Research Article

Cancer Epidemiology, Biomarkers & Prevention

Association between Body Mass Index and Mortality for Colorectal Cancer Survivors: Overall and by Tumor Molecular Phenotype

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Abstract

Background: Microsatellite instability (MSI) and *BRAF* mutation status are associated with colorectal cancer survival, whereas the role of body mass index (BMI) is less clear. We evaluated the association between BMI and colorectal cancer survival, overall and by strata of MSI, *BRAF* mutation, sex, and other factors.

Methods: This study included 5,615 men and women diagnosed with invasive colorectal cancer who were followed for mortality (maximum: 14.7 years; mean: 5.9 years). Prediagnosis BMI was derived from self-reported weight approximately one year before diagnosis and height. Tumor MSI and *BRAF* mutation status were available for 4,131 and 4,414 persons, respectively. Multivariable hazard ratios (HR) and 95% confidence intervals (CI) were estimated from delayed-entry Cox proportional hazards models.

Results: In multivariable models, high prediagnosis BMI was associated with higher risk of all-cause mortality in both sexes (per 5-kg/m^2; HR, 1.10; 95% CI, 1.06–1.15), with similar associations stratified by sex ($P_{interaction}$: 0.41), colon versus rectum ($P_{interaction}$: 0.86), MSI status ($P_{interaction}$: 0.84), and *BRAF* mutation status ($P_{interaction}$: 0.28). In joint models, with MS-stable/MSI-low and normal BMI as the reference group, risk of death was higher for MS-stable/MSI-low and obese BMI (HR, 1.32; *P* value: 0.0002), not statistically significantly lower for MSI-high and normal BMI (HR, 0.86; *P* value: 0.29), and approximately the same for MSI-high and obese BMI (HR, 1.00; *P* value: 0.98).

Conclusions: High prediagnosis BMI was associated with increased mortality; this association was consistent across participant subgroups, including strata of tumor molecular phenotype.

Impact: High BMI may attenuate the survival benefit otherwise observed with MSI-high tumors. *Cancer Epidemiol Biomarkers Prev; 24(8); 1229–38. ©2015 AACR.*

Introduction

High body mass index (BMI) is an established risk factor for colorectal cancer (1–4); however, associations are usually stronger for men than women and for colon than rectal cancers (2–5). Emerging data suggest the BMI-colorectal cancer association differs by microsatellite instability (MSI) status (6–10), with stronger associations typically shown for MS-stable than MSI-high tumors and other tumor phenotypes correlated with MS-stable (11). The impact of BMI on mortality after colorectal cancer diagnosis is less clear, possibly owing to the timing of BMI evaluation relative to diagnosis (12–15). When BMI was evaluated in the peri- or postdiagnosis period, generally null or only modest associations

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were shown (10, 12–14, 16–23). In contrast, when prediagnosis BMI was evaluated, studies typically showed higher risks of all-cause and colorectal cancer–specific mortality with high BMI (12–15, 24–26).

MSI is an established marker of colorectal cancer survival: patients with MSI-high tumors have a favorable prognosis compared with age- and stage-matched patients with MS-stable tumors (27–29). Similarly, patients with *BRAF* mutations, compared with patients with *BRAF* wild-type tumors, have poorer prognosis (29, 30). It is not known whether BMI or other lifestyle and behavioral factors modify the influences of MSI or *BRAF* on survival; it is plausible that lifestyle factors, including BMI, may differentially influence survival of patients according to tumor molecular features because those factors likely interact with the tumor cells' microenvironment.

Subgroup differences for the association between BMI and colorectal cancer incidence are consistently shown by strata of sex, site in the colorectum, and tumor molecular phenotype; however, it is not clear if these etiologic differences translate to the prognosis setting. This study examined the associations of BMI 2 years prior to enrollment (which is akin to BMI ∼1 year prior to diagnosis, and referred to here as "prediagnosis recent BMI"), BMI at age 20 years, and adult weight change with all-cause and colorectal cancer–specific mortality in a cohort of 5,615 adults who were diagnosed with incident, invasive colon or rectal adenocarcinoma. In addition, we examined whether associations differed by strata of sex, tumor site in the colorectum, smoking, disease stage, MSI, *BRAF*, and other factors.

Materials and Methods

Study population

Men and women in this study were identified from the Colon-Cancer Family Registry (C-CFR), an international resource for studies on colorectal cancer etiology and survival, initiated in 1997 (31). Case participants with incident colon or rectal cancer were identified via state or provincial cancer registries and invited to enroll. The mean time from diagnosis to enrollment for persons in this analysis was 0.92 years.

Of the 7,702 persons initially identified in the C-CFR that had returned an epidemiologic questionnaire, exclusions were made as follows: diagnosis prior to baseline in 1997 ($n = 97$); primary diagnosis with appendiceal or intestinal not-otherwise-specified cancer ($n = 56$); carcinoma *in situ* ($n = 29$); missing age or date of enrollment ($n = 8$); missing prediagnosis recent BMI ($n = 152$); missing end-of-follow-up date ($n = 121$); proxy respondent ($n = 124$); less than 30 days of follow-up time ($n = 365$); and time from diagnosis to enrollment greater than 2 years ($n = 1,135$). Thus, 5,615 C-CFR enrollees were included in this analysis.

Data collection

Data on demographics, race/ethnicity, personal and family history of cancer, medical history, reproductive factors, physical activity, diet, alcohol, tobacco, body weight, and height were collected via standardized personal interviews, telephone interviews, and/or mailed questionnaires (8, 31). The questionnaires are available online (32). Two measures of self-reported body weight were requested: prediagnosis recent weight (queried as body weight 2 years prior to enrollment, which corresponds to approximately 1 year prior to cancer diagnosis) and weight at age 20 years. All persons were asked to provide current height. All covariables used a prediagnosis referent period. After enrollment, the cohort was actively followed via periodic contact. Vital status, cause of death (COD), and date of death were ascertained through linkage with population-based registries, accrual of death certificates, contact with next-of-kin, and, more rarely, via other mechanisms (e.g., obituaries).

Written informed consent was obtained from all study participants and the institutional review boards at each center approved the studies.

Assessment of BMI and adult weight change

Prediagnosis recent BMI was calculated from prediagnosis recent weight in kilograms (kg) divided by height in meters (m) squared; BMI at age 20 years was similarly calculated using weight at age 20 years. BMI was categorized according to World Health Organization criteria (33). Adult weight change was calculated as prediagnosis recent weight minus weight at age 20 years (both in kg).

Assessment of tumor characteristics

Tumor tissue from the Jeremy Jass Memorial Pathology Bank characterized the tumor MSI and *BRAF* mutational status of 4,131 and 4,414 persons, respectively. Persons without MSI ($n = 1,484$) were, on average, younger than those with tumor blocks (mean age at study enrollment: 53.2 vs. 55.9 years; $P < 0.0001$); otherwise, there were no meaningful differences between those with and without MSI by sex, site, disease stage, or BMI. *BRAF* data were available for slightly more persons diagnosed with colon (79.8%) than rectal (76.3) cancer ($P = 0.003$); otherwise no meaningful differences were noted.

DNA for molecular testing was extracted from formalin-fixed paraffin-embedded tissues with use of the QIAamp Tissue kit (Qiagen) according to the manufacturer's instructions, as previously described (8). For the majority of case subjects with MSI ($n = 2,893$), tumor MSI was assessed by polymerase chain reaction (PCR) assays with the use of four mononucleotide markers (*BAT25*, *BAT26*, *BAT40*, and *BAT34C4*), five dinucleotide markers (*D5S346*, *D17S250*, *ACTC*, *D18S55*, and *D10S197*), and one complex marker (*MYCL*; ref. 8). Tumors were classified as MSI-high if ≥30% of the markers demonstrated instability (i.e., a change in marker repeat length was detected when comparing DNA from normal to tumor tissue), MSI-low if >0% and <30% demonstrated instability, and MS-stable if none exhibited instability (34). A minimum of four unequivocal results were required to characterize MSI. For a minority of persons ($n = 1,238$), MSI status was determined via immunohistochemistry (IHC) of the mismatch repair proteins MLH1, MSH2, MSH6, and PMS2. Positive staining for all proteins indicated MS-stable, whereas absence of staining for any protein indicated MSI-high (35, 36). IHC-based methods for detecting MSI-high and MS-stable show very high sensitivity and specificity with PCR-based methods (35). Tumor DNA was used to assess the *BRAF c.1799 T>A* (p.V600E) mutation using fluorescent allele-specific PCR, as described previously (37).

Colorectal cancer stage at the time of diagnosis was collected from state/provincial cancer registry information and/or from clinical/pathology records. When stage data were available both from registries and clinical/pathology records, the latter took precedence. Harmonized summary stage data were derived according to American Joint Committee on Cancer (AJCC) Tumor

Node Metastasis (TNM) criteria (38) or converted from SEER summary stage to TNM summary stage using an algorithm (39). Participants who were missing one or more of the individual components required to derive TNM summary stage (i.e., depth of invasion of the primary tumor, T-stage; presence of metastases in regional lymph nodes, N-stage; and presence of distant metastases, M-stage) were set to missing stage (20.7%).

Statistical analysis

Multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated using delayed-entry Cox proportional hazards models to estimate the associations of prediagnostic BMI and adult weight change with risk of death. Delayed-entry models accounted for the lag between diagnosis and enrollment. The time axis for all analyses was time-since-diagnosis and models were stratified on age at diagnosis. The proportional hazards assumption was tested with multiplicative interaction terms between BMI and time and Cox models with and without interaction terms were compared via the likelihood ratio test. Fully adjusted models included smoking status, tumor stage, study center, and sex (combined models), as parameterized in Table 1. Missing covariables were treated as a separate category. Inclusion of physical activity, red meat intake, education, race, and aspirin made no appreciable differences to the HRs and were not included in the final models. Follow-up time ended with date of death or last contact.

For analyses of colorectal cancer–specific mortality, follow-up time ended on the date of death from colon or rectal cancer as the primary underlying cause; persons who died from other causes or who were alive at last contact were censored in these analyses. Persons with unknown COD, and all persons enrolled in the USC/Stanford consortium (where no COD data were available), were excluded from the cause-specific analyses.

In categorical Cox models, persons who were underweight (<18.5 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) were compared with persons with normal BMI (18.5–24.9 kg/m^2). Obesity was further stratified as classes I (30–34.9 kg/m^2), II (35–39.9 kg/m^2), and III (≥40 kg/m^2) when the number of outcomes was greater than or equal to 10 per BMI category. Linear models examined the association of BMI, in 5 kg/m^2 increments, with mortality, excluding the underweight category. Wald tests assessed linear trends. Restricted cubic splines assessed potential nonlinearity of the relationship between BMI and all-cause mortality (40). For the cubic spline analysis, knots were selected at BMI values of 18.5, 22, 25, 30, and 40 while the referent was set at 22. The likelihood ratio test assessed nonlinearity via a model that contained only the linear term to a model with the linear and the cubic spline terms. Multiplicative interaction terms and the likelihood ratio test assessed whether the association between BMI and mortality differed by sex, MSI, *BRAF*, tumor site, smoking, and other factors. In sensitivity analyses, persons who were missing stage data were excluded. All *P* values were two-sided; *P* values less than 0.05 were considered statistically significant.

Results

In this cohort, 2,053 deaths occurred (1,233 deaths attributed to colorectal cancer, 533 deaths attributed to other causes; COD was unavailable for 287 deaths) during a mean of 5.9 years from study enrollment to end-of-study (minimum: 31 days; maximum: 14.7 years). Of the 2,053 deaths, the majority were verified through linkage with various population-based registries or accrual of death certificates (n = 1,401, 68%) while the remaining deaths were identified via next-of-kin contact (n = 389, 19%) or through other mechanisms, including review of obituaries (n = 263, 13%). As anticipated, MSI-high compared with MS-stable/MSI-low was associated with lower risk of all-cause mortality (HR, 0.68; 95% CI, 0.57–0.81), adjusted for stage, age, sex, BMI, smoking and study center, whereas *BRAF* mutation compared with *BRAF*-wild-type was associated with higher risk of all-cause mortality (HR, 1.32; 95% CI, 1.10–1.59), adjusted for MSI-status, stage, age, sex, BMI, smoking, and study center.

Table 1 shows socio-demographic, prediagnostic behavioral/lifestyle factors, and clinical factors for the study sample overall and stratified by prediagnosis recent BMI. Persons who were obese (BMI > 30 kg/m^2), compared with persons who had normal BMI (18.5–24.9 kg/m^2), were more likely to be men, ate more red meat, were less educated, were less likely to be current smokers, and were less physically active.

When testing the proportional hazards assumption, an interaction was observed for categorical BMI (excluding underweight BMI) and time (*P*: 0.003); however, after excluding the first 2 years of follow-up, the *P* value for the interaction was no longer statistically significant. From visually inspecting the Kaplan–Meier curves for categorical prediagnosis recent BMI (Fig. 1), it appears that the interaction between BMI and time is caused in the first 2 years of follow-up wherein the survival curves for the BMI categories essentially overlap. After approximately 2 or 3 years of follow-up, the curves begin to diverge, with the obese category showing the most marked decline (log rank, $P < 0.0001$).

Table 2 shows the associations of prediagnosis recent BMI, BMI at age 20 years, and adult weight change with all-cause and colorectal cancer–specific mortality. For women and men combined, there was a clear dose–response association between prediagnosis recent BMI and all-cause mortality: compared with a normal BMI, overweight, class I obesity, class II obesity, and class III obesity were associated with 12%, 19%, 43%, and 52% higher risks of mortality from all causes, respectively. The same general pattern was shown for BMI at age 20 years and all-cause mortality, albeit with less precision. Adult weight change, per 5 kg, was associated with a marginally higher risk of all-cause mortality. Generally, similar results were obtained for colorectal cancer–specific mortality, although CIs were wider with the smaller numbers of outcomes.

The joint impact of prediagnosis recent BMI and MSI status is shown in Table 3. Compared with persons with MS-stable/MSI-low and normal BMI, risk of death was higher for MS-stable/MSI-low and obesity (HR, 1.32), not statistically significantly lower for MSI-high and normal BMI (HR, 0.86), and essentially the same for MSI-high and obesity (HR, 1.00).

As shown in Fig. 2, there was no compelling evidence that the association between recent BMI per 5 kg/m^2 and all-cause mortality differed by site in the colon or rectum, stage, age at diagnosis, physical activity, red meat intake, or time from diagnosis to enrollment. Prediagnosis recent BMI was associated with higher risks of all-cause mortality among persons with both MS-stable/MSI-low (HR, 1.10) and MSI-high (HR, 1.24) tumors ($P_{interaction}$: 0.84). Similarly, BMI was associated with all-cause mortality for both strata of *BRAF* mutation status ($P_{interaction}$: 0.28), although the CIs for the smaller *BRAF* mutation group overlapped 1 (HR, 1.10; 95% CI, 0.91–1.33). There was some suggestion that risk of mortality with BMI might be higher for never smokers than ever

Table 1. Baseline characteristics of the cohort overall and by strata of prediagnosis recent BMI[a]

		Prediagnosis recent BMI				
Categories	**Total ($N = 5,615$) *N* (%)**	**<18.5 ($N = 83$) *N* (%)**	**18.5–<25 ($N = 1,897$) *N* (%)**	**25–<30 ($N = 2,152$) *N* (%)**	**≥30 ($N = 1,483$) *N* (%)**	***P*[b]**
Age at diagnosis, y						
<40	559 (10)	22 (26.5)	244 (12.9)	186 (8.6)	107 (7.2)	$P < 0.0001$
40–<50	1,800 (32.1)	26 (31.3)	663 (34.9)	620 (28.8)	491 (33.1)	
50–<60	1,339 (23.8)	6 (7.2)	387 (20.4)	531 (24.7)	415 (28)	
60–<70	1,312 (23.4)	15 (18.1)	392 (20.7)	553 (25.7)	352 (23.7)	
≥70	605 (10.8)	14 (16.9)	211 (11.1)	262 (12.2)	118 (8)	
Sex						
Men	2,928 (52.1)	17 (20.5)	733 (38.6)	1,367 (63.5)	811 (54.7)	$P < 0.0001$
Women	2,687 (47.9)	66 (79.5)	1,164 (61.4)	785 (36.5)	672 (45.3)	
Self-identified race						
White	4,549 (81)	67 (80.7)	1,506 (79.4)	1,787 (83)	1,189 (80.2)	$P < 0.0001$
Black or African American	376 (6.7)	3 (3.6)	78 (4.1)	140 (6.5)	155 (10.5)	
American Indian or Alaskan Native	20 (0.4)	0 (0)	2 (0.1)	10 (0.5)	8 (0.5)	
More than one race	162 (2.9)	1 (1.2)	63 (3.3)	49 (2.3)	49 (3.3)	
Unknown, other, or not reported	508 (9)	12 (14.5)	248 (13.1)	166 (7.7)	82 (5.5)	
Education[c]						
Less than high school	841 (15)	13 (15.7)	244 (12.9)	348 (16.2)	236 (15.9)	$P < 0.0001$
High school graduate	1,296 (23.1)	17 (20.5)	404 (21.3)	490 (22.8)	385 (26)	
Vocational/technical school	1,865 (33.2)	30 (36.1)	610 (32.2)	691 (32.1)	534 (36)	
Undergraduate or graduate	1,573 (28)	22 (26.5)	624 (32.9)	609 (28.3)	318 (21.4)	
Missing	40 (0.7)	1 (1.2)	15 (0.8)	14 (0.7)	10 (0.7)	
Smoking status[d]						
Never	2,357 (42)	33 (39.8)	851 (44.9)	860 (40)	613 (41.3)	$P < 0.0001$
Former	2,056 (36.6)	14 (16.9)	595 (31.4)	870 (40.4)	577 (38.9)	
Current	1,096 (19.5)	35 (42.2)	421 (22.2)	389 (18.1)	251 (16.9)	
Missing	106 (1.9)	1 (1.2)	30 (1.6)	33 (1.5)	42 (2.8)	
Red meat intake[e]						
<2 servings/week	787 (14)	22 (26.5)	325 (17.1)	276 (12.8)	164 (11.1)	$P < 0.0001$
2 or 3 servings/week	1,963 (35)	26 (31.3)	696 (36.7)	757 (35.2)	484 (32.6)	
>3–5 servings/week	1,262 (22.5)	17 (20.5)	403 (21.2)	499 (23.2)	343 (23.1)	
>5 servings/week	1,347 (24)	14 (16.9)	367 (19.3)	533 (24.8)	433 (29.2)	
Missing	256 (4.6)	4 (4.8)	106 (5.6)	87 (4)	59 (4)	
Physical activity[f]						
0–6 METs/week	1,207 (21.5)	18 (21.7)	358 (18.9)	446 (20.7)	385 (26)	$P < 0.0001$
6.1–20 METs/week	765 (13.6)	15 (18.1)	261 (13.8)	272 (12.6)	217 (14.6)	
20.1–44 METs/week	1,614 (28.7)	21 (25.3)	583 (30.7)	649 (30.2)	361 (24.3)	
>44 METs/week	1,510 (26.9)	20 (24.1)	537 (28.3)	604 (28.1)	349 (23.5)	
Missing	519 (9.2)	9 (10.8)	158 (8.3)	181 (8.4)	171 (11.5)	
Colon or rectal site[g]						
Colon	3,713 (66.1)	57 (68.7)	1,234 (65.1)	1,402 (65.1)	1,020 (68.8)	$P = 0.08$
Rectum	1,902 (33.9)	26 (31.3)	663 (34.9)	750 (34.9)	463 (31.2)	
TNM summary stage[h]						
I	1,205 (21.5)	21 (25.3)	424 (22.4)	475 (22.1)	285 (19.2)	$P = 0.28$
II	1,210 (21.5)	18 (21.7)	416 (21.9)	468 (21.7)	308 (20.8)	
III	1,431 (25.5)	17 (20.5)	459 (24.2)	565 (26.3)	390 (26.3)	
IV	609 (10.8)	8 (9.6)	205 (10.8)	214 (9.9)	182 (12.3)	
Missing	1,160 (20.7)	19 (22.9)	393 (20.7)	430 (20.0)	318 (21.4)	
MSI status						
MS-stable	3,226 (57.5)	50 (60.2)	1,114 (58.7)	1,239 (57.6)	823 (55.5)	$P = 0.41$
MSI-low	317 (5.6)	4 (4.8)	109 (5.7)	124 (5.8)	80 (5.4)	
MSI-high	588 (10.5)	6 (7.2)	210 (11.1)	215 (10)	157 (10.6)	
Missing	1,484 (26.4)	23 (27.7)	464 (24.5)	574 (26.7)	423 (28.5)	
BRAF						
Wild-type	4,018 (71.6)	57 (68.7)	1,368 (72.1)	1,545 (71.8)	1,048 (70.7)	$P = 0.96$
Mutation	396 (7.1)	6 (7.2)	135 (7.1)	149 (6.9)	106 (7.1)	
Missing	1,201 (21.4)	20 (24.1)	394 (20.8)	458 (21.3)	329 (22.2)	

[a]Derived from prediagnosis recent body weight (defined as "weight 2 years prior to enrollment") in kg divided by height in meters squared.
[b]χ^2 test for differences across strata.
[c]Defined as the highest completed level of education.
[d]Cigarette smoking was defined as ever smoking one cigarette per day for 3 months or longer. Current smoking was indicated when the participant smoked cigarettes in the period two years prior to enrollment (referent period); former smoking was indicated when smoking stopped before the referent period.
[e]One serving was defined as two to three ounces. Examples of red meat included beef, steak, hamburger, prime rib, and ham.
[f]Derived from responses to total years, total months, and duration per week of nine modes of activity for three periods of the lifespan (20–29, 30–49, 50 years or older).
[g]According to International Classification of Diseases for Oncology, Third Edition anatomic site codes: C180, C182, C183, C184, C185, C186, C187, C188, C189, C260 (colon); C199, C209 (rectum).
[h]Derived according to American Joint Commission on Cancer (AJCC) Tumor Node Metastasis (TNM) criteria or converted from SEER summary stage to TNM summary stage.

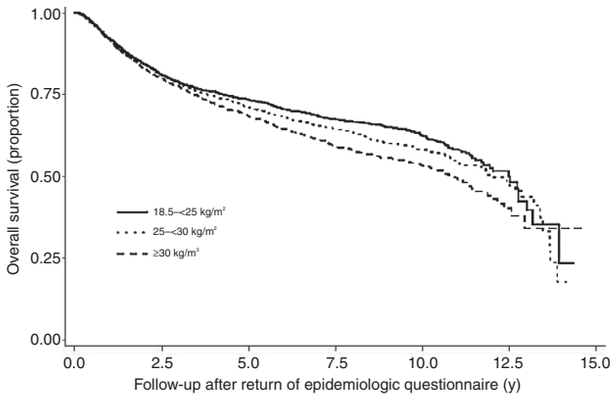

Figure 1.
The Kaplan–Meier survival curve for death from all-causes for men and women diagnosed with colorectal cancer in the C-CFR, 1997 to 2012.

smokers, although not statistically significant ($P_{interaction}$: 0.06). From Fig. 3, the relationship between prediagnosis recent BMI and all-cause mortality appears linear ($P_{linearity}$: <0.0001). In sensitivity analyses that excluded all persons with any missing stage data, the study results were essentially unchanged (data not shown), as expected because stage was not a confounder or effect modifier in this study.

Discussion

In this prospective cohort of 5,615 persons with invasive colon or rectal cancer, high BMI was associated with higher risks of all-cause and colorectal cancer–specific mortality in a dose–response and linear manner. Mortality estimates for prediagnosis recent BMI were consistent in magnitude across strata of sex, MSI, *BRAF*, stage, and other factors, suggesting that prediagnostic BMI is a robust indicator for colorectal cancer survival. These results also suggest that self-reported adult weight gain is not strongly associated with mortality risk for most colorectal cancer survivors.

The association between excess adiposity and colorectal cancer survival has been inconsistent despite several expert and consensus reports recommending that cancer survivors maintain or achieve a normal weight BMI (41, 42). Part of this inconsistency stems from differences in study methodology, predominantly the timing of BMI measurement relative to diagnosis (14). Studies that evaluated BMI after diagnosis in prospective cohorts (12, 13) or at around the time of diagnosis in adjuvant-treatment trials (16–18, 20) showed no evidence of association or only modestly higher risks of mortality with high BMI. In most previous studies where BMI was reported a year or more prior to colorectal cancer diagnosis, high BMI was associated with higher mortality (12, 13, 15, 24, 25). The magnitude of this association is similar across studies, including in this study, with HRs in the range of 1.2 to 1.5 for the association between obese BMI and all-cause mortality.

Several biologic mechanisms may explain the poorer prognosis from high BMI; some factors may also relate to colorectal cancer risk, including insulin and its associated growth factors and binding proteins, inflammation, oxidative stress, and impaired immune surveillance. Other, less explored, mechanisms include the potential for obesity to lead to the diagnosis of more biologically aggressive tumors, independent of stage and grade (29). To this end, higher BMI was associated with higher risk of the more-aggressive MS-stable tumors, but not associated with risk of the less-aggressive MSI-high tumors, in a previous study from the C-CFR (8), suggesting that BMI may not be as relevant in the context of developing an MSI-high tumor. In this analysis, we extend those findings to show BMI is relevant to colorectal cancer survival for patients with both MS-stable and MSI-high tumors, although the MSI-high group compared with the MS-stable group still maintains a prognostic advantage at each level of BMI. The role of BMI with colorectal cancer risk and survival according to various molecular markers has been examined in the Nurses' Health Study and the Health Professionals Follow-up Study. Using this extensive molecular pathologic epidemiology (MPE) resource, BMI was differentially associated with risks of colorectal cancer according to CTNNB1 (43) and FASN (11) expression status. Further work from this MPE resource showed that BMI differentially influences survival for colorectal cancer patients when groups are stratified by expression patterns of TP53 (44), CTNNB1 (45), p21 (46), STMN-1 (47), p27 (48), and FASN (49). Given the complex nature of colorectal cancer and the myriad of potential interactions that may occur between adiposity-markers and the tumor microenvironment, further work is clearly needed to better understand the biologic role of obesity on colorectal cancer risk and prognosis.

Clinical factors generally do not seem to explain the association between high BMI and poorer prognosis: compared with participants with a normal BMI enrolled on a clinical trial for colon cancer adjuvant treatment, obese participants had lower rates of leukopenia, nausea, and grade 3 or 4 toxicity and no differences were noted for emesis, diarrhea, stomatitis, and treatment-related death (16). Similarly, in a study of rectal cancer patients, BMI did not modify rates of nausea, emesis or diarrhea; however, obese persons were less likely to experience leukopenia, neutropenia, stomatitis, and any grade 3 or 4 toxicity (17).

One limitation of this study is that postdiagnosis body weight and potential confounders (e.g., physical activity and diet) were not comprehensively available. Body weight can change after diagnosis, due to the disease itself or as an effect of treatment. In the largest of the studies that had both pre- and postdiagnosis BMI for colorectal cancer survivors, prediagnosis BMI, but not postdiagnosis BMI, was associated with higher risk of mortality (12). This attenuation of association probably reflects illness-associated weight loss in the postdiagnosis setting (12, 50). With the evidence accumulated thus far, and given the established relationship between BMI and several causes of death beyond colorectal cancer, it seems reasonable to conclude that prediagnosis BMI is associated with higher risk of death among colorectal cancer survivors. Furthermore, because the postdiagnosis BMI analyses are likely confounded by illness, studies are needed that can distinguish between weight loss from illness/cachexia versus lifestyle modification (e.g., physical activity and/or caloric restriction) to clarify the prognostic role of weight-loss interventions for overweight/obese colorectal cancer survivors. Importantly, several observational studies have suggested that higher postdiagnosis physical activity among colorectal cancer survivors is associated with improved prognosis independent of BMI (13, 51, 52).

This study lacked detailed data on treatment, toxicity, surgical complications, and cancer recurrence; however, a recent pooled study of over 25,000 colon cancer patients enrolled on adjuvant treatment trials showed that adjuvant treatment did not confound or modify the association between BMI and all-cause mortality

Table 2. All-cause and colorectal cancer–specific mortality for persons with colorectal cancer by prediagnosis BMI and weight change: the C-CFR, 1997 to 2012

	Men and women combined				Women			Men		
	Deaths/person years	Multivariable HR (95% CI)[a]	P_{trend}[b]	$P_{interaction}$ with sex[c]	Deaths/person years	Multivariable HR (95% CI)[a]	P_{trend}[b]	Deaths/person years	Multivariable HR (95% CI)[a]	P_{trend}[b]
All-cause mortality										
BMI recent										
<18.5	39/429	1.62 (1.15–2.28)			31/351	1.76 (1.18–2.61)		—	—	
18.5–<25	629/11,420	1.00 (ref)			360/7,104	1.00 (ref)		269/4,316	1.00 (ref)	
25–<30	787/12,842	1.12 (1.00–1.25)			257/4,804	1.10 (0.93–1.30)		530/8,037	1.11 (0.95–1.29)	
≥30	598/8,522	1.29 (1.14–1.45)		0.36	259/3,828	1.33 (1.12–1.58)		339/4,695	1.23 (1.04–1.46)	
30–<35	364/5,654	1.19 (1.04–1.37)			130/2,170	1.25 (1.01–1.54)		234/3,484	1.16 (0.96–1.39)	
35–<40	141/1,790	1.43 (1.18–1.73)			68/1,003	1.31 (1.00–1.73)		73/786	1.59 (1.21–2.09)	
≥40	93/1,079	1.52 (1.21–1.90)		0.39	61/654	1.63 (1.21–2.19)		32/425	1.19 (0.81–1.74)	
Per 5 kg/m^2[d]		1.10 (1.06–1.15)	<0.0001	0.41		1.11 (1.05–1.17)	0.0002		1.09 (1.03–1.16)	0.004
BMI at age 20 y										
<18.5	130/2,213	1.06 (0.88–1.28)			93/1,655	1.04 (0.83–1.31)		37/558	1.16 (0.82–1.63)	
18.5–<25	1,342/23,556	1.00 (ref)			645/12,301	1.00 (ref)		697/11,255	1.00 (ref)	
25–<30	400/5,566	1.22 (1.08–1.37)			90/1,349	1.24 (0.98–1.56)		310/4,216	1.20 (1.04–1.38)	
≥30	116/1,228	1.57 (1.28–1.91)		0.08	47/417	2.02 (1.47–2.78)		69/811	1.32 (1.01–1.71)	
30–<35	90/956	1.67 (1.34–2.09)			34/303	2.07 (1.44–2.98)		56/652	1.48 (1.11–1.98)	
≥35	26/272	1.27 (0.85–1.91)		0.09	13/113	1.89 (1.03–3.47)		13/159	0.86 (0.48–1.55)	
Per 5 kg/m^2[d]		1.10 (1.04–1.16)	0.0007	0.002		1.23 (1.12–1.35)	<0.0001		1.03 (0.96–1.11)	0.4
Adult weight change[e]										
Lost weight	139/2,031	0.97 (0.79–1.20)			75/1,048	1.19 (0.89–1.60)		64/983	0.80 (0.59–1.09)	
0–<6 kg	393/6,593	1.00 (ref)			169/3,221	1.00 (ref)		224/3,372	1.00 (ref)	
6–<10 kg	327/5,464	1.00 (0.86–1.16)			151/2,645	1.09 (0.86–1.37)		176/2,820	0.94 (0.76–1.16)	
10–<20 kg	561/9,697	0.99 (0.87–1.13)			222/4,766	0.86 (0.69–1.06)		339/4,931	1.11 (0.93–1.32)	
≥20 kg	584/9,090	1.11 (0.97–1.27)		0.004	267/4,254	1.15 (0.93–1.41)		317/4,836	1.04 (0.87–1.25)	
Per 5 kg		1.02 (1.00–1.03)	0.02	0.72		1.01 (0.99–1.03)	0.5		1.02 (1.00–1.04)	0.06
Colorectal cancer–specific mortality										
BMI recent										
<18.5	15/388	0.90 (0.51–1.58)			12/313	1.04 (0.54–2.02)		—	—	
18.5–<25	383/10,540	1.00 (ref)			217/6,601	1.00 (ref)		166/3,939	1.00 (ref)	
25–<30	481/11,703	1.14 (0.99–1.31)			172/4,386	1.25 (1.01–1.55)		309/7,317	1.03 (0.84–1.26)	
≥30	354/7,674	1.19 (1.03–1.39)		0.41	158/3,422	1.28 (1.03–1.60)		196/4,251	1.09 (0.87–1.35)	
30–<35	215/5,062	1.12 (0.94–1.34)			82/1,939	1.27 (0.97–1.66)		133/3,123	1.02 (0.81–1.30)	
35–<40	90/1,636	1.36 (1.07–1.72)			41/892	1.20 (0.85–1.72)		49/744	1.53 (1.08–2.15)	
≥40	49/975	1.24 (0.91–1.69)		0.15	35/591	1.45 (0.98–2.15)		14/384	0.79 (0.45–1.39)	
Per 5 kg/m^2[d]		1.07 (1.02–1.13)	0.006	0.23		1.09 (1.02–1.17)	0.01		1.04 (0.96–1.13)	0.3
BMI at age 20 y										
<18.5	70/2,054	0.94 (0.73–1.22)			53/1,525	0.94 (0.69–1.27)		17/530	0.95 (0.57–1.58)	
18.5–<25	820/21,564	1.00 (ref)			411/11,319	1.00 (ref)		409/10,245	1.00 (ref)	
25–<30	238/5,064	1.10 (0.95–1.29)			52/1,215	1.05 (0.78–1.43)		186/3,849	1.09 (0.91–1.31)	
≥30	70/1,098	1.44 (1.11–1.85)		0.18	31/379	1.76 (1.18–2.62)		39/719	1.20 (0.84–1.70)	
30–<35	53/853	1.55 (1.16–2.07)			—	—		—	—	
≥35	17/245	1.15 (0.70–1.90)		0.30	—	—		—	—	
Per 5 kg/m^2[d]		1.08 (1.00–1.16)	0.04	0.01		1.20 (1.06–1.36)	0.004		1.00 (0.91–1.10)	0.99
Adult weight change[e]										
Lost weight	72/1,831	0.93 (0.70–1.23)			39/991	1.10 (0.74–1.63)		33/840	0.83 (0.54–1.27)	
0–<6 kg	244/6,035	1.00 (ref)			109/2,946	1.00 (ref)		135/3,088	1.00 (ref)	
6–<10 kg	201/5,096	0.97 (0.80–1.18)			92/2,478	1.08 (0.81–1.45)		109/2,618	0.95 (0.73–1.24)	
10–<20 kg	357/8,873	1.03 (0.87–1.22)			144/4,344	0.95 (0.73–1.24)		213/4,529	1.11 (0.88–1.40)	
≥20 kg	334/8,202	1.03 (0.87–1.23)		0.19	167/3,858	1.16 (0.89–1.50)		167/4,344	0.94 (0.73–1.20)	
Per 5 kg		1.02 (1.00–1.03)	0.09	0.23		1.02 (0.99–1.05)	0.1		1.01 (0.98–1.03)	0.5

[a]Adjusted for sex, TNM stage, cigarette smoking, C-CFR study site, and age at diagnosis (strata statement).
[b]Wald *P* value for linear trend, excluding underweight BMI.
[c]Calculated from -2 log likelihood ratio test comparing models with and without interaction terms between BMI (or weight change) and sex.
[d]Underweight BMI (<18.5 kg/m^2) not included in model.
[e]Adjusted for factors listed in "a" and additionally adjusted for BMI at age 20.

(20). Dose capping for adjuvant therapy among obese colorectal cancer patients was demonstrated to have no material influence on a variety of outcomes, including colon cancer recurrence and all-cause mortality (18). Another limitation of this study was that participants were asked to recall their body weight before cancer diagnosis. Cross-sectional data show that self-reported BMI values are typically slightly lower than directly measured values (53); under-reporting of self-reported BMI may overestimate associations of overweight BMI with risk of mortality and concurrently underestimate the association for obese BMI. Good-to-excellent agreement was reported, however, in studies with similar demographic characteristics to this study for self-reported and directly measured values of height and weight (54, 55). Furthermore, prospective studies with height and weight data reported many years prior to colorectal cancer diagnosis (12, 13, 15, 24, 25) have shown similar associations to those reported in this study,

Table 3. Joint associations of BMI and MSI status on all-cause mortality: the C-CFR, 1997 to 2012

	MS-stable and MSI-low		MSI-high	
	Deaths/person years	Multivariable HR (95% CI)[a]	Deaths/person years	Multivariable HR (95% CI)[a]
Recent BMI				
18.5–<25	425/7,530	1.00 (ref)	60/1,556	0.86 (0.65–1.14)
25–<30	532/8,419	1.19 (1.04–1.36)	44/1,547	0.58 (0.42–0.80)
≥30	376/5,481	1.32 (1.14–1.53)	47/1,062	1.00 (0.74–1.37)

[a]Adjusted for sex, TNM stage, cigarette smoking, C-CFR study site, and age at diagnosis (strata statement).

providing some re-assurance that recall bias is less likely to be a major concern.

Distinct advantages of this study include its large sample size and the availability of data on MSI, *BRAF*, smoking, and other potential effect modifiers, which allowed for the examination of whether the subgroup differences often observed in incidence studies applied to prognosis. The meta-analysis by Parkin and colleagues (14) identified summary HRs for the association between BMI per 5 kg/m^2 and all-cause mortality by sex (women, HR: 1.16; men, HR: 1.07) that were similar to our findings, suggesting that sex is not an effect modifier in prognosis studies, in contrast to results from incidence studies where associations are typically higher for men than women (2–5). Few studies have examined whether risk of mortality with BMI differed by site within the colorectum (12, 24, 25). In this study, we observed essentially the same mortality estimates for the colon and rectum. The Cancer Prevention Study-II Nutrition Cohort observed stronger associations between BMI and mortality for persons diagnosed with rectal than colon cancers (12), similar to the results from Haydon and colleagues (25). Doria-Rose and colleagues (24) showed that BMI was associated with higher mortality among women diagnosed with colon, but not rectal, cancer. We are not aware of a clear explanation for these discrepant findings; it is plausible that chance is playing a role. Future work, preferably with pooled data from multiple prospective studies, will be needed to clarify this issue.

In this study, there were no statistical interactions between prediagnostic BMI and *BRAF* or MSI, suggesting that high BMI is associated with worse prognosis regardless of these tumor subtypes. For patients with MSI-high tumors, this observation may be clinically relevant, particularly for stage II disease because MSI-high status is recommended to identify patients who do not need or benefit from 5-FU–based adjuvant therapy (56). Accordingly, obesity in stage II colon cancer patients has potential implications for treatment that should be considered in future studies. We report suggestive, albeit not statistically significant, evidence that smoking may modify the link between BMI and all-cause mortality. This phenomenon occurs in more general populations (57–59) and is attributed to smoking dose being correlated with lower BMI and with higher risk of death. It is important to note that several subgroup comparisons were made in this analysis and these results may be due to chance.

In conclusion, in this cohort of colorectal cancer survivors, high prediagnosis BMI was associated with higher all-cause and colorectal cancer–specific mortality; these associations were consistent across strata of sex, tumor molecular phenotype, TNM summary stage, site in the colorectum, age at diagnosis, and red meat intake. Importantly, high BMI attenuated the survival advantage otherwise observed among persons with MSI-high tumors. Further research is needed to address the biologic causes and clinical implications of this association.

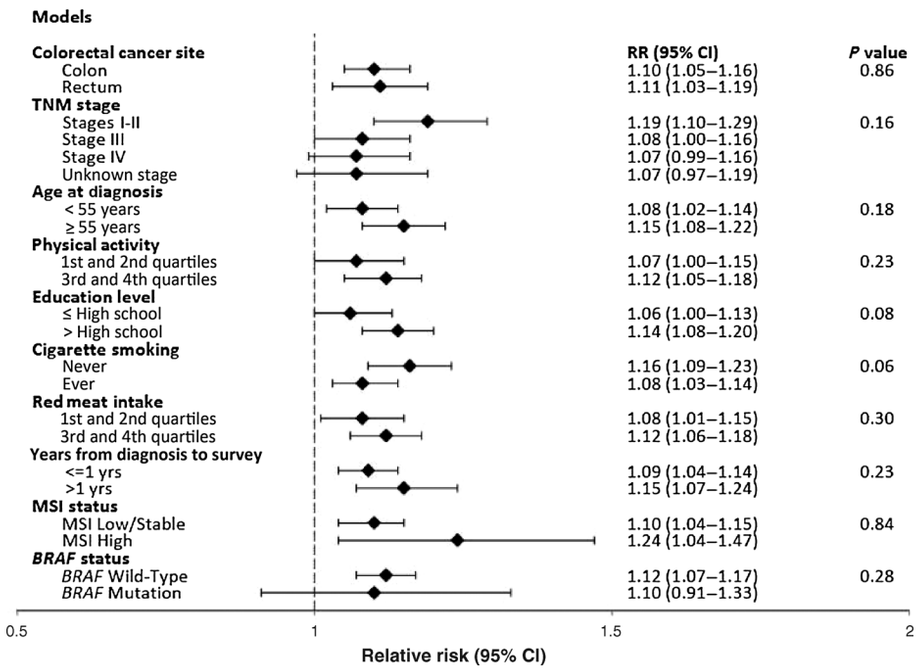

Figure 2.
Relative risks (RR) and 95% CIs for deaths from all causes per 5 kg/m^2 of BMI for persons diagnosed with colorectal cancer in the C-CFR, 1997 to 2012. *P* values for heterogeneity are calculated by comparing the likelihood ratio statistic from models with and without interaction terms. Models are adjusted for sex, TNM stage, cigarette smoking, C-CFR study site, and age at diagnosis (strata statement).

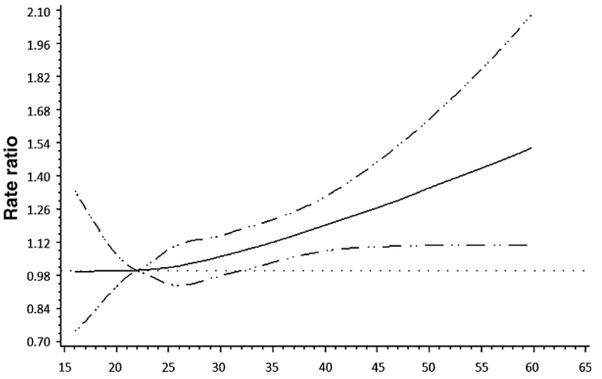

Figure 3.
Restricted cubic spline analysis of recent prediagnosis BMI and all-cause mortality for men and women diagnosed with colorectal cancer in the C-CFR, 1997 to 2012. Solid line indicates HR while dashed line indicates 95% CIs.

Disclosure of Potential Conflicts of Interest

P.J. Limburg reports receiving commercial research support from Ironwood Pharmaceuticals; has ownership interest (including patents) in Exact Sciences; and is a consultant/advisory board member for Everyday Health, LLC. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The content of this article does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the C-CFR, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the C-CFR.

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