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ORIGINAL RESEARCH

Untreated Hypertension and Subsequent Incidence of Colorectal Cancer: Analysis of a Nationwide Epidemiological Database

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BACKGROUND: Studies of the association of hypertension with incident colorectal cancer (CRC) may have been confounded by including individuals taking antihypertensive medication, at high risk for CRC (ie, colorectal polyps and inflammatory bowel disease), or with shared risk factors (eg, obesity and diabetes). We assessed whether adults with untreated hypertension are at higher risk for incident CRC compared with those with normal blood pressure (BP), and whether any association is evident among individuals without obesity or metabolic abnormalities.

METHODS AND RESULTS: Analyses were conducted using a nationwide health claims database collected in the JMDC Claims Database between 2005 and 2018 (n=2 220 112; mean age, 44.1±11.0 years; 58.4% men). Participants who were taking antihypertensive medications or had a history of CRC, colorectal polyps, or inflammatory bowel disease were excluded. Each participant was categorized as having normal BP (systolic BP [SBP]<120 mm Hg and diastolic BP [DBP] <80 mm Hg, n=1 164 807), elevated BP (SBP 120–129 mm Hg and DBP <80 mm Hg, n=341 273), stage 1 hypertension (SBP 130–139 mm Hg or DBP 80–89 mm Hg, n=466 298), or stage 2 hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg, n=247 734). Over a mean follow-up of 1112±854 days, 6899 incident CRC diagnoses occurred. After multivariable adjustment, compared with normal BP, hazard ratios for incident CRC were 0.93 (95% CI, 0.85–1.01) for elevated BP, 1.07 (95% CI, 0.99–1.15) for stage 1 hypertension, and 1.17 (95% CI, 1.08–1.28) for stage 2 hypertension. The hazard ratios for incident CRC for each 10-mm Hg-higher SBP or DBP were 1.04 (95% CI, 1.02–1.06) and 1.06 (95% CI, 1.03–1.09), respectively. These associations were present among adults who did not have obesity, high waist circumference, diabetes, or dyslipidemia.

CONCLUSIONS: Higher SBP and DBP, and stage 2 hypertension are associated with a higher risk for incident CRC, even among those without shared risk factors for CRC. BP measurement could identify individuals at increased risk for subsequent CRC.

Key Words: blood pressure ■ colorectal cancer ■ epidemiology ■ hypertension ■ onco-hypertension

Colorectal cancer (CRC) is the third most common form of cancer and the second most common cause of cancer death worldwide, with an estimated 1.8 million new cases and 861 000 deaths each year.[1] Risk factors for CRC include obesity, diabetes, smoking, excessive drinking, and physical inactivity. A recent meta-analysis of 25 observational studies with a total of 1.95 million participants found that individuals with hypertension had a 15% higher risk of CRC compared with their normotensive counterparts.[2] However, the prior studies of hypertension–CRC have several limitations. First, other risk factors, including obesity

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CLINICAL PERSPECTIVE

What Is New?

- The analysis of a nationwide epidemiological database suggests that higher blood pressure is associated with higher risk for incident colorectal cancer events among untreated adults.
- This association was present among adults who did not have obesity, high waist circumference, diabetes, or dyslipidemia.

What Are the Clinical Implications?

- Untreated high blood pressure is associated with an increased risk of colorectal cancer.
- Control of blood pressure in such patients may have added advantage beyond cardiovascular benefits.

Nonstandard Abbreviations and Acronyms

CRC	colorectal cancer
EPIC	European Prospective Investigation Into Cancer and Nutrition

and diabetes, which could affect both blood pressure (BP) and cancers,[3–5] may confound the relationship between hypertension and cancer. Second, prior studies included individuals taking antihypertensive medication, and some classes of antihypertensive drugs (eg, diuretics and renin–angiotensin–aldosterone inhibitors) have been associated with cancer risk.[6–9] Third, some of the aforementioned studies included individuals at high risk for CRC, including those with a history of colorectal polyps, Crohn's disease, and ulcerative colitis. Fourth, the definition of hypertension in the prior hypertension–CRC association studies differs from that in the 2017 American College of Cardiology/American Heart Association BP guideline.[10] Thus, translating evidence from prior studies into current clinical practice is challenging. Using data from the health claims database of the JMDC Claims Database (JMDC; Tokyo, Japan) that excluded individuals with colorectal polyps, Crohn's disease, and ulcerative colitis,[11–14] we assessed whether adults with untreated hypertension, defined using the 2017 American College of Cardiology/American Heart Association BP guideline, are at higher risk for incident CRC events compared with those with normal BP. We also assessed whether the association between hypertension and CRC is present in individuals without obesity or metabolic abnormalities.

METHODS

This database is available for anyone who purchases it from the JMDC (https://www.jmdc.co.jp/en/index).

Study Population

The Japanese government provides universal health insurance for all registered inhabitants. Each employer is obliged by law to provide an annual health checkup to its employees. Medical and pharmacy claims data and annual health checkup data from employees' health insurance programs were obtained in an anonymous format from the JMDC.[15] This study is a retrospective observational analysis of a health claims database between January 2005 and August 2018. The JMDC Claims Database includes individual health insurance claims from >60 insurers. The JMDC Claims Database includes demographics, medical history, medications, hospital claims with *International Classification of Diseases, Tenth Revision* (*ICD-10*) coding, and death information. For the current analyses, we selected records of individuals (n=2 528 157) who underwent assessments of BP. We excluded individuals taking antihypertensive medications (n=246 870), those <20 years of age (n=22 198), and those with a history of colorectal disease including CRC (*ICD-10* codes C18, C19, C20), colorectal polyp (*ICD-10* codes K635, K621), ulcerative colitis (*ICD-10* code K51), or Crohn's disease (*ICD-10* code K50) (n=38 977). The flowchart defining the sample that was used in the analyses is shown in Figure 1. After all exclusion criteria were applied, data from 2 220 112 individuals were analyzed in this study.

Ethics

We conducted this study according to the ethical guidelines of our institution (approval by the Ethical Committee of the University of Tokyo: 2018-10862) and in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because all data in the JMDC database were anonymized and de-identified. All data were compliant with the International Conference on Harmonization guidelines.[16]

BP and Other Measurements

Resting BP was measured by healthcare professionals such as nurses twice at each health checkup according to the procedure recommended by the Ministry of Health, Labour, and Welfare, and the Japanese Society of Cardiovascular Disease Prevention as previously described.[13] The average of 2 measurements was recorded. Participants were categorized as having normal BP, elevated BP, stage 1 hypertension, or stage 2 hypertension according to the 2017 American

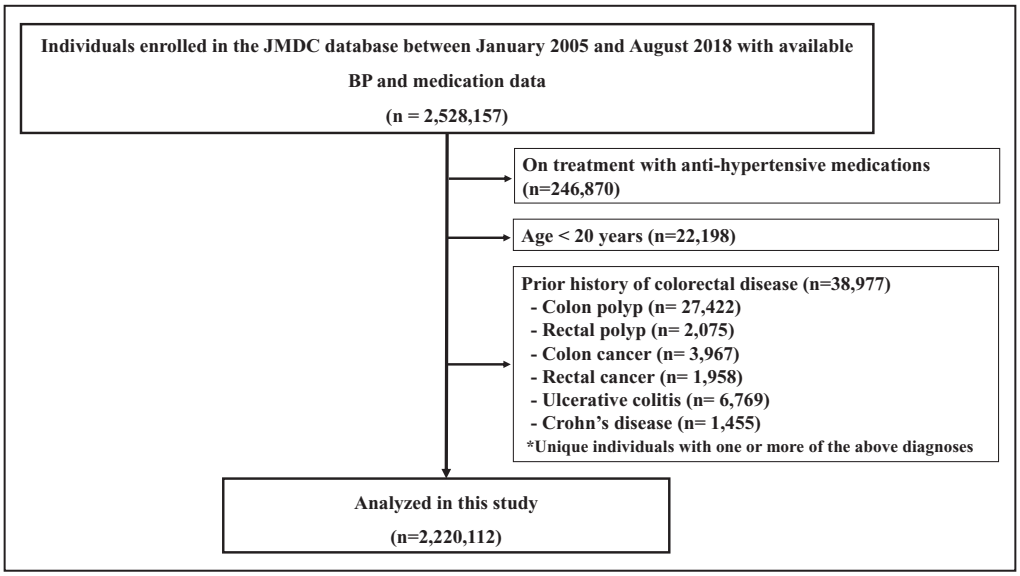


Figure 1. Flowchart.
We extracted records of individuals (n=2 528 157) who underwent health checkups between 2005 and 2018. We excluded individuals taking antihypertensive medications (n=246 870), those <20 years of age (n=22 198), and those with a history of colorectal disease including colon cancer, rectal cancer, colon polyp, rectal polyp, ulcerative colitis, or Crohn's disease (n=38 977). After these exclusions, 2 220 112 subjects were analyzed in this study. BP indicates blood pressure; and JMDC, Japan Medical Data Center.

College of Cardiology/American Heart Association BP guideline.[10] The normal BP group included participants with systolic BP <120 mm Hg and diastolic BP <80 mm Hg. The elevated BP group included participants with systolic BP 120 to 129 mm Hg and diastolic BP <80 mm Hg. The stage 1 hypertension group included participants with systolic BP 130 to 139 mm Hg or diastolic BP 80 to 89 mm Hg. The stage 2 hypertension group included participants with systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg. Information on cigarette smoking (current or noncurrent) and alcohol consumption (every day or not every day) was self-reported. Obesity was defined as body mass index (BMI) ≥25 kg/m^2. High waist circumference was defined as ≥85 cm for men and ≥90 cm for women.[17] Diabetes was defined as a fasting glucose level of ≥126 mg/dL or use of glucose-lowering medications. Dyslipidemia was defined as low-density lipoprotein cholesterol level ≥140 mg/dL, high-density lipoprotein cholesterol level <40 mg/dL, triglycerides ≥150 mg/dL, or use of lipid-lowering medications. We defined physical inactivity as not engaging in 30 minutes of exercise 2 or more times a week or not walking ≥1 hour per day.[12] We defined nonoptimal eating behaviors as meeting at least one of the following criteria[12]: (1) skipping breakfast ≥3 times per week, (2) late night dinner (having dinner within 2 hours before one's bedtime) ≥3 times per week, and (3) bedtime snacking (eating snacks after dinner) ≥3 times per week.

Outcomes

Outcomes were collected between January 2005 and August 2018. The primary outcome was CRC of any stage (*ICD-10* codes C18, C19, C20). We collected the information of the primary outcomes by claims records included in the JMDC database. The JMDC database could track all of the individual's clinical information (such as diagnosis of CRC) even if the individual sees different medical providers as long as the individual has the same insurance coverage.

Statistical Analysis

Summary statistics for characteristics of participants in the BP groups were calculated. The statistical significance of differences among groups was determined using analysis of variance for continuous variables and χ^2 tests for categorical variables. The cumulative incidence of CRC events for the BP groups was calculated using the Kaplan-Meier method. We conducted Cox regression analyses to identify the association of BP levels with subsequent risk of CRC. Follow-up time was censored on the date an event (CRC diagnosis) was ascertained. Hazard ratios (HRs) were calculated in an unadjusted model, an age- and sex-adjusted model, and after adjustment for potential confounders including age, sex, obesity, high waist circumference, diabetes, dyslipidemia, prior history of myocardial infarction (*ICD-10* codes I210, I211, I212, I213, I214, I219), current cigarette smoking, alcohol drinking, physical

inactivity, nonoptimal eating behaviors, and aspirin use at baseline. We conducted 6 sensitivity analyses. First, because the association of hypertension with CRC may differ by sex,[18,19] we conducted analyses for women and men separately. Second, to minimize the potential influence of latent CRC, we excluded participants whose observational period was shorter than 1 year or shorter than 2 years. Third, we excluded participants who had obesity, high waist circumference, diabetes, or dyslipidemia at baseline. Fourth, we imputed missing data for covariates using multiple imputation with chained equations and 20 iterations, as previously described.[20–22] HRs and standard errors were obtained using Rubin's rules. Fifth, we excluded participants diagnosed with CRC but no treatment history confirmed. Colon resection (procedure code: K719), colorectal mucosal resection (procedure code: K721), rectal resection (procedure code: K740), or others (procedure codes: K726, K728, K732, and K736) were defined as surgery for CRC. Use of fluorouracil, irinotecan, oxaliplatin, or capecitabine were defined as chemotherapy for CRC. Sixth, we added 235 448 participants who were on antihypertensive medication, ≥20 years of age, and had no history of CRC, colorectal polyp, or inflammatory bowel disease in the analysis. A P value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS software version 25 (IBM, Armonk, NY) and Stata version 16 StataCorp, College Station, TX).

RESULTS

Characteristics of the study participants (n=2 220 112) are shown in Table 1. The mean age was 44.1±11.0 years, and 1 297 204 participants (58.4%) were men. Using BP measurements at baseline, participants were categorized as having normal BP (n=1 164 807), elevated BP (n=341 273), stage 1 hypertension (n=466 298), or stage 2 hypertension (n=247 734). Participants with elevated BP, stage 1 hypertension, and stage 2 hypertension were older and more likely to be men, current smokers, and habitual drinkers than their counterparts with normal BP. Participants in the elevated BP and stage 1 and stage 2 hypertension groups had higher BMI, waist circumference, plasma glucose, glycated hemoglobin, and serum low-density lipoprotein cholesterol and triglyceride levels, and lower serum high-density lipoprotein cholesterol levels compared with their counterparts in the normal BP group.

During a mean (SD) follow-up of 1112 (854) days, 6899 CRC diagnoses occurred. The cumulative incidence of CRC was progressively higher in the higher BP categories (Figure 2). The event rates for incident CRC were highest in the stage 2 hypertension group (1.71 per 1000 person-years), followed by the stage 1 hypertension group (1.22 per 1000 person-years), the elevated BP group (0.91 per 1000 person-years), and the normal BP group (0.82 per 1000 person-years) (Table 2). Univariate Cox regression analyses showed that, compared with normal BP, the presence of elevated BP, stage 1 hypertension, or stage 2 hypertension was associated with a higher risk for incident CRC events. Age- and sex-adjusted Cox regression analyses showed that, compared with normal BP, stage 1 hypertension or stage 2 hypertension were associated with a higher risk for incident CRC. In the full multivariable Cox regression analyses (model 3), compared with normal BP, stage 2 hypertension was associated with higher CRC risk (HR, 1.17; 95% CI, 1.08–1.28) (Table 2, Table S1).

Higher systolic and diastolic BP were associated with a higher risk for incident CRC (Table 3). After multivariable adjustment, each 10-mm Hg-higher systolic and diastolic BP were associated with increased risk for incident CRC (HR for systolic BP, 1.04; 95% CI, 1.02–1.06 and HR for diastolic BP, 1.06; 95% CI, 1.03–1.09).

We performed 6 sensitivity analyses. First, after multivariable adjustment, each 10-mm Hg-higher systolic BP was associated with a higher risk for incident CRC events in men (HR, 1.06; 95% CI, 1.04–1.08), but there was no evidence of an association among women (HR, 1.01; 95% CI, 0.98–1.04). Also, each 10-mm Hg-higher diastolic BP was associated with incident CRC in men (HR, 1.07; 95% CI, 1.04–1.11) but not in women (HR, 1.04; 95% CI, 0.996–1.09). Compared with normal BP, stage 1 hypertension (HR, 1.10; 95% CI, 1.00–1.20) and stage 2 hypertension (HR, 1.24; 95% CI, 1.12–1.37) were associated with a higher risk for CRC events in men, but there was no evidence of an association among women (Table 4). Second, we excluded 471 604 participants whose follow-up period for CRC was <365 days, leaving a sample size of 1 748 508 participants. During a mean (SD) follow-up of 997 (789) days, 4780 CRC diagnoses occurred. Multivariable Cox regression analyses showed that 10-mm Hg-higher in systolic BP and diastolic BP were associated with a higher risk for incident CRC (HR, 1.04; 95% CI, 1.01–1.06 and HR, 1.07; 95% CI, 1.04–1.11, respectively). Multivariable Cox regression analyses demonstrated that stage 2 hypertension was associated with a higher risk for incident CRC (HR, 1.17; 95% CI, 1.06–1.30) compared with normal BP (Table S2). We excluded participants with a follow-up period for CRC shorter than 2 years, and analyzed 1 330 566 participants who had a follow-up period for CRC ≥730 days. Even in this model, the main result did not change (Table S3). Third, we analyzed 818 116 participants who did not have obesity, high waist circumference, diabetes, or dyslipidemia at baseline. During a mean follow-up of 1126±847 days, 2300 CRC diagnoses occurred. Multivariable Cox regression analysis showed

Table 1. Characteristics of Study Participants

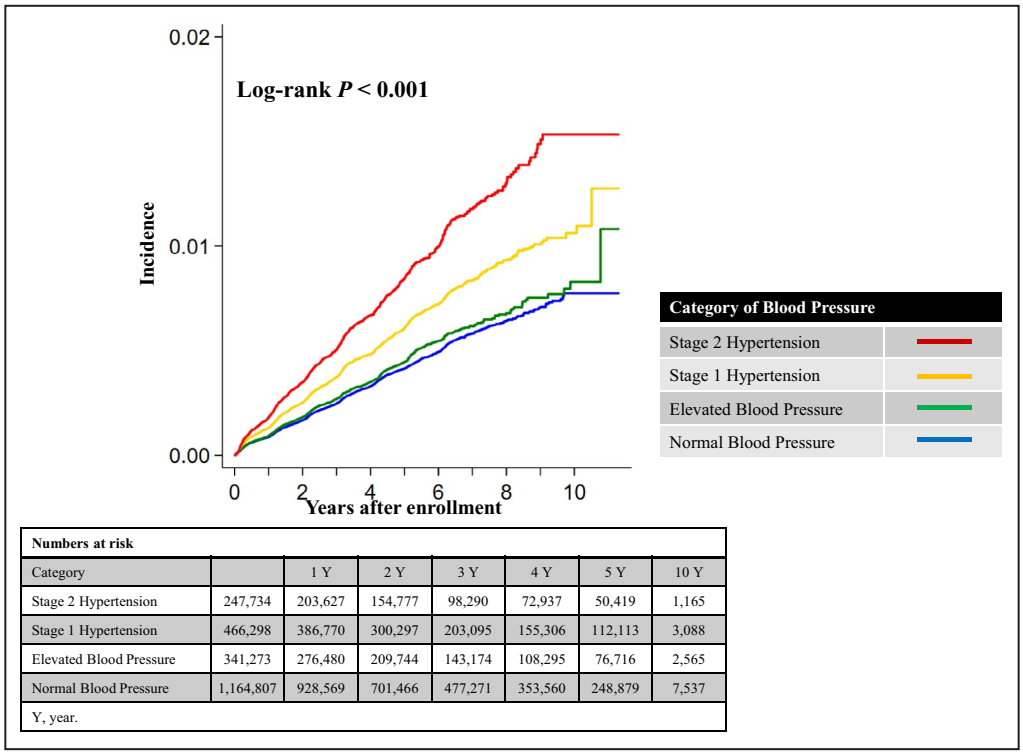
	Missing	Normal BP, n=1 164 807	Elevated BP, n=341 273	Stage 1 hypertension, n=466 298	Stage 2 hypertension, n=247 734	*P* Value
Age, y	0	42.0 (10.6)	43.3 (11.6)	46.7 (10.4)	50.0 (9.8)	<0.001
Male sex, n (%)	0	555 861 (47.7)	228 466 (66.9)	333 696 (71.6)	179 181 (72.3)	<0.001
Body mass index, kg/m^2	967	21.5 (3.0)	23.0 (3.4)	23.8 (3.7)	24.8 (4.2)	<0.001
Obesity, n (%)	967	139 638 (12.0)	83 560 (24.5)	149 258 (32.0)	104 341 (42.1)	<0.001
Waist circumference, cm	215 354	77.4 (8.5)	81.5 (9.3)	83.6 (9.6)	86.2 (10.5)	<0.001
High waist circumference, n (%)	215 354	153 054 (14.8)	86 005 (28.8)	164 134 (37.8)	112 733 (47.5)	<0.001
SBP, mm Hg	0	107 (8)	124 (3)	128 (7)	146 (13)	<0.001
DBP, mm Hg	0	65 (7)	72 (5)	81 (5)	92 (9)	<0.001
Diabetes, n (%)	457 332	17 694 (1.9)	10 099 (4.0)	20 180 (5.4)	17 158 (8.7)	<0.001
Dyslipidemia, n (%)	79 926	325 483 (29.2)	130 857 (40.3)	221 345 (48.6)	137 667 (56.4)	<0.001
Myocardial infarction, n (%)	0	587 (0.1)	199 (0.1)	342 (0.1)	240 (0.1)	<0.001
Cigarette smoking, n (%)	16 779	286 740 (24.8)	98 260 (29.1)	136 652 (29.5)	73 236 (29.8)	<0.001
Alcohol drinking, n (%)	282 492	171 522 (16.8)	65 443 (21.8)	118 863 (29.4)	73 629 (34.7)	<0.001
Physical inactivity, n (%)	386 719	525 426 (54.2)	151 072 (53.5)	211 583 (55.8)	113 450 (56.2)	<0.001
Nonoptimal eating behavior, n (%)	499 469	464 203 (51.3)	140 936 (53.6)	189 720 (52.9)	100 734 (52.1)	<0.001
Aspirin use, n (%)	0	2095 (0.2)	899 (0.3)	1658 (0.4)	996 (0.4)	<0.001
Laboratory data						
Glucose, mg/dL	462 857	91 (13)	94 (16)	97 (19)	101 (23)	<0.001
HbA1c, %	427 497	5.4 (0.5)	5.5 (0.6)	5.6 (0.7)	5.7 (0.8)	<0.001
Low-density lipoprotein cholesterol, mg/dL	80 117	115 (30)	121 (32)	125 (32)	129 (33)	<0.001
High-density lipoprotein cholesterol, mg/dL	74 163	66 (16)	62 (16)	62 (17)	61 (17)	<0.001
Triglycerides, mg/dL	74 655	88 (64)	108 (82)	123 (99)	140 (117)	<0.001

Data are expressed as mean (standard deviation) or number (percentage). *P* values were calculated using the analysis of variance for continuous variables and χ^2 test for categorical variables. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg), elevated BP (untreated SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). BP indicates blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; and SBP, systolic blood pressure.

that 10-mm Hg-higher systolic and diastolic BP were associated with higher risk for incident CRC (HR, 1.04; 95% CI, 1.01–1.07 and HR, 1.08; 95% CI, 1.03–1.13, respectively). Among this population, stage 2 hypertension was associated with a higher risk for incident CRC (HR, 1.32; 95% CI, 1.13–1.53) compared with normal BP (Table S4). Fourth, after imputing missing data, there were 6899 incident CRC diagnoses. Results with and without imputing missing covariates were similar in terms of the point estimate for CRC events for BP categories (Table S5). Fifth, among 6899 participants diagnosed with CRC in this study population, we confirmed that 4963 participants (71.9%) underwent surgical treatment or chemotherapy for CRC. Accordingly, we excluded 1936 participants diagnosed with CRC but no treatment history confirmed from the study population. In this population, the association of hypertension, systolic BP, and diastolic BP with incident CRC still existed (Table S6). Sixth, compared with participants having normal BP, those treated with antihypertensive medication had a higher incidence of CRC (HR, 1.14; 95% CI, 1.04–1.23). In this study population, systolic BP per 10 mm Hg (HR, 1.03; 95% CI, 1.02–1.05) and diastolic BP per 10 mm Hg (HR, 1.06; 95% CI, 1.03–1.08) were associated with CRC (Table S7). However, if we analyzed only the study population treated with antihypertensive medications, neither systolic BP per 10 mm Hg (HR, 1.01; 95% CI, 0.98–1.05) nor diastolic BP per 10 mm Hg (HR, 1.02; 95% CI, 0.97–1.08) was associated with incident CRC.

DISCUSSION

In this nationwide analysis of a health claims database including adults who had an annual health checkup, those with untreated hypertension had a higher risk for incident CRC events, even after adjustment for multiple potential confounders. This association was present among adults who did not have obesity, high waist circumference, diabetes, or dyslipidemia. The associations between BP and CRC may differ by sex. In men, the associations of CRC risk and higher systolic and



Numbers at risk

Category		1 Y	2 Y	3 Y	4 Y	5 Y	10 Y
Stage 2 Hypertension	247,734	203,627	154,777	98,290	72,937	50,419	1,165
Stage 1 Hypertension	466,298	386,770	300,297	203,095	155,306	112,113	3,088
Elevated Blood Pressure	341,273	276,480	209,744	143,174	108,295	76,716	2,565
Normal Blood Pressure	1,164,807	928,569	701,466	477,271	353,560	248,879	7,537

Y, year.

Figure 2. Kaplan-Meier curves for colorectal cancer.
The cumulative probability of colorectal cancer events for each blood pressure (BP) group was calculated using the Kaplan-Meier method. A log-rank test was used to calculate the *P* value (*P*<0.001). Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg), elevated BP (untreated SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

diastolic BP, stage 1 hypertension, and stage 2 hypertension were statistically significant, whereas these associations were not statistically significant in women.

In a multicenter case-control study conducted in Italy and Switzerland and including 1378 cases of colon cancer, 878 cases of rectal cancer, and 4661 controls, Pelucchi et al, reported that hypertension was associated with higher odds risk for CRC in men (odds ratio [OR], 1.36; 95% CI, 1.10–1.68) but not in women (OR, 0.92; 95% CI, 0.73–1.16).[18] Hypertension was defined as the use of antihypertension medication, without taking BP levels into account. The HRs were adjusted for age, study center, education, smoking habit, alcohol drinking, occupational physical activity, and nonalcohol energy intake. However, shared risk factors, including adiposity and diabetes that could increase the

Table 2. Frequency of Events, Corresponding Incidence Rates, and Hazard Ratios for Colorectal Cancer Events Among Participants by BP Category

	Normal BP, n=1 164 807	Elevated BP, n=341 273	Stage 1 hypertension, n=466 298	Stage 2 hypertension, n=247 734
No. of events	2867 (0.2)	947 (0.3)	1815 (0.4)	1270 (0.5)
Incidence rate	0.82	0.91	1.22	1.71
Model 1 (unadjusted)	1 [Reference]	1.10 (1.03–1.19)	1.49 (1.40–1.58)	2.07 (1.94–2.21)
Model 2	1 [Reference]	0.95 (0.88–1.03)	1.08 (1.01–1.14)	1.22 (1.14–1.31)
Model 3	1 [Reference]	0.93 (0.85–1.01)	1.07 (0.99–1.15)	1.17 (1.08–1.28)

The incidence rate was per 1000 person-years. Unadjusted and adjusted hazard ratios (95% CIs) associated with BP group are shown. Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for age, sex, obesity, high waist circumference, diabetes, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, nonoptimal eating behavior, and aspirin use. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg), elevated BP (untreated SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

Table 3. Hazard Ratios for Colorectal Cancer Events for Systolic and Diastolic Blood Pressure

	Systolic blood pressure, per 10 mm Hg	Diastolic blood pressure, per 10 mm Hg
Model 1 (unadjusted)	1.17 (1.15–1.18)	1.25 (1.23–1.27)
Model 2	1.04 (1.02–1.05)	1.07 (1.04–1.09)
Model 3	1.04 (1.02–1.06)	1.06 (1.03–1.09)

Unadjusted and adjusted hazard ratios (95% CIs) associated with a 10-mm Hg increase in systolic and diastolic blood pressure, respectively, are shown. Model 1 is unadjusted. Model 2 includes adjustment for age and sex. Model 3 includes adjustment for age, sex, obesity, high waist circumference, diabetes, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, nonoptimal eating behavior, and aspirin use.

prevalence of not only hypertension but also CRC,[23–25] were not included in adjusted analyses. In the EPIC (European Prospective Investigation Into Cancer and Nutrition) study, Christakoudi et al, reported that each 10-mm Hg-higher systolic and diastolic BP were associated with increased risk for CRC incidence in men (HR, 1.03; 95% CI, 1.01–1.06 and HR, 1.05; 95% CI, 1.01–1.10, respectively) but not in women (HR, 0.99; 95% CI, 0.97–1.02 and HR, 1.03; 95% CI, 0.99–1.08, respectively).[26] Among EPIC participants, 43% were taking antihypertensive medications, and those with colorectal polyps, Crohn's disease, and ulcerative colitis were not excluded.

The current study extends our knowledge by demonstrating that, in individuals not taking antihypertensive medication and who do not have colorectal polyps, Crohn's disease, and/or ulcerative colitis, higher systolic and diastolic BP as well as stage 2 hypertension were associated with CRC risk. There was evidence of differences in the strength of the associations of BP groups with CRC events by sex. Stage 1 and 2 hypertension were each associated with a higher risk for CRC events in men but not in women. Higher systolic and diastolic BP were associated with CRC in men, whereas the associations in women were weaker and not statistically significant. These findings suggest that the strength of the associations of BP with CRC events may be stronger in men compared with women. However, given the secondary nature of the interaction analyses, the current results require further testing in an independent cohort to determine whether associations between BP and CRC differ by sex.

In the current study, hypertension preceded the development of CRC. However, the precise pathophysiological mechanisms underlying the association between hypertension and CRC remain unknown. The findings of this observational study are insufficient to infer a causal relationship between hypertension and CRC. Furthermore, our analysis showed that participants on treatment with antihypertensive medication were also associated with an elevated risk of CRC compared with those having normal BP. In addition, the relationship of systolic and diastolic BP with incident CRC disappeared in participants on treatment with antihypertensive medication. We need further investigations to clarify (1) whether a history of hypertension is associated with incident CRC, (2) if BP-lowering intervention could reduce the risk of CRC, and (3) whether antihypertensive medication itself might affect the incidence of CRC.

The results of the current study have clinical implications. CRC is both a common cancer and a major

Table 4. Sex-Specific Hazard Ratios for Colorectal Cancer Events for BP Category, SBP, and DBP

Men						
	BP category					
	Normal BP, n=555 861	Elevated BP, n=228 466	Stage 1 hypertension, n=333 696	Stage 2 hypertension, n=179 181	SBP, per 10 mm Hg	DBP, per 10 mm Hg
Adjusted hazard ratio (95% CI)	Reference	0.93 (0.83–1.04)	1.10 (1.00–1.20)	1.24 (1.12–1.37)	1.06 (1.04–1.08)	1.07 (1.04–1.11)
Women						
	BP category					
	Normal BP, n=608 946	Elevated BP, n=112 807	Stage 1 hypertension, n=132 602	Stage 2 hypertension, n=68 553	SBP, per 10 mm Hg	DBP, per 10 mm Hg
Adjusted hazard ratio (95% CI)	Reference	0.95 (0.82–1.11)	1.03 (0.90–1.17)	1.04 (0.88–1.23)	1.01 (0.98–1.04)	1.04 (1.00–1.09)

Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg), elevated BP (untreated SBP 120–129 mm Hg and DBP <80 mm Hg), stage 1 hypertension (untreated SBP 130–139 mm Hg or DBP 80–89 mm Hg), or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). Adjusted hazard ratios for colorectal cancer were calculated by including adjustments for age, obesity, high waist circumference, diabetes, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, non-optimal eating behavior, and aspirin use. BP indicates blood pressure; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

cause of death. Therefore, early detection of and intervention for CRC are important. If future studies demonstrate a reduction in CRC cancer risk attributable to BP-lowering therapy, the case for population-level hypertension control will be further strengthened. The association between BP and incident CRC was more evident in men compared with women. It is presently unknown whether offering CRC screening to men with hypertension before the current age-based screening criteria would lead to fewer CRC deaths.

The strengths of this study include the large, nationwide, longitudinal health-screening database with high participation and outcome ascertainment rates because of electronic linkages to medical claims data. This study also has several limitations. Measurements at a single occasion were used for BP categorization, which might not fully reflect a person's long-term levels. In the health checkup system, BP was measured according to the recommended standard protocol of the Japanese Ministry of Health, Labour, and Welfare by healthcare professionals, and the average of 2 BP measurements on a single occasion was recorded as we previously described.[27] However, adherence to the protocol could be limited in a real-world clinical setting on a nationwide scale. We identified CRC using *ICD-10* codes registered in the JMDC Claims Database. Generally, recorded diagnoses of administrative databases, including the JMDC Claims Database, are thought to be less well validated. Thus, uncertainty remains about the accuracy of the diagnosis for CRC. However, a previous study reported that the validity of the diagnoses of the administrative database in Japan was high. Particularly, the sensitivity and specificity of cancer diagnoses were 83.5% and 97.7%, respectively.[28] We obtained several data including antihypertensive medications from questionnaires at health checkups, and therefore, misclassification could have occurred. Possible residual confounding, including diet, gut microbiome, and socioeconomic status, may affect the association between BP and CRC events. The JMDC Claims Database primarily included employed, working-age adults. Therefore, selection bias (healthy-worker bias) should be considered. In addition, because the population in this study was young, the incidence of CRC was lower than that found in previous epidemiological data from a Japanese population.[3] Further studies are required to assess the generalizability of these results to other races, ethnicities, educational levels, and incomes. Data on death attributable to CRC were not available in this database. Because the sensitivity analysis that included people with follow-up periods ≥365 or ≥730 days confirmed the main results, and the difference in the cumulative incidence of CRC among the 4 groups shown in Kaplan-Meier curves widened with time without attenuation, we believe that the influence of latent CRC was not so large. However, the period of observation was relatively short. Therefore, we cannot eliminate the possibility of clinically undetected CRC at baseline, which could influence the findings. Further studies with longer observational periods are needed to confirm our results. We could not track the individual if he or she left the original insurance coverage. An initiation of antihypertensive medication during the observation period would influence the results. However, we were unable to assess this point in this study. Given the low prevalence of obesity in Japan, we defined obesity as BMI ≥25 kg/m^2 in this study. However, obesity is usually defined as BMI ≥30 kg/m^2. Therefore, we redefined obesity as BMI ≥30 kg/m^2 and included it in the multivariable model. In this model, the results did not change, and stage 2 hypertension was associated with a higher risk of CRC (HR, 1.17; 95% CI, 1.08–1.28) compared with normal BP.

CONCLUSIONS

Higher systolic and diastolic BP, as well as stage 2 hypertension, were each associated with a higher risk for incident CRC among medication-naïve adults. BP measurement could identify individuals at increased risk for subsequent CRC.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S7

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SUPPLEMENTAL MATERIAL

Table S1. Multivariable Cox Regression Model for Colorectal Cancer Events

	Hazard Ratio	95% Confidence Interval
Blood Pressure Category		
Normal Blood Pressure	1 [Reference]	
Elevated Blood Pressure	0.93	0.85-1.01
Stage 1 Hypertension	1.07	0.99-1.14
Stage 2 Hypertension	1.17	1.08-1.28
Age	1.08	1.08-1.08
Men	1.04	0.97-1.12
Obesity	1.04	0.95-1.13
High Waist Circumference	1.13	1.04-1.22
Diabetes Mellitus	1.24	1.11-1.39
Dyslipidemia	0.95	0.90-1.01
Prior Myocardial Infarction	1.16	0.54-2.49
Cigarette Smoking	1.14	1.06-1.22
Alcohol Drinking	1.28	1.20-1.37
Physical Inactivity	1.05	0.99-1.12
Non-Optimal Eating Behavior	1.02	0.96-1.08
Aspirin Use	1.19	0.82-1.73

Normal blood pressure was defined as untreated systolic blood pressure <120 mmHg and diastolic blood pressure < 80 mmHg. Elevated blood pressure was defined as untreated systolic blood pressure of 120-129 mm Hg and diastolic blood pressure < 80 mmHg. Stage 1 hypertension was defined as untreated systolic blood pressure of 130-139 mmHg or diastolic blood pressure of 80-89 mmHg. Stage 2 hypertension was untreated systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

Table S2. Hazard Ratios for Colorectal Cancer Events for Blood Pressure Category, Systolic Blood Pressure, and Diastolic Blood Pressure in Participants with Follow-Up Period for Colorectal Cancer ≥ 365 days

	BP Category				Systolic blood pressure (per 10 mmHg)	Diastolic blood pressure (per 10 mmHg)
	Normal BP (n=904,866)	Elevated BP (n=267,840)	Stage 1 Hypertension (n=376,975)	Stage 2 Hypertension (n=198,827)		
Adjusted Hazard Ratio (95% CI)	Reference	0.94 (0.84-1.05)	1.08 (0.99-1.18)	1.17 (1.06-1.30)	1.04 (1.01-1.06)	1.07 (1.04-1.11)

We excluded 471,604 participants who had colorectal cancer within the first year of follow-up. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg; elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg; or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). Adjusted hazard ratios for colorectal cancer were calculated by including adjustments for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, non-optimal eating behavior, and aspirin use. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval.

Table S3. Hazard Ratios for Colorectal Cancer Events for Blood Pressure Category, Systolic Blood Pressure, and Diastolic Blood Pressure in Participants with Follow-Up Period for Colorectal Cancer ≥ 730 days

	BP Category				Systolic blood pressure (per 10 mmHg)	Diastolic blood pressure (per 10 mmHg)
	Normal BP (n=683,713)	Elevated BP (n=203,170)	Stage 1 Hypertension (n=292,586)	Stage 2 Hypertension (n=151,097)		
Adjusted Hazard Ratio (95% CI)	Reference	0.94 (0.82-1.07)	1.08 (0.97-1.20)	1.17 (1.03-1.33)	1.03 (1.00-1.06)	1.06 (1.02-1.11)

We excluded participants with follow-up period for CRC shorter than two years, and analyzed 1,330,566 participants who had follow-up period for CRC ≥ 730 days. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg; elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg; or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). Adjusted hazard ratios for colorectal cancer were calculated by including adjustments for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, non-optimal eating behavior, and aspirin use. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval.

Table S4. Hazard Ratios for Colorectal Cancer Events for Blood Pressure Category, Systolic Blood Pressure, and Diastolic Blood Pressure in in Participants Not Having Metabolic Disorders

	BP Category				Systolic blood pressure (per 10 mmHg)	Diastolic blood pressure (per 10 mmHg)
	Normal BP (n=542,024)	Elevated BP (n=104,736)	Stage 1 Hypertension (n=123,515)	Stage 2 Hypertension (n=47,841)		
Adjusted Hazard Ratio (95% CI)	Reference	0.91 (0.78-1.05)	1.05 (0.93-1.19)	1.32 (1.13-1.53)	1.04 (1.01-1.07)	1.08 (1.03-1.13)

We excluded 1,401,996 participants with obesity, high waist circumference, diabetes mellitus, or dyslipidemia at baseline. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg; elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg; or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). Adjusted hazard ratio for colorectal cancer were calculated by including adjustments for age, sex, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, non-optimal eating behavior, and aspirin use. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval.

Table S5. Hazard Ratios for Colorectal Cancer Events for Blood Pressure Category after Multiple Imputation for Missing Data

	BP Category			
	Normal BP (n=1,164,807)	Elevated BP (n=341,273)	Stage 1 Hypertension (n=466,298)	Stage 2 Hypertension (n=247,734)
Adjusted Hazard Ratio (95% CI)	Reference	0.92 (0.85-1.00)	1.04 (0.98-1.12)	1.12 (1.04-1.22)

We imputed covariates for missing data collected at baseline (left column in Table 1) for the 2,220,112 participants. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg; elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg; or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). Adjusted hazard ratios for colorectal cancer were calculated by including adjustment for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, non-optimal eating behavior, and aspirin use. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval.

Table S6. Hazard Ratios for Colorectal Cancer Events for Blood Pressure Category, Systolic Blood Pressure, and Diastolic Blood Pressure in Participants After Excluding Those Diagnosed with Colorectal Cancer But No Treatment History Confirmed

	BP Category				Systolic blood pressure (per 10 mmHg)	Diastolic blood pressure (per 10 mmHg)
	Normal BP (n=1,163,922)	Elevated BP (n=341,018)	Stage 1 Hypertension (n=465,801)	Stage 2 Hypertension (n=247,435)		
Adjusted Hazard Ratio (95% CI)	Reference	0.98 (0.88-1.09)	1.09 (1.00-1.19)	1.24 (1.12-1.37)	1.05 (1.03-1.07)	1.07 (1.04-1.11)

After excluding 1,936 participants diagnosed with CRC but no treatment history confirmed, we analyzed 2,218,176 patients. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg; elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg; or stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg). Adjusted hazard ratios for colorectal cancer were calculated by including adjustments for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, non-optimal eating behavior, and aspirin use. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval.

Table S7. Hazard Ratios for Colorectal Cancer Events for Blood Pressure Category, Systolic Blood Pressure, and Diastolic Blood Pressure in Participants Including People Treated with Antihypertensive Medication

	BP Category					Systolic blood pressure (per 10 mmHg)	Diastolic blood pressure (per 10 mmHg)
	Normal BP (n=1,164,807)	Elevated BP (n=341,273)	Stage 1 Hypertension (n=466,298)	Stage 2 Hypertension (n=247,734)	Antihypertensive medications (235,448)		
Adjusted Hazard Ratio (95% CI)	Reference	0.93 (0.85-1.02)	1.07 (0.99-1.15)	1.18 (1.08-1.29)	1.14 (1.04-1.23)	1.03 (1.02-1.05)	1.06 (1.03-1.08)

We added 235,448 participants who were on antihypertensive medication, aged ≥20 years and having no history of CRC, colorectal polyp, and inflammatory bowel disease in the analysis. Participants were categorized as having normal BP (untreated SBP <120 mm Hg and DBP <80 mm Hg; elevated BP (untreated SBP 120-129 mm Hg and DBP <80 mm Hg); stage 1 hypertension (untreated SBP 130-139 mm Hg or DBP 80-89 mm Hg); stage 2 hypertension (untreated SBP ≥140 mm Hg or DBP ≥90 mm Hg); or on treatment with antihypertensive medication. Adjusted hazard ratios for colorectal cancer were calculated by including adjustments for age, sex, obesity, high waist circumference, diabetes mellitus, dyslipidemia, prior myocardial infarction, cigarette smoking, alcohol drinking, physical inactivity, non-optimal eating behavior, and aspirin use. BP=blood pressure; SBP=systolic blood pressure; DBP=diastolic blood pressure; CI=confidence interval.