because of limited data. A study demonstrated that most patients with diabetes (96.3% of all study participants) had received statin-based antidyslipidemic therapy (statin monotherapy and combination therapy), whereas only 4.7% received nonstatin lipid-lowering agents [36]. It might be because statin-based treatments were predominantly used in Koreans. Instead of nonstatin lipid-lowering agents, we adopted total cholesterol as the second-best option. Because of the problem of data access, we could not include hormone therapy as a confounder. The preceding meta-analysis suggested a reduced risk of colorectal cancer among women taking postmenopausal hormones [37]. However, according to a previous study of the national use of hormonal therapy in postmenopausal women in 2010, only 4.5% of women aged older than 50 years were receiving postmenopausal hormonal medication in Korea [38]. We thought that hormonal effects would be minimal if the rate of hormone therapy in postmenopausal women was not high. Second, we could not discriminate the types of statin, which are lipophilic, hydrophilic, or mixed. Previous studies have reported that statin types can have different effects on development, progression, and mortality of malignant neoplasms [39]. A previous cohort study in the Women's Health Initiative showed a marginal reduction in the risk of colorectal cancer associated with lipophilic statins [16]. Subsequent studies may require more accurate study design by including detailed medical records and classifying statins. Third, we could not check whether statin users took their medications as prescribed. To minimize misclassification, we used MPR, which is well correlated with patient compliance [40]. Fourth, there is limited information about colorectal cancer risk, such as history of inflammatory bowel disease, aspirin use, and meat consumption because the NHIS-HEALS cohort did not provide this information. Because the NHIS cohort was not linked to the data of Korea Central Cancer Registry by the National Cancer Center, there is possibility of misdiagnosis for colorectal cancer. For this reason, colorectal cancer in this study was defined using only the main diagnosis with the ICD-10 codes C18.0-C20.0 to reduce the possibility of false positives.

Nevertheless, this study demonstrated that real-world statin usage was prospectively associated with anatomical site-specific risk reduction of colorectal cancer development over a relatively long duration (median follow-up duration 12.7 years). Another strength is that this study included data from a large population, and the NHIS-HEALS cohort provided by NHIS is based on real-world measurement in the clinical setting. Korean public authorities recommend obligatory medical insurance to cover the entire Korean population. Because of this, the cohort well represents the entire Korean population.

In conclusion, statin high users with hypercholesterolemia had lower risk of colorectal cancers, especially proximal colon cancer in men and rectal cancer in both sexes.

Conflict of interest and disclosure

No conflicts of interest have been reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.04.002.

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