Colorectal Cancer Risks According to Sex Differences in Patients With Type II Diabetes Mellitus: A Korean Nationwide Population-Based Cohort Study

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INTRODUCTION: Developing colorectal cancer (CRC) poses challenges for patients with type II diabetes mellitus (T2DM). We investigated CRC risk factors in patients with T2DM.

METHODS: We retrospectively collected data from the National Health Insurance Corporation database, comprising approximately 97% of the Korean population. T2DM and CRC were defined according to *International Classification of Disease* codes (10th Revision) and claims data. Obesity was defined using body mass index (BMI); abdominal obesity was defined according to waist circumference. Other variables were defined using demographic, anthropometric, and laboratory data.

RESULTS: Overall, 2,591,149 patients with T2DM were analyzed. During the follow-up period (median, 5.4 years), 24,236 CRC cases were identified. Aging (≥70 years), male sex, smoking, alcohol consumption, hypertension, and insulin and/or sulfonylurea use were significant risk factors for CRC. In males, smoking and alcohol consumption were more likely to lead to CRC, whereas a BMI increase was a more significant risk factor in females. Females with a BMI ≥ 25 kg/m² and abdominal obesity were associated with an 18% increased risk of CRC compared with patients with normal weight and normal waist circumference (hazard ratio = 1.184, 95% confidence interval 1.123–1.25), whereas male patients with a BMI ≥ 25 kg/m² and abdominal obesity were associated with an 8% increased risk (hazard ratio = 1.087, 95% confidence interval 1.049–1.127).

DISCUSSION: Patients had CRC risk factors that differed according to sex. Smoking and heavy alcohol consumption were risks of CRC in males. Female patients with a BMI ≥ 25 kg/m² and abdominal obesity were at a higher risk of developing CRC than males.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer in Korea, and the CRC burden is rapidly increasing (1,2). According to a report published in 2011, the prevalence of type II diabetes mellitus (T2DM) in the Korean population aged ≥30 years was 12.4%, which was considered to be relatively high (3).

Several studies have previously reported an increased risk of CRC development in patients with T2DM compared with healthy individuals (4,5). Hyperinsulinemia due to insulin resistance in patients with T2DM may have a tumorigenic effect by affecting epithelial cell proliferation in CRC (6). Moreover, overexpression of insulin receptors may affect the development of CRC (7). Some Korean studies have also shown a positive correlation between T2DM and CRC (8–10). Therefore, the development of CRC in

Korean patients with T2DM can pose specific challenges. Obesity increases the risk of CRC (11) and has been reported to be a risk factor for CRC in patients with T2DM (5). However, most data have been reported on populations living in developed Western countries where the obesity criterion is higher (body mass index [BMI] ≥ 30 kg/m²) than for the Korean population (BMI ≥ 25 kg/m²) (12,13). Therefore, further research involving Asian populations is required.

In Korea, all health insurance associations have been integrated into the National Health Insurance Corporation (NHIC). The National Health Insurance Service covers the whole population as a social insurance benefit system. The NHIC database includes all claims data such as the *International Classification of Disease* (*ICD*) codes, information of treatment prescriptions, and details of national medical checkups (14,15). This information is available for

researchers once study protocols have been approved by an official review committee and upon receipt of payment for the data.

We analyzed the risk factors for CRC in a Korean cohort with T2DM using the NHIC database, and we investigated the effects of obesity on the risk of developing CRC.

METHODS

Data source and collection of the study population

The NHIC database stores data comprising approximately 97% of the enrolled Korean population who receive a semicompulsory medical examination biennially.

Data were collected from the medical records of 4,171,087 individuals with type II diabetes who were aged 20 years or older and had undergone an NHIC medical examination biennially or annually between 2009 and 2012. Of these individuals, 149,046 were excluded because of missing values such as laboratory findings. We also excluded those with overlapping data, where 2 or more examinations had been performed within the observation period (n = 1,393,059), and individuals who had been diagnosed previously (n = 37,833). Finally, 2,591,149 individuals were included in the study (Figure 1). The enrolled patients were followed up until December 2015 to examine the developing CRC.

The study was reviewed and approved by the Institutional Research Ethics Board of the Catholic University of Korea (VC17ZESI0110).

Definition of T2DM and CRC

T2DM was defined as ≥1 claim per year for the prescription of antidiabetic medications based on the *ICD 10th Revision* (*ICD-10*), codes E11 to E14, or a fasting glucose level ≥126 mg/dL (obtained from the health examination database).

The primary outcome was newly diagnosed CRC, which was defined using *ICD-10* codes (C180-200) and the National Cancer Registry database.

Covariates

The covariates used in the multivariate analysis were collected using a standardized self-reported questionnaire and data derived from the medical examination. The covariates were as follows: age (years), sex, smoking (never, former, and current), alcohol consumption (none, mild, and heavy), regular exercise (no and yes), yearly income (lower quintile vs the remaining quintiles), residency (rural and urban), BMI, waist circumference (WC), hypertension, dyslipidemia, complications of diabetes (history of stroke and cardiovascular events), antidiabetic medications (insulin, sulfonylurea, metformin, meglitinide, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, and acarbose), and duration of diabetes (years).

Individuals whose alcohol consumption was <30 g per day were defined as mild drinkers, whereas individuals whose alcohol consumption was >30 g per day were defined as heavy drinkers. Regular exercise was based on the frequency and intensity of activity per week. We defined hypertension when at least 1 claim per year for the prescription of an antihypertensive agent under *ICD-10* codes I10-I15 was confirmed. Dyslipidemia was defined when at least 1 claim had been documented per year for the prescription of antidyslipidemic agents under *ICD-10* codes E78 (16). Information concerning history of stroke and cardiovascular events was obtained from the self-reported questionnaire. The use of antidiabetic medication was defined as involving at least 1 claim per year for the relevant prescription.

In our study, we defined obesity using a BMI cutoff of 25 kg/m². Abdominal obesity was defined as a WC of ≥90 cm for men and a WC of ≥80 cm for women (17).

Statistical analyses

Data were presented as mean ± SD for normally distributed continuous variables and as proportions for categorical variables. The Student *t* test was used to analyze continuous variables, and the differences between nominal variables were compared using the χ^2 test. Incidence rates for cancers were calculated by dividing the number of events by person-years at risk. An age-sex adjusted model was used to reduce the variables, which was then analyzed in a multivariate analysis. A Cox regression model was used to determine the independent association of covariates with the risk of cancer incidence. This was undertaken through controlling for age, sex, BMI, smoking, alcohol consumption, exercise, income, hypertension, dyslipidemia, history of stroke and cardiovascular events, nephropathy, retinopathy, T2DM medications, and T2DM disease duration. The association between obesity/abdominal obesity and CRC was analyzed after controlling for variables such as age, sex, smoking, alcohol consumption, and exercise. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org). A 2-sided *P* value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics

During the follow-up period (median, 5.4 years), 24,236 cases of CRC had occurred. The incidence of CRC in patients with T2DM was 2.3 per 1,000 person-years. Baseline characteristics of the study participants are shown in Table 1. In the age-sex adjusted model, the risk of CRC was significantly associated with the following: aging, male sex (adjusted hazard ratio [aHR] = 1.840, 95% confidence interval [CI] 1.751–1.848), former smoker (aHR = 1.138, 95% CI 1.097–1.181), current smoker (aHR = 1.137, 95% CI 1.096–1.18), mild alcohol consumption (aHR = 1.173, 95% CI 1.137–1.21), heavy alcohol consumption (aHR = 1.333, 95% CI 1.271–1.398), BMI ≥ 30 kg/m² (aHR = 1.110, 95% CI 1.048–1.176), abdominal obesity (aHR = 1.093, 95% CI 1.064–1.122), hypertension (aHR = 1.089, 95% CI 1.059–1.119), and a duration of T2DM of ≥5 years (aHR = 1.050, 95% CI 1.022–1.078) (Table 2).
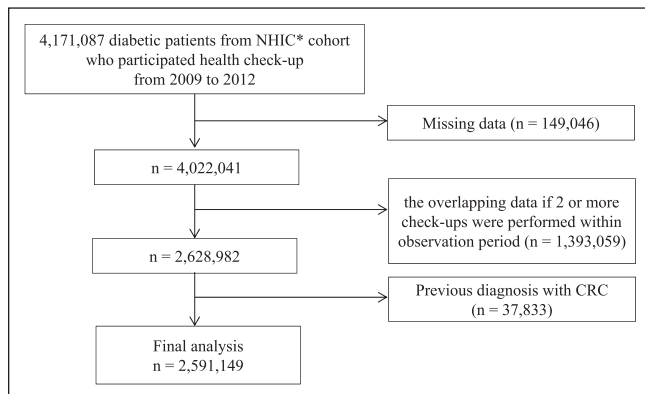
Figure 1. Flowchart showing the enrollment process for the study cohort. *NHIC, National Health Insurance Corporation. CRC, colorectal cancer.

Table 1. Baseline characteristics of the study participants

	CRC	
	No (n = 2,566,913)	Yes (n = 24,236)
Age, y		
<40	165,442 (6.45)	174 (0.72)
40–<50	475,357 (18.52)	1,552 (6.4)
50–<60	759,073 (29.57)	5,868 (24.21)
60–<70	686,253 (26.73)	9,233 (38.1)
≥70	480,788 (18.73)	7,409 (30.57)
Male (n, %)	1,537,995 (59.92)	16,162 (66.69)
Smoking (n, %)		
Nonsmoker	1,428,972 (55.67)	12,913 (53.28)
Former smoker	476,573 (18.57)	5,569 (22.98)
Current smoker	661,368 (25.77)	5,754 (23.74)
Alcohol consumption		
Non	1,471,798 (57.34)	13,717 (56.6)
Mild	874,483 (34.07)	8,226 (33.94)
Heavy	220,632 (8.6)	2,293 (9.46)
Regular exercise, yes (n, %)	657,478 (25.61)	6,559 (27.06)
Lower quintile of yearly income (n, %)	685,918 (26.72)	6,315 (26.06)
Residency, rural (n, %)	1,437,507 (56.07)	13,541 (55.94)
BMI (kg/m^2, mean ± SD)	25.08 ± 3.34	24.92 ± 3.18
Obesity (n, %)	1,238,895 (48.26)	11,341 (40.74)
WC (cm, mean ± SD)	85.48 ± 8.54	86.46 ± 8.3
Abdominal obesity (n, %)	1,232,574 (48.02)	12,039 (49.67)
Hypertension (n, %)	1,464,079 (57.04)	16,021 (66.1)
Dyslipidemia (n, %)	1,097,726 (42.76)	10,172 (41.97)
Diabetic complications (n, %)		
Stroke	55,701 (2.8)	598 (2.97)
Cardiovascular events	128,134 (6.41)	1,412 (7)
Duration of DM ≥ 5 y (n, %)	792,988 (30.89)	9,215 (38.02)
Antidiabetic drugs (n, %)		
Insulin	206,861 (8.06)	2,297 (9.48)
Sulfonylurea	1,067,102 (41.57)	12,507 (51.61)
Metformin	1,187,807 (46.27)	12,374 (51.06)
Meglitinide	57,174 (2.23)	659 (2.72)
Thiazolidinedione	163,852 (6.38)	1,766 (7.29)
Dipeptidyl peptidase-4 inhibitor	243,102 (9.47)	2,156 (8.9)
Acarbose	286,939 (11.18)	3,445 (14.21)

BMI, body mass index; CRC, colorectal cancer; DM, diabetes mellitus; WC, waist circumference.

Risk factors for CRC in patients with T2DM

In the Cox regression model, aging, male sex (hazard ratio [HR] = 1.571, 95% CI 1.511–1.633), BMI ≥ 30 kg/m² (HR = 1.100, 95% CI 1.033–1.172), former smoker (HR = 1.108, 95% CI 1.064–1.154), current smoker (HR = 1.101, 95% CI 1.056–1.148), mild alcohol consumption (HR = 1.136, 95% CI 1.096–1.176), heavy alcohol consumption (HR = 1.266, 95% CI 1.2–1.337), hypertension (HR = 1.07, 95% CI 1.037–1.104), and insulin treatment (HR = 1.078, 95% CI 1.027–1.131) and/or sulfonylurea (HR = 1.091, 95% CI 1.057–1.127) were significant risk factors for CRC. Dyslipidemia (HR = 0.949, 95% CI 0.922–0.977) and a history of stroke (HR = 0.894, 95% CI 0.822–0.972) and a cardiovascular event (HR = 0.910, 95% CI 0.86–0.963) were associated with a decreased risk of CRC.

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Table 2. Risk factors for colorectal cancer in patients with diabetes (age- and sex-adjusted model)

	Events	Duration (years)	IR (per 1,000 person-years)	HR (95% CI)
Age, y				
<40	174	656,560.29	0.26502	1 (ref.)
40–<50	1,552	1,921,491.88	0.80771	3.231 (2.763–3.778)
50–<60	5,868	3,114,366.69	1.88417	7.861 (6.762–9.138)
60–<70	9,233	2,908,770.29	3.17419	14.010 (12.06–16.275)
≥70	7,409	1,931,028.58	3.83682	17.994 (15.482–20.913)
Sex				
Male	16,162	6,262,914.49	2.58059	1.840 (1.751–1.848)
Female	8,074	4,269,303.24	1.89118	1 (ref.)
Smoking				
Nonsmoker	12,913	5,932,193.96	2.17677	1 (ref.)
Former smoker	5,569	1,943,496.99	2.86545	1.138 (1.097–1.181)
Current smoker	5,754	2,656,526.79	2.16599	1.137 (1.096–1.18)
Alcohol consumption				
Non	13,717	6,071,603.81	2.25921	1 (ref.)
Mild	8,226	3,564,910.35	2.30749	1.173 (1.137–1.21)
Heavy	2,293	895,703.57	2.56	1.333 (1.271–1.398)
Regular exercise				
No	17,677	7,786,741.87	2.27014	1 (ref.)
Yes	6,559	2,745,475.86	2.38902	1.014 (0.986–1.044)
Income status				
Others	17,921	7,739,873.39	2.31541	1 (ref.)
Lowest quantile	6,315	2,792,344.34	2.26154	1.015 (0.986–1.044)
Residence				
Urban	10,666	4,637,791.77	2.2998	1 (ref.)
Rural	13,541	5,884,482.18	2.30114	0.986 (0.962–1.012)
BMI in 5 levels (kg/m^2)				
<18.5	352	146,750.15	2.39863	0.887 (0.796–0.987)
18.5–<23	6,252	2,610,101.44	2.39531	1 (ref.)
23–<25	6,291	2,678,567.59	2.34864	1.014 (0.979–1.05)
25–<30	9,874	4,322,782.4	2.28418	1.064 (1.031–1.099)
≥30	1,467	774016.15	1.89531	1.110 (1.048–1.176)
Abdominal obesity				
No	12,197	5,440,153.89	2.24203	1 (ref.)
Yes	12,039	5,092,063.84	2.36427	1.093 (1.064–1.122)
Hypertension				
No	8,215	4,499,080.13	1.82593	1 (ref.)
Yes	16,021	6,033,137.6	2.6555	1.089 (1.059–1.119)
Dyslipidemia				
No	14,064	6,019,672.22	2.33634	1 (ref.)
Yes	10,172	4,512,545.5	2.25416	0.988 (0.963–1.014)
Stroke				
No	19,518	8,178,783.71	2.38642	1 (ref.)
Yes	598	222,804.41	2.68397	0.854 (0.787–0.927)

Table 2. (*continued*)

	Events	Duration (years)	IR (per 1,000 person-years)	HR (95% CI)
Cardiovascular events				
No	18,751	7,899,126.98	2.37381	1 (ref.)
Yes	1,412	520,747.64	2.71149	0.881 (0.834–0.93)
Duration of DM				
<5 y	15,021	7,193,683.55	2.08808	1 (ref.)
≥5 y	9,215	3,338,534.18	2.76019	1.050 (1.022–1.078)
Insulin				
No	21,939	9,690,716.46	2.26392	1 (ref.)
Yes	2,297	841,501.27	2.72965	1.080 (1.035–1.128)
Sulfonylurea				
No	11,729	5,892,106.6	1.99063	1 (ref.)
Yes	12,507	4,640,111.13	2.69541	1.108 (1.08–1.137)
Metformin				
No	11,862	5,578,914.63	2.12622	1 (ref.)
Yes	12,374	4,953,303.1	2.49813	1.039 (1.013–1.066)
Meglitinide				
No	23,577	10,280,127.39	2.29345	1 (ref.)
Yes	659	252,090.33	2.61414	0.995 (0.921–1.075)
Thiazolidinedione				
No	22,470	9,795,408.07	2.29393	1 (ref.)
Yes	1,766	736,809.66	2.39682	1.007 (0.959–1.057)
Dipeptidyl peptidase-4 inhibitor				
No	22,080	9,605,330.98	2.29872	1 (ref.)
Yes	2,156	926,886.75	2.32607	1.040 (0.995–1.087)
Acarbose				
No	20,791	9,267,460.73	2.24344	1 (ref.)
Yes	3,445	1,264,757	2.72384	1.036 (1–1.075)

BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; IR, incidence rate; ref, reference.

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In male patients, smoking (former smoker [HR = 1.117, 95% CI 1.07–1.165] and current smoker [HR = 1.125, 95% CI 1.076–1.176]) and alcohol consumption (mild drinking [HR = 1.15, 95% CI 1.107–1.195] and heavy drinking [HR = 1.288, 95% CI 1.219–1.362]) were more likely to lead to the development of CRC than in females. Treatment with metformin (HR = 0.955, 95% CI 0.918–0.993) was related to a decreased risk of CRC in male patients. In female patients, an increase in BMI was a significant risk factor for CRC compared to male patients (Table 3).

Effect of BMI and WC on the risk of CRC in patients with T2DM
The risk of CRC according to the different BMI and WC levels was analyzed to determine whether BMI or WC had a stronger association with CRC (Figure 2). Increased BMI levels tended to be more associated with developing CRC in females than in males (Figure 2a), and a high WC was a significant risk factor for all patients with CRC (Figure 2b).

Considering both BMI and WC, BMI ≥ 25 kg/m² or abdominal obesity alone did not affect the risk of CRC regardless of sex (Table 4). However, patients with BMI ≥ 25 kg/m² and abdominal obesity were associated with a 10% increased risk of CRC compared with patients with a normal weight and a normal WC (HR = 1.105, 95% CI 1.073–1.138). Male patients with a BMI ≥ 25 kg/m² and abdominal obesity were associated with an 8% increased risk of CRC compared with patients with normal weight and normal WC (HR = 1.087, 95% CI 1.049–1.127), whereas female patients with a BMI ≥ 25 kg/m² and abdominal obesity were associated with an 18% increased risk (HR = 1.184, 95% CI 1.123–1.25). A BMI ≥ 25 kg/m² and abdominal obesity had a synergistic effect on developing CRC, and female patients with a BMI ≥ 25 kg/m² and abdominal obesity were at a higher risk of developing CRC than male patients.

DISCUSSION
It has been reported that T2DM increases the risk of CRC by 30%–40% (18,19). In this study, the incidence of CRC in patients with T2DM was relatively high (2.3 per 1,000 person-years) compared with the reported 0.6 per 1,000 person-years of those surveyed among the Korean population in 2012 (20).

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Table 3. Risk factors for colorectal cancer in patients with diabetes (multivariate Cox regression model)

	HR (95% CI)		
	Total	Male	Female
Age, y			
<40	1 (ref.)	1 (ref.)	1 (ref.)
40–<50	3.194 (2.648–3.852)	3.271 (2.65–4.038)	1.971 (1.299–2.99)
50–<60	7.804 (6.511–9.354)	8.580 (7.003–10.512)	3.556 (2.37–5.334)
60–<70	14.127 (11.787–16.932)	16.491 (13.459–20.206)	5.501 (3.67–8.247)
≥70	18.469 (15.391–22.162)	21.489 (17.505–26.379)	7.396 (4.93–11.095)
Male	1.571 (1.511–1.633)		
BMI in 5 levels (kg/m^2)			
<18.5	0.939 (0.829–1.062)	0.941 (0.81–1.093)	0.929 (0.745–1.159)
18.5–<23	1 (ref.)	1 (ref.)	1 (ref.)
23–<25	0.989 (0.951–1.028)	0.974 (0.929–1.02)	1.032 (0.962–1.106)
25–<30	1.034 (0.998–1.072)	0.999 (0.956–1.044)	1.132 (1.064–1.205)
≥30	1.100 (1.033–1.172)	1.055 (0.965–1.153)	1.194 (1.088–1.31)
Smoking (no)			
Former smoker	1.108 (1.064–1.154)	1.117 (1.07–1.165)	1.143 (0.94–1.389)
Current smoker	1.101 (1.056–1.148)	1.125 (1.076–1.176)	1.028 (0.894–1.182)
Alcohol consumption (no)			
Mild	1.136 (1.096–1.176)	1.15 (1.107–1.195)	1.065 (0.977–1.161)
Heavy	1.266 (1.2–1.337)	1.288 (1.219–1.362)	1.079 (0.727–1.603)
Regular exercise (yes)	0.970 (0.94–1.001)	0.957 (0.921–0.993)	0.986 (0.931–1.045)
Lowest quintile of yearly income	0.983 (0.952–1.015)	0.984 (0.946–1.024)	0.959 (0.908–1.012)
Hypertension (yes)	1.070 (1.037–1.104)	1.102 (1.061–1.145)	1.012 (0.958–1.069)
Dyslipidemia (yes)	0.949 (0.922–0.977)	0.942 (0.909–0.977)	0.971 (0.925–1.019)
Stroke (yes)	0.894 (0.822–0.972)	0.920 (0.832–1.016)	0.839 (0.72–0.978)
Cardiovascular events (yes)	0.910 (0.86–0.963)	0.900 (0.837–0.967)	0.934 (0.853–1.023)
Insulin (yes)	1.078 (1.027–1.131)	1.091 (1.026–1.16)	1.050 (0.97–1.136)
Sulfonylurea (yes)	1.091 (1.057–1.127)	1.133 (1.088–1.179)	1.023 (0.969–1.079)
Metformin (yes)	0.979 (0.949–1.01)	0.955 (0.918–0.993)	1.015 (0.963–1.07)
Meglitinide (yes)	0.977 (0.9–1.062)	0.984 (0.887–1.091)	0.963 (0.838–1.106)
Thiazolidinedione (yes)	0.962 (0.913–1.013)	0.964 (0.904–1.028)	0.950 (0.87–1.038)
Dipeptidyl peptidase-4 inhibitor (yes)	1.032 (0.981–1.086)	1.012 (0.949–1.08)	1.063 (0.98–1.153)
Acarbose (yes)	1.001 (0.961–1.042)	1.015 (0.964–1.068)	0.973 (0.909–1.041)
Duration of DM (≥5 y)	1.009 (0.976–1.042)	0.993 (0.954–1.035)	1.039 (0.983–1.098)

BMI, body mass index; CI, confidence interval; HR, hazard ratio; DM, diabetes mellitus; ref, reference.

Aging, male sex, and smoking are well-known risk factors for CRC in the general population (21). Metabolic disturbance such as dyslipidemia, hypertension, T2DM, and obesity have been reported to be risk factors for CRC not only among populations in developed Western countries but also among Korean populations (5,22,23). To our knowledge, this study is the first to investigate Korean patients with T2DM and assess the risk of CRC. In this study, established risk factors such as aging, male sex, smoking, or hypertension in the general population were also identified as significant risk factors. Interestingly, the significant risk factors differed according to sex. In men, smoking and alcohol consumption increased the risk of CRC and regular exercise decreased the risk, indicating that lifestyle itself had a significant effect on developing CRC. In terms of alcohol consumption, some previous studies have reported a cutoff of 50 g per day for drinking, above which the risk of CRC increases (24,25). However, we revealed that even lower doses of alcohol intake (<30 g per day) would increase the risk. Obesity, represented as a high BMI, also increased the risk of CRC; however, this was a more significant risk factor in women. Considering these results, physicians may be able to tailor their advice to their male and female patients with T2DM more effectively to reduce the development of CRC.
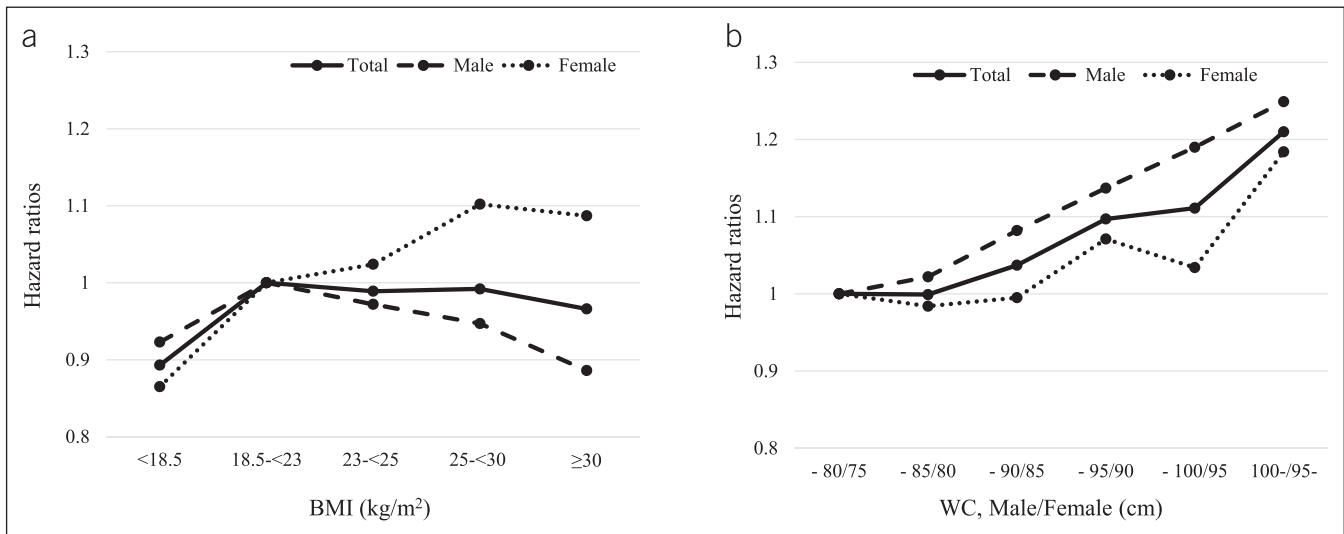
Figure 2. Effect of BMI and WC on the risk of CRC in patients with T2DM. (**a**) Development of CRC depending on changing BMI; adjusted for age, sex, smoking, alcohol consumption, regular exercise, and BMI. (**b**) Development of CRC depending on changing WC; adjusted for age, sex, smoking, alcohol consumption, regular exercise, and WC. BMI, body mass index; CRC, colorectal cancer; WC, waist circumference.

The effect of antidiabetic medication on the development of CRC has been studied. Metformin has been shown to lower the incidence of CRC, and insulin or insulin secretagogues have been identified as risk factors for CRC (26–29). Similarly, in this study, insulin and sulfonylurea were identified as significant risk factors for CRC, and metformin significantly lowered the risk for men in the multivariate analysis.

Patients with a history of dyslipidemia, stroke, and cardiovascular events were found to have a low incidence of CRC. This may have been due to the increasing possibility of death owing to the life-threatening nature of the complications, low CRC detection rate due to fewer colonoscopy examinations in patients with comorbidities or because of aspirin/statin use. Several studies have reported that the use of aspirin and statins is a preventive factor in CRC development (30,31).

A noteworthy aspect of our study concerns how obesity was found to affect CRC in patients with T2DM. The prevalence of obesity in Korea has been gradually increasing (32). Obesity is associated with not only metabolic diseases but also with cancers, resulting in increased medical expenditure (33–36), and has become socially more problematic in Korea. Generally, visceral obesity has been considered to be a more important factor in colorectal carcinogenesis than a high BMI (37). We also found that abdominal obesity correlated more with developing CRC than a high BMI in patients with T2DM. However, distinct from other studies considering only 1 variable or each variable separately (WC or BMI) (5,13,23,37,38), a high WC and BMI had a synergistic effect on developing CRC, and this effect was highly sensitive in females, whereas a high BMI (≥ 25 kg/m^2) or abdominal obesity alone did not increase the risk of CRC.

The underlying mechanisms concerning the relationship between obesity and CRC are not well known. It has been suggested that metabolic syndrome, insulin resistance, and altered levels of adipocytokines may play a role in obesity-associated colorectal carcinogenesis (13). A recent study reported that obesity, especially higher WC, was more associated with CRC in females, and explained as being due to hormonal metabolism. Postmenopausal women who

comprised most females in that study had changes in fat distribution, resulting in increased visceral fat depots, and this central obesity was related to an increase in androgenic activity in postmenopausal women (38). Similarly, most female patients enrolled in the study were also aged >50 years, and these factors might explain these results. Although the decreased protective effect of estrogen, attributable to the induction of apoptosis and inhibition of cell proliferation (39), might explain the results in that study, it is not clear why obesity was a greater CRC risk factor in female patients with T2DM. Although different sex susceptibility to CRC has been discussed in terms of obesity, a meta-analysis showed that BMI appeared to be consistently associated with an increased risk of CRC in men, but less so in women (13). Similarly, a recent Korean study showed that a high BMI (≥ 25 kg/m^2) significantly increased the risk of CRC in men but not in women in the general population (23). Further studies are required to explain different sex susceptibility in relation to T2DM.

The major strengths of our study comprise the following: (i) this is the first study to analyze the risk factors of CRC in patients with T2DM using a nationwide, population-based cohort; (ii) we analyzed the data using a large number of covariates as we were able to use the data and include information derived from detailed questionnaires in the national checkup program; and (iii) we identified the difference in risk factors according to sex and also confirmed the effect of BMI and WC on elevated risk of CRC in patients with T2DM. The results of the study may be a useful foundation for developing clinical management guidelines that focus on advising patients with T2DM on the risks of developing CRC. Our study had some limitations, as follows: (i) the NHIC database does not include HbA1c values, and therefore, we defined T2DM with *ICD* codes, claims indicating diabetes medications, and fasting glucose levels; (ii) our registry only held data that indicated whether antidiabetic medication had been used or not. The precise duration of medication and the combination effect of medications were not considered in the analysis; and (iii) our registry did not include the changes in BMI and WC during the study period. Nevertheless, this was a large-scale population-based study, and the results are likely to be meaningful.

Table 4. Impact of obesity on the risk of colorectal cancer in patients with DM

Obesity[a]	Abdominal obesity[b]	Total				Male				Female			
		Events	Duration (years)	IR (per 1,000 person-years)	HR[c] (95% CI)	Events	Duration (years)	IR (per 1,000 person-years)	HR[c] (95% CI)	Events	Duration (years)	IR (per 1,000 person-years)	HR[c] (95% CI)
No	No	9,798	4,179,446.32	2.34433	1 (ref.)	7,752	2,913,568.46	2.66065	1 (ref.)	2,046	1,265,877.86	1.61627	1 (ref.)
	Yes	3,097	1,255,972.86	2.46582	1 (0.959–1.043)	1,261	345,376.22	3.65109	1.043 (0.983–1.107)	1,836	910,596.64	2.01626	1.038 (0.974–1.106)
Yes	No	2,399	1,260,707.57	1.9029	0.947 (0.905–0.99)	2,141	1,092,185.36	1.96029	0.958 (0.913–1.005)	258	168,522.21	1.53096	1.058 (0.929–1.204)
	Yes	8,942	3,836,090.98	2.33102	1.105 (1.073–1.138)	5,008	1,911,784.45	2.61954	1.087 (1.049–1.127)	3,934	1,924,306.53	2.04437	1.184 (1.123–1.25)
	P-value				<0.0001				<0.0001				<0.0001

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; IR, incidence rate; ref, reference.
[a]Obesity was defined with a body mass index cutoff of 25 kg/m^2.
[b]Abdominal obesity defined as ≥90 cm for men and ≥80 cm for women.
[c]Adjusted for age, sex, smoking, alcohol consumption, and exercise.

In conclusion, our nationwide and population-based cohort study showed that patients with T2DM were associated with specific risk factors that differed depending on sex. A high BMI and abdominal obesity had a synergistic effect on elevating the risk of CRC, and female patients (BMI ≥ 25 kg/m^2) with abdominal obesity were at a higher risk of developing CRC than male patients. Our results may be useful for clinicians working to prevent CRC and educate patients with T2DM of the sex-specific risk factors of CRC in such instances.

CONFLICTS OF INTEREST

Study Highlights

WHAT IS KNOWN

✓ Developing CRC poses challenges for patients with T2DM.

WHAT IS NEW HERE

✓ Significant risk factors for patients with CRC and T2DM included smoking and alcohol consumption in men and increased BMI in women.

✓ Considering both BMI and WC, female patients with a BMI ≥ 25 kg/m^2 and abdominal obesity were at a higher risk of developing CRC than male patients.

TRANSLATIONAL IMPACT

✓ Individual risk factors for CRC in men and women should be kept in mind in the management of patients with T2DM.

REFERENCES

1. Shin A, Kim KZ, Jung KW, et al. Increasing trend of colorectal cancer incidence in Korea, 1999-2009. Cancer Res Treat 2012;44:219–26.
2. Jung KW, Won YJ, Kong HJ, et al. Cancer statistics in Korea: Incidence, mortality, survival, and prevalence in 2015. Cancer Res Treat 2018;50:303–16.
3. Jeon JY, Ko SH, Kwon HS, et al. Prevalence of diabetes and prediabetes according to fasting plasma glucose and HbA1c. Diabetes Metab J 2013;37:349–57.
4. Larsson SC, Orsini N, Wolk A. Diabetes mellitus and risk of colorectal cancer: A meta-analysis. J Natl Cancer Inst 2005;97:1679–87.
5. Peeters PJ, Bazelier MT, Leufkens HG, et al. The risk of colorectal cancer in patients with type 2 diabetes: Associations with treatment stage and obesity. Diabetes Care 2015;38:495–502.
6. Tran TT, Naigamwalla D, Oprescu AI, et al. Hyperinsulinemia, but not other factors associated with insulin resistance, acutely enhances colorectal epithelial proliferation in vivo. Endocrinology 2006;147:1830–7.
7. Kiunga GA, Raju J, Sabljic N, et al. Elevated insulin receptor protein expression in experimentally induced colonic tumors. Cancer Lett 2004;211:145–53.

8. Jee SH, Ohrr H, Sull JW, et al. Fasting serum glucose level and cancer risk in Korean men and women. JAMA 2005;293:194–202.

9. Shin HY, Jung KJ, Linton JA, et al. Association between fasting serum glucose levels and incidence of colorectal cancer in Korean men: The Korean Cancer Prevention Study-II. Metab Clin Exp 2014;63:1250–6.

10. Woo H, Lee J, Lee J, et al. Diabetes mellitus and site-specific colorectal cancer risk in Korea: A Case-control study. J Prev Med Public Health 2016;49:45–52.

11. Larsson SC, Wolk A. Obesity and colon and rectal cancer risk: A meta-analysis of prospective studies. Am J Clin Nutr 2007;86:556–65.

12. Kim MK, Lee WY, Kang JH, et al. 2014 Clinical practice guidelines for overweight and obesity in Korea. Endocrinol Metab (Seoul) 2014;29:405–9.

13. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut 2013;62:933–47.

14. Song SO, Jung CH, Song YD, et al. Background and data configuration process of a nationwide population-based study using the Korean national health insurance system. Diabetes Metab J 2014;38:395–403.

15. Lee J, Lee JS, Park SH, et al. Cohort profile: The National Health Insurance Service-National Sample Cohort (NHIS-NSC), South Korea. Int J Epidemiol 2017;46:e15.

16. Yang HK, Han K, Kwon HS, et al. Obesity, metabolic health, and mortality in adults: A nationwide population-based study in Korea. Sci Rep 2016;6:30329.

17. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—A new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet Med 2006;23:469–80.

18. Yuhara H, Steinmaus C, Cohen SE, et al. Is diabetes mellitus an independent risk factor for colon and rectal cancer? Am J Gastroenterol 2011;106:1911–21; quiz 1922.

19. Yang YX, Hennessy S, Lewis JD. Type 2 diabetes mellitus and the risk of colorectal cancer. Clin Gastroenterol Hepatol 2005;3:587–94.

20. Jung KW, Won YJ, Kong HJ, et al. Cancer statistics in Korea: Incidence, mortality, survival, and prevalence in 2012. Cancer Res Treat 2015;47:127–41.

21. Yeoh KG, Ho KY, Chiu HM, et al. The Asia-Pacific Colorectal Screening score: A validated tool that stratifies risk for colorectal advanced neoplasia in asymptomatic Asian subjects. Gut 2011;60:1236–41.

22. Yang HJ, Choi S, Park SK, et al. Derivation and validation of a risk scoring model to predict advanced colorectal neoplasm in adults of all ages. J Gastroenterol Hepatol 2017;32:1328–35.

23. Shin CM, Han K, Lee DH, et al. Association among obesity, metabolic health, and the risk for colorectal cancer in the general population in Korea using the national health insurance service-national sample cohort. Dis Colon Rectum 2017;60:1192–200.

24. Cai S, Li Y, Ding Y, et al. Alcohol drinking and the risk of colorectal cancer death: A meta-analysis. Eur J Cancer Prev 2014;23:532–9.

25. Fedirko V, Tramacere I, Bagnardi V, et al. Alcohol drinking and colorectal cancer risk: An overall and dose-response meta-analysis of published studies. Ann Oncol 2011;22:1958–72.

26. Currie CJ, Poole CD, Gale EA. The influence of glucose-lowering therapies on cancer risk in type 2 diabetes. Diabetologia 2009;52:1766–77.

27. Libby G, Donnelly LA, Donnan PT, et al. New users of metformin are at low risk of incident cancer: A cohort study among people with type 2 diabetes. Diabetes Care 2009;32:1620–5.

28. Chang CH, Lin JW, Wu LC, et al. Oral insulin secretagogues, insulin, and cancer risk in type 2 diabetes mellitus. J Clin Endocrinol Metab 2012;97:E1170–5.

29. Yang YX, Hennessy S, Lewis JD. Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology 2004;127:1044–50.

30. Drew DA, Cao Y, Chan AT. Aspirin and colorectal cancer: The promise of precision chemoprevention. Nat Rev Cancer 2016;16:173–86.

31. Poynter JN, Gruber SB, Higgins PD, et al. Statins and the risk of colorectal cancer. N Engl J Med 2005;352:2184–92.

32. Kang HT, Shim JY, Lee HR, et al. Trends in prevalence of overweight and obesity in Korean adults, 1998-2009: the Korean National Health and Nutrition Examination Survey. J Epidemiol 2014;24:109–16.

33. Logue J, Murray HM, Welsh P, et al. Obesity is associated with fatal coronary heart disease independently of traditional risk factors and deprivation. Heart 2011;97:564–8.

34. Després JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–7.

35. Park MH, Falconer C, Viner RM, et al. The impact of childhood obesity on morbidity and mortality in adulthood: A systematic review. Obes Rev 2012;13:985–1000.

36. Noori N, Hosseinpanah F, Nasiri AA, et al. Comparison of overall obesity and abdominal adiposity in predicting chronic kidney disease incidence among adults. J Ren Nutr 2009;19:228–37.

37. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:920–31.

38. Park JY, Mitrou PN, Keogh RH, et al. Self-reported and measured anthropometric data and risk of colorectal cancer in the EPIC-Norfolk study. Int J Obes (Lond) 2012;36:107–18.

39. Kennelly R, Kavanagh DO, Hogan AM, et al. Oestrogen and the colon: Potential mechanisms for cancer prevention. Lancet Oncol 2008;9:385–91.