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Relationship of pre-diagnostic body mass index with survival after colorectal cancer: Stage-specific associations

Jonathan M Kocarnik[1,2], **Andrew T Chan**[3,4], **Martha L Slattery**[5], **John D Potter**[2], **Jeffrey Meyerhardt**[6,7], **Amanda Phipps**[1,2], **Hongmei Nan**[8,9], **Tabitha Harrison**[2], **Thomas E Rohan**[10], **Lihong Qi**[11], **Lifang Hou**[12], **Bette Caan**[13], **Candyce H Kroenke**[13], **Howard Strickler**[10], **Richard B Hayes**[14], **Robert E Schoen**[15], **Dawn Q Chong**[4,16], **Emily White**[1,2], **Sonja I Berndt**[17], **Ulrike Peters**[1,2], and **Polly A Newcomb**[1,2]

[1]Department of Epidemiology, University of Washington, Seattle, WA

[2]Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA

[3]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Boston, MA

[4]Division of Gastroenterology, Massachusetts General Hospital, Boston, MA

[5]Department of Internal Medicine, University of Utah Health Sciences Center, Salt Lake City, UT

[6]Dana-Farber Cancer Institute, Boston, MA

[7]Brigham and Women's Hospital, Boston, MA

[8]Department of Epidemiology, Richard M. Fairbanks School of Public Health, Indiana University, Indianapolis, IN

[9]Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN

[10]Department of Epidemiology & Population Health, Albert Einstein College of Medicine, Bronx, NY

[11]Department of Public Health Sciences, School of Medicine, University of California Davis, Davis, CA

[12]Department of Preventive Medicine and the Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, IL

[13]Division of Research, Kaiser Permanente Northern California, Oakland, CA

[14]Division of Epidemiology, New York University School of Medicine, New York, NY

[15]Department of Medicine and Epidemiology, University of Pittsburgh Medical Center, Pittsburgh, PA

[16]Division of Medical Oncology, National Cancer Centre Singapore, Singapore

[17]Division of Cancer Epidemiology & Genetics, National Cancer Institute, Bethesda, MD

Corresponding Author: Jonathan Kocarnik, 1100 Fairview Ave N, Mailstop M4-B402, Seattle, WA 98199, USA, Phone: 206-667-5257, Fax: 206-667-7850, jkocarni@fredhutch.org.

Abstract

Higher body mass index (BMI) is a well-established risk factor for colorectal cancer (CRC), but is inconsistently associated with CRC survival. In 6 prospective studies participating in the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO), 2,249 non-Hispanic white CRC cases were followed for a median 4.5 years after diagnosis, during which 777 died, 554 from CRC-related causes. Associations between pre-diagnosis BMI and survival (overall and CRC-specific) were evaluated using Cox regression models adjusted for age at diagnosis, sex, study, and smoking status (current/former/never). The association between BMI category and CRC survival varied by cancer stage at diagnosis (I–IV) for both all-cause (*P*-interaction=0.03) and CRC-specific mortality (*P*-interaction=0.04). Compared to normal BMI (18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9) was associated with increased mortality among those with stage I disease, and decreased mortality among those with stages II–IV disease. Similarly, obesity (BMI ≥30) was associated with increased mortality among those with stages I–II disease, and decreased mortality among those with stages III–IV disease. These results suggest the relationship between BMI and survival after CRC diagnosis differs by stage at diagnosis, and may emphasize the importance of adequate metabolic reserves for colorectal cancer survival in patients with late-stage disease.

Keywords

Body mass index (BMI); cancer stage; colorectal cancer (CRC); mortality; survival

Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide, as the third most commonly diagnosed cancer and the fourth most common cause of cancer death [1]. In the United States alone, roughly 133,000 new cases and 50,000 deaths are expected in 2015 [2]. A large number of modifiable risk factors have been identified for CRC incidence, but evidence for factors influencing survival following CRC diagnosis is still accumulating. With more than 1.2 million CRC survivors living in the United States [3], understanding risk factors for mortality in this population is of considerable public health importance. Potentially, one such risk factor is higher body mass index (BMI; kg/m^2), which has been established as associated with increased CRC risk [4, 5]. While higher BMI is clearly associated with increased risk for incident disease, BMI has been inconsistently associated with survival after CRC diagnosis [6, 7]. Indeed, several studies have reported that moderately higher BMI may actually be associated with better survival following a CRC diagnosis [8, 9], a counterintuitive relationship that has been termed an ‘obesity paradox’ when observed in cardiovascular and other diseases [10, 11].

To further characterize the relationship between BMI and CRC survival, we evaluated whether pre-diagnosis BMI was associated with either overall or CRC-specific survival in 6 prospective cohort studies participating in the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) [12]. We focused only on pre-diagnosis BMI because previous research has suggested that pre-diagnosis, but not post-diagnosis BMI, is associated with CRC survival [6, 7]. Because five-year survival rates differ widely by cancer stage at

diagnosis [2, 3], we also performed stage-stratified analyses to assess BMI-survival associations in the context of disease progression at diagnosis.

Materials and Methods

Study participants

The Genetic Epidemiology of Colorectal Cancer Consortium (GECCO) is a large collaborative consortium evaluating genetic and environmental risk factors for colorectal cancer [12]. For the present analysis, existing survival data were available on 3,494 men and women diagnosed with incident colorectal cancer from six prospective epidemiologic cohort studies participating in GECCO. These studies were: the Health Professionals Follow-up Study (HPFS) [13]; the Nurses' Health Study (NHS) [14]; the Physicians' Health Study (PHS) [15]; the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) [16, 17]; the VITamins And Lifestyle (VITAL) study [18]; and the Women's Health Initiative (WHI) [19, 20]. These large cohort studies contributed CRC-focused nested case-control subsets of their data as part of their participation in GECCO. Selection criteria for cases and controls in these subsets have been described in detail previously [12, 21], and specifically included the availability of biospecimens for genotyping. For this survival analysis, inclusion was further restricted to CRC patients with survival outcomes data available. All participants self-reported their race as non-Hispanic white. This study was approved by Institutional Review Boards at participating institutions, and all participants provided their informed consent.

Data collection

Demographic and epidemiologic data were obtained prior to diagnosis via questionnaire, either at enrollment into each study (PLCO, VITAL, WHI) or at a subsequent follow-up blood draw (HPFS, NHS, PHS). Basic characteristics such as age, sex, and smoking status (current, former, or never smoker), were collected, and self-reported weight and height were used to calculate pre-diagnostic BMI (weight in kilograms divided by height in meters squared; kg/m^2). Incident invasive colorectal adenocarcinoma cases were identified in each study by either: self-report with subsequent medical record review (PLCO); self-report with subsequent study physician review of medical record and pathology report (HPFS, NHS, PHS); self-report with central physician adjudication (WHI); or linkage to the Surveillance, Epidemiology, and End Results (SEER) cancer registry (VITAL). Age at diagnosis and primary tumor location (proximal colon, distal colon, or rectum) were similarly collected. Cancer stage (I–IV) was assigned according to American Joint Committee on Cancer (AJCC) criteria by study physicians (HPFS, NHS, PHS), community physicians (PLCO), or cancer registrars (VITAL, WHI). Vital status was ascertained by each study (except VITAL) through active follow-up with study participants, and supplemented through linkages to the National Death Index (NDI); VITAL ascertained vital status through linkage to Washington State death records. The present analysis considered both CRC-specific mortality (death attributable to CRC) and overall mortality (death from any cause), as reported by state death records (VITAL) or NDI (WHI), or as determined by committee review of medical records and death certificates (HPFS, NHS, PHS, PLCO).

Data definitions and statistical analyses

BMI values (in kg/m^2) were grouped into the four World Health Organization categories: underweight (BMI < 18.5), normal (18.5 – 24.9), overweight (25.0 – 29.9), and obese (≥ 30.0) [22]. BMI was modeled comparing overweight and obese individuals (separately) to normal-weight individuals; underweight participants were excluded due to small sample size (n=19). Sensitivity analyses considered smaller subcategories among the normal (low-normal (18.5 – 22.9) and high-normal (23.0 – 24.9)) [23] and obese BMI categories (obese I (30.0 – 34.9), obese II (35.0 – 39.9), and obese III (≥ 40.0)) [24]. Cancer stage at diagnosis was analyzed as AJCC stage I, II, III, or IV.

To limit potential bias due to illness-associated weight loss, participants whose BMI was measured within the 1 year preceding diagnosis were excluded (n = 533). To reduce potential bias due to misclassification, participants whose BMI was measured more than 10 years before diagnosis were also excluded (n = 466). After these overlapping exclusions, 194 participants were missing information on cancer stage (n = 141), BMI (n = 38), or smoking status (n = 20), leaving 2,249 CRC cases for analyses. Descriptive statistics were generated using standard methods. We used Cox regression to calculate the hazard ratios (HR) and 95% confidence intervals (95% CI) for the associations between BMI and both CRC-specific and overall mortality. Analyses were adjusted or stratified by cancer stage at diagnosis and adjusted for age at diagnosis, sex, study, and smoking status. To investigate whether the relationship between BMI and CRC survival differed by cancer stage, we modeled an interaction term between categorical BMI and grouped-linear stage at diagnosis (2 degrees of freedom). Interaction *P*-values are 2 sided, with *P*-values < 0.05 considered statistically significant. Proportional hazards assumptions for main effects were verified by testing for a non-zero slope of the scaled Schoenfeld residuals on ranked failure times. Analyses were performed using Stata version 14 [25].

Results

The characteristics of the study participants are reported in Table 1. Briefly, a total of 2,249 CRC cases were followed for a median of 4.5 years after diagnosis (interquartile range 2.2 – 7.2). Of these, 772 died during follow-up (34%), 550 from CRC (24%). The mean age at diagnosis (70.6 years) was on average 5.8 years after mean age at study entry (64.8 years). The proportion of individuals in the normal-weight category tended to be higher in the three health professional cohort studies (HPFS, NHS, PHS; range 46–57%) than in the population-based studies (PLCO, VITAL, WHI; range 28–33%).

For overall survival, we observed statistically significantly lower all-cause mortality for overweight (HR for death = 0.85; 95% CI: 0.72, 1.00), but not obesity (HR = 0.98; 95% CI: 0.81, 1.19; Table 2) compared to normal BMI. However, we further observed that the association between BMI category and all-cause mortality differed by cancer stage at diagnosis (*P*-interaction for obesity*stage = 0.03). Among individuals with stage I CRC, we observed significantly higher mortality for both overweight (HR = 1.58; 95% CI: 1.00, 2.50) and obesity (HR = 1.86; 95% CI: 1.06, 3.27) compared to normal BMI (Table 3). Conversely, among individuals with stage III or IV CRC, both overweight and obesity were associated with lower all-cause mortality compared to normal BMI, though only the

association comparing overweight versus normal BMI among stage III cases was statistically significant (HR = 0.70; 95% CI: 0.51, 0.95). Among individuals with stage II cancer, overweight compared to normal BMI trended towards lower mortality while obesity trended towards higher mortality.

For CRC-specific survival we observed very similar associations to those for overall survival, finding statistically significantly lower CRC-specific mortality for overweight (HR = 0.76; 95% CI: 0.63, 0.93) but not obesity (HR = 0.84; 95% CI: 0.67, 1.05) compared to normal BMI. Also similarly, the relationship between BMI category and CRC-specific mortality varied by stage at diagnosis (*P*-interaction for obesity*stage = 0.04). Overweight compared to normal BMI again suggested higher CRC-specific mortality among those with stage I CRC and lower mortality for those with stage II, III, or IV CRC, with statistically significantly lower CRC-specific mortality among those with stage II (HR = 0.48; 95% CI: 0.25, 0.90) or stage III disease (HR = 0.69; 95% CI: 0.49, 0.98). Similarly, obesity compared to normal BMI showed higher mortality among those with stage I and II CRC but lower mortality for those with stage III or IV CRC (HR for stage IV = 0.70; 95% CI: 0.50, 0.98).

To evaluate potential misclassification of BMI due to the amount of time elapsed between BMI measurement and CRC diagnosis, we performed sensitivity analyses with differing exclusion criteria on this time difference (Web Table 1). Overall, the direction and magnitude of the HR estimates were generally consistent regardless of the time window used, with the stage I results showing the largest changes in effect size. Using more stringent boundaries on time between BMI measurement and CRC diagnosis (excluding those measured within the 2 years prior to diagnosis, greater than 5 years before diagnosis, or both) generally resulted in consistent or larger effect sizes. Conversely, loosening these boundaries (either excluding only those measured within the 1 year prior to diagnosis, or no exclusions) generally resulted in consistent or smaller effect sizes. Due to missing information in several studies, we were unable to adjust for potential confounding factors such as physical activity. In a subset of the sample, however, sensitivity analyses adjusting for MET hours per week generally showed no substantial differences. Additional analyses adjusting for aspirin use, or exploring differences by sex, BMI classification, or tumor location, similarly showed no large differences in the results (data not shown).

Discussion

In this large collaborative consortium of colorectal cancer studies, we found that the association between BMI categories and CRC survival varied according to cancer stage at diagnosis. Compared to normal BMI, higher BMI was associated with higher mortality among those with early-stage CRC (overweight stage I, obese stages I–II), while higher BMI was associated with lower mortality among those with later-stage CRC (overweight stages II–IV, obese stages III–IV). The directions of these relationships were consistent for both all-cause and CRC-specific survival. Our confidence in these results is supported by the large size of the study population, the population-based nature of the contributing studies, the completeness of follow-up, and the prospective nature of the included studies.

To our knowledge, this is the first study to show that the association between BMI and CRC survival depends on cancer stage at diagnosis. Although most previous studies report that results did not differ by cancer stage [6], our results differed substantially by cancer stage at diagnosis. Among participants with early-stage disease, our findings are similar in magnitude to previous reports of lower survival with higher BMI [6]. With increasing stage at diagnosis, however, our results trended in the opposite direction, showing improved survival with higher BMI levels. Our results suggest that some of the 'obesity paradox' for colorectal cancer survival may be due, at least in part, to differences in the relationship of BMI with CRC survival by cancer stage at diagnosis. Previous studies modeling BMI as a continuous variable or not adequately accounting for stage at diagnosis may have obscured this stage-dependent relationship.

In addition, this is the largest study to date to show statistically-significant associations of overweight and obese BMI with lower all-cause and CRC-specific mortality in colorectal cancer survivors using pre-diagnosis BMI. Most previous analyses using pre-diagnosis BMI have reported higher mortality with higher BMI levels [7, 8, 26–30], and obesity in particular, though several have also observed non-significant associations of decreased mortality for overweight vs. normal BMI [8, 28]. One study did report significant associations of higher BMI with increased survival, but only in smaller subgroups, such as overweight African American women, overweight Japanese or Hawaiian men, or obese Latino men [29]. Differences in methodology across these studies, however, lessen the comparability of our results. For example, some of these previous studies excluded rectal cancers [27], excluded distant-stage CRC cases [7], combined multiple race/ethnicity groups [29], or included underweight individuals in the normal weight group [30]. Importantly, none of these studies stratified their main analyses by cancer stage at diagnosis.

This relationship between BMI and CRC survival by stage at diagnosis might be expected to be important since treatment, toxicity, and metabolic requirements vary by stage of disease. Fundamentally, body adiposity is related to energy balance and metabolic reserve: energy intake beyond current metabolic requirements can be stored as fat for future use. While this is a useful system when energy sources are scarce, in energy-rich environments (as is the case in Westernized populations) this can lead to chronic excess adiposity [31]. Higher adiposity has been associated with increased incidence and mortality of several diseases, including cardiovascular disease and many types of cancer [5, 32–34]. This relationship between adiposity and survival may not be linear, however, appearing instead to be U or J-shaped [34–37]. During periods of illness, elevated adiposity may actually be beneficial for meeting short-term metabolic needs [11], such as in context of CRC where the body is undergoing disease-related stress, as well as therapies that may preclude meeting nutritional needs (e.g., nausea induced by chemotherapy). These physiologic stresses likely differ according to the cancer stage at diagnosis and treatment received.

Localized CRC can generally be treated via surgical resection [38], and has a high 5-year survival rate (90.1% [2]). Because most patients with local CRC do not die from the cancer itself, other diseases associated with higher BMI levels (e.g., cardiovascular disease) have an opportunity to manifest in the years following successful CRC treatment. In our results, we observed higher increases in mortality risk for obese than overweight BMI, which were

statistically significant for all-cause but not CRC-specific mortality. Furthermore, comparing higher levels of obesity (obese I/II/III) to normal BMI among those with stage I or II disease suggested progressively higher mortality risk.

For regional stage II and III disease, 5-year survival is still relatively high (70.8% [2]). Patients are variously treated with surgery, radiotherapy, and/or chemotherapy regimens [38], some of which have generalized systemic effects leading to weight loss, loss of appetite, nausea, diarrhea, and other symptoms [39]. These may reduce the patient's ability to obtain the nutrients they need, relying instead on stored body fat for metabolic needs. Higher BMI may therefore provide an increased ability to cope with the physiologic stressors of treatment. However, our results of significantly increased survival for overweight but not obesity vs. normal BMI might suggest an upper limit to the potential benefit of excess metabolic capacity in this context.

In contrast, treatment for distant-stage CRC can be palliative rather than curative [38], and five-year survival is very low (13.1% [2]). For these individuals, risk of death from CRC may be high regardless of body weight, and thus any risk of death from BMI-related disease might be outweighed by the risk of CRC-related mortality. In the context of stage IV CRC, it may be that those with higher adiposity are able to live relatively longer than those with lower metabolic reserves. Mechanistically, individuals with increased adiposity may better tolerate the effects of disease-related weight loss, while individuals with low BMI may be more susceptible to frailty- or cachexia-related mortality [40]. Alternatively, it is also possible that patients who were able to remain obese until diagnosis of later-stage CRC may have less-aggressive and less-catabolic tumors. Obesity might thus be a marker for the metabolic behavior of the tumor, potentially informing prognosis.

One of the challenges in assessing the association between adiposity and CRC survival is ensuring an appropriate and accurate measurement of adiposity. Given that weight loss around the time of CRC diagnosis is common, the time gap between BMI measurement and CRC diagnosis is an important consideration [6]. Uncontrolled, using BMI measured too close to diagnosis could lead to biased results due to reverse causation, while BMI assessed too long before diagnosis may increase measurement error. Sensitivity analyses suggest our results are not substantially impacted by either of these issues.

In addition, the way in which BMI is categorized can have a large impact on associations between categories [41]. As such, standard BMI categories may be insufficient for differentiating healthy levels of adiposity, and may be misclassifying adiposity exposures in research settings. Furthermore, BMI is only a crude measurement of body fat, and does not capture differences in body composition (muscle vs. fat) or fat distribution (subcutaneous vs. visceral), which can also vary by age, sex, physical activity, and other factors [40, 42]. A person's percentage of body fat generally increases with age, for example, and females generally have a higher percentage of body fat than males for the same BMI value [42]. Given the U-shaped association of BMI with survival, it has also been proposed that the lower bound of the normal group may be too low to exclude those of unhealthily-low weight, and that the 'normal' category be further broken down into low- and high-normal BMI in survival studies [23]. Sensitivity analyses suggested greater effect size estimates for overall

and CRC-specific mortality among stage I and IV cases when comparing overweight and obesity to low- than high-normal BMI.

These results are similar to those of a prospective study reporting a statistically significantly reduced mortality risk of overweight vs. normal BMI in a Korean population (HR = 0.62, 95% CI: 0.41, 0.93) where the BMI category boundaries were lower (normal 18.2 – 22.9, overweight 23.0 – 27.4) [43]. Similarly, in a pooled analysis of overall mortality in 1.1 million Asians, low-normal BMI values were associated with a significantly increased risk of death (all-cause) compared to high-normal BMI (low ≤ 22.5, normal 22.5 – 24.9) [36]. Several other large prospective [34] or meta-analysis [41] studies have also shown decreased survival (overall) among those who are underweight, including clinical trial [44] and prospective [27] studies of CRC survival. Together, these results support the hypothesis that adequate metabolic reserves play an important role in CRC survival, and furthermore suggest that relevant thresholds of adiposity may differ by sex and race/ethnicity. As such, the associations we observed could be due to a detrimental effect of low BMI (even within the normal category) rather than a beneficial effect of overweight/obesity per se, and may therefore be particularly relevant to those at the lower end of the ‘normal’ BMI range.

A strength of this study is the large number of cases with detailed follow-up time, allowing for greater precision and numerous subgroup analyses. Another major strength is the use of prospectively-collected pre-diagnostic BMI, which should reduce the potential for reverse causation due to illness-associated weight loss. Our ability to evaluate different time windows between BMI measurement and diagnosis further speaks to the robustness of our results. These strengths are important since several previous studies of BMI and CRC survival have been criticized for small sample sizes or for the potential for recall bias and reverse causality [6].

One potential limitation of our study was the inability to adjust for treatment received, which would have allowed us to further explore our hypothesis that the stage-dependent association results observed may be due to metabolic capacity to cope with systemic treatment effects. This may be a particular concern because of evidence from studies in other cancer types suggesting that under-dosing of chemotherapy in obese patients negatively impacts survival [45]. We attempted to lessen this limitation by stratifying our analyses by cancer stage at diagnosis, given that individuals within a given cancer stage should receive roughly similar treatment approaches [46]. We were also unable to adjust for potential confounding factors such as physical activity, or account for long-term BMI, changes in BMI over time, or tumor phenotype. Given evidence that certain molecular subtypes of tumors are associated with different survival characteristics [47], future studies will need to explore whether these tumor characteristics affect the association between BMI and CRC survival.

In conclusion, our results show that the association between BMI and CRC survival varies by stage at diagnosis, with higher BMI associated with higher mortality in those with early-stage CRC and lower mortality in those with later-stage disease. These results may suggest interplay between stage at diagnosis, treatment, patient metabolic reserve, and mortality risk. Future studies should further explore these relationships by incorporating tumor subtype, treatment received, and considering additional measurements of body fat and composition.

While maintaining a healthy body weight remains important for lowering the risk of developing CRC, further research is needed to determine what a healthy body weight means in the context of recent disease. Our results suggest that some degree of adiposity may be advantageous for survival once CRC has manifested.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations Used

95% CI	95% Confidence Interval
AJCC	American Joint Committee on Cancer
BMI	Body Mass Index
CRC	Colorectal Cancer
GECCO	Genetics and Epidemiology of Colorectal Cancer Consortium
HPFS	Health Professionals Follow-up Study
HR	Hazard Ratio
NDI	National Death Index
NHS	Nurses' Health Study
PHS	Physicians' Health Study
PLCO	The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial
SEER	Surveillance, Epidemiology, and End Results Program
VITAL	VITamins and Lifestyle Study
WHI	The Women's Health Initiative

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Novelty and Impact

This study evaluated the association of pre-diagnostic body mass index with post-diagnostic survival using data on 2,249 colorectal cancer cases from the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO). Importantly, and in contrast to previous studies, this relationship was found to significantly differ according to cancer stage at diagnosis: higher body mass index was associated with increased mortality among those with early-stage disease, but with decreased mortality among those with late-stage disease.

Table 1

Demographic and Epidemiologic Characteristics of Included Study Participants.

	HPFS	NHS	PHS	PLCO	VITAL	WHI	Total
Total cases [a]	92	134	102	737	178	1006	2249
No. deaths (%)	47 (51)	58 (43)	72 (71)	226 (31)	64 (36)	305 (30)	772 (34)
No. CRC deaths (%)	29 (32)	40 (30)	54 (53)	158 (21)	39 (22)	230 (23)	550 (24)
Median years follow-up	5.5	8.9	5.9	4.7	4.6	3.9	4.5
Sex (% female)	0	100	0	44	46	100	69
Mean age at reference (SD)	65.5 (8.5)	59.7 (6.3)	61.4 (8.7)	64.1 (5.2)	66.0 (6.4)	66.1 (6.6)	64.8 (6.6)
Mean age at diagnosis (SD)	71.5 (8.5)	66.1 (6.2)	67.3 (8.9)	70.2 (5.7)	70.6 (6.6)	71.7 (7.0)	70.6 (6.9)
Smoking status (%)							
Current	5 (05)	22 (16)	10 (10)	75 (10)	17 (10)	71 (07)	200 (09)
Former	47 (51)	55 (41)	63 (62)	330 (45)	98 (55)	450 (45)	1043 (46)
Never	40 (43)	57 (43)	29 (28)	332 (45)	63 (35)	485 (48)	1006 (45)
Body mass index category (%)							
Normal (18.5–24.9)	42 (46)	77 (57)	55 (54)	207 (28)	52 (29)	334 (33)	767 (34)
Overweight (25.0–29.9)	40 (43)	42 (31)	43 (42)	343 (47)	75 (42)	351 (35)	894 (40)
Obese (≥ 30.0)	10 (11)	15 (11)	4 (04)	187 (25)	51 (29)	331 (32)	588 (26)
Stage at diagnosis (%)							
I	30 (33)	32 (24)	24 (24)	225 (31)	59 (33)	328 (33)	698 (31)
II	19 (21)	40 (30)	26 (25)	214 (29)	45 (25)	285 (28)	629 (28)
III	23 (25)	38 (28)	30 (29)	196 (27)	46 (26)	257 (26)	590 (26)
IV	20 (22)	24 (18)	22 (22)	102 (14)	28 (16)	136 (14)	332 (15)
Tumor site (%)							
Distal	34 (37)	43 (32)	40 (39)	184 (25)	46 (26)	248 (25)	595 (26)
Proximal	35 (38)	59 (44)	45 (44)	427 (58)	101 (57)	564 (56)	1231 (55)
Rectal	22 (24)	30 (22)	13 (13)	109 (15)	29 (16)	188 (19)	391 (17)
Not specified	1 (01)	2 (01)	4 (04)	17 (02)	2 (01)	6 (01)	32 (01)

Abbreviations: HPFS, Health Professionals Follow-up Study; NHS, Nurses' Health Study; PHS, Physicians' Health Study; PLCO, The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; VITAL, VITamins and Lifestyle Study; WHI, The Women's Health Initiative.

[a] Represents cases after exclusions (n = 1,051) and missing observations (n = 194).

Table 2

Hazard Ratios for Overall and Colorectal Cancer-Specific Mortality, Adjusted by Cancer Stage at Diagnosis.

Overall Survival				
n (events)	**2,249 (772)**			
	HR[a]	**95% CI**	***P*-value**	***P*-interaction[b]**
Normal (Ref.)				
Overweight	0.85	0.72 – 1.00	**0.049**	0.26
Obese	0.98	0.81 – 1.19	0.86	**0.03**
CRC-specific Survival				
n (events)	2,249 (550)			
	HR[a]	95% CI	*P*-value	*P*-interaction[b]
Normal (Ref.)				
Overweight	0.76	0.63 – 0.93	**0.01**	0.61
Obese	0.84	0.67 – 1.05	0.12	**0.04**

Abbreviations: HR, Hazard Ratio; 95% CI: 95% Confidence Interval.

[a]Adjusted for age at diagnosis, sex, smoking history (current/former/never), study, and cancer stage at diagnosis (I/II/III/IV).

[b]Wald P-value for the interaction term added to the model (BMI*stage).

Table 3

Hazard Ratios for Overall and Colorectal Cancer-Specific Mortality, Stratified by Cancer Stage at Diagnosis.

Overall Survival	**Stage I**			**Stage II**			**Stage III**			**Stage IV**		
n (events)	**698 (108)**			**629 (150)**			**590 (228)**			**332 (286)**		
	HR[a]	**95% CI**	***P*-value**	**HR[a]**	**95% CI**	***P*-value**	**HR[a]**	**95% CI**	***P*-value**	**HR[a]**	**95% CI**	***P*-value**
Normal (Ref.)												
Overweight	1.58	1.00 – 2.50	**0.048**	0.69	0.46 – 1.02	0.07	0.70	0.51 – 0.95	**0.02**	0.92	0.70 – 1.20	0.53
Obese	1.86	1.06 – 3.27	**0.03**	1.36	0.90 – 2.06	0.14	0.90	0.64 – 1.26	0.53	0.76	0.55 – 1.05	0.10
CRC-specific survival	Stage I			Stage II			Stage III			Stage IV		
n (events)	698 (32)			629 (68)			590 (181)			332 (269)		
	HR[a]	95% CI	*P*-value	HR[a]	95% CI	*P*-value	HR[a]	95% CI	*P*-value	HR[a]	95% CI	*P*-value
Normal (Ref.)												
Overweight	1.47	0.61 – 3.54	0.39	0.48	0.25 – 0.90	**0.02**	0.69	0.49 – 0.98	**0.04**	0.87	0.66 – 1.15	0.34
Obese	2.50	0.93 – 6.77	0.07	1.33	0.74 – 2.39	0.33	0.78	0.53 – 1.15	0.21	0.70	0.50 – 0.98	**0.04**

Abbreviations: HR, Hazard Ratio; 95% CI, 95% Confidence Interval.

[a]Adjusted for age at diagnosis, sex, study, and smoking history (current/former/never).