Research Article

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Body Mass Index and Microsatellite Instability in Colorectal Cancer: A Population-based Study

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Abstract

Background: Previous studies reported a positive association of body mass index (BMI) with microsatellite-stable (MSS) but not with microsatellite-instable (MSI-high) colorectal cancer. However, information from population-based studies conducted in representative age groups is so far limited.

Methods: We conducted a population-based case–control study (DACHS) in Southern Germany, including 1,215 patients with incident colorectal cancer and 1,891 matched controls with no upper age limit. Information on risk factors of colorectal cancer was obtained in standardized interviews. Microsatellite instability was analyzed using a mononucleotide marker panel.

Results: Median age among cases was 69 years, and 115 cases were classified MSI-high (9.5%). In multivariate analyses, BMI was positively associated with both risk of MSI-high colorectal cancer [per 5 kg/m^2: OR, 1.71; 95% confidence interval (CI), 1.35–2.17] and risk of MSS colorectal cancer (OR, 1.20; 95% CI, 1.07–1.33). The association with MSI-high colorectal cancer was limited to women (OR, 2.04; 95% CI, 1.50–2.77; P interaction = 0.02) and most pronounced among ever users of postmenopausal hormone replacement therapy (OR, 4.68; 95% CI, 2.36–9.30; P interaction = 0.01). In case-only analyses, BMI was more strongly associated with MSI-high colorectal cancer than with MSS colorectal cancer among women (OR, 1.84; 95% CI, 1.13–1.82; P interaction = 0.01).

Conclusions: This population-based study confirms previous findings of increased risk of MSS colorectal cancer with obesity between both sexes and suggests that overweight and obesity may also be associated with increased risk of MSI-high colorectal cancer among women.

Impact: These findings extend available data on the association of BMI and microsatellite instability in colorectal cancer and may suggest a link between overweight and obesity with sporadic MSI-high colorectal cancer in women. *Cancer Epidemiol Biomarkers Prev; 22(12); 2303–11. ©2013 AACR.*

Introduction

Colorectal cancer is a heterogeneous disease that can be classified into distinct subtypes with different underlying molecular alterations, such as microsatellite instability, chromosomal instability, and the CpG-island methylator phenotype (CIMP; ref. 1). It is conceivable that colorectal cancers developing from the same molecular pathways are likely to be similar with regard to their etiologic factors, response to therapy, or prognosis (2).

Many studies have investigated associations of risk factors and colorectal cancer by anatomic subsite of the tumor (e.g., colon/rectum, proximal/distal; refs. 3–5), which may partly reflect associations with different molecular types of carcinogenesis. For example, obesity is an established risk factor of colorectal cancer (6); however, studies showed variation of relative risks by sex and cancer site (7). Discrimination by molecular subtypes could provide an even clearer distinction of colorectal cancers and their associations with risk factors than tumor subsite alone (8, 9).

Knowledge of associations of risk factors and molecular subtypes of colorectal cancer could contribute to more targeted prevention, better specification of individually underlying risk factors in post-diagnosis communication, better understanding of the interaction of risk factors and carcinogenic processes. Furthermore, it could inform future intervention studies.

High-level microsatellite instability (MSI-high) is a genetic phenotype resulting from DNA mismatch repair

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deficiency and a hallmark alteration of cancers arising in the setting of hereditary nonpolyposis colorectal cancer (HNPCC; Lynch syndrome, approximately 3% of colorectal cancers). In this context, tumor development typically has an early onset. On the other hand, MSI-high is also present in about 10% of sporadic colorectal cancers, predominantly among women and among patients with a late age of onset, even though pathogenesis of sporadic MSI-high colorectal cancer is fundamentally different from pathogenesis of Lynch syndrome–associated MSI-high colorectal cancer.

In a recent case–control study within the Colon Cancer Family Registry (CCFR) from the United States, body mass index (BMI) was associated with microsatellite-stable (MSS) colorectal cancer but not with MSI-high colorectal cancer (10). However, because of the possibility of oversampling hereditary colorectal cancer (i.e., MSI-high cases with Lynch syndrome) and of undersampling sporadic colorectal cancers of older age groups, the results may not reflect what would be found in a population at average risk. Therefore, more results from older age groups and further population-based studies are required than currently available (11, 12) to evaluate the role of overweight and obesity with regard to microsatellite instability in colorectal cancer.

We aimed to further investigate the association of BMI and microsatellite instability in colorectal cancer among women and men in a large population-based study from Germany with a representative age distribution.

Materials and Methods

Study design and study population

We conducted a population-based case–control study in the Rhine-Neckar region in southwestern Germany. Details of the study design and participation rates have been reported previously (13, 14). Briefly, patients ages 30 or older with a histologically confirmed first diagnosis of primary colorectal cancer between 2003 and 2007, who were physically and mentally able to participate and to communicate in German, were recruited in all 22 hospitals of the study region offering colorectal cancer surgery. Community-based control subjects were randomly selected from population registries and frequency matched to cases with respect to age, sex, and county of residence. Controls with a history of colorectal cancer were excluded; otherwise inclusion and exclusion criteria were the same as in cases. Participants with hereditary colorectal cancer syndromes were not excluded. The patients recruited constitute about 50% of the expected eligible patients in the study area. The participation rate among eligible control participants was slightly more than 50%. The study was approved by the ethics committees of the Medical Faculty at the University of Heidelberg and of the Medical Chambers of Baden-Wuerttemberg and Rhineland-Palatinate. Written informed consent was obtained from each participant and included the analysis of tumor tissue from patients with colorectal cancer.

Data collection

Patients were informed about the study by the physicians in charge of their treatment, in most cases during hospital stay after surgery. Personal interviews were conducted by trained interviewers during hospitalization, or, if patients had already left hospital, at their homes. Controls were contacted by the study center through mail and follow-up calls, and interviews were scheduled at their homes. The standardized interviews included a detailed medical and family history, as well as a lifetime history of sociodemographic and lifestyle factors. A self-administered questionnaire including key information was obtained from a minority of control participants not willing to participate in a personal interview. In addition, we collected discharge letters and pathology reports of the cases, and endoscopy reports of up to three previous colorectal endoscopies of both cases and controls. The index date was the date of diagnosis among cases and the date of the interview among controls.

Information on weight at preceding ages (10-year intervals) and current height was obtained from self-reports during the interview. To calculate BMI of cases and controls (kg/m^2), weight at least 5 years before the index year was used (e.g., for a person age 85 years we used weight at age 80, if 84 years old we used weight at age 70; range 5–14 years, median 10 years). This measure of body weight was preferred over current weight because cancer-related symptoms before and after diagnosis or therapy of colorectal cancer can cause weight changes. As preceding weight was comprehensively assessed during the interviews only, we restricted the analyses to interviewed cases (all 1,945 patients) and controls ($N = 1{,}891$, 508 controls with short questionnaire were not included).

Collection and processing of tumor samples

Formalin-fixed paraffin–embedded (FFPE) samples of the colorectal tumor were collected from the pathology departments of the cooperating clinics and transferred to the tissue bank of the National Center for Tumor Diseases (NCT) in Heidelberg. DNA was isolated from one section of the tumor tissue block after areas with highest tumor cell concentration (at least 70% tumor cells) had been microscopically identified. DNA isolation was performed using a commercial DNA Extraction Kit (DNeasy; Qiagen) according to the manufacturer's protocol. Microsatellite instability was determined in 1,215 consecutively recruited cases using a mononucleotide marker panel (BAT25, BAT26, and CAT25) in sections of the tumor block. The marker panel used differentiates MSI-high from non–MSI-high tumors with a sensitivity of 98.2% and a specificity of 100%, and with 100% concordance of MSI-high tumors compared with the National Cancer Institute/International Collaborative Group on HNPCC (NCI/ICG-HNPCC) marker panel (BAT25, BAT26, D17S250, D2S123, and D5S346) for the evaluation of microsatellite instability in colorectal cancer (15). A more detailed description is available elsewhere (16). The very high

accuracy of the marker panel has also been confirmed by additional independent studies (17–19).

Statistical analysis

We first compared the distribution of potential risk factors and protective factors among patients with MSS colorectal cancer, MSI-high colorectal cancer, and controls and assessed heterogeneity of results (see Table 1).

Unconditional multiple logistic regression was used to estimate ORs for the association of risk factors with risk of MSI-high and MSS tumors. Covariates other than the matching factors age and sex were included in the model in a backward variable selection procedure if the OR was changed by ≥10% after elimination from the model, or if the distribution among either MSI-high or MSS cases was statistically significantly different from that among the controls ($P < 0.05$). ORs were adjusted for age and sex, and for the following additional known or potential confounders: school education (≤9/10–11/12+ years), previous colorectal endoscopy (yes/no), previous general health screening examination (yes/no), history of colorectal cancer in a first-degree relative (yes/no), ever regular smoking (current/former/never), regular use of nonsteroidal anti-inflammatory drugs (NSAID; 2+ times per week for at least one year, ever/never), and use of hormone replacement therapy (HRT; ever/never). Other covariates like diabetes, physical activity, and alcohol consumption did not materially influence the estimates and were not included in the models. Heterogeneity of associations of BMI with MSI-high and MSS colorectal cancer was assessed in case-only analyses. In sensitivity analyses, we additionally adjusted for cancer stage and cancer location to control for potential confounding, because location and stage were differentially associated with MSI-high and MSS colorectal cancer.

To account for possible interaction, we conducted additional stratified analyses by age groups (<70 years/70+ years), history of colorectal cancer in a first-degree family member (yes/no) and, among postmenopausal women, by ever use of HRT (ever/never). Detailed information about gynecologic history and HRT use was available from the interviews and medical records (14). Any previous use of estrogen alone or in combination with other drugs for any time period was considered ever use of HRT. Women were classified postmenopausal if menstrual bleeding had stopped naturally, if bilateral oophorectomy, radiation therapy or chemotherapy had been performed, or if women were older than 55 years. Menopausal status can be masked if a hysterectomy was the cause for the end of the menstrual cycle or if HRT was started before natural menopause. Therefore, we also classified women ages 55 years or younger as postmenopausal if their menstrual bleedings had stopped and they additionally used HRT for more than 4 years (the duration of perimenopause for most women).

The analyses were carried out with the statistical software package SAS 9.2 (SAS Institute Inc.) using PROC FREQ for descriptive analyses and χ^2 tests (PROC TTEST for analyses of age differences), and PROC LOGISTIC for multivariable logistic regression analyses. Interaction was evaluated after inclusion of a multiplicative term into the model, consisting of BMI and the effect modifier under study. All tests were two-sided and P values of <0.05 were considered statistically significant.

Results

Overall, 1,215 patients, 115 of whom were MSI-high (9.5%), and 1,891 controls were included in the analyses. Median age among cases and controls was 69 and 70 years, respectively. Controls had better education and had undergone large-bowel endoscopy more often than cases (Table 1). Patients had more often a first-degree relative with a history of colorectal cancer than the controls and included a higher proportion of current smokers. The proportions of women and obese subjects were higher among patients with MSI-high colorectal cancer than among controls or cases with MSS colorectal cancer. MSI-high tumors were strongly associated with proximal location (proximal colon: cecum to transversal colon; distal colon: left flexure to sigmoid colon; rectum; rectum including rectosigmoid), female sex, and lower tumor stage.

Compared with normal weight participants, risk of both MSS colorectal cancer and MSI-high colorectal cancer was higher with increasing BMI (Table 2). Per 5 kg/m^2 increment in BMI, risks of MSS, and MSI-high colorectal cancer were statistically significantly elevated by 20% and 71%, respectively. For MSS colorectal cancer, the associations were similar in subgroup analyses among women and men (P interaction = 0.35). For MSI-high colorectal cancer, associations were stronger than with MSS colorectal cancer among women only (OR, 2.04; 95% confidence interval (CI), 1.50–2.77; P interaction = 0.02). Compared with normal weight women, obese women even had a 4-fold increased risk of MSI-high colorectal cancer. In case-only analyses, increasing BMI was more strongly associated with MSI-high colorectal cancer than with MSS colorectal cancer among women (per 5 BMI points: OR, 1.84; 95% CI, 1.34–2.52), but not among men (OR, 0.95; 95% CI, 0.64–1.41; P interaction = 0.01). Additional adjustment for proximal and distal location and tumor stage did not alter the case-only results (data not shown).

The observed associations per 5 kg/m^2 increment in BMI were not statistically different in age groups less than 70 and 70+ years, or according to a history of colorectal cancer in a first-degree relative (Table 3). However, among postmenopausal women, largely differential effects were observed about risk of MSI-high colorectal cancer according to use or nonuse of HRT (OR, 4.68; 95% CI, 2.36–9.30 and OR, 1.50; 95% CI, 1.05–2.15, respectively, P interaction = 0.01).

Table 1. Characteristics of the study population

	MSS colorectal cancer	MSI-high colorectal cancer	Controls	*P*		
				MSS vs. controls	MSI-high vs. controls	MSS vs. MSI-high
	N = 1,100 (%)	*N* = 115 (%)	*N* = 1,891 (%)			
Age, y						
<50	44 (4)	3 (3)	68 (4)			
50–59	162 (15)	17 (15)	283 (15)			
60–69	364 (33)	34 (30)	590 (31)			
70–79	366 (33)	33 (29)	632 (33)			
80+	164 (15)	28 (24)	318 (17)			
Median (range)	69 (33–94)	71 (37–89)	70 (34–98)	0.82	0.11	0.10
Sex						
Female	459 (42)	64 (56)	774 (41)			
Male	641 (58)	51 (44)	1,117 (59)	0.67	<0.01	<0.01
Colorectal cancer stage						
I	170 (19)	12 (13)	– (–)			
II	281 (32)	51 (57)	– (–)			
III	297 (33)	23 (26)	– (–)	–	–	<0.01
IV	140 (16)	4 (4)	– (–)			
Colorectal cancer location[a]						
Proximal colon	275 (31)	79 (88)	– (–)			
Distal colon	258 (29)	11 (10)	– (–)	–	–	<0.01
Rectum	353 (40)	2 (2)	– (–)			
School education, y[b]						
≤9	760 (69)	87 (76)	1,129 (60)			
10–11	186 (17)	12 (11)	378 (20)	<0.01	<0.01	0.18
12–13	154 (14)	15 (13)	380 (20)			
History of colorectal cancer in a first-degree relative[c]						
No/unknown	937 (86)	98 (85)	1,677 (89)			
Yes	158 (14)	17 (15)	211 (11)	0.01	0.24	0.92
Previous large-bowel endoscopy[d]						
No/unknown	887 (81)	77 (67)	905 (48)			
Yes	211 (19)	38 (33)	986 (52)	<0.01	<0.01	<0.01
BMI (kg/m^2)						
<25	370 (34)	27 (24)	666 (35)			
25–<30	510 (46)	51 (44)	899 (48)	0.16	<0.01	<0.01
30+	220 (20)	37 (32)	326 (17)			
Cigarette smoking[e]						
Never	465 (42)	54 (47)	846 (45)			
Former	455 (42)	41 (36)	806 (43)	0.02	0.17	0.48
Current	176 (16)	20 (17)	235 (12)			
NSAIDs[f]						
Never	850 (78)	86 (75)	1,314 (70)			
Ever	246 (22)	29 (25)	570 (30)	<0.01	0.25	0.50
Hormone replacement therapy (postmenopausal women)[g]						
Never	284 (68)	46 (72)	342 (48)			
Ever	134 (32)	18 (28)	377 (52)	<0.01	<0.01	0.53

[a]Missing for 2 MSS cases. Proximal colon: cecum to transversal colon; distal colon: left flexure to sigmoid colon; rectum: rectosigmoid, rectum.
[b]Missing for 1 MSI-high case and 4 controls.
[c]Missing for 5 MSS cases and 3 controls.
[d]Missing for 2 MSS cases.
[e]Missing for 4 MSS cases and 4 controls.
[f]Missing for 4 MSS cases and 7 controls.
[g]Missing for 5 MSS cases and 2 controls.

Table 2. Association of BMI with MSS and MSI-high colorectal cancer

	Controls	MSS colorectal cancer		MSI-high colorectal cancer		MSI-high vs. MSS colorectal cancer
	N (%)	*N* (%)	OR[a] (95% CI)	*N* (%)	OR[a] (95% CI)	OR[a] (95% CI)
Women and men						
<25 kg/m^2	666 (35)	370 (34)	1.00	27 (23)	1.00	1.00
25–<30 kg/m^2	899 (48)	510 (46)	1.03 (0.85–1.24)	51 (44)	1.56 (0.95–2.57)	1.57 (0.95–2.61)
30+ kg/m^2	326 (17)	220 (20)	1.23 (0.97–1.56)	37 (32)	2.97 (1.72–5.12)	2.58 (1.48–4.48)
Per 5 kg/m^2[b]	1,891	1,100	1.20 (1.07–1.33)	115	1.71 (1.35–2.17)	1.44 (1.13–1.82)
P interaction (sex–BMI)[c]			0.35		0.02	0.01
Women						
<25 kg/m^2	346 (45)	212 (46)	1.00	13 (20)	1.00	1.00
25–<30 kg/m^2	306 (40)	159 (35)	0.83 (0.62–1.11)	27 (42)	2.23 (1.10–4.51)	2.71 (1.31–5.63)
30+ kg/m^2	122 (16)	88 (19)	1.25 (0.86–1.81)	24 (38)	4.70 (2.21–9.98)	4.51 (2.07–9.86)
Per 5 kg/m^2[b]	774	459	1.15 (0.97–1.35)	64	2.04 (1.50–2.77)	1.84 (1.34–2.52)
Men						
<25 kg/m^2	320 (29)	158 (25)	1.00	14 (27)	1.00	1.00
25–<30 kg/m^2	593 (53)	351 (55)	1.20 (0.93–1.55)	24 (47)	0.99 (0.49–1.97)	0.79 (0.39–1.58)
30+ kg/m^2	204 (18)	132 (20)	1.29 (0.93–1.77)	13 (25)	1.52 (0.68–3.41)	1.16 (0.51–2.63)
Per 5 kg/m^2[b]	1,117	641	1.25 (1.08–1.45)	51	1.22 (0.82–1.81)	0.95 (0.64–1.41)

[a]ORs are adjusted for matching factors age and sex, and, in addition, for school education, history of large-bowel endoscopy, participation in health screening examinations, history of colorectal cancer in a first-degree relative, smoking, ever regular use of NSAIDs, and ever use of hormone replacement therapy.

[b]Categories for the analysis of the 5 kg/m^2 increments of BMI were <25 kg/m^2 (category I), 25–<30 kg/m^2 (II), 30–<35 kg/m^2 (III), and 35+ kg/m^2 (IV).

[c]Tests for statistical interaction were performed with BMI per 5 kg/m^2 increments.

Discussion

In this population-based study, we found a strongly elevated risk of MSI-high colorectal cancer associated with BMI. However, the association was limited to women. In fact, the risk of MSI-high colorectal cancer was even stronger than of MSS colorectal cancer, for which a moderately increased risk was observed among women and men from the age of 70 years on, and was particularly pronounced among postmenopausal women who ever used HRT. The observed differences were independent of additional tumor characteristics such as cancer location and stage and suggest a link between overweight and obesity with sporadic MSI-high colorectal cancer among women.

Approximately 10% to 15% of colorectal cancers are MSI-high, and 10% to 25% of MSI-high colorectal cancers are associated with the Lynch syndrome (2). These tumors are caused by a combined germline and somatic mutational inactivation of the mismatch repair genes and usually have an early age of onset (20). The remaining MSI-high cancers are sporadic tumors following silencing of *MLH1* through aberrant promoter methylation (21, 22). Thus, different initiating mechanisms of MSI-high carcinogenesis exist, and it is conceivable that lifestyle risk factors, such as overweight and obesity, have a different, presumably less pronounced influence on hereditary as compared with sporadic carcinogenesis. In fact, increasing evidence suggests that obesity can alter DNA methylation, even though mechanisms are poorly understood yet (23, 24).

Our findings about MSI-high colorectal cancer are not in line with a recent study by Campbell and colleagues that found no association of BMI and MSI-high colorectal cancer (10). In this case–control study conducted within a registry focusing on hereditary colorectal cancer, patients had a low median age (median: 55 years; ≥70 years: 13%) and a high proportion of subjects had a history of colorectal cancer in a first-degree relative (cases: >30%; controls: 100%; refs. 25, 26). In the study reported here, patients with a first diagnosis of incident colorectal cancer and controls were recruited with no upper age limit (median: 69 years; ≥70 years: 50%; proportion of cases and controls reporting colorectal cancer in a first-degree relative: 14% and 11%, respectively). However, subgroup-specific analyses in our study defined by history of colorectal cancer in a first-degree relative did not reveal major differences, and female subjects younger than 70 years and 70+ years showed similarly strong associations with respect to risk of MSI-high colorectal cancer (Table 3).

Table 3. Association of BMI (per 5 kg/m^2) with MSS and MSI-high colorectal cancer according to age group, history of colorectal cancer in a first-degree relative, and by use of hormone replacement therapy among postmenopausal women

	Controls	MSS colorectal cancer		MSI-high colorectal cancer		MSI-high vs. MSS colorectal cancer
	N	*N* (%)[a]	OR[b,c] (95% CI)	N (%)[a]	OR[b,c] (95% CI)	OR[b,c] (95% CI)
Women and men						
<70 y	941	570 (91)	1.09 (0.94–1.26)	54 (9)	1.52 (1.08–2.13)	1.37 (0.97–1.92)
70+ y	950	530 (90)	1.32 (1.12–1.56)	61 (10)	1.86 (1.32–2.63)	1.51 (1.07–2.12)
P interaction (age–BMI)[d]			0.10		0.30	0.59
Women						
<70 y	397	222 (90)	1.07 (0.85–1.35)	24 (10)	2.02 (1.26–3.25)	1.80 (1.10–2.94)
70+ y	377	237 (86)	1.26 (0.99–1.61)	40 (14)	2.04 (1.34–3.09)	1.75 (1.13–2.69)
P interaction (age–BMI)[d]			0.17		0.86	0.41
Men						
<70 y	544	348 (92)	1.15 (0.94–1.40)	30 (8)	1.09 (0.66–1.81)	0.97 (0.58–1.63)
70+ y	573	293 (93)	1.38 (1.10–1.73)	21 (7)	1.50 (0.78–2.87)	1.07 (0.55–2.07)
P interaction (age–BMI)[d]			0.33		0.38	0.81
History of colorectal cancer in a first-degree relative						
Yes	211	158 (90)	1.32 (0.97–1.79)	17 (10)	1.74 (0.88–3.43)	1.27 (0.64–2.51)
No	1,677	937 (90)	1.19 (1.05–1.33)	98 (10)	1.72 1.33–2.23	1.44 (1.12–1.86)
P interaction (family history–BMI)[d]			0.82		0.81	0.70
Hormone replacement therapy (postmenopausal women)						
Ever	377	134 (88)	1.22 (0.90–1.65)	18 (12)	4.68 (2.36–9.30)	3.12 (1.62–6.01)
Never	342	284 (86)	1.07 (0.86–1.32)	46 (14)	1.50 (1.05–2.15)	1.42 (0.97–2.08)
P interaction (HRT–BMI)[d]			0.90		0.01	<0.01

[a]Prevalence of MSS colorectal cancer or MSI-high colorectal cancer within a subgroup.

[b]ORs are adjusted for matching factors age and sex, and, in addition, for school education, history of large-bowel endoscopy, participation in health screening examinations, history of colorectal cancer in a first-degree relative, smoking, ever regular use of NSAIDs, and ever use of hormone replacement therapy.

[c]Categories for the analysis of the 5 kg/m^2 increments of BMI were <25 kg/m^2 (category I), 25–<30 kg/m^2 (II), 30–<35 kg/m^2 (III), and 35+ kg/m^2 (IV).

[d]Tests for statistical interaction were performed with BMI per 5 kg/m^2 increments, and the dichotomous variables age <70/70+ years, history of colorectal cancer in a first-degree relative, and ever use of hormone replacement therapy, respectively.

An earlier epidemiologic study investigating the association of BMI and MSI-high colon cancer had been conducted in a slightly younger population (mean age at diagnosis about 64 years; >70 years: 34%), and reported effect directions in the highest BMI groups that were similar to our study (11). Associations with risk of MSI-high colon cancer were, however, not statistically significant (OR, 1.3; 95% CI, 0.8–1.9 among women; OR, 1.0; 95% CI, 0.6–1.6 among men), whereas risk of MSS tumors was increased among both women and men (OR, 1.3; 95% CI, 1.0–1.7 and OR, 1.9; 95% CI, 1.5–2.4, respectively). It has to be noted that the BMI of the reference group among women in this study (<30 kg/m^2) was much higher than in our study. Another recent investigation pooling data from two cohort studies with similar age distribution from the Netherlands and Australia, respectively, found a moderately increased risk with MSS cancer and no association with MSI-high cancer, but results were not statistically different (P heterogeneity = 0.53; ref. 12). Also, no sex-specific differences were observed.

Obesity increases levels of endogenous estrogen and may thereby influence colorectal cancer risk (27). Slattery and colleagues suggested that higher levels of estrogen prevent MSI-high colorectal cancer in older women, and

that risk of MSI-high colorectal cancer is elevated if estrogens are lacking (28). However, we found that obesity and, even more, use of HRT on top of obesity was associated with an increase in risk of MSI-high colorectal cancer among postmenopausal women. Despite the different findings, use of HRT seems to have an influence on the association of obesity and risk of MSI-high among older women.

Apart from hormonal factors, different characteristics of the studied populations likely have contributed to the different results with respect to MSI-high colorectal cancer, including different proportions of hereditary and sporadic MSI-high cancers, or of other cancer features. Furthermore, differences in cancer risk factors, such as differences in age and sex, family history, and environmental or lifestyle factors, might have contributed to the apparent differences in results.

Considering that the majority of MSI-high tumors are sporadic tumors, their association with obesity in women needs further investigation. Interestingly, fatty acid synthase (FASN) is a key enzyme for de novo lipogenesis that is upregulated in conditions of excess energy, is regulated by estrogen and progesterone in hormone-sensitive cells, and may be one link to the association of obesity and colorectal cancer (29, 30). In colorectal cancer samples from population-based cohort studies, FASN was more frequently overexpressed in MSI-high than in MSS tumors, although sex-specific associations of FASN expression and MSI-high colorectal cancer were not reported (31).

Our study has strengths and limitations. Among the strengths are its population-based setting, an age structure that is very close to that of patients with incident colorectal cancer, the recruitment of unrelated cases and controls matched by gender, age, and county of residence, the extensive collection of information during in-person interviews and from medical records, and consequently the ability to adjust for major confounders in the multivariate analyses.

Although participation of 50% of eligible controls who had to agree to home visits is probably close to what can be achieved in a large unselected population of older adults with no upper age limit, we cannot rule out potential selection bias. However, compared with controls that provided information on current weight only in a self-administered questionnaire, controls reporting current weight in the full interview—who may potentially differ from those who provided key information only in a self-administered questionnaire—were more often obese (20% vs. 15%). This pattern suggests underestimation rather than overestimation of effects in the present study. About 50% of all eligible cases in the study region were recruited in 22 hospitals. Recruitment of patients was rather dependent on the clinicians' time and motivation whereas only a minority of patients refused to participate. However, end-stage patients were likely not capable or less willing to participate and were slightly underrepresented.

BMI was calculated using self-reported weight within a time window of 5 to 14 years before diagnosis (cases) or recruitment (controls) to avoid misclassification by potential cancer-related weight changes. In previous validation studies, reporting of former weight was considered generally accurate; however, women seem to slightly underestimate their past weight, particularly women with a higher BMI (32, 33). If potential misclassification of BMI among cases and controls is nondifferential as expected, estimates would be biased toward no association and would rather underestimate than overestimate effects. Still, as this is an observational study, exposure assessment and confounder adjustment are likely less than perfect, and unmeasured confounders may have biased results. Additional information about relevant molecular features of colorectal cancer would have enabled further specification of the pathways to colorectal cancer that are associated with overweight and obesity. However, due to the low case numbers with MSI-high colorectal cancer, subgroup analyses have already been very limited and multiple comparisons may have led to chance findings.

In conclusion, this population-based study confirms previous findings of a moderately increased risk of MSS colorectal cancer with obesity among both sexes and suggests that overweight and obesity could be associated with increased risk of sporadic MSI-high colorectal cancer in women. The association was stronger with MSI-high than with MSS colorectal cancer, was particularly pronounced in women with HRT use, and has not been observed in previous studies. Other studies are required to confirm the observed associations with MSI-high colorectal cancer among women. Sampling of study populations seems to play a major role in studies evaluating risk factors of MSI-high colorectal cancer. Further research should aim at elucidating the mechanisms underlying the observed differences, especially with respect to sex.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M. Hoffmeister, H. Bläker, C. Toth, J. Chang-Claude, H. Brenner
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Hoffmeister, H. Bläker, M. Kloor, C. Toth, E. Herpel, H. Brenner
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Hoffmeister, H. Bläker, W. Roth, C. Toth, B. Frank, H. Brenner
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Hoffmeister, H. Bläker, C. Toth, E. Herpel, P. Schirmacher
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