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Article

Body mass index and molecular subtypes of colorectal cancer

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Abstract

Background: Obesity is an established risk factor for colorectal cancer (CRC), but the evidence for the association is inconsistent across molecular subtypes of the disease.

Methods: We pooled data on body mass index (BMI), tumor microsatellite instability status, CpG island methylator phenotype status, *BRAF* and *KRAS* mutations, and Jass classification types for 11 872 CRC cases and 11 013 controls from 11 observational studies. We used multinomial logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) adjusted for covariables.

Results: Higher BMI was associated with increased CRC risk (OR per 5 kg/m^2 = 1.18, 95% CI = 1.15 to 1.22). The positive association was stronger for men than women but similar across tumor subtypes defined by individual molecular markers. In analyses by Jass type, higher BMI was associated with elevated CRC risk for types 1-4 cases but not for type 5 CRC cases (considered familial-like/Lynch syndrome microsatellite instability-H, CpG island methylator phenotype-low or negative, *BRAF*-wild type, *KRAS*-wild type, OR = 1.04, 95% CI = 0.90 to 1.20). This pattern of associations for BMI and Jass types was consistent by sex and design of contributing studies (cohort or case-control).

Conclusions: In contrast to previous reports with fewer study participants, we found limited evidence of heterogeneity for the association between BMI and CRC risk according to molecular subtype, suggesting that obesity influences nearly all major pathways involved in colorectal carcinogenesis. The null association observed for the Jass type 5 suggests that BMI is not a risk factor for the development of CRC for individuals with Lynch syndrome.

Colorectal cancer (CRC) is a heterogeneous disease that evolves through increasing genomic instability (1,2). These include microsatellite instability (MSI), which results from impaired DNA mismatch repair (MMR), and the CpG island methylator phenotype (CIMP), which results from extensive hypermethylation of promoter CpG island sites, causing inactivation of specific tumor suppressor genes. MSI status is commonly defined as MSI-high (MSI-H) or MSI-stable or low (MSS/MSI-L). MSI-H CRC is found in approximately 15% of cases (approximately 12% sporadic, approximately 3% familial-like/Lynch) (3,4). Additionally, somatic mutations in the *BRAF* and *KRAS* genes are major pathological features of CRC tumors with relevance to prognosis and prediction.

Overweight and obesity have been consistently associated with higher risk of CRC (5-7), but the evidence from studies that examined associations between body mass index (BMI) and molecular subtypes of CRC has been inconsistent. For MSI status, a recent meta-analysis of 6 studies reported positive associations of similar magnitudes for BMI with MSI-H vs MSS CRC, but high heterogeneity between studies was detected (8). For CIMP status, a recent analysis in the Darmkrebs: Chancen der Verhutung durch Screening Study (DACHS) case-control study reported a stronger positive association between BMI and CIMP-high CRC compared with CIMP-low or negative tumors for women only (9). However, no evidence of heterogeneity by CIMP status was found in a Netherlands Cohort Study analysis (10). For *KRAS* or *BRAF* tumor mutation status, the DACHS study found little evidence of heterogeneity with the association of BMI and CRC (9), whereas a Swedish cohort analysis reported differences in the BMI and CRC relationship according to *KRAS* or *BRAF* mutation status, with further heterogeneity found according to sex (11).

This inconsistent pattern of results reported across individual studies may be due to small study effects and chance, publication bias, between-study differences in tumor marker classifications, true population differences, and/or differential effects of confounding. The smaller sample sizes of previous studies precluded an examination of the associations between BMI and Jass subtypes [1-5; defined by the joint presentations of MSI, CIMP, *BRAF*, and *KRAS* status (2)]. A more detailed analysis according to Jass types would separate sporadic (Jass type 1) MSI-H tumors (also CIMP-high/*BRAF*-mutated) from familial-like/Lynch syndrome (Jass type 5) MSH-H tumors (also CIMP-low or negative). Such an approach is crucial because this could explain the heterogeneity in the BMI and MSI-H CRC associations reported by previous studies (8,9,12,13).

Here, we analyzed individual-level, harmonized data for 11 872 CRC cases and 11 013 controls from 11 observational studies within the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) to examine the association between BMI and CRC overall and by tumor molecular subtypes.

Methods

Study participants

This study sample included CRC cases and controls within GECCO and CCFR with available tumor marker and BMI data (Table 1; Supplementary Table 1, available online). Additional information on contributing studies is included in the Supplementary Methods (available online). All participants provided written informed consent. Each study was approved by a research ethics committee or institutional review board.

Collection and harmonization of tumor marker data

Data collection and harmonization of GECCO and CCFR tumor marker data have been described elsewhere (14,15). Briefly, MSI

Table 1. Baseline characteristics of cases and controls[a]

Characteristics	Cases	Controls
Total No.	11 872	11 013
Age, mean (SD), y	60.5 (12.2)	63.2 (10.9)
Sex, No. (%)		
Men	6209 (52.3)	5617 (51)
Women	5663 (47.7)	5396 (49)
Study, No. (%)		
CCFR	5073 (42.7)	2180 (19.8)
CPSII	790 (6.7)	929 (8.4)
DACHS	1966 (16.6)	2744 (24.9)
DALS	1083 (9.1)	1148 (10.4)
EDRN	188 (1.6)	329 (3)
EPIC_Sweden	145 (1.2)	381 (3.5)
HPFS	585 (4.9)	591 (5.4)
MCCS	490 (4.1)	670 (6.1)
NFCCR	489 (4.1)	461 (4.2)
NHS	764 (6.4)	1197 (10.9)
NSHDS	299 (2.5)	383 (3.5)
Body mass index, No. (%)		
18.5 to <25 kg/m^2	4154 (35)	4510 (41)
25 to <30 kg/m^2	4991 (42)	4650 (42.2)
≥30 kg/m^2	2727 (23)	1853 (16.8)
Tobacco smoking, No. (%)		
Never	4947 (41.7)	5156 (46.8)
Past or current	6386 (53.8)	5524 (50.2)
Unknown	539 (4.5)	333 (3)
Dietary intake		
Red meat, mean (SD), servings/d	0.8 (0.6)	0.7 (0.6)
Processed meat, mean (SD), servings/d	0.5 (0.4)	0.4 (0.4)
Fruits, mean (SD), servings/d	1.7 (1.5)	1.8 (1.6)
Vegetables, mean (SD), servings/d	2.3 (1.9)	2.4 (2.0)
Fiber, mean (SD), g/d	23.3 (10.8)	23.1 (10.3)
Total energy, mean (SD), kcal/d	2133 (866)	2015 (767)
Education level, No. (%)		
Less than high school graduate	2382 (20.1)	1776 (16.1)
High school graduate	2872 (24.2)	2605 (23.7)
Vocational or technical school or some college/university	2971 (25)	2310 (21)
Undergraduate or graduate degree	3394 (28.6)	4063 (36.9)
Missing	253 (2.1)	259 (2.4)
First degree relative with colorectal cancer, No. (%)		
No	8777 (73.9)	9323 (84.7)
Yes	2712 (22.8)	1134 (10.3)
Missing	383 (3.2)	556 (5)
Location of colorectal cancer, No. (%)		
Proximal colon	4510 (38)	—
Distal colon	3525 (29.7)	—
Rectum (includes rectosigmoid junction)	3331 (28.1)	—
Missing	506 (4.3)	—
Colorectal cancer stage, No. (%)		
Stage 1 or local	2747 (23.1)	—
Stage 2/3 or regional	6785 (57.2)	—
Stage 4 or distant	1214 (10.2)	—
Missing	1126 (9.5)	—
Microsatellite instability, No. (%)		
MSI-H	1809 (15.2)	—
MSS/MSI-L	8967 (75.5)	—
Missing	1096 (9.2)	—
CpG island methylator phenotype, No. (%)		
High	1386 (11.7)	—
Low/negative	7160 (60.3)	—
Missing	3326 (28.0)	—
BRAF, No. (%)		
Mutated	1297 (10.9)	—
Wild type	9423 (79.4)	—
Missing	1152 (9.7)	—
KRAS, No. (%)		
Mutated	2961 (24.9)	—
Wild type	6011 (50.6)	—
Missing	2900 (24.4)	—

[a] CCFR = Colon Cancer Family Registry; CPSII = Cancer Prevention Study II; DACHS = Darmkrebs: Chancen der Verhutung durch Screening Study; DALS = Diet Activity and Lifestyle Study; EDRN = Early Detection Research Network; EPIC = European Prospective Investigation into Cancer and Nutrition; HPFS = Health Professionals Follow-up Study; MCCS = Melbourne Collaborative Cohort Study; MSS = microsatellite stable; NFCCR = Newfoundland Familial Colorectal Cancer Study; NHS = Nurses' Health Study; NSHDS = Northern Sweden Health and Disease Study.

testing was primarily conducted using polymerase chain reaction following accepted guidelines (CCFR, Cancer Prevention Study-II [CPS-II], Melbourne Collaborative Cohort Study [MCCS], Nurses' Health Study [NHS]) (16) with 4 or more interpretable markers typically required to classify tumors (Supplementary Table 2, available online). DACHS used a mononucleotide panel of 3 markers. Tumors were classified as MSI-H if 30% or more of the markers showed instability. Other studies used immunohistochemistry for the correlated DNA MMR proteins (Northern Sweden Health and Disease Study [NSHDS], European Prospective Investigation into Cancer and Nutrition [EPIC]-Sweden, and subsets of CCFR and MCCS).

CIMP status was determined using methylation analyses as described in the Supplementary Materials (Supplementary Table 3, available online). Briefly, the CCFR, CPS-II, Health Professionals Follow-up Study, MCCS, NSHDS, EPIC-Sweden, and NHS used MethyLight to determine CIMP status. CPS-II, Health Professionals Follow-up Study, NSHDS, EPIC-Sweden, and NHS used an 8-gene panel; CCFR and MCCS used a 5-gene panel. DACHS determined CIMP status using a different 5-gene panel (17). CIMP categories for our analyses were CIMP-high and CIMP-low or negative.

Studies assessed *BRAF* and *KRAS* mutations using polymerase chain reaction, sequencing, and immunohistochemistry. Most studies evaluated *BRAF* via c.1799T>A (p.V600E) mutations in exon 15 and *KRAS* via mutations in codons 12 and 13, although any mutation identified by one of the studies in *BRAF* and *KRAS* genes was included. We further defined 5 combined colorectal tumor subtypes consistent with Jass classifications (2,18): type 1 ("sporadic"-MSI-H, CIMP-high, *BRAF*-mutated, *KRAS*-wild type), type 2 (MSS/MSI-L, CIMP-high, *BRAF*-mutated, *KRAS*-wild type), type 3 (MSS/MSI-L, CIMP-low or negative, *BRAF*-wild type, *KRAS*-mutated), type 4 (MSS/MSI-L, CIMP-low or negative, *BRAF*-wild type, *KRAS*-wild type), and type 5 ("Lynch syndrome"-MSI-H, CIMP-low or negative, *BRAF*-wild type, *KRAS*-wild type).

Exposure data

Data collection and harmonization are described elsewhere (14,15,19). Briefly, demographic and environmental risk factors were self-reported at in-person interviews or via questionnaires. Data were collected relevant to the time of study entry or recalled for a time period generally 1 to 2 years before study enrolment. The timing of height and body weight measurements for each contributing study ranged from 5 to 14 years before enrolment in the DACHS case-control study to baseline measurements in prospective cohort studies (Supplementary Table 1, available online).

A multistep iterative data-harmonization procedure was applied, reconciling each study's unique protocols and data collection instruments. Multiple quality-control checks were performed, and outlying values of variables were truncated to the minimum or maximum value of an established range for each variable. Variables were combined into a single dataset with common definitions, standardized coding, and standardized permissible values. BMI was calculated from self-reports or direct measures of body weight (kg) divided by height-squared (m^2), with individuals with BMI less than 18.5 kg/m^2 excluded from the analysis because of the observed nonlinear associations at the lower end of the BMI continuum in these data and elsewhere (20,21). Other variables included age, sex, education, smoking, physical activity, regular use of aspirin or nonsteroidal anti-inflammatory drugs, postmenopausal hormone therapy use (women), diabetes, first-degree family history of CRC, and history of endoscopy (colonoscopy or sigmoidoscopy). Dietary covariables were ascertained using food frequency questionnaires or diet history diaries or records. We defined age as age at CRC diagnosis for cases and age at enrolment for controls.

Statistical analyses

We used logistical and multinomial models to estimate odds ratios (OR) and 95% confidence intervals (CIs) for the association between BMI and CRC overall and with CRC subtypes defined by tumor markers: MSI-H vs MSS/MSI-L, CIMP high vs low or negative, and *BRAF* or *KRAS* mutated vs nonmutated. Analyses were conducted for sexes combined and separately. Heterogeneity by sex was assessed by calculating χ^2 statistics. BMI was defined continuously (per 5 kg/m^2; primary analyses) and categorically (18.5 to <25 [reference group], 25 to <30, and ≥30 kg/m^2). For the Jass type analyses, type 4 was used as the reference group in the case-only analysis, whereas in the multinomial analysis, controls were used as the reference group. Both analyses used multinomial logistic regression to compare odds of exposure in each molecular pathological subtype with the reference group while accounting for covariables. The multivariable models included a set of a priori–determined CRC risk factors: age, sex, smoking status, education, and red meat intake as covariates. Additional adjustment for family history of CRC; history of endoscopy; aspirin or nonsteroidal anti-inflammatory drug use; energy intake; and consumption of alcohol, processed meat, fruits, and vegetables resulted in virtually unchanged odds ratio estimates. Analyses between BMI and individual molecular subtypes of CRC according to study were also undertaken. For Jass type–defined pathways of CRC, we conducted analyses stratified by case-control and cohort studies. We used Bonferroni corrected *P* values (<.05/12 = .004; 4 subtypes being tested in the sexes combined, and men and women separately) to assess statistical significance for the case-only analyses of the primary subtypes (MSI, CIMP-status *BRAF*, and *KRAS*). For secondary analyses, we considered a 2-sided *P* value less than .05 as statistically significant. In a sensitivity analysis using multivariable logistic regression models, we calculated study-specific odds ratios for the associations between BMI and CRC tumor molecular subtypes and then pooled using random effects meta-analysis models. Analyses were performed using R v4.0.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Compared with controls, CRC cases were younger; were more likely to be men, heavier (≥30 kg/m^2), past or current smokers, and to have a first-degree relative with CRC; and were less likely to have attained an undergraduate or graduate degree (Table 1). Among cases, 15.2% were MSI-H (n = 1809), 11.7% were CIMP-high (n = 1386), 10.9% were *BRAF*-mutated (n = 1297), and 24.9% were *KRAS*-mutated (n = 2961). Baseline characteristics according to contributing study are presented in Supplementary Table 4 (available online).

Higher BMI was associated with elevated CRC risk in multivariable models (OR per 5 kg/m^2 = 1.18, 95% CI = 1.15 to 1.22; OR for ≥30 vs 18.5 to <25 kg/m^2 = 1.47, 95% CI = 1.36 to 1.59; $P_{trend} < .001$), with a stronger positive association observed for men than women ($P_{heterogeneity} = .02$) (Table 2). BMI was positively associated with CRC risk for all individual molecular subtypes, with minimal evidence of heterogeneity observed. For women, a stronger positive association was observed for CIMP-high cases (OR per 5 kg/m^2 = 1.23, 95% CI = 1.15 to 1.33) compared with CIMP-low or negative cases (OR per 5 kg/m^2 = 1.14, 95% CI = 1.08 to 1.19). This heterogeneity was higher than the Bonferroni-corrected *P* value threshold ($P_{difference} = .008$) and largely driven by results from the DACHS study ($P_{difference}$ with DACHS excluded = .22). Results for the association between BMI and individual molecular subtypes of CRC according to study are presented in Supplementary Table 5 (available online). Similar associations between BMI and individual molecular subtypes of CRC were found when individual study odds ratios were calculated and then pooled in a meta-analysis (Supplementary Table 6, available online).

Analyses for Jass types of CRC presenting with MSI-H found positive associations for type 1 cases (OR per 5 kg/m^2 = 1.24, 95% CI = 1.12 to 1.36) but not for type 5 cases (OR per 5 kg/m^2 = 1.04, 95% CI = 0.90 to 1.20) (Figure 1; Supplementary Table 7, available online). Null associations for Jass type 5 CRC were also observed when case-control (OR per 5 kg/m^2 = 1.02, 95% CI = 0.87 to 1.21) and cohort (OR per 5 kg/m^2 = 1.08, 95% CI = 0.79 to 1.47) studies were analyzed separately (Supplementary Table 8, available online). Higher BMI was associated with elevated risk of Jass types 2, 3, and 4–defined CRC (Figure 1; Supplementary Table 7, available online). A similar pattern of associations was observed between BMI and Jass-classified CRC according to sex (Supplementary Table 7, available online) and when individual study odds ratios were calculated and pooled in a meta-analysis (Supplementary Table 9, available online).

Discussion

In our analysis of pooled individual-level data from 11 872 CRC cases and 11 013 controls, higher BMI was associated with increased CRC risk, with little evidence of heterogeneity across molecular subtypes observed. Higher BMI was consistently associated with elevated risks of Jass types 1-4 CRC, suggesting that obesity influences all major pathways. The null association found for the Jass type 5 indicates that high BMI may not be a risk factor for the development of CRC for individuals with Lynch syndrome.

Inconsistent results were previously reported regarding the associations between BMI and CRC by CIMP status. While a case-control analysis reported a positive association between BMI with CIMP-low or negative, but not CIMP-high, colon cancers (22), a Netherlands Cohort Study prospective analysis reported relatively consistent associations between BMI and CRC according to CIMP status (10). These earlier investigations were not stratified by sex. Our sex-specific analyses, similarly to the DACHS study (9), found a stronger positive association for BMI with CIMP-high

Table 2. Association between body mass index and molecular subtypes of colorectal cancer[a,b]

		Microsatellite instability		CpG island methylator phenotype		*BRAF*		*KRAS*	
Exposure	**CRC OR (95% CI)**	**MSS/MSI-L OR (95% CI)**	**MSI-H OR (95% CI)**	**CIMP-low/negative OR (95% CI)**	**CIMP-high OR (95% CI)**	***BRAF*-wild type OR (95% CI)**	***BRAF*-mutated OR (95% CI)**	***KRAS*-wild type OR (95% CI)**	***KRAS*-mutated OR (95% CI)**
Both sexes									
No. cases	11 872	8967	1809	7160	1386	9423	1297	6011	2961
18.5 to <25 kg/m^2	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
25 to <30 kg/m^2	1.18 (1.11 to 1.25)	1.18 (1.11 to 1.26)	1.20 (1.06 to 1.35)	1.20 (1.11 to 1.29)	1.20 (1.05 to 1.37)	1.20 (1.12 to 1.28)	1.17 (1.02 to 1.34)	1.24 (1.15 to 1.34)	1.13 (1.03 to 1.24)
≥30 kg/m^2	1.47 (1.36 to 1.59)	1.47 (1.35 to 1.59)	1.55 (1.34 to 1.78)	1.39 (1.27 to 1.52)	1.67 (1.43 to 1.96)	1.47 (1.36 to 1.60)	1.54 (1.31 to 1.81)	1.54 (1.40 to 1.69)	1.40 (1.25 to 1.57)
P_{trend}	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Per 5 kg/m^2	1.18 (1.15 to 1.22)	1.19 (1.15 to 1.23)	1.18 (1.12 to 1.24)	1.17 (1.12 to 1.21)	1.23 (1.16 to 1.31)	1.18 (1.15 to 1.23)	1.20 (1.13 to 1.28)	1.20 (1.16 to 1.25)	1.17 (1.12 to 1.22)
$P_{difference}$[c]		.91		.04		.35		.22	
Men									
No. cases	6209	4923	764	3954	528	5118	474	3144	1563
18.5 to <25 kg/m^2	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
25 to <30 kg/m^2	1.19 (1.09 to 1.31)	1.22 (1.11 to 1.34)	1.06 (0.88 to 1.28)	1.20 (1.09 to 1.33)	1.16 (0.93 to 1.43)	1.19 (1.09 to 1.31)	1.25 (1.00 to 1.57)	1.28 (1.15 to 1.42)	1.11 (0.97 to 1.27)
≥30 kg/m^2	1.51 (1.35 to 1.70)	1.53 (1.35 to 1.72)	1.43 (1.14 to 1.79)	1.42 (1.25 to 1.62)	1.56 (1.19 to 2.04)	1.52 (1.35 to 1.72)	1.44 (1.08 to 1.91)	1.52 (1.33 to 1.74)	1.44 (1.22 to 1.71)
P_{trend}	<.001	<.001	.004	<.001	.002	<.001	.01	<.001	<.001
Per 5 kg/m^2	1.24 (1.18 to 1.30)	1.25 (1.18 to 1.31)	1.16 (1.05 to 1.28)	1.22 (1.15 to 1.29)	1.22 (1.09 to 1.38)	1.24 (1.17 to 1.31)	1.20 (1.06 to 1.35)	1.24 (1.16 to 1.31)	1.21 (1.13 to 1.31)
$P_{difference}$[c]		.19		.89		.6		.54	
Women									
No. cases	5663	4044	1045	3206	858	4305	823	2867	1398
18.5 to <25 kg/m^2	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)	1 (referent)
25-<30 kg/m^2	1.17 (1.07 to 1.28)	1.16 (1.05 to 1.28)	1.27 (1.08 to 1.49)	1.20 (1.08 to 1.33)	1.23 (1.03 to 1.46)	1.22 (1.11 to 1.35)	1.10 (0.93 to 1.32)	1.21 (1.09 to 1.35)	1.17 (1.02 to 1.34)
≥30 kg/m^2	1.44 (1.29 to 1.60)	1.43 (1.27 to 1.60)	1.57 (1.31 to 1.89)	1.36 (1.20 to 1.55)	1.74 (1.43 to 2.11)	1.44 (1.28 to 1.62)	1.60 (1.32 to 1.95)	1.57 (1.39 to 1.78)	1.37 (1.17 to 1.61)
P_{trend}	<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001	.001
Per 5 kg/m^2	1.15 (1.11 to 1.20)	1.16 (1.11 to 1.21)	1.17 (1.10 to 1.25)	1.14 (1.08 to 1.19)	1.23 (1.15 to 1.33)	1.16 (1.11 to 1.21)	1.19 (1.11 to 1.28)	1.19 (1.13 to 1.24)	1.14 (1.08 to 1.21)
$P_{difference}$[c]		.41		.008		.14		.18	

[a] Controls are used as reference for all odds ratios. CI = confidence interval; CIMP = CpG island methylator phenotype; CRC = colorectal cancer; MSI = microsatellite instability; MSS = microsatellite stable; OR = odds ratio.
[b] Odds ratios are adjusted for study, age, sex, smoking status, education, and red meat intake.
[c] Case-only analyses used to calculate $P_{difference}$.

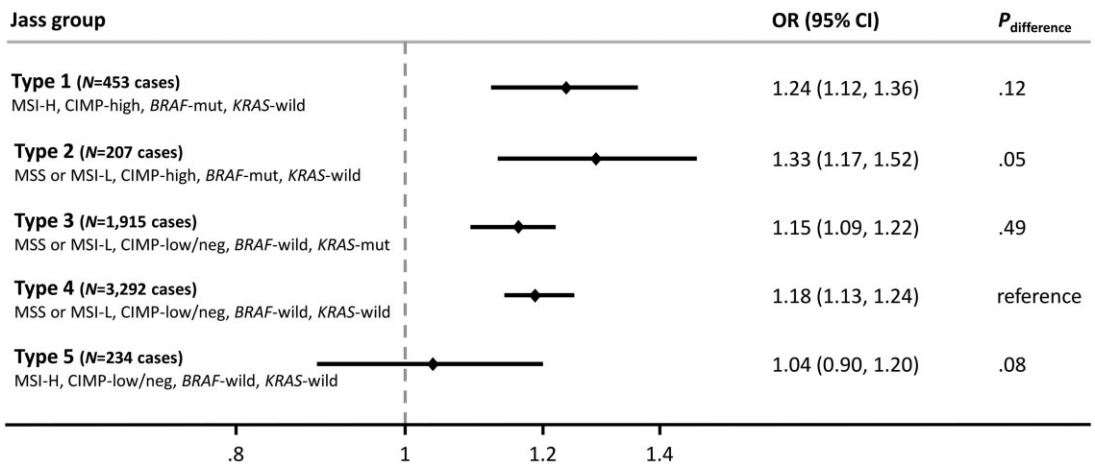

Figure 1. Association between body mass index and Jass classified types of colorectal cancer. Controls were used as reference for all odds ratios. Odds ratios were adjusted for study, age, sex, smoking status, education, and red meat intake. Multinomial logistic regression was used to compare each type with the reference group (Type 4; $P_{difference}$). CI = confidence interval; CIMP = CpG island methylator phenotype; MSI = microsatellite instability; MSS = microsatellite stable; mut = mutated; OR = odds ratio; wild = wild type.

compared with CIMP-low or negative CRC for women only. Importantly, this heterogeneity of association by CIMP status was mainly driven by our inclusion of the DACHS study. When we excluded DACHS, there was little evidence of divergent associations between BMI and CRC by CIMP status, suggesting the differential association was specific to only the DACHS study.

The relatively few previous studies that examined associations between BMI and CRC risk according to *KRAS* and *BRAF* tumor mutation status have reported discordant results. For example, a Malmö Diet and Cancer cohort analysis (n = 494 CRC cases) reported a stronger positive association between BMI and CRC for mutated *KRAS* than for wild-type tumors for men but not women (11). In contrast, the DACHS study (n = 2217 CRC cases) reported no evidence of heterogeneity according to *KRAS* mutation status for men yet for women found that BMI was positively associated with wild-type *KRAS* but not *KRAS* mutated tumors (9). For *BRAF*, a Malmö Diet and Cancer cohort analysis reported that BMI was positively associated with wild-type *BRAF* CRC for men and women (11). The DACHS study reported a stronger positive association for *BRAF* mutated tumors compared with wild-type tumors, but this heterogeneity was not statistically significant after correction for multiple comparisons (9). Our current pooled analysis, which included more than 8900 and more than 10 700 CRC cases with data on *KRAS* and *BRAF* tumor mutations, respectively, found consistent positive associations according to mutation status of these 2 oncogenes, suggesting high BMI is positively associated with CRC with and without *KRAS* or *BRAF* mutations.

For MSI status, like our findings, a meta-analysis of 4 previous studies reported similar positive associations between BMI and CRC for MSI-H and MSS/MSI-L tumors (8). Across individual studies included and not included in this meta-analysis, heterogeneous findings for the BMI and MSI-H CRC associations have been reported (8,9,12,23,24). In particular, divergent results were reported by 2 of the larger case-control studies, with higher BMI associated with MSI-H CRC in the population-based DACHS study (9,13) but a null association found by the CCFR, a large case-control study of CRC families likely enriched for individuals with Lynch syndrome (12,25).

Part of the discordance in the association of BMI by MSI status might be explained by the predominant source of MSI-H cases in each study. In our analyses according to Jass types, for the first time to our knowledge, the BMI and CRC association was investigated after further separating sporadic MSI-H tumors from the less common familial-like/Lynch MSI-H tumors. Consistent with the earlier results from the CCFR study (12), we observed a null association between BMI and risk of familial-like/Lynch syndrome (type 5) MSI-H CRC, with similar null associations found according to sex and for case-control and cohort (which excluded all CCFR participants by design) studies when analyzed separately. The current findings for increasing BMI and higher risk of Jass type 1 tumors, which are largely considered sporadic MSI-H, were also consistent with the earlier DACHS findings, which would have been largely comprised of sporadic MSI-H tumors. That is, from these studies, it seems that high BMI is a risk factor for sporadic MSI-H tumors but perhaps less relevant to risk of tumors developing on a background of Lynch syndrome.

Interpretation of the null association between BMI and Jass type 5/Lynch syndrome MSI-H tumors in this study is further complicated by previous studies of apparent Lynch syndrome families, defined by germline mutations in a MMR gene or by being a member of Amsterdam criteria I or revised Bethesda guidelines families (26-28). In those few previous studies, including a recent meta-analysis of 4 studies in Lynch syndrome patients, a positive association was reported between obesity (compared with the nonobese group) and CRC/adenoma for men (relative risk = 2.09, 95% CI = 1.23 to 3.55) but a weaker association for women (relative risk = 1.41, 95% CI = 0.46 to 4.27) (28). More than 89% of the cases in this previous meta-analysis were included in 2 earlier CCFR publications (26,27); those studies defined Lynch syndrome according to clinical family history criteria (26) or by MMR carrier status (27). Notably, these studies had several design features that may have contributed to the apparently discordant results with this study. First, the study by Win and colleagues (27) used a retrospective cohort, time-to-event study design with noncases drawn from Lynch family members who did not have a CRC diagnosis. Those study participants may be leaner and otherwise more health conscious, owing to their genetic predisposition to cancer, compared with controls in this study who would generally not have a strong family history of CRC. Second, the larger study by Campbell and colleagues (26) used Amsterdam and Bethesda criteria to identify potential

Lynch syndrome families, and thus the interpretation of those results is not specific to Lynch syndrome. Additionally, neither study considered tumor MSI status as a separate outcome. Collectively, these results suggest that high BMI is not associated with MSH-H tumors consistent with Lynch syndrome, but, given the many disease outcomes and cancers associated with obesity (29), persons predisposed to Lynch syndrome should still be advised to maintain a healthy body weight.

Beyond Lynch syndrome, our results suggest that obesity can affect all other major pathways of CRC tumorigenesis, including the traditional adenoma to cancer pathway and the serrated pathway. However, our analysis used broad categories to define molecular subtypes. Next-generation sequencing of tumor samples will allow a deeper classification of tumor subtypes by identifying somatically mutated genes. Examining associations between BMI and newly identified CRC subtypes could provide important insights into the molecular mechanisms underlying the BMI and CRC positive association.

Ours was the largest study yet to investigate associations between BMI and molecular subtypes of CRC. The large sample size obtained by pooling individual-level data from 11 studies, harmonized data, and standardized statistical analytical approach meant our analyses are less prone to between-study heterogeneity and publication biases. Crucially, the large sample size allowed an examination of the association between BMI and all 5 Jass types, providing insights into how excess adiposity is associated with different pathways of tumorigenesis. Limitations of our analysis include that 5 of the 11 studies in our analysis used a case-control design, which may be vulnerable to reverse causality; however, the positive association we found between BMI and CRC in the current analysis for case-control studies was of similar strength to that from prospective studies (6,30), indicating that any bias from reverse causation is likely small. A further limitation was that data on central adiposity measurements (eg, waist circumference) were not available to be included in our study. Finally, as is common for studies including tumor samples, tissue samples were not available for all CRC cases within contributing studies and may have been related with stage and/or size of tumor; however, prior investigations in some of the contributing studies reported that lifestyle and demographic characteristics differed little between CRC cases for whom tumor samples could or could not be obtained (31-33).

In conclusion, we found little evidence of heterogeneity for the positive association between BMI and CRC according to individual molecular tumor subtypes. Analyses by Jass type suggest that obesity influences all major pathways involved in colorectal carcinogenesis. The lack of association found for Jass type 5 tumors suggests that high BMI may not be a risk factor for the development of CRC for individuals with an inherited predisposition to Lynch syndrome. Further studies are needed to confirm this finding and increase understanding of the role of obesity in Lynch syndrome cancers.

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Data availability

Tumor marker and epidemiologic data is available upon request and permission. Please contact gecco@fredhutch.org to request the standardized proposal form. The principal investigators of each contributing study will evaluate and approve the proposal, and data access will be managed centrally.

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