Analysis of body mass index and mortality in patients with colorectal cancer using causal diagrams

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Abstract

Importance—Physicians and investigators have sought to determine the relationship between body mass index (BMI) and colorectal cancer (CRC) outcomes, but methodologic limitations including sampling selection bias, reverse causality, and "collider" bias have prevented the ability to draw definitive conclusions.

Objective—We evaluated the impact of BMI at the time of, and following colorectal cancer (CRC) diagnosis, on mortality in a complete population using causal diagrams.

Design—Retrospective observational study with prospectively collected data

Setting—Kaiser Permanente Northern California

Participants—3,408 men and women diagnosed 2006-2011 with stages I-III colorectal cancer who had surgery

Exposures—BMI at diagnosis, and 15 months following diagnosis

Main Outcomes and Measures—Hazard ratios for all-cause and CRC-specific mortality, relative to normal-weight patients, adjusted for sociodemographics, disease severity, treatment, and pre-diagnosis BMI.

Results—At-diagnosis BMI was associated with all-cause mortality in a nonlinear fashion, with underweight (BMI<18.5 kg/m^2, hazard ratio [HR]=2.65, 95% confidence interval [CI]:1.63-4.31) and class II/III obese (BMI 35 kg/m^2, HR=1.33, 95% CI: 0.89-1.98) patients exhibiting elevated mortality risks, compared with low normal-weight (BMI 18.5-<23 kg/m^2) patients. In contrast,

high-normal-weight (BMI 23-<25 kg/m^2, HR=0.77, 95% CI: 0.56-1.06), low-overweight (BMI 25-<28 kg/m^2, HR=0.75, 95% CI:0.55-1.04), and high-overweight (BMI 28-<30 kg/m^2, HR=0.52, 95% CI: 0.35-0.77) patients had lower mortality risks, and class I obese (BMI 30-<35 kg/m^2) patients showed no difference in risk. Spline analysis confirmed a U-shaped relationship in participants (p-value, test for nonlinearity<0.001) with lowest mortality at BMI=28 kg/m^2. Associations with CRC-specific mortality were similar. Associations of post-diagnosis BMI and mortality were also similar, but class I obese had significantly lower all-cause and cancer-specific mortality risks.

Conclusions and Relevance—Overweight patients consistently had the lowest mortality after a CRC diagnosis. Though strong scientific evidence shows that exercise in cancer patients should be encouraged, findings suggest, among overweight CRC patients, that recommendations for weight loss in the immediate post-diagnosis period may be unwarranted.

Keywords

Body mass index; weight; survival; mortality; colorectal cancer

Introduction

Body mass index (BMI) is positively associated with the risk of colorectal cancer[1-9]. For that reason, investigators have hypothesized that overweight/obesity leads to worse colorectal cancer (CRC) prognosis. However, though previous studies have shown an apparently elevated mortality risk in class II/III obese (BMI 35 kg/m^2) patients[10-12], associations of class I obesity (BMI 30-<35 kg/m^2) and survival are mixed; some studies show a higher mortality risk[6, 10, 13-16] and others show no higher[17] or a possible lower[18] mortality risk, depending in part on when BMI is measured relative to diagnosis. Overweight and obese CRC patients have shown lower mortality risks[11, 18] compared with normal- or underweight patients when BMI is measured following diagnosis but concerns are that this "obesity paradox" could reflect sampling selection bias, reverse causality, and/or collider bias[19-21]. We sought to employ methods to overcome these concerns in our evaluation of the impact of BMI on post-diagnosis mortality.

First, many studies of weight and CRC survival are conducted in samples recruited after diagnosis causing concerns that only the healthiest may enroll. Such sampling selection bias could produce an obesity paradox if the sickest overweight patients are less likely to enroll than the sickest normal-weight patients or they die prior to enrollment. Second, underweight or normal-weight patients may have higher mortality, compared with overweight patients because they may include cachectic patients nearing death, i.e., reverse causality[22]. A third concern is collider bias[20]; in the presence of an unmeasured risk factor for CRC diagnosis (see eFigure 1 in the supplement), selecting a population based on a CRC diagnosis could introduce a spurious association between an exposure (e.g., post-diagnosis BMI) and an outcome (e.g., death) that could reverse the direction of association, making a harmful exposure appear protective[21]. I.e., collider bias may occur if overweight/obesity leads to higher disease incidence, but unmeasured risk factors occurring disproportionately in normal-weight patients are more strongly related to mortality than is overweight/obesity. In this case, spuriousness can be avoided with adjustment for pre-diagnosis BMI (eFigure 1).

Using electronic medical record (EMR) data collected as a part of routine clinical care within the Kaiser Permanente Northern California (KPNC) population, we examined the effect of BMI at, and following, diagnosis on all-cause and CRC-specific mortality in KPNC CRC patients diagnosed from 2006-2011, using several strategies to overcome bias. These included the use of data from a complete population of CRC patients with longitudinally-collected data, examination of associations in stage I patients not expected to be at imminent risk of death, stratification by weight loss status, and the use of causal diagrams to identify sufficient adjustment sets[23] of covariates. Related to this, we were able to adjust for prospectively collected data on pre-diagnosis BMI, a unique feature of our data.

We hypothesized higher mortality risks in underweight and class II/III obese CRC patients, and a lower risk in overweight, vs. normal-weight, patients.

Methods

Study Population

The study population consisted of all patients ages 18-80 from KPNC diagnosed from 2006-2011 with stage I-III invasive CRC whose cancer was confirmed by computed tomography, who received surgery, and for whom an electronic weight and height were available at diagnosis. Case ascertainment began in 2006, one year after weights routinely became available in the EMR, to enable inclusion of pre-diagnosis weight in analyses. A third of the California population are KP members; members represent the underlying population except at socioeconomic extremes[24]. Approximately 5% of patients were missing at-diagnosis BMI data in a year. Loss to follow-up was <3%. 49.7% of study participants were female and 50.3% male. A waiver of written informed consent was obtained and the study was approved by the KPNC institutional review board.

Data Collection

Body mass index—Height and weight were measured by a medical assistant at each medical visit. BMI was computed in kilograms per height in meter squared. Patients were included in analyses if they had a recorded BMI <6 months of a CRC diagnosis prior to surgery. BMI closest to the diagnosis date (range -5.3 to 6.0 months, median=0.0 mo) was used in analyses of at-diagnosis BMI. BMI measured 9 months before CRC diagnosis (range 9.0-68.9 months prior, median=-12.5 mo) was used to assess pre-diagnosis BMI, and BMI measured approximately fifteen months following diagnosis (range 9.0-27.0 months, median=14.7 mo), post-treatment, was used to assess post-diagnosis BMI.

We initially categorized BMI using World Health Organization (WHO) categories[25]. However, the optimal weight for CRC patients is unknown and large BMI categories may obscure risk in the case of U- or J-shaped relationships, so we categorized BMI into finer categories (<18.5, 18.5-<23, 23-<25, 25-<28, 28-<30, 30-<35, and 35+) consistent with those used in a recent meta-analysis of weight and mortality[26], and to distinguish risks for lower (18.5-<23 kg/m^2) and upper (23-<25 kg/m^2) normal-weight, as well as lower (25-<28 kg/m^2) and upper (28-<30 kg/m^2) overweight.

Clinical variables and endpoints—KPNC Cancer Registry data and the EMR were reviewed for information on prognostic factors, including disease stage, tumor characteristics, surgical procedures, and treatment (chemotherapy, radiation therapy). Data on overall and CRC-specific mortality were obtained from the KPNC computerized mortality file, which is comprised of data from the California State Department of Vital Statistics, U.S. Social Security Administration, and KPNC utilization data sources. Colorectal cancer death was attributed to persons if CRC was listed as a cause of death on the death certificate.

Other covariate data—EMR data were accessed for information on numerous potential confounders including demographics (self-reported race is included in the EMR) and smoking status. The Charlson index was used to measure (any vs. no) comorbidity. Physical activity data (minutes per week of moderate or vigorous activity) were available in 22% of the population.

Statistical analysis

We used analysis of covariance to examine linear covariates by categories of at-diagnosis BMI adjusted for age. For categorical variables, we examined covariate distributions by categories of at-diagnosis BMI.

We used Cox proportional hazards regression models to examine associations between BMI at the time of, and following diagnosis, and all-cause and CRC-specific mortality. For analyses of at-diagnosis BMI, time was computed from time of diagnosis. In analyses of post-diagnosis BMI, time was computed from the time of the follow-up BMI measure to time of event or study end.

To address possible reverse causality, we evaluated associations in those with stage I cancer. Typically, researchers eliminate deaths occurring early after measurement of a risk factor. Though this can lead to collider bias[20], this strategy is commonly used so we nonetheless conducted sensitivity analyses eliminating deaths occurring within the first six months and the first year to facilitate comparison to other studies.

Potential confounding variables in models were selected based on subject matter expertise encoded in directed acyclic graphs (DAGs)[27], diagrams that help elucidate the causal structure relating variables under study. We compared models controlling for age, race, and sex, to those adjusted additionally for stage, grade, cancer site (colon; distal or proximal, and rectal), smoking, and physical activity. To address concerns about the potential for collider bias because of the restriction of analyses to diagnosed CRC patients (Supplementary eFigure 1), we adjusted for pre-diagnosis BMI when evaluating the effects of both at- and post-diagnosis BMI. Adjustment for chemotherapy and radiation were not suggested by the DAG in the analysis of at-diagnosis BMI based on the time order of covariates. We nonetheless included these variables in models based on convention; adjustment had no substantive effect on associations. We considered adjustment for comorbidity but sought to avoid overadjustment since CRC and comorbidities have mechanisms in common related to BMI.

We used both standard WHO[25], and expanded, BMI categories. We also examined possible nonlinear relationships between BMI and survival, nonparametrically, and by sex, with restricted cubic splines[28], a technique enabling specification of a relationship between two variables when the function is nonlinear. Tests for nonlinearity used the likelihood ratio test, comparing the model with the linear term to one with linear and cubic spline terms.

Finally, we conducted analyses of at-diagnosis BMI and outcomes, stratified in separate analyses by sex, age (<65 vs. 65 years), race, stage, comorbidity, treatment status, CRC site, and weight loss status between diagnosis and post-diagnosis. Heterogeneity in associations in stratified analyses were examined via introduction of cross-product terms for BMI categories and stratification variables in regression models and evaluation of significance with likelihood ratio χ^2 tests. We conducted sensitivity analyses restricting to the population with complete information on pre-diagnosis BMI. We also conducted tests of proportionality with variable by time interactions. Tests of statistical significance were two-sided. Significant results denote p-values 0.05.

Results

Of the 3,408 CRC patients, 617 died (411 from CRC), with follow-up ranging from 0-8.7 years, with a median 4.5 years follow-up. For analyses of post-diagnosis BMI and mortality (N=3,157), 482 died (317 from CRC), and follow-up ranged from 0-7.9 years, with a median 3.5 years follow-up.

Baseline characteristics

Examining covariates, age was inversely associated with at-diagnosis BMI. Women were more likely to be underweight, normal weight, and class II/III obese, compared with men. Asians were more likely to be underweight or normal-weight; Whites, Blacks, and Hispanics were more likely to be class II/III obese. Those with stages II and III cancers were more likely to be underweight or normal weight compared with those with stage I cancer. However, those with stage III cancer were more likely to be obese (BMI 30 kg/m^2) than those with earlier stage cancer. Predictably, levels of smoking and physical activity were higher in underweight and normal-weight patients. Distal cancers were more common among obese patients; those with BMI<25 kg/m^2 were more likely to have proximal colon or rectal cancers. Underweight and class II/III obese patients were less likely to receive chemotherapy (Table 1).

BMI and all-cause mortality

Using WHO criteria, in models adjusted for age, sex, and race, at-diagnosis BMI was associated with all-cause and CRC-specific mortality in a nonlinear fashion, with underweight (BMI<18.5 kg/m^2) and class II/III obese (BMI 35 kg/m^2) patients exhibiting elevated, and overweight (BMI 25-<30 kg/m^2) patients showing reduced, mortality risks, compared with normal-weight (BMI 18.5-<25 kg/m^2) patients. Mortality risks of class I obese and normal-weight patients were similar. In multivariable-adjusted analyses, associations were similar though the association for overall mortality in overweight patients was somewhat attenuated (Table 2). After comorbidity adjustment, the association between

class II/III obesity and all-cause mortality was no longer significant (HR=1.27, 95% CI: 0.88-1.84).

Using expanded BMI categories, in models adjusted for age, sex, and race, at-diagnosis BMI was also associated with all-cause and CRC-specific mortality in a nonlinear fashion. Multivariable-adjusted results were qualitatively similar (Table 2). Underweight (BMI<18.5 kg/m^2, hazard ratio [HR]=2.65, 95% confidence interval [CI]:1.63-4.31) and class II/III obese (BMI 35 kg/m^2, HR=1.33, 95% CI:0.89-1.98) patients exhibited elevated mortality risks; high-normal-weight (BMI 23-<25 kg/m^2, HR=0.77, 95% CI:0.56-1.06), low-overweight (BMI 25-<28 kg/m^2, HR=0.75, 95% CI:0.55-1.04), and high-overweight (BMI 28-<30 kg/m^2, HR=0.52, 95% CI:0.35-0.77) patients showed reduced mortality risks; and class I obese (BMI 30-<35 kg/m^2) patients showed no difference in risk, compared with low-normal-weight (BMI 18.5-<23 kg/m^2) patients. Mortality risk did not differ comparing high-normal-weight and low-overweight patients (Wald χ2=0.03, p=0.87).

In spline analyses of all-cause mortality, risk was lowest among CRC patients with a BMI=28 kg/m^2 (Figure 1), evident in men (eFigure 2) and women (eFigure 3). Tests for linear trend suggested linear relationships of BMI with mortality hazard overall (p=0.01) and women (p=0.01) but not in men (p=0.21). In all cases, spline analyses provided evidence of a nonlinear component (p<0.001 for nonlinear association [men, p<0.001; women, p=0.02].

Patterns of associations of post-diagnosis (Table 3) BMI and all-cause mortality were similar to results for at-diagnosis BMI and all-cause mortality. However, class I obese patients had a lower mortality risk, and class II/III obese patients showed no higher mortality risk compared with low normal-weight patients.

BMI and CRC-specific mortality

Associations of both at-diagnosis and post-diagnosis BMI with CRC-specific mortality were similar to those for analyses of all-cause mortality. However, in post-diagnosis analyses, class I obese patients had a significantly lower mortality risk and class II/III obese patients showed no higher and a possibly lower mortality risk compared with the reference (Tables 2-3).

Stratified analyses

In stratified analyses, there were few differences by age, race, sex, stage, comorbidity, treatment, or weight loss status (Table 4, eTable 1). However, there was strong evidence of statistical interaction by primary tumor site. The nonlinear pattern of BMI and mortality was apparent in all sites, but elevated risks for underweight and class II/III obesity were most evident in proximal cases whereas reduced risks for overweight and class I obese were most evident in distal and rectal cancers cases (p-interaction=0.005) (Table 4).

In sensitivity analyses excluding early deaths, we noted little qualitative change or attenuation in associations for at-diagnosis weight and mortality. Associations for underweight and mortality in post-diagnosis analyses were somewhat attenuated when we excluded first year deaths, but other associations were similar (data not shown). Results in

sensitivity analyses were also similar (data not shown). With stratification on grade, proportional hazards assumptions were met.

Discussion

Consistent with hypotheses, CRC patients who were underweight or class II/III obese at diagnosis had worse overall prognosis than normal-weight patients. By contrast, neither all-cause nor disease-specific mortality were elevated for class II/III obese CRC patients >1 year after diagnosis. Overweight patients consistently had the best prognosis, with the lowest risks of all-cause and CRC-specific mortality, though the mortality risks of low-overweight and high-normal-weight CRC patients did not differ. We were able to overcome limitations of previous studies with the availability of a complete CRC patient population, prospectively measured pre-diagnosis weight data, and methods which may improve causal claims regarding the effects of BMI on post-CRC-diagnosis mortality. These findings, in the largest CRC cohort to date with data on weight prior to, at the time of, and following diagnosis, provide support that overweight does not confer an increased mortality risk, and may support an obesity paradox, in CRC patients.

Previous investigators have generally shown that underweight and class II/III obese CRC patients have a higher mortality risk when BMI is assessed prior to[13, 29, 30] or near the time of[10-12, 14, 31] diagnosis. Risks for underweight are higher than for other patients. Our findings are generally consistent with these, though we found elevated mortality risks for underweight patients at all timepoints, in contrast with previous findings showing diminished effects in post-diagnosis analyses. Consistent with our findings, several though not all previous studies have shown lower overall and/or disease-specific mortality risks in overweight[18, 30, 32, 33], and even mildly obese[33], CRC patients when BMI has been evaluated after diagnosis. However, results from these analyses have been a source of concern among researchers interested in causal methods who have argued that inverse associations are due to collider bias[21, 34].

With sufficient covariate adjustment, including pre-diagnosis BMI, we found robust evidence that prognosis is best in CRC patients who are overweight at, and after, the time of diagnosis. In this study, overweight CRC patients had a lower mortality risk among stage I patients, whether or not we eliminated early mortality, and among those with or without weight loss, suggesting results were not attributable to reverse causality. Our strong inverse findings for overweight and both all-cause and disease-specific mortality are novel, obtained using improved methodologies.

A lack of association of overweight around diagnosis and outcomes in previous studies may be due to small sample sizes[11, 17, 32] and to broad categorization of weight groups; most studies have defined normal-weight CRC patients with BMI 18.5-<25 kg/m^2, though some omit lower normal-weight patients in this category[10, 11, 14, 15]. Our findings, including a nonsignificant inverse association in overweight patients with similar categorization, but strong inverse findings in all other analyses, suggest that traditional BMI categories are insufficiently granular to understand mortality risk in CRC patients since the nature of the relationship appears convincingly nonlinear. Intriguingly, some studies with long (median 8

years) follow-up have shown weak, significant or borderline significant positive findings of overweight and mortality[10, 12]. However, hazard ratios of approximately 1.0 suggest that these estimates are influenced by the tail at the high end of the BMI distribution or that they might represent time-averaged effects of being overweight and/or obese on patients outcomes with increasing risks further from diagnosis. Long-term studies of BMI and CRC survival, with regularly updated BMI measures, are needed.

By examining associations in a population unaffected by sample selection bias and using causal methods to address confounding, we provide support that results are biologically meaningful. In the context of disease, overweight may confer survival benefits[35-48], attributed to better nutritional status[36], more optimal medical treatment[49], greater endothelial progenitor cells[50], lower thromboxane production[51], higher ghrelin sensitivity[52], and lower concentrations of tumor necrosis factor-α[53, 54]. CRC patients with extra weight may have greater muscle and fat mass enabling them to cope with the metabolic demands of tumor progression and treatment[49-54]. However, though mortality was lowest in the overweight, risk was similarly low in high-normal-weight patients, suggesting that a BMI in this range may minimize the risks entailed in managing disease.

A study strength was the ability to examine prospectively measured weight at, and following diagnosis, with outcomes, adjusted for pre-diagnosis BMI. Other study strengths include a large sample size, data on treatment and comorbidities, weights and height measured by a medical assistant, and follow-up to 8.7 years. Study limitations include lack of physical activity data for the full cohort. However, adjustment for this variable did not affect results in the subset with these data (data not shown). As with all observational studies, residual confounding is possible. We were unable to control for detailed treatment information. However, Glymour found that the level of unmeasured confounding would have to be very large to explain the obesity paradox[55] and covariate adjustment in our study had little influence on associations.

In summary, extremes in weight at diagnosis were associated with elevated all-cause and CRC-specific mortality in a large population of stage I-III CRC patients. By contrast, overweight CRC patients had the best prognosis. Studies are needed to understand the mechanisms underlying these results, particularly studies of body composition. Though strong scientific evidence shows that exercise in cancer patients should be encouraged, findings suggest, among overweight CRC patients, that recommendations for weight loss in the immediate post-diagnosis period may be unwarranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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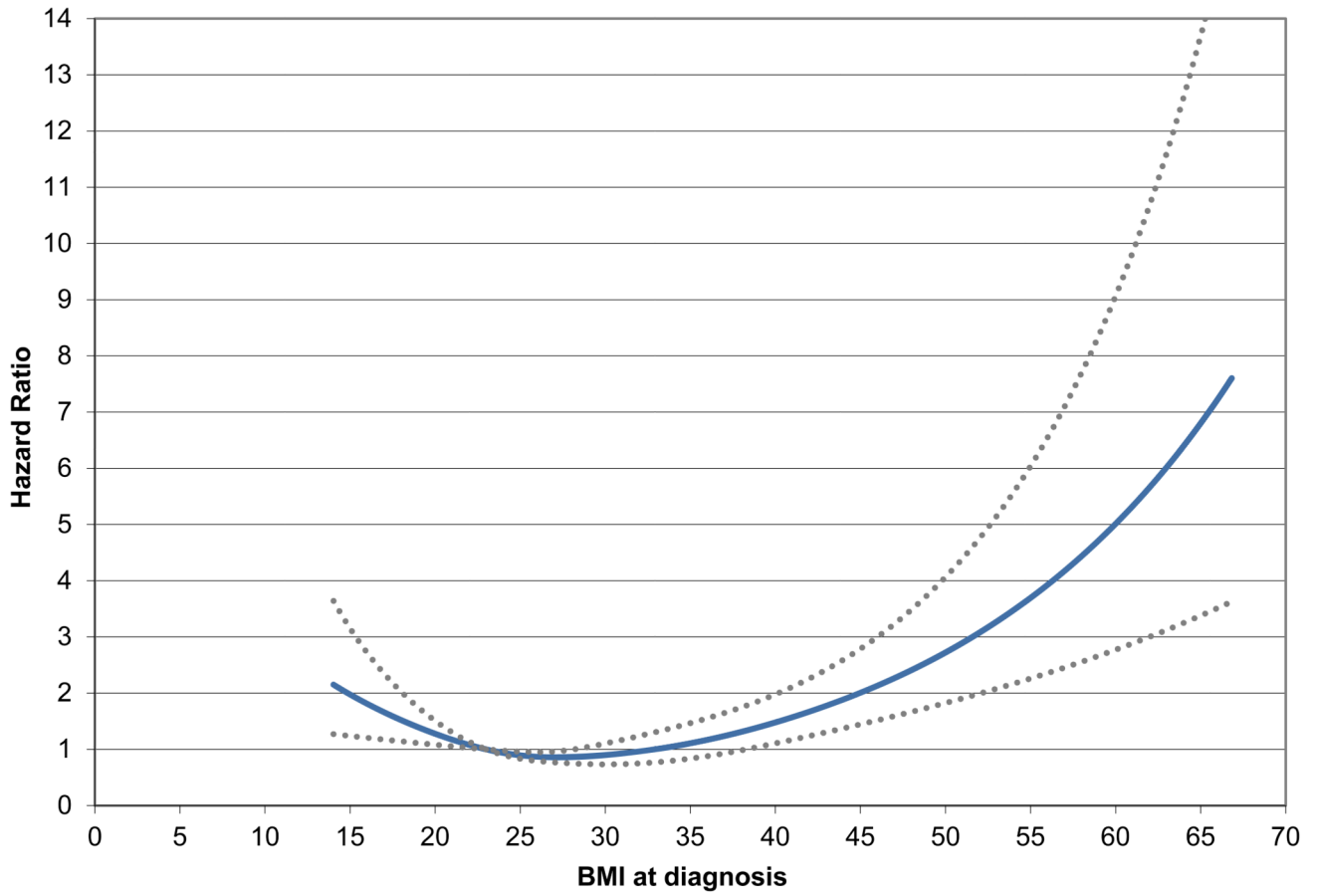
Figure 1.
Spline curve of BMI at diagnosis and overall mortality, p-value, test for nonlinearity <0.0001. Adjusted for age, sex, race, stage, site, grade, chemotherapy, radiation, pre-diagnosis BMI, smoking, and physical activity.

Table 1

Selected characteristics according to categories of BMI at diagnosis in the Kaiser Permanente Northern California population (N=3,408)

| | BMI at diagnosis (kg/m²) – WHO categories | | | | |
	<18.5	18.5-<25	25-<30	30-<35	>=35
N	67	1,050	1,214	671	408
N, pre-diagnosis BMI	45	729	823	461	287
N, post-diagnosis BMI	50	974	1,141	623	369
Age at diagnosis	65	64	63	62	60
Mean pre-diagnosis BMI	18.5	23.6	28.1	32.8	40.7
Mean BMI at diagnosis	17.4	22.6	27.4	32.1	40.4
Female (%)	77.3	58.3	40.4	44.6	58.7
Race					
White	57.4	62.5	65.1	69.0	70.0
Black	8.8	5.8	6.4	8.5	10.6
Hispanic	2.9	6.8	12.4	15.3	13.0
Asian/Pacific Islander	30.9	24.6	15.5	6.7	4.7
Stage					
I	26.5	28.4	30.7	31.3	31.4
II	38.2	33.5	33.2	27.3	28.7
III	35.3	38.2	36.1	41.3	40.0
Grade					
I	2.9	7.0	7.6	7.2	7.4
II	75.5	75.4	75.9	74.5	75.0
III	16.2	11.1	10.2	11.0	11.5
IV	1.5	1.8	1.2	1.6	1.0
Unknown	5.9	4.7	5.1	5.7	5.2
Site					
Proximal	52.9	46.3	43.2	42.8	47.1
Distal	17.7	24.4	27.2	28.7	29.4
Rectal	29.4	29.3	29.6	28.5	23.5
Treatment					

	BMI at diagnosis (kg/m²) – WHO categories				
	<18.5	**18.5-<25**	**25-<30**	**30-<35**	**>=35**
Chemotherapy	38.5	45.6	44.0	45.7	40.5
Radiation	15.9	16.0	16.1	14.6	10.2
Physical activity (min/wk)					
0	33.3	24.0	24.4	34.2	46.2
>0-<120	22.2	31.3	34.6	34.2	36.9
120	44.4	44.6	41.0	31.5	17.9
Smoking status					
Never	37.3	48.4	47.0	43.8	46.6
Past	43.3	37.3	42.3	45.0	42.1
Current	19.4	14.3	10.8	11.0	10.8

Table 2

Hazard ratios (HR) of at-diagnosis body mass index and mortality* (N=3,408)

	N	Event	Age, race, sex adjusted HR	95% CI	MV-adjusted HR	95% CI
All-cause mortality						
BMI (kg/m²)—WHO categories**						
<18.5	67	32	3.55	(2.44, 5.17)	3.01	(1.88, 4.83)
18.5-<25	1,050	198	ref		ref	
25-<30	1,214	179	0.75	(0.61, 0.92)	0.81	(0.64, 1.03)
30-<35	671	119	0.94	(0.74, 1.19)	1.03	(0.77, 1.38)
35+	406	89	1.36	(1.06, 1.76)	1.63	(1.13, 2.33)
BMI (kg/m²)—expanded categories						
<18.5	67	32	3.06	(2.07, 4.53)	2.65	(1.63, 4.31)
18.5-<23	553	118	Ref		ref	
23-<25	497	80	0.71	(0.54, 0.95)	0.77	(0.56, 1.06)
25-<28	787	125	0.70	(0.54, 0.91)	0.75	(0.55, 1.04)
28-<30	427	54	0.54	(0.39, 0.74)	0.52	(0.35, 0.77)
30-<35	671	119	0.80	(0.62, 1.04)	0.81	(0.57, 1.15)
35+	406	89	1.17	(0.88, 1.55)	1.33	(0.89, 1.98)
CRC-specific mortality						
BMI (kg/m²)—WHO categories						
<18.5	67	20	3.29	(2.05, 5.28)	3.35	(1.92, 5.87)
18.5-<25	1,050	130	ref		Ref	
25-<30	1,214	116	0.74	(0.57, 0.95)	0.77	(0.57, 1.03)
30-<35	671	92	1.07	(0.81, 1.40)	1.06	(0.75, 1.50)
35+	406	53	1.14	(0.82, 1.58)	1.47	(0.96, 2.27)
BMI (kg/m²)—expanded categories						
<18.5	67	20	3.02	(1.84, 4.96)	3.18	(1.78, 5.69)
18.5-<23	553	73	ref		Ref	

	N	Event	Age, race, sex adjusted HR	95% CI	MV-adjusted HR	95% CI
23–<25	497	57	0.83	(0.58, 1.17)	0.89	(0.60, 1.31)
25–<28	787	84	0.76	(0.55, 1.05)	0.81	(0.55, 1.19)
28–<30	427	32	**0.51**	**(0.34, 0.78)**	**0.45**	**(0.28, 0.74)**
30–<35	671	92	0.97	(0.71, 1.33)	0.88	(0.58, 1.32)
35+	406	53	1.04	(0.73, 1.49)	1.12	(0.61, 2.06)

*
Age-adjusted HR adjusted for age (continuous), sex, and race (White (ref), Black, Hispanic, Asian/Pacific Islander, Other). MV-adjusted analysis adjusted additionally for stage (I (ref), II, III), grade (1, 2 (ref), 3, 4), chemotherapy (no (ref), yes), radiation (no (ref), yes), disease site (proximal (ref), distal, rectal), smoking (never (ref), past, current), physical activity (0, >0 to <120, 120+ minutes/wk), and pre-diagnosis BMI (<18.5, 18.5–<25 (ref), 25–<30, 30–<35, 35+ kg/m^2).

**
Note: Adjustment for comorbidity attenuated the association of those with BMI 35+ for all-cause mortality to HR=1.27, 95% CI: 0.88–1.84 and for other cause mortality in analyses (data not shown). Adjustment for comorbidity had minimal influence on associations with colorectal cancer-specific mortality.

Table 3

Post-diagnosis body mass index (BMI) and mortality outcomes (N=3,157)

	N	Event	Age, race, sex adjusted HR	95% CI	MV-adjusted HR	95% CI
All-cause mortality						
BMI (kg/m2)						
<18.5	78	38	3.71	(2.52, 5.45)	3.38	(2.19, 5.20)
18.5-<23	539	108	Ref		Ref	
23-<25	411	60	0.70	(0.51, 0.96)	0.72	(0.52, 1.02)
25-<28	721	90	0.56	(0.42, 0.75)	0.56	(0.41, 0.77)
28-<30	396	44	0.46	(0.32, 0.66)	0.39	(0.26, 0.58)
30-<35	643	78	0.57	(0.42, 0.77)	0.51	(0.35, 0.73)
35+	400	72	0.96	(0.70, 1.30)	0.85	(0.56, 1.30)
CRC-specific mortality						
<18.5	78	25	3.25	(2.00, 5.27)	3.21	(1.88, 5.47)
18.5-<23	539	70	Ref		Ref	
23-<25	411	38	0.70	(0.47, 1.04)	0.69	(0.46, 1.05)
25-<28	721	53	0.53	(0.37, 0.76)	0.50	(0.34, 0.75)
28-<30	396	30	0.53	(0.34, 0.82)	0.42	(0.26, 0.67)
30-<35	643	60	0.67	(0.47, 0.96)	0.56	(0.36, 0.85)
35+	400	45	0.86	(0.59, 1.27)	0.84	(0.51, 1.37)

[*]
Age-adjusted HR adjusted for age (continuous), sex, and race (White (ref), Black, Hispanic, Asian/Pacific Islander, Other). MV-adjusted analysis adjusted additionally for stage (I (ref), II, III), grade (1, 2 (ref), 3, 4), chemotherapy (no (ref), yes), radiation (no (ref), yes), disease site (proximal (ref), distal, rectal), smoking (never (ref), past, current), physical activity (0, >0 to <120, 120+ minutes/wk), and pre-diagnosis BMI (<18.5, 18.5-<23 (ref), 23-<25, 25-<28, 28-<30, 30-<35, 35+ kg/m^2).

Table 4

Stratified analyses of weight and all-cause mortality (N=3,408)*

	<18.5	18.5-<23	23-<25	25-<28	28-<30	30-<35	35	p**
BMI at diagnosis (kg/m2)								
Site								
Proximal, N	36	264	223	333	191	288	191	
Events	22	57	42	61	30	56	51	
HR	**4.82**	1.00	1.02	1.02	0.77	1.07	1.76	**0.005**
95% CI	**(2.57, 9.02)**		(0.65, 1.61)	(0.64, 1.61)	(0.44, 1.33)	(0.64, 1.76)	(0.99, 3.13)	
Distal, N	11	132	124	205	125	192	120	
Events	2	28	13	21	11	35	16	
HR	0.86	1.00	**0.40**	**0.38**	**0.32**	0.86	0.49	
95% CI	(0.19, 3.76)		**(0.19, 0.85)**	**(0.19, 0.79)**	**(0.13, 0.75)**	(0.41, 1.83)	(0.20, 1.24)	
Rectal, N	20	157	150	249	111	191	95	
Events	8	33	25	43	13	28	22	
HR	1.73	1.00	0.75	0.65	**0.37**	**0.47**	1.39	
95% CI	(0.61, 4.86)		(0.42, 1.35)	(0.36, 1.18)	**(0.16, 0.82)**	**(0.24, 0.93)**	(0.67, 2.91)	
Stage								
I, N	18	137	161	232	140	210	128	
Events	5	18	13	19	9	13	10	
HR	**4.04**	1.00	0.57	0.48	0.39	0.56	1.25	0.58
95% CI	**(1.12, 14.6)**		(0.24, 1.34)	(0.20, 1.18)	(0.14, 1.10)	(0.20, 1.54)	(0.39, 4.00)	
II, N	25	192	160	277	127	183	117	
Events	15	27	21	42	17	26	27	
HR	**2.81**	1.00	0.85	1.00	0.95	1.41	**2.24**	
95% CI	**(1.31, 6.04)**		(0.45, 1.63)	(0.53, 1.90)	(0.45, 2.01)	(0.68, 2.92)	**(1.02, 4.93)**	
III, N	24	224	176	278	160	278	161	
Events	12	73	46	64	28	80	52	
HR	1.87	1.00	0.76	0.69	**0.37**	0.66	1.01	
95% CI	(0.81, 4.31)		(0.50, 1.15)	(0.45, 1.04)	**(0.22, 0.62)**	(0.43, 1.03)	(0.61, 1.68)	

*
Models adjusted for age (continuous), sex, and race (White (ref), Black, Hispanic, Asian/Pacific Islander, Other), stage (I (ref), II, III), grade (1, 2 (ref), 3, 4), chemotherapy (no (ref), yes), radiation (no (ref), yes), and disease site (proximal (ref), distal, rectal), smoking (never (ref), past, current), physical activity (0, >0 to <120, 120+ minutes/wk), and pre-diagnosis BMI (<18.5, 18.5-<23 (ref), 23-<25, 25-<28, 28-<30, 30-<35, 35+ kg/m^2) though models were not adjusted for the stratification variable.

**
p-value, Likelihood Ratio χ^2 test for interaction

†
There were no significant differences in analyses stratified by age (< vs. 65 years) (p-value, test for interaction=0.83), race (p=0.18), comorbidity status (p=0.64), chemotherapy (p=0.41) or radiotherapy (p=0.63).