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Explaining the obesity paradox: The association between body composition and colorectal cancer survival (C-SCANS study)

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Abstract

Background—Body composition may partially explain the U-shaped association between BMI and colorectal cancer (CRC) survival.

Methods—Muscle and adiposity at CRC diagnosis and survival were examined in a retrospective cohort using Kaplan Meier curves, multivariable Cox regression, and restricted cubic splines in 3,262 early stage (I-III) male (50%) and female (50%) patients. Sarcopenia was defined using optimal stratification and sex- and BMI-specific cut points. High adiposity was defined as the highest tertile of sex-specific total adipose tissue (TAT). Primary outcomes were overall mortality (OM) and CRC specific mortality (CRCsM).

Results—Forty-two percent of patients were sarcopenic. During 6.0 years of follow-up, 788 deaths occurred, including 433 from CRC. Sarcopenic patients had a 27% (HR 1.27; 95% CI 1.09, 1.48) higher risk of OM, than those who were not sarcopenic. Females with both low muscle and high adiposity had a 64% higher risk of OM (HR 1.64; 95% CI 1.05, 2.57) when compared to females with adequate muscle and lower adiposity. The lowest risk of OM was seen in patients with a BMI between 25-<30-kg/m^2, a range associated with the greatest number of patients (58.6%) who were not at increased risk of OM due to either low muscle or high adiposity.

Conclusions—Sarcopenia is prevalent among non-metastatic CRC patients, and should, along with adiposity be a standard oncological marker.

Impact—Our findings suggest a biological explanation for the obesity paradox in CRC and refute the notion that the association between overweight and lower mortality is due solely to methodological biases.

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Introduction

Although overweight and obesity are associated with a higher risk of developing colorectal cancer (CRC), the association between body mass index (BMI) and CRC survival is U- or J-shaped; the most favorable outcomes are often in those who are overweight or even those with class I obesity (1–3). This is referred to as the obesity paradox (4). Some posit that these survival benefits are due to selection bias, uncontrolled confounding, and/or reverse causality (5–7). Others argue that extra weight provides the necessary muscle and adipose reserves (8) to counteract the negative metabolic consequences of cancer and cancer-associated treatments.

Unfortunately, BMI, a measure readily available in CRC patients, does not accurately measure either adiposity or muscle mass (9). The few studies that have been able to directly measure body composition have demonstrated that low muscle mass (10–16) or higher visceral adiposity (17–23) are associated with worse survival. Most of these studies, however, have been very small (n<250) and conducted in advanced cancer patients with poor prognosis. Understanding the role body composition plays in non-metastatic patients, for whom prognosis is generally favorable, may lead to earlier, more effective interventions. This is the largest investigation of muscle mass and adiposity, measured at diagnosis, on overall mortality (OM) and CRC- specific mortality (CRCsM). This representative sample of early stage CRC patients (n=3,276), with its ability to distinguish these body composition compartments may help to resolve the obesity paradox.

Materials and Methods

Cohort and End Points

This retrospective cohort study included patients from Kaiser Permanente Northern California (KPNC), an integrated managed health care organization. A comparison of KPNC data and Bay Area metropolitan statistical area census data demonstrates that KPNC is closely representative of the general population in a number of demographic and socioeconomic categories, including gender and race/ethnicity but members have a slightly higher education and income level (24). This study, Colorectal Cancer- Sarcopenia And Near-term Survival (C-SCANS), included all patients diagnosed at KPNC between 2006–2011 with stage I-III invasive CRC who had a surgical resection (n=4,465). We excluded 693 patients who did not have an abdominal or pelvic CT scan, collected as part of the routine staging workup, which was needed to measure body composition. Exclusions also included 411 participants without a valid weight measure around the CT scan and 99 whose scans were unreadable due to poor image quality. This left 3,262 patients in the final analytic sample. Excluded participants were older, had colon versus rectal cancer and had Stage I vs. Stage II or III disease. The study was approved by the KPNC Institutional Review Board.

Deaths were obtained continuously from KPNC electronic mortality files which combine internal data, California state death data, and Social Security Administration data to determine a patient’s vital status. Deaths were considered “CRC-specific” if CRC was listed as an underlying or contributing cause of death on the death certificate.

Body Composition Assessment/CT Image Analysis

"At diagnosis" muscle mass and adipose tissue were measured from a CT scan taken within four months of diagnosis and before any chemotherapy or radiation (median = 0.25 months, range from -2.0 to 3.8 months); 83% of the scans occurred prior to surgery. A single, trained researcher (JX) quantified the cross-sectional area of muscle and adipose tissue in centimeters squared (cm^2) at the third lumbar vertebra (L3) discriminating components by tissue-specific Hounsfield Units ranges using SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada) (25). Single-slice abdominal cross-sectional areas at the L3 vertebra are strongly correlated with whole body volumes of muscle mass and adipose tissue (26). Skeletal muscle areas included rectus abdominus, erector spinae muscles, quadratus lumborum, psoas, and internal, transverse and external oblique muscle groups. The skeletal muscle index (SMI) was defined as muscle mass at the L3 in cm^2 divided by height in $meters^2$. Adipose tissue was segmented to distinguish separate measures of visceral (intra-abdominal) adipose tissue (VAT), subcutaneous adipose tissue (SAT) and intramuscular adipose tissue (IMAT). Total adiposity (TAT) was measured as the sum of VAT, SAT and IMAT. Fifty images were randomly selected to be quantified by a second trained researcher, within strata defined by age, BMI and vital status. The coefficients of variation (CV%) were 1.2, 2.7 and 1.1 for muscle, SAT and VAT, respectively.

Definition of Sarcopenia

To define sarcopenia, we used optimal stratification, a statistical procedure that selects a cutpoint for a continuous variable (in this instance, the SMI) from a fixed set of possible values, drawn, for this analysis, from sex- and BMI-specific (<30, ≥ 30-kg/m^2) strata. For each candidate cutpoint, the log rank statistic testing the between group difference in overall survival was computed, and the cutpoint that had the maximum absolute value of the log rank statistic was chosen as the optimal cutpoint (27) for establishing presence or absence of sarcopenia. This approach is common for defining low muscle mass in cancer (28, 29).

Covariate Assessment

KPNC electronic data sources, including patients' electronic medical record (EMR) and the Cancer Registry, provided information on height, weight, disease stage, tumor characteristics, surgical procedures, and treatment. Height and weight measured at the clinical visit closest to the diagnosis scan were used to calculate BMI. Pre-diagnosis weight change was defined as the subtraction of diagnosis weight from the weight taken 18 months prior to diagnosis. Demographic factors (age, race/ethnicity and sex), smoking history, and relevant laboratory data were also obtained from the EMR.

Statistical Analysis

In addition to defining sarcopenia as a dichotomous variable (yes/no), muscle mass and TAT were categorized into sex-specific tertiles for analysis; the lowest tertile of TAT and the highest tertile of muscle mass were used as reference groups. We also categorized patients into 4 mutually-exclusive body composition phenotypes based on the presence or absence of low muscle mass and high TAT: 1) "Low muscle" defined as the lowest tertile of muscle mass (<155 cm^2 for men and <103 cm^2 for women); 2) "High adiposity" defined as the

highest tertile of TAT (>463 cm^2 for men and >423 cm^2 for women); 3) “Low muscle and high adiposity”; and 4) “Normal” defined as the highest two tertiles of muscle mass and the lowest two tertiles of adiposity. The “Normal” category, with its adequate muscle mass and lower adipose tissue, also served as the reference group. To examine whether there were differences in effects by specific adiposity compartments, we used the same body composition phenotype categories described above but instead replaced the highest sex-specific tertile of TAT with the highest sex-specific tertile of VAT (>243 cm^2 for men and >136 cm^2 for women) and then separately with SAT (>203 cm^2 for men and >269 cm^2 for women). We assessed associations of sarcopenia and adiposity with time to event. Follow-up began on the date of CRC diagnosis, and continued until death or December 15, 2015, whichever was earlier. Time to failure as a function of sarcopenia and the muscle mass and adiposity variables was evaluated using Kaplan-Meier curves and compared by log-rank tests. Unadjusted and multivariable-adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for risk of mortality associated with sarcopenia or the adiposity variables were estimated using Cox proportional hazards models. Muscle mass tertiles were treated as a continuous score to calculate p for trend.

Covariates were chosen a priori based on previous research and included age at diagnosis, sex, race, stage, treatment, and cancer site. Models were then simultaneously adjusted for muscle mass, adipose tissue, and partitioned BMI with weight from muscle mass and adipose tissue removed.

The existence of nonlinear relationships between sarcopenia and body composition measures and OM were assessed by the addition of restricted cubic splines and use of the likelihood ratio test that compared models with the linear terms only, to those with both linear and cubic spline terms. Effect modification was assessed using cross-product terms for body composition measures and the following covariates: sex; age at diagnosis (<60, 60−<70 and ≥70 years); BMI category (18.5−<25, 25−<30 and ≥30 kg/m^2); weight change prior to diagnosis (stable, 5% loss, 5% gain); cancer stage (I, II/III); tumor site (rectal vs. colon); and chemotherapy (any vs. none); p-values for the corresponding Wald tests are reported.

All statistical analyses were performed using SAS (version 9.3; SAS Institute Inc.). Statistical significance was established with 2-sided tests with α=0.05.

Results

Median follow-up time was 6.0 years (range 0.0–9.9), during which there were 788 deaths, including 433 from CRC. At diagnosis, 42.4% of the participants were sarcopenic with men having a higher prevalence (45.3%) than women (39.5%, p=0.001). Table 1 shows that patients with sarcopenia were older (66.4 years versus 59.8; p<.0001), and more likely to be white (45.3%) or Asian (46.0%), than Black (28.2%) or Hispanic (30.7%), and to have Stage II or III vs. Stage I disease (44.1% vs 38.5% respectively). Other factors associated with sarcopenia included cancer site, smoking status and a neutrophil/lymphocyte ratio ≥5, an indicator of systemic inflammation (30).

Kaplan-Meier curves demonstrated that patients with sarcopenia had worse survival (Figure 1A) than those without sarcopenia (log rank p<0.0001); those with low muscle mass, high adiposity or both high adiposity and low muscle mass had worse survival (Figure 1B) compared to the Normal group (log rank p<0.0001).

Table 2 presents multivariate Cox proportional hazards analyses examining the associations of sarcopenia, muscle mass area and body composition phenotypes with OM and CRCsM. Sarcopenic patients had a 27% (HR 1.27; 95% CI 1.09, 1.48) greater risk of OM and a 46% (HR 1.46; 95% CI 1.19, 1.79) greater risk of CRCsM than those who were not sarcopenic. When muscle mass was alternatively categorized by tertiles, similar results were seen. Those in the lowest tertile of muscle mass had a statistically significant 32% greater risk of OM (HR 1.32; 95% CI 1.07, 1.64) and a 54% greater risk CRCsM (HR 1.54; 95% CI 1.16, 2.05) compared to those in the highest tertile. No significant interactions of the effects of sarcopenia on survival by sex, age, BMI, pre-diagnosis weight change, stage, cancer site, or receipt of chemotherapy (Supplemental Table 1) were observed.

Compared to the Normal group, patients with high adiposity had increased risks of OM (HR 1.21; 1.01, 1.46) and CRCsM (HR 1.28; 95% CI 1.00, 1.64) whereas patients with both low muscle mass and high adiposity had slightly higher risks of both OM (HR 1.40; 95% CI 1.03, 1.90) and CRCsM (HR 1.79; 95% CI 1.20, 2.67) than those with low muscle mass alone. However, findings varied by sex. In men, neither those with high adiposity nor those with both low muscle mass and high adiposity had significantly higher OM or CRCsM. In contrast, women characterized as having high adiposity (HR 1.30; 95% CI 0.99, 1.71) and those characterized as having both low muscle mass and high adiposity (HR 1.64; 95% CI 1.05, 2.57) had a higher risk of OM. Results were more elevated for CRCsM.

When categorizing patients into body composition phenotypes by their level of VAT or SAT (Supplemental Table 2) patients with high VAT alone had marginally significant increased risk (HR 1.22; 95% CI 0.99, 1.49), whereas patients with high SAT alone had no increased risk (HR 0.94; 95% CI 0.77, 1.15).

Figure 2 displays restricted cubic splines that allow for non-linear relationships of SMI and TAT with OM, stratified by sex. The SMI association with OM among men appeared to be U-Shaped for SMI (p-value for curvature 0.05). For women, the association curve for SMI was linear, and a statistical test for curvature confirmed no evidence of non-linearity (p-value for curvature 0.88). TAT shows non-linear associations with OM in both men and women (p-values for curvature 0.0002 and 0.0001 respectively). In men, compared to the reference of the median TAT value (381 cm^2), there is no evidence of a difference in risk of OM for those with TAT values between the 50th and 90th percentile range of the distribution; TAT is associated with increased risk of death only for those at the very high end (TAT values >675 cm^2; 91^{st} percentile) of the population distribution. In contrast, women with TAT slightly above the median had a higher risk of death compared to women at the reference median TAT value (332 cm^2), and the risk of death rose with higher TAT.

The restricted cubic spline displayed in Figure 3A demonstrates that the lowest risk of OM is between a BMI of 25-<30 kg/m^2. As shown in the accompanying histogram (Figure 3B),

when we graph the body composition phenotypes, the majority of patients in the overweight range (BMI of 25-<30 kg/m^2) are in the Normal group, having adequate muscle mass and lower adiposity (58.6%). Only 22.1% had low muscle mass, 13.3% had high adiposity, and 6.0% were characterized by both low muscle mass and high adiposity (Supplemental Table 3).

Discussion

These results show definitively, for the first time, that low muscle mass or sarcopenia is highly prevalent among non-metastatic colorectal cancer patients, and that the adverse effect of low muscle mass is not restricted to CRC patients with cachexia but threatens survival in non-metastatic CRC patients as well. Forty-five % of newly diagnosed men and 40% of women were sarcopenic; and compared to those without sarcopenia, they had an almost 30% increased risk of OM and 50% increased risk of CRCsM. This prevalence is considerably higher than reported in healthy individuals of similar age (~15%) (31). This study is also the first to establish sarcopenia risk cutpoints derived from a large population-based sample that can be applied to newly diagnosed Stage I-III CRC patients to identify those with low muscle mass. Lastly, the body composition findings suggest a compelling explanation for the obesity paradox in CRC and refute the notion that the observed association between overweight and a lower mortality risk is due solely to methodological biases.

Our findings are consistent with the few other existing studies in colorectal patients of the impact of muscle mass on survival outcomes, most of which have been small and in advanced-stage patients. The largest study prior to the current study (n=805) (14), which included a sample of patients with primary colorectal cancer who underwent colorectal resection, reported that sarcopenia was independently associated with both disease-free survival (HR 1.53; 95% CI 1.06, 2.39) and overall survival (HR 1.75; 95% CI 1.25, 2.31). Several additional studies (10–12, 15, 16) also consistently demonstrated that sarcopenia predicted significantly worse survival. Furthermore, a recent meta-analyses of 7,843 patients with solid tumors from 38 studies, showed sarcopenia was associated with poor OM (HR = 1.44; 95% CI 1.32, 1.56; $p < 0.001$) (32). Several tumor- and treatment-specific factors likely lead to increased muscle catabolism and progressive muscle loss in CRC. Multiple biological mechanisms provide support for this hypothesis. For example, muscle wasting in cancer patients results from nutrient mobilization of skeletal tissue, both directly as amino acids and indirectly as glucose derived from the exploitation of liver gluconeogenesis that reaches the tumor through the bloodstream (33). For a long time, this process has been merely considered to occur in end-stage tumors. However, Mayers et al. (34) recently demonstrated that up to 2–5 years before pancreatic cancer diagnosis, when disease is undetectable, pancreatic tumor cells mobilize amino acids derived from skeletal muscle to support tumor growth. Surgical resection for CRC also represents a time when patients may be subject to further muscle loss due to bed rest and decreased activity. After 7 days of bed rest, Ferrando et al. (35) reported a significant 3% decrease in MRI thigh muscle volume and Tanner et al. (36) reported a loss of ~4% leg lean mass. Lastly, several studies have proposed that cancer therapy may have direct effects on skeletal muscle or may cause a pro-inflammatory state that leads to proteolysis. Recent work highlights significant skeletal muscle loss during the course of chemotherapy (11, 37, 38).

Notably the current study suggests that while high levels of TAT may increase mortality risk, the level of TAT at which risk occurs may differ for men and women. TAT does not appear to increase risk significantly until approximately the 90th percentile of the distribution in men whereas for women the risk appears to increase close to the median. This could be due to the observation that the ratio of muscle mass to adipose tissue is higher for men at any given SMI than for women, which could suggest that higher muscularity is protective unless adiposity is extremely high. Sex differences in mortality risk associated with adiposity deserve further exploration. Few studies have measured adiposity directly and examined associations with cancer survival and these have been characterized by small sample sizes (17–23). Six out of 7 reported an inverse association between VAT and either overall or disease-specific survival; however, in one of these studies, lower survival was apparent only in Stage 2 patients while in Stage 3 patients there was higher survival associated with higher VAT (22). These studies are in agreement with our data which demonstrate that the observed association of high TAT with higher OM is mostly due to those with high VAT and not high SAT.

Previously published data from our study population demonstrates that a BMI in the overweight range of 25 and <30 kg/m^2 is associated with the lowest mortality risk (3). Strikingly within this BMI range, body composition appears to explain why a BMI higher than normal is associated with the lowest mortality: 72% of patients in that BMI category had adequate muscle reserves, presumably providing the capacity to counter the catabolic consequences of both tumor growth and cancer treatments, and only 19% had adiposity levels sufficiently high to impact risk of survival. These results do not imply that a BMI in the range of 25-<30 kg/m^2 is ideal for everyone for optimal cancer outcomes. Rather, the findings demonstrate that BMI is a poor surrogate for both muscle mass and adiposity, and should not be used to assess survival risk or target patients for interventions. More direct measures of body composition are needed to assess nutritional status.

Several limitations must be noted. First, our study is observational. As in all observational studies, there is the possibility of unmeasured confounding. However, to fully account for our findings these unmeasured factors would need to be quite large (39). Our results were robust to adjustment for numerous potential confounding variables including tumor and medical characteristics and in sensitivity analyses, exercise. Second, reverse causality (a more aggressive cancer leading to lower muscle mass) may still in part be responsible for our observed associations. However, we observed consistent findings by stage, whether or not we eliminated early mortality, and among those with or without weight loss prior to diagnosis. Third, we had to exclude approximately 15% of potentially eligible patients due to the lack of a diagnostic CT scan. Those patients who did not receive a scan were more likely to have colon versus rectal cancer, were older and earlier stage and likely perceived by their physicians to be lower risk. However, there still remains considerable representation across stage site and age among those included in the analyses. Finally, we used a data-driven approach to define sarcopenia, an approach frequently used in studies of cancer survival; however, our results are similar whether we categorize patients into tertiles of muscle or examined muscle continuously, suggesting a dose-response relationship present regardless of the choice of cut-point.

In conclusion, the results of our work and that of others in CRC (10–16) and other cancers (40, 41), show that the prevalence of sarcopenia is high in these patients and is associated with poorer survival. Thus, information on muscle derived from CT analysis provides significant prognostic information, and should be considered, along with adiposity as a standard oncologic biomarker (42). Inadequate muscle reserves occur not only in end-stage disease where sarcopenia and cancer cachexia are well-described, but represent an occult problem present in newly diagnosed non-metastatic cancer patients across all levels of BMI. The establishment of a new sarcopenia ICD-10 Code represents a major recognition of its importance and need for treatment. CT scans are readily available for colorectal cancer patients for both staging and surveillance, commercially available programs (25) are currently available to assess body composition, and abbreviated (43) and automated (44) assessment methods are emerging. In the era of precision medicine, we need to move beyond BMI and utilize more precise body composition techniques to assess muscle (45) mass, as well as directly measure adiposity to help to guide treatment plans to optimize survival outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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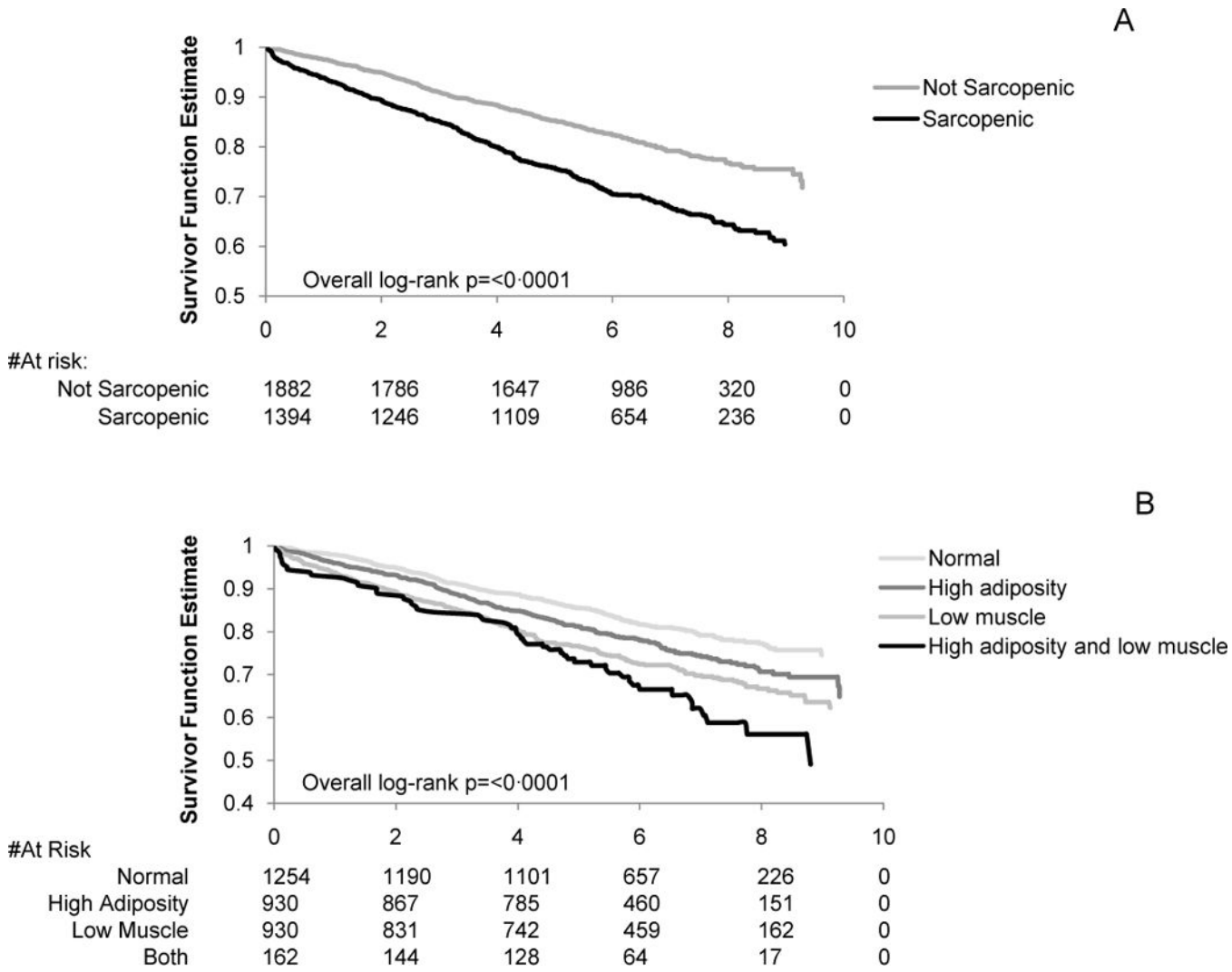

Figure 1.

A Kaplan-Meier curves for sarcopenia and all-cause mortality

B Kaplan-Meier curves for body composition phenotypes and all-cause mortality

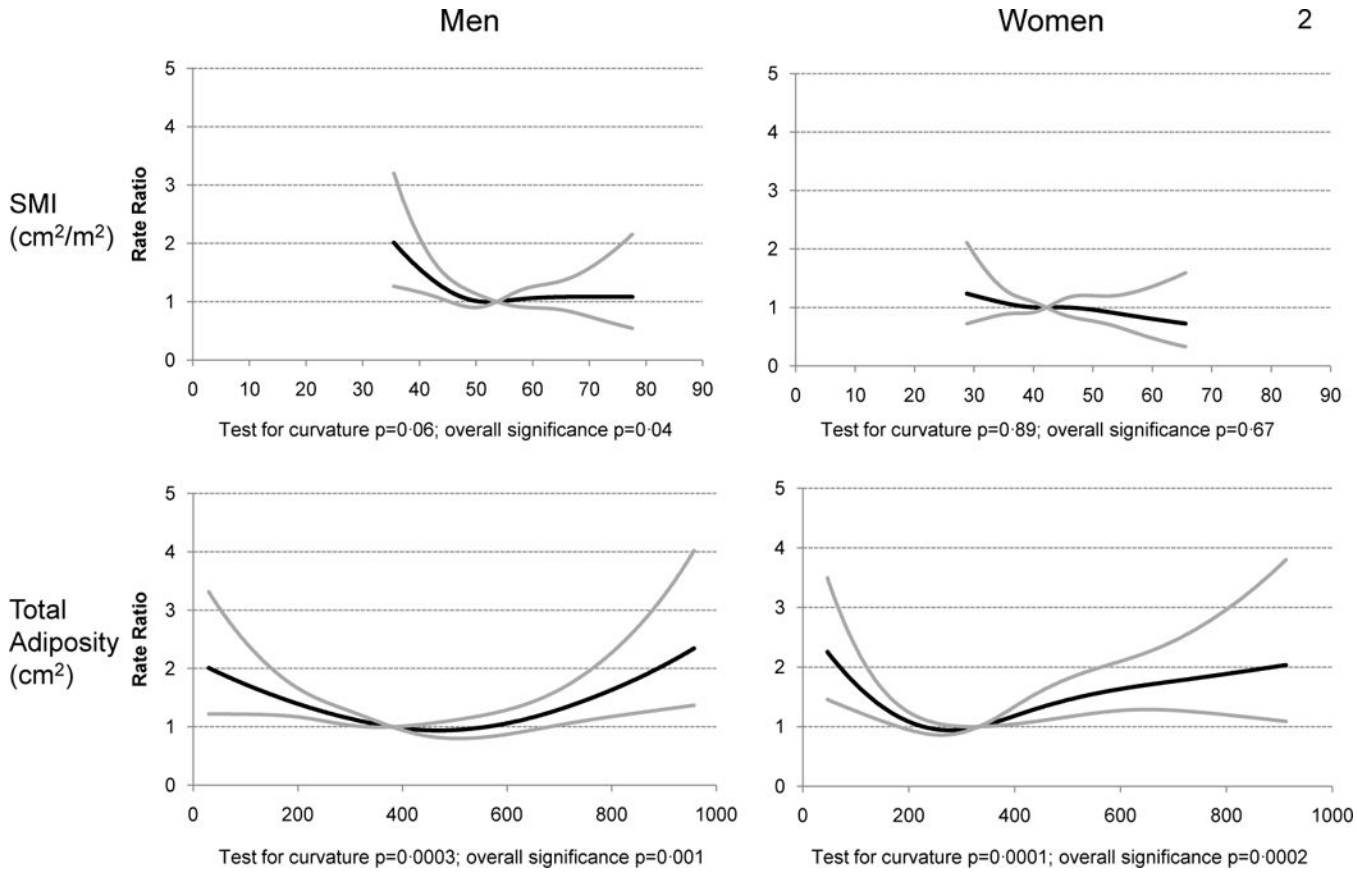

Figure 2.

Restricted cubic splines for body composition and overall mortality, by sex. Reference is sex-specific median; graphs have 4 knots and are truncated at 1st and 99th percentiles; adjusted for age, stage, site, treatment and partitioned BMI. SMI graphs additionally adjusted for total adiposity in tertiles; total adiposity graphs adjusted for muscle in tertiles.

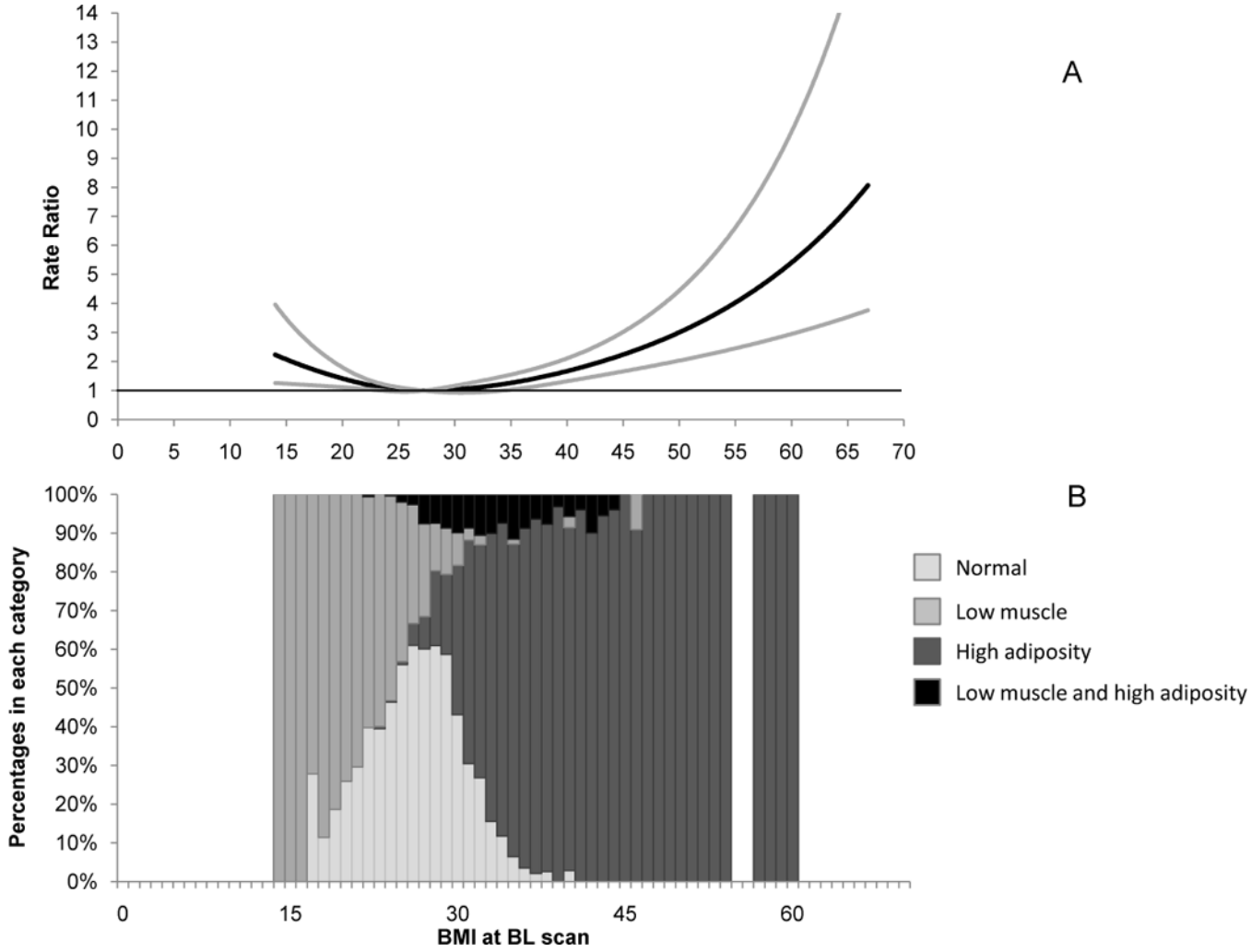

Figure 3.

A Restricted cubic spline for BMI has 4 knots and a reference value of 27; adjusted for age, sex, race, stage, grade, site, treatment, pre-diagnosis BMI, smoking and physical activity. Reference value is the overall median (27.2); test for curvature $p < 0.0001$; overall significance $p < 0.0001$.

B Histogram for body composition phenotypes by BMI

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Table 1

Characteristics of the Cohort, by Sarcopenia Status

	Total		Sarcopenic*		Not Sarcopenic		
	n=3,262		n=1,383		n=1,879		
	n	Row%	n	Row%	n	Row%	p-value
Age at diagnosis, years							
Mean (SD)	62.6 (11.4)		66.4 (10.4)		59.8 (11.3)		<0.0001
Age at diagnosis							
<60 years	1238	100.0	332	26.8	906	73.2	<0.0001
60-<70 years	941	100.0	420	44.6	521	55.4	
>=70 years	1083	100.0	631	58.3	452	41.7	
Sex							
Male	1634	100.0	740	45.3	894	54.7	0.001
Female	1628	100.0	643	39.5	985	60.5	
Race/ethnicity							
White	2118	100.0	960	45.3	1158	54.7	<0.0001
Black	234	100.0	66	28.2	168	71.8	
Hispanic	365	100.0	112	30.7	253	69.3	
Asian/PI	520	100.0	239	46.0	281	54.0	
Other	21	100.0	5	23.8	16	76.2	
AJCC Stage							
I	979	100.0	377	38.5	602	61.5	0.003
II or III	2283	100.0	1006	44.1	1277	55.9	
Site of cancer							
Rectal	947	100.0	353	37.3	594	62.7	<0.0001
Colon	2315	100.0	1030	44.5	1285	55.5	
Weight change in 18m pre-diagnosis							
Stable	1150	100.0	484	42.1	666	57.9	0.22
>=5% loss	548	100.0	255	46.5	293	53.5	
>=5% gain	137	100.0	60	43.8	77	56.2	
Smoking status							

	Total		Sarcopenic*		Not Sarcopenic		
	n=3,262		n=1,383		n=1,879		
	n	Row %	n	Row%	n	Row%	p-value
Never	1516	100.0	602	39.7	914	60.3	0.01
Former	1347	100.0	608	45.1	739	54.9	
Current	396	100.0	173	43.7	223	56.3	
Charlson comorbidity score							
0	1770	100.0	744	42.0	1026	58.0	0.48
1–2	946	100.0	416	44.0	530	56.0	
>=3	321	100.0	144	44.9	177	55.1	
Neutrophil/Lymphocyte Ratio							
<5	2250	100.0	880	39.1	1370	60.9	<0.0001
>=5	919	100.0	466	50.7	453	49.3	

*SMI cutpoints for sarcopenia:	Men	Women
Normal and overweight	<52.3	<38.6
Obese	<54.3	<46.6

Table 2

Body Composition and Mortality

		Overall Mortality		CRC-specific Mortality	
	At Risk	**#Events**	**HR (95% CI)**	**#Events**	**HR (95% CI)**
Sarcopenic					
No	1879	362	Referent	200	Referent
Yes	1383	426	1.27 (1.09, 1.48)	233	1.46 (1.19, 1.79)
Muscle (cm^2)					
Low tertile 1	1086	328	1.32 (1.07, 1.64)	176	1.54 (1.16, 2.05)
Middle tertile 2	1088	249	1.13 (0.93, 1.37)	135	1.19 (0.92, 1.55)
High tertile 3	1088	211	Referent	122	Referent
p for trend			0.01		0.003
Body composition phenotypes					
Normal	1251	239	Referent	134	Referent
Low muscle	925	272	1.33 (1.10, 1.61)	144	1.46 (1.13, 1.88)
High adiposity	925	221	1.21 (1.01, 1.46)	123	1.28 (1.00, 1.64)
Low muscle and high adiposity	161	56	1.40 (1.03, 1.90)	32	1.79 (1.20, 2.67)
Body composition phenotypes, AMONG MEN					
Normal	637	130	Referent	78	Referent
Low muscle	453	137	1.34 (1.02, 1.74)	68	1.30 (0.91, 1.87)
High adiposity	452	110	1.13 (0.87, 1.46)	57	1.08 (0.76, 1.52)
Low muscle and high adiposity	92	30	1.25 (0.82, 1.90)	16	1.33 (0.76, 2.34)
Body composition phenotypes, AMONG WOMEN					
Normal	614	109	Referent	56	Referent
Low muscle	472	135	1.38 (1.06, 1.81)	76	1.69 (1.17, 2.45)
High adiposity	473	111	1.30 (0.99, 1.71)	66	1.56 (1.09, 2.25)
Low muscle and high adiposity	69	26	1.64 (1.05, 2.57)	16	2.62 (1.48, 4.65)

Models adjusted for age at dx (continuous), sex (ref=Men), race (ref=White), stage (ref=I), chemotherapy (ref=No), radiation (ref=No), site of cancer (ref=Rectal) and partitioned BMI. Sarcopenia and muscle models adjusted for total adiposity in tertiles (ref=Low).

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