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ARTICLE

Case–Control Study of Overweight, Obesity, and Colorectal Cancer Risk, Overall and by Tumor Microsatellite Instability Status

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Background Being overweight or obese is an established risk factor for colorectal cancer, more so for men than for women. Approximately 10%–20% of colorectal tumors display microsatellite instability (MSI), defined as the expansion or contraction of small repeated sequences in the DNA of tumor tissue relative to nearby normal tissue. We evaluated associations between overweight or obesity and colorectal cancer risk, overall and by tumor MSI status.

Methods The study included 1794 case subjects with incident colorectal cancer who were identified through population-based cancer registries and 2684 of their unaffected sex-matched siblings as control subjects. Recent body mass index (BMI), BMI at age 20 years, and adult weight change were derived from self-reports of height and weight. Tumor MSI status, assessed at as many as 10 markers, was obtained for 69.7% of the case subjects and classified as microsatellite (MS)-stable (0% of markers unstable; n = 913), MSI-low (>0% but <30% of markers unstable; n = 149), or MSI-high (≥30% of markers unstable; n = 188). Multivariable conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (95% CIs). All statistical tests were two-sided.

Results Recent BMI, modeled in 5 kg/m^2 increments, was positively associated with risk of colorectal cancer for men and women combined (OR = 1.24; 95% CI = 1.15 to 1.34), for women only (OR = 1.20; 95% CI = 1.10 to 1.32), and for men only (OR = 1.30; 95% CI = 1.15 to 1.47). There was no interaction with sex (P = .22). Recent BMI, per 5 kg/m^2, was positively associated with the risk of MS-stable (OR = 1.38; 95% CI = 1.24 to 1.54) and MSI-low (OR = 1.33; 95% CI = 1.04 to 1.72) colorectal tumors, but not with the risk of MSI-high tumors (OR = 1.05; 95% CI = 0.84 to 1.31).

Conclusion The increased risk of colorectal cancer associated with a high BMI might be largely restricted to tumors that display the more common MS-stable phenotype, suggesting further that colorectal cancer etiology differs by tumor MSI status.

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The DNA mismatch repair system is involved in the etiology of colorectal cancer (1). Defective DNA mismatch repair is associated with microsatellite instability (MSI), a distinct tumor phenotype whereby short repetitive DNA sequences undergo an increase or decrease in repeat length. Approximately 10%–20% of colorectal tumors display MSI, usually as a result of epigenetic modification of *MLH1*, a gene that encodes a mismatch repair protein (2,3), or, less often, because the affected individual has a germline mutation in a DNA mismatch repair gene (3,4). The majority of colorectal tumors develop despite having competent mismatch repair; these tumors, known as microsatellite (MS)-stable, arise through chromosomal instability and do not display marked gains or losses in MS regions. The Bethesda consensus panel of MS markers for assessing MSI was proposed over a decade ago as a uniform way to characterize colorectal tumors as MSI-high (defined as instability for at least 30% of the assessed markers), MSI-low (defined as instability at more than 0% and less than 30% of the assessed markers), or MS-stable (no instability in any of the assessed markers) (5). There is strong evidence to suggest that tumor MSI status is a predictor of colorectal cancer survival (6) and of response

CONTEXT AND CAVEATS

Prior knowledge

Overweight and obesity are established risk factors for colorectal cancer, more so for men than for women. Approximately 10%–20% of colorectal tumors have microsatellite instability (MSI), a distinct tumor phenotype characterized by an expansion or contraction of small repeated sequences in the tumor DNA relative to adjacent normal tissue that is associated with defective DNA mismatch repair.

Study design

A case–control study of subjects with incident colorectal cancer and their unaffected sex-matched siblings to evaluate associations between being overweight or obese (defined according to body mass index) and adult weight change and colorectal cancer risk, overall and by tumor MSI status, assessed at up to 10 markers and classified as microsatellite-stable, MSI-low, or MSI-high.

Contribution

Recent body mass index and adult weight gain since age 20 years were positively associated with an increased risk of colorectal cancer. Recent body mass index was positively associated with increased risks of microsatellite-stable and MSI-low tumors, but not with the risk of MSI-high tumors.

Implications

Colorectal cancer risk may differ by tumor MSI status.

Limitations

Body weight and height were self-reported. For approximately one-quarter of the case subjects, the baseline interview occurred 2–5 years after the colorectal cancer diagnosis. Survival bias might have contributed to an underestimate of the risk of colorectal cancer associated with obesity.

From the Editors

to fluorouracil-based adjuvant chemotherapy for colon cancer (7). Yet, with the possible exception of cigarette smoking (8–10), there are limited data on whether lifestyle risk factors for colorectal cancer differ according to tumor MSI status.

According to a report by the World Cancer Research Fund and the American Institute for Cancer Research (11), there is convincing observational evidence to suggest that being overweight [defined by the World Health Organization (12) as a body mass index [BMI] of 25–29.9 kg/m^2] or obese [defined as BMI $\geq$30 kg/m^2 (12)] is associated with the risk of colorectal cancer. However, these associations are thought to vary by sex (13,14) and tumor subsite within the colorectum (13,14). To our knowledge, only one study (10) to date has evaluated associations between BMI and the risk of colorectal cancer stratified by tumor MSI status. That study, which predated the adoption of the Bethesda consensus panel of markers for MSI, reported that among men, BMI was positively associated with the risk of MSI-negative colon cancer but was not associated with the risk of MSI-positive colon cancer; among women, BMI was weakly associated with the risk of both MSI-positive and MSI-negative colon tumors (10). Given the rarity of data on this topic, we evaluated associations between BMI and adult weight gain and the risk of colorectal cancer overall and by tumor MSI status.

Subjects and Methods

Study Population

The study participants were women and men drawn from the Colon Cancer Family Registry, an international resource for studies on the etiology of colorectal cancer that was initiated in 1997 and is described in detail elsewhere (15). Briefly, the Colon Cancer Family Registry includes six recruitment centers: Cancer Care Ontario (Toronto, Canada; the Memorial University of Newfoundland [St John's, Newfoundland] was added as a sister site to Cancer Care Ontario in 2000), the Fred Hutchinson Cancer Research Center (Seattle, WA), the Mayo Clinic (Rochester, MN), the University of Hawaii (Honolulu, HI), the University of Melbourne (Melbourne, Australia), and the University of Southern California Consortium (Los Angeles, CA).

Population-based case subjects with incident colon or rectal cancer were recruited into the study, beginning in 1997, through state or provincial cancer registries. All case subjects were interviewed by study staff within 5 years of diagnosis; 73% of the case subjects were interviewed within 2 years of diagnosis. Data for this study were abstracted from the central data repository of the Colon Cancer Family Registry in October 2007; these data included subjects who had been diagnosed with colon or rectal cancer as recently as July 2005. After enrollment into the study, case subjects were asked to assist in the recruitment of their relatives. The control subjects for this study were siblings of the case subjects who had not been affected by cancer, with the additional requirements that the case subjects and sibling control subjects were of the same sex and reported that they had the same biological parents.

Overall, epidemiological and outcome data were available through the Colon Cancer Family Registry on 1794 confirmed colorectal cancer case subjects and 2684 of their unaffected siblings as control subjects. In sex-specific analyses, we had data for 877 male case subjects and 1299 of their unaffected brothers and for 917 female case subjects and 1385 of their unaffected sisters.

Data Collection

Data on demographics, race and ethnicity, personal and familial history of cancer, medical history, reproductive history, physical activity, diet, alcohol, tobacco, and anthropometry were collected from each subject via standardized personal interviews (University of Southern California Consortium), telephone interviews (University of Southern California Consortium, Fred Hutchinson Cancer Research Center, University of Melbourne, and Mayo Clinic), and mailed questionnaires (University of Hawaii, Cancer Care Ontario, Memorial University of Newfoundland, and Mayo Clinic). The questionnaires are available at the following URL: https://cfrisc.georgetown.edu/isc/dd.questionnaires.do;jsessionid=6D7A43E5E68A70842BEC745C882F035F. Two measures of self-reported body weight were requested during the interview and on the questionnaire: recent weight (defined as weight approximately 1 year before study participation for control subjects or 1 year before colorectal cancer diagnosis for case subjects) and weight at approximately age 20 years. All participants were asked to provide their current height.

Assessment of BMI and Adult Weight Change

Recent BMI was calculated from recent body weight in kilograms divided by height in meters squared; and BMI at age 20 years was calculated in a similar manner by using body weight at age 20 years. BMI measures were categorized as 15–18.49 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), 25–29.9 kg/m^2 (overweight), or 30 kg/m^2 or higher (obese) according to World Health Organization criteria (12). We also evaluated associations between colorectal cancer risk and adult weight change (calculated as recent weight minus weight at age 20 years, both in kilograms).

Assessment of Tumor MSI

Case Subject Material. Tumor blocks and pathology reports, obtained from the Jeremy Jass Memorial Pathology Bank of the Colon Cancer Family Registry, were available to characterize the tumor MSI status of 1250 (69.7%) of the 1794 case subjects. Case subjects without tumor blocks (n = 544) were, on average, younger than case subjects with tumor blocks and MSI data (mean age at study enrollment: 52.9 vs 57.1 years; $P < .001$); otherwise, there were no discernible differences between case subjects with and without MSI data in terms of sex, BMI, or adult weight gain values.

DNA Extraction. Formalin-fixed paraffin-embedded tissue was serially cut into 10-μm thick sections and mounted to two or more slides. One slide was stained with hematoxylin and eosin, and areas of neoplastic (>40%) and normal tissue were identified by pathologists at the various study sites. The corresponding areas containing marked normal and tumor tissue from the unstained sections were then scraped and placed into separate tubes for DNA extraction with the use of a QIAamp Tissue kit (Qiagen, Valencia, CA) according to the manufacturer's instructions.

Microsatellite Instability. Tumor MSI status was assessed by polymerase chain reaction assays at the Colon Cancer Family Registry sites (Cancer Care Ontario; Memorial University of Newfoundland; Mayo Clinic [where tumor samples from the Fred Hutchinson Cancer Research Center and the University of Hawaii were also tested], University of Melbourne, and the Cleveland Clinic [where the University of Southern California Consortium tumor samples were tested]), essentially as described previously (16) with the use of four mononucleotide markers (BAT25, BAT26, BAT40, and BAT34C4), five dinucleotide markers (D5S346, D17S250, ACTC, D18S55, and D10S197), and one penta-mono-tetra compound–repeat marker (MYCL). Primers tagged with various fluorescent dyes were ordered from Applied Biosystems (Applied Biosystems, Foster City, CA), and polymerase chain reaction products were analyzed on an ABI 3100 (Applied Biosystems). Primer sequences are provided in Supplementary Table 1 (available online). Tumors were classified as MSI-high if 30% or more of the markers demonstrated instability, MSI-low if more than 0% and less than 30% of the markers demonstrated MSI, and MS-stable if none of the markers exhibited MSI (5). A minimum of four unequivocal results were required to characterize the tumor MSI status.

Written informed consent was obtained from all study participants at each study center, and the study protocol was approved at each Colon Cancer Family Registry site.

Statistical Analysis

Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated from conditional logistic regression models that accounted for the sibling matching (SAS software, PHREG procedure, version 9.2; SAS Institute Inc, Cary, NC) and adjusted for age at study enrollment (continuous), history of colorectal endoscopy screening procedure (yes, no, or unknown), cigarette smoking status (current, former, never, or unknown), and, in women, postmenopausal hormone use (current, former, never, or unknown). These variables were selected at the onset of the study because they are well-established risk factors for colorectal cancer (17). In conditional logistic regression models that assessed the risk of colorectal cancer from adult weight gain, BMI at age 20 years was included as a covariate. In additional analyses, inclusion of self-identified race, average number of servings of red meat consumed per week, nonsteroidal anti-inflammatory drug use, lifetime average metabolic equivalent hours of physical activity per week, and education level had no substantial effect on the point estimates.

P values for tests of linear trend were estimated by way of a two-sided Wald test for regression models that included continuous measures of recent BMI, BMI at age 20 years, and adult weight gain. Risk estimates are presented in 5-unit increments for the BMI and adult weight gain measures for ease of interpretation and to facilitate comparisons with recent meta-analyses (13,14). Interactions between sex and each of the BMI variables and adult weight gain were tested by -2 log likelihood ratio test statistics that compared models with and without interaction terms. Because of potential nonlinear associations due to the underweight (BMI <18.5 kg/m^2) and weight loss categories, we excluded these groups from the continuous risk estimates and from models with linear interaction terms.

We estimated stratum-specific odds ratios to evaluate potential effect modification of BMI and adult weight change by tumor MSI status by including interaction terms in the conditional logistic regression models. Heterogeneity of the odds ratios by tumor MSI status was evaluated by using a likelihood ratio test that compared a model that included the interaction terms for the stratum-specific associations with one that included the main effects of the respective excess body weight variable. All statistical tests were two-sided.

Results

The median age at study enrollment among women was 55 years (range = 26–83 years) for case subjects and 54 years (range = 19–90 years) for control subjects; among men, the median age of case subjects was 56 years (range = 21–87 years) and of control subjects, 55 years (range = 19–87 years). Select descriptive data for case subjects and sibling control subjects are shown in Table 1.

We first examined associations between BMI (recent and at age 20 years) and adult weight change and the risk of colorectal cancer, overall and stratified by sex (Table 2). For men and women combined, compared with recent normal BMI status (BMI of 18.5–24.9

Table 1. Descriptive characteristics of the study sample by sex and case status*

	Men		Women	
	Case subjects (n = 877)	Control subjects (n = 1299)	Case subjects (n = 917)	Control subjects (n = 1385)
Characteristic	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Age at study enrollment, y				
18–29	8 (0.9)	16 (1.2)	5 (0.5)	16 (1.2)
30–39	36 (4.1)	93 (7.2)	55 (6.0)	125 (9.0)
40–49	208 (23.7)	313 (24.1)	248 (27.0)	382 (27.6)
50–59	284 (32.4)	406 (31.2)	264 (28.8)	398 (28.7)
60–69	227 (25.9)	300 (23.1)	224 (24.4)	297 (21.4)
≥70	114 (13.0)	171 (13.2)	121 (13.2)	167 (12.1)
Colon Cancer Family Registry site				
Memorial University of Newfoundland, St John's, Canada	34 (3.9)	53 (4.1)	26 (2.8)	48 (3.5)
Cancer Care Ontario, Toronto, Canada	114 (13.0)	158 (12.2)	158 (17.2)	231 (16.7)
University of Southern California Consortium, Los Angeles, CA	120 (13.7)	148 (11.4)	133 (14.5)	180 (13.0)
Universities of Queensland and Melbourne, Australia	150 (17.1)	233 (17.9)	139 (15.2)	211 (15.2)
University of Hawaii, Honolulu, HI	42 (4.8)	66 (5.1)	33 (3.6)	48 (3.5)
Mayo Clinic, Rochester, MN	89 (10.1)	144 (11.1)	106 (11.6)	168 (12.1)
Fred Hutchinson Cancer Research Center, Seattle, WA	328 (37.4)	497 (38.3)	322 (35.1)	499 (36.0)
Tumor MSI status				
MS-stable	479 (54.6)	—	434 (47.3)	—
MSI-low	75 (8.6)	—	74 (8.1)	—
MSI-high	65 (7.4)	—	123 (13.4)	—
Unknown	258 (29.4)	—	286 (31.2)	—
Tumor location in the colon or rectum†				
Right colon	223 (25.4)	—	322 (35.1)	—
Left colon	203 (23.1)	—	230 (25.1)	—
Rectum	291 (33.2)	—	214 (23.3)	—
Colon NOS	116 (18.2)	—	151(16.5)	—
No. of first-degree relatives with a history of colorectal cancer				
0	609 (69.4)	—	639 (69.7)	—
≥1	268 (30.6)	—	278 (30.3)	—
Self-identified race				
American Indian or Alaskan Native	58 (6.6)	94 (7.2)	32 (3.5)	49 (3.5)
Black or African American	11 (1.2)	18 (1.4)	22 (2.4)	35 (2.5)
White	767 (87.5)	1125 (86.6)	817 (89.1)	1223 (88.3)
More than one race	10 (1.1)	13 (1.0)	10 (1.1)	11 (0.8)
Unknown, other, or not reported	31 (3.5)	49 (3.8)	36 (3.9)	67 (4.8)
Endoscopy screened‡§				
Yes	133 (15.2)	305 (23.5)	131 (14.3)	270 (19.5)
No	741 (84.5)	991 (76.3)	784 (85.5)	1113 (80.4)
Diabetes‡,‖				
Yes	94 (10.7)	111 (8.6)	79 (8.6)	92 (6.6)
No	781 (89.1)	1186 (91.3)	835 (91.1)	1291 (93.2)
Average no. of servings of red meat per week‡,¶				
<2	94 (10.7)	168 (12.9)	131 (14.3)	223 (16.1)
2 or 3	271 (30.9)	404 (31.1)	361 (39.4)	517 (37.3)
>3–5	208 (23.7)	289 (22.2)	225 (24.5)	308 (22.2)
>5	286 (32.6)	395 (30.4)	169 (18.4)	269 (19.4)
NSAID use‡#				
Never	492 (56.1)	724 (55.7)	532 (58.0)	769 (55.5)
Former	164 (18.7)	226 (17.4)	207 (22.6)	296 (21.4)
Current	219 (25.0)	343 (26.4)	176 (19.2)	314 (22.7)
Postmenopausal hormone use‡,**				
Never	—	—	529 (57.7)	852 (61.5)
Former	—	—	129 (14.1)	148 (10.7)
Current	—	—	164 (17.9)	245 (17.7)

(Table continues)

Table 1 (continued).

Characteristic	Men		Women	
	Case subjects (n = 877)	Control subjects (n = 1299)	Case subjects (n = 917)	Control subjects (n = 1385)
	No. (%)	No. (%)	No. (%)	No. (%)
Cigarette smoking status‡,††				
Never	306 (34.9)	470 (36.2)	448 (48.8)	663 (47.9)
Former	378 (43.1)	549 (42.3)	299 (32.6)	460 (33.2)
Current	169 (19.3)	262 (20.2)	161 (17.6)	238 (17.2)
Lifetime average MET hours of physical activity per week‡,‡‡				
0–6	205 (23.4)	280 (21.6)	227 (24.7)	356 (25.7)
6.1–20	198 (22.6)	304 (23.4)	277 (30.2)	377 (27.2)
20.1–44	211 (24.1)	302 (23.3)	180 (19.6)	280 (20.2)
>44	203 (23.2)	287 (22.1)	139 (15.2)	222 (16.0)
Education level‡,§§				
Less than high school graduate	124 (14.1)	198 (15.2)	138 (15.0)	221 (16.0)
High school graduate	187 (21.3)	290 (22.3)	255 (27.8)	358 (25.8)
Vocational or technical school or some college or university	277 (31.6)	386 (29.7)	297 (32.4)	467 (33.7)
Undergraduate or graduate degree	279 (31.8)	406 (31.2)	219 (23.9)	319 (23.0)

* Some counts do not add to totals because of missing data. MET = metabolic equivalent; MS= microsatellite; MSI = microsatellite instability; NOS = not otherwise specified; NSAID = nonsteroidal anti-inflammatory drug; — = not applicable.

† According to *International Classification of Diseases for Oncology, Third Edition* (18) anatomical site codes: C180, C182, C183, C184, C185 (right colon); C186, C187 (left colon); C199, C209 (rectum); C188, C189, C260 or missing (colon NOS).

‡ Self-reported via questionnaire or interview, depending on study center. The referent date for case subjects was approximately 1 year before diagnosis of colorectal cancer; for siblings (control subjects), the referent date was approximately 1 year before their enrollment into the study.

§ Defined as a prior colonoscopy or sigmoidoscopy procedure for reasons consistent with asymptomatic screening (eg, part of routine physical examination).

‖ Self-report that diabetes mellitus was diagnosed by a physician, excluding gestational diabetes.

¶ One serving was defined as two to three ounces (the size of a deck of cards). Examples of red meat included beef, steak, hamburger, prime rib, and ham.

Defined as use of aspirin- or ibuprofen-containing drugs at least twice per week for 1 month or longer. Current use was indicated when NSAID use was reported in the referent period (defined as approximately 1 year before diagnosis for case subjects or enrollment for control subjects); former use was indicated when NSAIDs were only used before the referent period.

** Defined as use of any form of hormones containing estrogen only (eg, Premarin) or estrogen–progestin (eg, Provera or Prometrium) for treatment of menopausal symptoms, removal of ovaries, heart disease prevention, or osteoporosis. Current and former categories were defined as described above for NSAID use.

†† Cigarette smoking was defined as ever smoking one cigarette per day for 3 months or longer. Current and former categories were defined as described above for NSAID use.

‡‡ Derived from responses to total years, total months, and duration per week of nine modes of activity (walking, running, cycling, swimming, racquet sports, aerobic activities [eg, group exercise and calisthenics], team sports [eg, rugby, soccer, football], vigorous house work, and other activities that increased heart rate and induced sweating) for three periods of the lifespan (20–29, 30–49, 50 years or older).

§§ Defined as the highest completed level of education.

kg/m^2), recent obesity (a BMI of 30 kg/m^2 or more) was associated with increased risk of colorectal cancer (OR = 1.53; 95% CI = 1.26 to 1.86). When the data were stratified by sex, the same comparison yielded lower risk estimates for women (OR = 1.34; 95% CI = 1.03 to 1.75) than for men (OR = 1.79; 95% CI = 1.33 to 2.40); however, the interaction term with sex and recent BMI was not statistically significant ($P_{\text{interaction}}$ = .10). Recent BMI, modeled as a continuous variable in 5 kg/m^2 increments, was positively associated with the risk of colorectal cancer for men and women combined (OR = 1.24; 95% CI = 1.15 to 1.34), for women only (OR = 1.20; 95% CI = 1.10 to 1.32), and for men only (OR = 1.30; 95% CI = 1.15 to 1.47).

For men and women combined, a higher BMI at age 20 years was positively associated with the risk of colorectal cancer; however, in the sex-specific analyses, the 95% confidence intervals for the odds ratios largely included 1. BMI at age 20 years, modeled as a continuous variable in 5 kg/m^2 increments, was positively associated with the risk of colorectal cancer in men and women combined (OR = 1.13; 95% CI = 1.01 to 1.27) but was not statistically significantly associated with the risk of colorectal cancer in women (OR = 1.11; 95% CI = 0.95 to 1.30) or in men (OR = 1.15; 95% CI = 0.97 to 1.35). Compared with an adult weight gain of 0–5 kg, an adult weight gain of 21 kg or more was associated with colorectal cancer risk in men (OR = 2.23; 95% CI = 1.58 to 3.14) but not in women (OR = 1.08; 95% CI = 0.80 to 1.47).

We next examined associations between excess body weight and colorectal cancer risk by tumor MSI status (Table 3). In general, the data suggested that recent BMI and adult weight gain were associated with the risk of MS-stable colorectal tumors but not with the risk of MSI-high colorectal tumors. More specifically, recent BMI per 5 kg/m^2 increment was similarly associated with the risk of MS-stable (OR = 1.38; 95% CI = 1.24 to 1.54) and MSI-low (OR = 1.33; 95% CI = 1.04 to 1.72) colorectal tumors but not with risk of MSI-high colorectal tumors (OR = 1.05; 95%

Table 2. Risk estimates for incident colorectal cancer according to body mass index (BMI) and adult weight change*

	Men and women combined				Women			Men		
	No. of case subjects/ No. of control subjects, n = 1794/2684	OR (95% CI)	P_{trend}†	$P_{interaction\ with\ sex}$‡	No. of case subjects/ No. of control subjects, n = 917/1385	OR (95% CI)	P_{trend}†	No. of case subjects/ No. of control subjects, n = 877/1299	OR (95% CI)	P_{trend}†
BMI (kg/m^2), recent§										
<18.5	26/27	1.51 (0.82 to 2.76)			24/22	1.77 (0.91 to 3.45)		2/5	0.51 (0.09 to 2.89)	
18.5–24.99	627/1051	1.00 (referent)		.10	404/651	1.00 (referent)		223/400	1.00 (referent)	
25–29.99	660/1022	1.16 (0.99 to 1.36)			252/415	1.00 (0.80 to 1.25)		408/607	1.33 (1.06 to 1.68)	
≥30	434/529	1.53 (1.26 to 1.86)			212/281	1.34 (1.03 to 1.75)		222/248	1.79 (1.33 to 2.40)	
Per 5 kg/m^2	1721/2602	1.24 (1.15 to 1.34)	<.001	.22	868/1347	1.20 (1.10 to 1.32)	<.001	853/1255	1.30 (1.15 to 1.47)	<.001
BMI (kg/m^2), age 20 y‖										
<18.5	111/223	0.70 (0.54 to 0.91)			87/184	0.65 (0.48 to 0.88)		24/39	0.85 (0.48 to 1.50)	
18.5–24.99	1284/1944	1.00 (referent)		.58	703/1024	1.00 (referent)		581/920	1.00 (referent)	
25–29.99	292/376	1.28 (1.07 to 1.55)			87/108	1.30 (0.94 to 1.81)		205/268	1.29 (1.02 to 1.62)	
≥30	71/83	1.48 (1.02 to 2.16)			31/42	1.39 (0.81 to 2.36)		40/41	1.58 (0.93 to 2.70)	
Per 5 kg/m^2	1647/2403	1.13 (1.01 to 1.27)	.03	.76	821/1174	1.11 (0.95 to 1.30)	.20	826/1229	1.15 (0.97 to 1.35)	.10
Adult weight change										
Weight loss	198/321	0.94 (0.73 to 1.22)			94/161	0.70 (0.49 to 1.00)		104/160	1.40 (0.95 to 2.06)	
0–5 kg	251/441	1.00 (referent)		.009	158/228	1.00 (referent)		93/213	1.00 (referent)	
6–10 kg	298/483	1.09 (0.87 to 1.37)			155/241	0.88 (0.64 to 1.20)		143/242	1.47 (1.05 to 2.07)	
11–20 kg	506/752	1.22 (0.99 to 1.50)			249/387	0.93 (0.70 to 1.23)		257/365	1.72 (1.25 to 2.36)	
≥21 kg	462/582	1.48 (1.18 to 1.85)			229/327	1.08 (0.80 to 1.47)		233/255	2.23 (1.58 to 3.14)	
Per 5 kg	1517/2258	1.07 (1.04 to 1.11)	<.001	.49	791/1183	1.06 (1.01 to 1.12)	.01	726/1075	1.08 (1.03 to 1.14)	.003

* Odds ratios adjusted for age, endoscopy screening, cigarette smoking, and postmenopausal hormone use (women only). Odds ratios for adult weight gain were additionally adjusted for BMI at age 20 years. Some counts do not add to totals because of missing information. CI = confidence interval; OR = odds ratio.

† Calculated from two-sided Wald χ^2 statistic based on conditional logistic regression models with BMI or weight gain as continuous measures. BMI less than 18.5 and weight loss were excluded from linear models with BMI and adult weight gain, respectively.

‡ Calculated from −2 log likelihood ratio test comparing models with and without an interaction term between sex and the excess body weight variable. BMI less than 18.5 and weight loss were excluded from interaction models with BMI and adult weight gain, respectively.

§ Calculated from self-reported height and weight approximately 1 year before colorectal cancer diagnosis for case subjects or approximately 1year before study enrollment for sibling control subjects.

‖ Calculated from self-reported height and weight at approximately age 20 years for case subjects and sibling control subjects.

Table 3. Risk estimates for incident colorectal cancer according to body mass index (BMI) and adult weight change, stratified by tumor MSI status*

	MS-stable			MSI-low			MSI-high				
	No. of case subjects/ No. of control subjects, n = 913/1376	OR (95% CI)	P_{trend}†	No. of case subjects/ No. of control subjects, n =149/230	OR (95% CI)	P_{trend}†	No. of case subjects/ No. of control subjects, n = 188/274	OR (95% CI)	P_{trend}†	$P_{interaction}$ with MSI level‡	$P_{interaction}$ with MSI level, excluding MSI-low‡
BMI (kg/m^2), recent§											
<18.5	17/14	2.25 (0.98 to 5.17)		1/1	0.92 (0.06 to 14.70)		1/6	Undefined			
18.5–24.99	287/541	1.00 (referent)		55/89	1.00 (referent)		76/93	1.00 (referent)		.15	.04
25–29.99	349/535	1.35 (1.07 to 1.71)		53/88	1.10 (0.65 to 1.84)		64/115	0.79 (0.45 to 1.28)			
≥30	235/252	2.04 (1.54 to 2.71)		37/47	1.81 (0.92 to 3.56)		42/59	0.93 (0.51 to 1.69)			
Per 5 kg/m^2	871/1328	1.38 (1.24 to 1.54)	<.001	145/224	1.33 (1.04 to 1.72)	.03	182/267	1.05 (0.84 to 1.31)	.65	.08	.02
BMI (kg/m^2), age 20 y‖											
<18.5	62/110	0.78 (0.54 to 1.13)		10/23	0.64 (0.28 to 1.47)		14/25	0.67 (0.32 to 1.44)			
18.5–24.99	647/1007	1.00 (referent)		102/163	1.00 (referent)		137/204	1.00 (referent)		.63	.70
25–29.99	151/192	1.44 (1.11 to 1.87)		26/30	1.59 (0.82 to 3.08)		28/36	1.29 (0.71 to 2.36)			
≥30	34/38	1.42 (0.84 to 2.39)		9/8	3.73 (1.04 to 13.42)		7/6	2.07 (0.59 to 7.29)			
Per 5 kg/m^2	832/1237	1.14 (0.98 to 1.33)	.10	137/201	1.58 (1.04 to 2.41)	.03	172/246	1.10 (0.81 to 1.50)	.54	.31	.88
Adult weight change											
Weight loss	103/183	0.92 (0.64 to 1.32)		15/25	0.98 (0.38 to 2.57)		20/24	0.88 (0.38 to 2.02)			
1–5 kg	117/224	1.00 (referent)		18/34	1.00 (referent)		29/39	1.00 (referent)		.39	.47
6–10 kg	144/248	1.04 (0.75 to 1.44)		29/43	1.65 (0.72 to 3.77)		37/49	1.02 (0.49 to 2.12)			
11–20 kg	253/388	1.20 (0.89 to 1.61)		45/56	1.62 (0.76 to 3.49)		50/90	0.86 (0.44 to 1.67)			
≥21 kg	254/274	1.79 (1.29 to 2.47)		37/63	1.36 (0.60 to 3.05)		45/68	1.01 (0.50 to 2.06)			
Per 5 kg	768/1134	1.15 (1.09 to 1.21)	<.001	129/196	0.97 (0.86 to 1.09)	.61	161/246	1.06 (0.95 to 1.18)	.30	.03	.18

* Odds ratios adjusted for age, endoscopy screening, and cigarette smoking. Odds ratios for adult weight gain were further adjusted for BMI at age 20 years. Some counts do not add to totals because of missing information. CI = confidence interval; MSI = microsatellite instability; MS-stable = microsatellite stable; OR = odds ratio.

† Calculated from two-sided Wald χ^2 statistic based on conditional logistic regression models with BMI or weight gain as continuous measures. BMI less than 18.5 and weight loss were excluded from linear models with BMI and adult weight gain, respectively.

‡ Calculated from −2 log likelihood ratio test comparing models with and without an interaction term between MSI and the excess body weight variable. BMI less than 18.5 and weight loss were excluded from interaction models with BMI and adult weight gain, respectively.

§ Calculated from self-reported height and weight approximately 1year before colorectal cancer diagnosis for case subjects or approximately 1year before study enrollment for sibling control subjects.

‖ Calculated from self-reported height and weight at approximately age 20 years for case subjects and sibling control subjects.

CI = 0.84 to 1.31). Comparable, albeit somewhat less consistent, trends were observed for BMI at age 20 years and adult weight gain across tumor MSI strata.

We observed no statistically significant associations between recent BMI (when modeled categorically and continuously) and the risk of MSI-high colorectal tumors when the MSI-high data were further stratified by family history of colorectal cancer (one or more first-degree relative affected by colorectal cancer for case subjects vs no family history among cases subjects), *MLH1* promoter methylation status (methylated vs unmethylated), or mismatch repair gene germline mutation status [carrier of a germline mutation in *MLH1*, *MSH2*, or *MSH6* (3) vs no germline mutation], although the numbers in the subgroups were small (Supplementary Table 2, available online).

Discussion

Consistent with previous observational studies (13,14), our findings indicate that BMI and adult weight gain are associated with an increased risk of colorectal cancer; a novel aspect of our study is the inclusion of tumor MSI data and the finding that overweight and obesity were associated with increased risks of MS-stable and MSI-low tumors, but not with the risk of MSI-high tumors. These data add further evidence that excess body weight is a potentially avoidable cause of colorectal cancer. The risk estimate for recent BMI was higher for men than for women (but the difference was not statistically significant), consistent with results of a recent pooled analysis of data from seven prospective studies of metachronous colorectal adenomas (19) and of meta-analyses of prospective studies of colorectal cancer (13,14). As we have discussed in detail elsewhere (20), this risk attenuation for women may be due to the protective effect of estrogenic precursors that are produced by adipose tissue in counterbalancing the otherwise risk-enhancing properties of obesity. Alternatively, it is possible that BMI might be less associated with central adiposity in women than in men (21), and several studies suggest that for both sexes, central adiposity is more strongly associated with colorectal cancer risk than BMI (22,23). We cannot address this issue directly because we did not collect data on waist circumference (a common measure of central adiposity in population-based studies).

We found that BMI at age 20 years and adult weight gain were associated with the risk of colorectal cancer in men and women combined. The categorical sex-specific analyses suggested that adult weight gain is associated with colorectal cancer risk for men but not women. However, when modeled continuously, adult weight gain was associated with colorectal cancer risk for men and for women; these results for women should be interpreted cautiously because the linear associations are inconsistent with their respective categorical associations. For men, these observations add to the relatively sparse data in the literature, suggesting that adult weight gain is associated with an increased risk of colon adenoma (24,25) and colorectal cancer (20,24,26,27). Given the rarity of studies on this topic for women, additional studies on the associations between adult weight gain and BMI in early adulthood with risk of colorectal cancer are warranted.

The only other study to our knowledge that examined associations between BMI and the risk of colorectal cancer by tumor MSI status (10) reported that in men, BMI was positively associated with MSI-negative tumors but not with MSI-positive tumors (odds ratios were 1.9 [95% CI = 1.5 to 2.4] and 1.0 [95% CI = 0.6 to 1.6], respectively). We observed the same pattern of associations for men and women combined for MS-stable and MSI-high. For women, the study by Slattery et al. (10) reported that BMI was relatively equivalently and weakly associated with the risk of MSI-negative (OR = 1.3; 95% CI = 1.0 to 1.7) and MSI-positive (OR = 1.3; 95% CI = 0.8 to 1.9) tumors. The discrepant results between this study and the study by Slattery et al. may be explained by the MSI definitions used in the two studies: This study characterized three levels of MSI (MS-stable, MSI-low, and MSI-high), whereas Slattery et al. (10) characterized only two levels (MSI-negative and MSI-positive, which correspond to MS-stable and MSI-high, respectively, in this study). Our data also indicated that risk estimates were similar for MSI-low and MS-stable tumors, although the sample size for MSI-low was considerably smaller than MS-stable. The collective evidence from these two studies suggests that BMI is most strongly associated with the risk of MS-stable colorectal tumors; however, given the relatively small numbers of MSI-high tumors in these studies, these results might be due to chance, and future studies with larger sample sizes are needed to confirm these findings.

Several mechanisms have been proposed to explain the association between BMI, adult weight gain, and colorectal cancer risk, including insulin and the insulin-like growth factor system, adipokines (eg, leptin, adiponectin), inflammation (eg, C-reactive protein), oxidative stress, and steroid hormones, as discussed in recent comprehensive reviews (28,29). Perhaps more relevant here are experimental data regarding differing associations for excess body weight and risk of MS-stable vs MSI-high tumors, including results from studies in mice (30,31). For example, an obesity-causing mutation in the leptin receptor was required for the development of colon neoplasia in adenomatous polyposis coli (APC)-mutant mice (an experimental model of human adenomatous polyposis prone to MS-stable malignancies that occur predominantly in the small intestine) (30). Mice that had the APC mutation, but lacked the leptin receptor mutation and therefore had normal body weight, developed only noncolorectal tumors (30). An earlier study of DNA mismatch repair–deficient mice fed a high fat and low calcium diet or an energy-restricted diet suggested no effect of diet or weight change on the development of intestinal adenomas or cancers, despite marked differences in overall survival between mice fed the different diets (31). Results of these two animal studies are in agreement with our findings of an association between recent BMI and increased risk of MS-stable tumors and no association between recent BMI and risk of MSI-high tumors. The combined evidence suggests that obesity is a strong risk factor for colorectal tumors that display the MS-stable phenotype.

The underlying basis for the increased risk of MS-stable tumors associated with overweight or obesity and the lack of an association with MSI-high tumors remain largely speculative. However, one possible explanation includes the matrix metalloproteinase system, which is involved in diet-induced obesity through remodeling of the extracellular matrix that surrounds the expanding adipose tissue (32) and in the degradation of the extracellular matrix during colorectal cancer metastasis (33).

mRNA levels of several metalloproteinases were differentially expressed in a mouse model of diet-induced obesity (34), and gene expression analysis has further shown that *MMP-7* expression is increased in MS-stable colorectal cancer cell lines compared with non-neoplastic cell lines, but not in MSI-high cell lines compared with non-neoplastic cell lines (35). Another potential biological source of our observations of increased risk of MS-stable tumors from overweight and obesity and no associations for risk of MSI-high tumors involves telomeres (the physical ends of chromosomes): An inverse association between telomere length and body weight was reported recently (36), and shorter telomere length, in turn, has been linked to chromosomal instability and MS-stable colorectal tumors but not to MSI-high colorectal tumors (37). If the differential associations for BMI and tumor MSI reported here are replicated in future studies, additional studies will be needed to better understand the differing etiologies of MS-stable and MSI-high colorectal cancers.

Limitations of this study include the use of self-reported body weight and height, along with the somewhat prolonged interval (2–5 years) between colorectal cancer diagnosis and baseline interview for some subjects (27%). A recent cross-sectional study suggested that BMI measures based on self-reports of height and weight are, on average, 1.3 kg/m^2 lower than directly measured values (38). Underreporting of self-reported BMI may overestimate associations between being overweight and the risk of colorectal cancer compared with studies that have direct measures of body weight. However, generally good-to-excellent agreement between self-reported and directly measured values of height and weight has been reported in study populations that were demographically similar to the one used in this study (39,40). Furthermore, prospective studies (41,42) with direct measures of height and weight reported estimates of associations between BMI and colorectal cancer risk that are similar to those reported in this study.

An additional limitation of this study is the possibility of survival bias because some potential case subjects may have died before they had the opportunity to enroll in this study. Because obesity is associated with poorer survival after diagnosis of colorectal cancer (43), survival bias might have contributed to an underestimate of the risk of colorectal cancer associated with obesity. We would expect survival bias to have less of an impact on analyses of case subjects with MSI-high tumors because of the better survival of these patients compared with patients with MS-stable tumors (6). The lack of association between BMI and risk of MSI-high tumors, therefore, appears unlikely to be explained by survival bias.

The strengths of this study include the large number of colorectal cancer case subjects with detailed assessments of their tumor MSI status according to standardized protocols. We also used a control series comprising unaffected same-sex siblings of the case subjects. The use of such a control group reduces potential unmeasured confounding from factors that include genetic variation and early-life exposures to potential risk factors (44).

In summary, our data suggest that BMI approximately 1 year before a colorectal cancer diagnosis is associated with the risk of this disease, slightly more so for men than for women. Long-term weight status, as reflected by BMI at age 20 years and adult weight gain, is also associated with the risk of colorectal cancer. Our data also suggest that the associations between BMI and adult weight gain and the risk of colorectal cancer differ between MS-stable and MSI-high tumors, as defined by the Bethesda panel, further suggesting differing underlying etiologies for colorectal cancer according to tumor MSI.

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