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The Association of Abdominal Adiposity With Mortality in Patients With Stage I–III Colorectal Cancer

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Abstract

Background: The quantity and distribution of adipose tissue may be prognostic measures of mortality in colorectal cancer patients, and such associations may vary by patient sex.

Methods: This cohort included 3262 stage I–III colorectal cancer patients. Visceral and subcutaneous adipose tissues were quantified using computed tomography. The primary endpoint was all-cause mortality. Restricted cubic splines estimated statistical associations with two-sided *P* values.

Results: Visceral adipose tissue was prognostic of mortality in a reverse L-shaped pattern (nonlinear *P* = .02); risk was flat to a threshold (~260 cm²) then increased linearly. Subcutaneous adipose tissue was prognostic of mortality in a J-shaped pattern (nonlinear *P* < .001); risk was higher at extreme (<50 cm²) but lower at intermediate values (>50 to ≤560 cm²). Patient sex modified the prognostic associations between visceral adipose tissue (*P*_{interaction} = .049) and subcutaneous adipose tissue (*P*_{interaction} = .04) with mortality. Among men, visceral adiposity was associated with mortality in a J-shaped pattern (nonlinear *P* = .003), whereas among women, visceral adiposity was associated with mortality in a linear pattern (linear *P* = .008). Among men, subcutaneous adiposity was associated with mortality in an L-shaped pattern (nonlinear *P* = .01), whereas among women, subcutaneous adiposity was associated with mortality in a J-shaped pattern (nonlinear *P* < .001).

Conclusions: Visceral and subcutaneous adipose tissue were prognostic of mortality in patients with colorectal cancer; the shape of these associations were often nonlinear and varied by patient sex. These results offer insight into the potential biological mechanisms that link obesity with clinical outcomes in patients with cancer, suggesting that the dysregulated deposition of excess adiposity is prognostic of mortality.

Body mass index (BMI) is a surrogate measure for total body adiposity (1). In a pooled analysis of 25 291 patients with early-stage colon cancer, men with class II or III obesity (BMI ≥35.0 kg/m²) were 16% more likely to die compared with men of normal weight (BMI 18.5–24.9 kg/m²); however, no such association was observed in women (2). BMI does not distinguish muscle from adiposity, nor does it differentiate visceral and subcutaneous adipose tissue regions (3). Men preferentially store adiposity viscerally, whereas women store adiposity subcutaneously (4). Visceral adiposity secretes a variety of protumorigenic metabolites relative to subcutaneous adiposity (5–7), which may

explain, in part, why BMI is prognostic in men but not in women (8).

The quantity and distribution of adipose tissue may be powerful prognostic measures of mortality in patients with colorectal cancer (9,10). However, studies to date have offered conflicting insight (11), concluding that excess visceral adiposity increases (12), decreases (13), or has no influence (14,15) on the risk of poor clinical outcomes. Emerging evidence also suggests that excess subcutaneous adiposity decreases the risk of poor clinical outcome (16,17). Adiposity is correlated with muscle, and it is not known if the prognostic effects of adipose tissue

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quantity and distribution are independent of muscle (18). The current study tested the hypothesis that visceral and subcutaneous adipose tissue, measured using abdominal computed tomography (CT) imaging, are prognostic of mortality in 3262 patients with stage I–III colorectal cancer and that such prognostic associations are modified by patient sex.

Methods

Study Population and Design

The cohort—Colorectal, Sarcopenia, Cancer and Near-term Survival—was derived from the Kaiser Permanente Northern California (KPNC) cancer registry, with ascertainment of all patients diagnosed with stage I–III invasive colorectal cancer between the years 2006 and 2011, age 18–80 years, who underwent surgical resection for colorectal cancer (n = 4465). We excluded 693 patients without abdominal or pelvic CT images, 411 patients without valid measures of body mass, and 99 patients whose CT images were unreadable because of poor image quality. The final analytic sample included 3262 patients (Supplementary Figure 1, available online). A waiver of written informed consent was obtained by the study investigators. This study was approved by the KPNC and University of Alberta institutional review boards.

Measures of Body Composition

Height (meters) and weight (kilograms) were measured at the time of diagnosis by medical assistants per KPNC clinic standards. BMI was calculated as kilograms per square meter of height (kg/m^2). Body composition was measured using CT images originally collected for clinical purposes with sliceomatic software (V5.0, TomoVision, Montreal, Canada). A single-slice transverse image at the third lumbar vertebra was used, because tissue cross-sectional areas at this lumbar region correlate with whole-body (19) and visceral and subcutaneous tissue volumes both in men and women (20). Tissues were demarcated with a semiautomated procedure using Hounsfield Unit thresholds of -29 to 150 for muscle tissue, -150 to -50 for visceral adipose tissue, and -190 to -30 for subcutaneous adipose tissue. A random subsample of 50 CT images was analyzed by two investigators blinded to outcome, and the remaining images were analyzed by a single trained investigator blinded to outcome. The coefficients of variation for visceral adipose tissue area and subcutaneous adipose tissue area were 1.1% and 2.7%, respectively (21).

Covariates

The KPNC electronic medical record was used to obtain baseline information on age, sex, race and ethnicity, and smoking history. The KPNC cancer registry was used to obtain information on the anatomical site of cancer, cancer stage, and the administration of chemotherapy and radiation. Conditions from the Charlson comorbidity index were obtained from the electronic medical record with a 36-month lookback interval from the time of cancer diagnosis (22). The above-described covariate data were 99.9% complete. The measurement of physical activity was implemented across KPNC beginning in October 2009; consequently, only 447 (13.7%) of our cohort had physical activity measures available from 36 months before colorectal cancer diagnosis and up to 12 months after diagnosis. Sensitivity

analyses were conducted including physical activity measures as a covariate. Additional sensitivity excluded patients who had a BMI classified as underweight at colorectal cancer diagnosis ($<18.5 \text{ kg}/\text{m}^2$).

Study Outcomes

The primary study outcome was all-cause mortality, defined as the time from CT image acquisition to death from any cause. The secondary study outcome was colorectal cancer-specific mortality, defined as the time from CT image acquisition to death attributable to colorectal cancer. Deaths were identified from the California state death registry, National Death Index using Social Security Administration data, and KPNC electronic mortality files through December 31, 2016. Deaths were classified as cancer specific if colorectal cancer was documented as an underlying or contributing cause of death on the death certificate through January 31, 2015.

Statistical Analysis

Investigators often model visceral and subcutaneous adipose tissue using categorical variables. However, categorization induces discontinuities in mortality risk between exposure categories that reduce statistical power and are often difficult to justify biologically and interpret clinically. In contrast to prior studies, we modeled visceral and subcutaneous adipose tissue as continuous variables using restricted cubic splines. Cubic splines accommodate nonlinearity and provide statistically efficient and visually intuitive descriptions of prognostic associations (23). Model parsimony and the Akaike information criterion were used to select the optimal number of knots for visceral and subcutaneous adipose tissue. In the absence of available literature, knot locations could not be biologically prespecified and were based on default locations using data-derived quantities (23).

Multivariable-adjusted Cox proportional hazards models were used to evaluate associations between baseline visceral and subcutaneous adipose tissue and mortality risk. Models were adjusted for age, race and ethnicity, cancer site, cancer stage, chemotherapy, radiation therapy, smoking history, Charlson comorbidity index, and height. In addition to muscle area, we simultaneously adjusted statistical models for visceral adipose tissue and subcutaneous adipose tissue to evaluate their independent effects. Linearity and nonlinearity were inspected visually using spline plots and examined statistically using likelihood ratio tests (23). The assumption of proportional hazards was examined by visual inspection of graphical log-log plots and tested statistically in a generalized linear regression of the scaled Schoenfeld residuals on time (24). Sensitivity analyses that included physical activity as a covariate used the missing-indicator method (25). The Pearson correlation coefficient was used to quantify the strength of the association between visceral and subcutaneous adipose tissues.

Effect modification was examined by including the multiplicative interaction terms in the regression models and examined using the likelihood ratio test. Based on prior studies that identified sex-by-BMI interactions (2,26), sex was prespecified as the primary effect modifier of interest. Baseline characteristics were compared between men and women using the χ^2 test for categorical variables and the *t* test for continuous variables. In post hoc analyses, we also examined the following subgroups: age, cancer site, cancer stage, smoking history, and muscle

Table 1. Baseline demographic, disease, behavioral, and anthropometric characteristics overall and stratified by sex

Characteristic	Overall cohort (N = 3262)	Sex stratified		P*
		Men (N = 1634)	Women (N = 1628)	
Mean age (SD), y	62.6 ± 11.4	62.0 ± 11.3	63.2 ± 11.5	.002
Race, no. (%)				.59
White	2118 (65.0)	1063 (65.1)	1055 (64.8)	
Asian	520 (16.0)	261 (16.0)	259 (15.9)	
Hispanic	365 (11.2)	193 (11.8)	172 (10.6)	
Black	234 (7.2)	105 (6.4)	129 (7.9)	
Other or unknown	25 (0.6)	12 (0.7)	13 (0.8)	
Site, no. (%)				<.001
Colon	2315 (71.0)	1082 (66.2)	1233 (75.7)	
Rectum	947 (29.0)	552 (33.8)	395 (24.3)	
Stage, no. (%)				.18
I	979 (30.0)	501 (30.7)	478 (29.4)	
II	1030 (31.6)	531 (32.5)	499 (30.6)	
III	1253 (38.4)	602 (36.8)	651 (40.0)	
Chemotherapy, no. (%)	1703 (52.2)	866 (53.0)	837 (51.4)	.36
Radiation, no. (%)	506 (15.5)	312 (19.1)	194 (11.9)	<.001
Smoking history, no. (%)				<.001
Never	1516 (46.5)	634 (38.8)	882 (54.2)	
Former	1347 (41.3)	771 (47.2)	576 (35.4)	
Current	396 (12.2)	226 (13.8)	170 (10.4)	
Unknown	3 (0.1)	3 (0.2)	0 (0.0)	
Charlson comorbidity index, no. (%)				.32
0	1995 (61.2)	981 (60.0)	1014 (62.3)	
1	946 (29.0)	482 (29.5)	464 (28.5)	
≥2	321 (9.8)	171 (10.5)	150 (9.2)	
Mean height (SD), m	1.69 ± 0.10	1.76 ± 0.08	1.62 ± 0.07	<.001
Mean body mass (SD), kg	80.9 ± 20.6	88.7 ± 19.2	73.4 ± 19.2	<.001
Mean body mass index (SD), kg/m ²	28.1 ± 6.0	28.3 ± 5.2	27.9 ± 6.7	.09
Mean muscle area (SD), cm ²	140.7 ± 38.2	168.6 ± 30.6	112.7 ± 20.3	<.001
Mean visceral adipose tissue area (SD), cm ²	155.7 ± 110.0	201.3 ± 116.2	110.0 ± 80.6	<.001
Mean subcutaneous adipose tissue area (SD), cm ²	212.6 ± 120.3	187.4 ± 105.3	237.8 ± 128.9	<.001

*The χ^2 test was used to compare distributions of categorical variables and a t test for distributions of continuous variables. All statistical tests were two-sided.

area. Because of known limitations in statistical power, the threshold for statistical significance for interactions was prespecified at P less than .10 (27). To conclude the presence of effect modification, a statistically significant likelihood ratio test P value and clinically meaningful visual differences in effect size estimates from the spline plots were required (28). All statistical tests were two-sided.

Results

Characteristics of the Study Cohort

The average (SD) age of the 3262 participants was 62.6 (11.4) years, and 49.9% were women (Table 1). Baseline CT images were obtained a median of 6 days (interquartile range = 0–12 days) after biopsy-proven diagnosis of colorectal cancer. During a median follow-up of 6.9 years (interquartile range = 5.3–8.4 years), 879 (26.9% of the cohort) deaths occurred, with 451 (51.3% of all deaths) attributable to colorectal cancer (Supplementary Table 1, available online).

The median BMI was 27.2 kg/m² (range = 14.0–59.6 kg/m²), muscle area was 135.9 cm² (range = 60.3–319.6 cm²), visceral adipose tissue was 138.6 cm² (range = 0.1–676.7 cm²), and subcutaneous adipose tissue was 184.9 cm² (range = 0.0–931.1 cm²). Visceral and subcutaneous adipose tissue were

moderately and positively correlated ($r=0.37$, 95% CI = 0.34 to 0.40, $P < .001$). Demographic, clinical, and behavioral characteristics were associated with visceral and subcutaneous adipose tissue area (Supplementary Table 2, available online).

Prognostic Effects of Adipose Tissue Distribution on Mortality

Visceral adipose tissue was prognostic of all-cause mortality in a reverse L-shaped pattern (nonlinear $P = .02$); risk was flat to a threshold (~ 260 cm²), then increased linearly (Figure 1; Supplementary Table 3, available online). Subcutaneous adipose tissue was prognostic of all-cause mortality in a J-shaped pattern (nonlinear $P < .001$); risk was higher at the extreme (< 50 cm²) but lower at intermediate values (> 50 to ≤ 560 cm²; Supplementary Table 4, available online). Subcutaneous adipose tissue (nonlinear $P = .02$) but not visceral adipose tissue (linear $P = .24$, nonlinear $P = .32$) was prognostic of colorectal cancer-specific mortality (Supplementary Figure 2, available online). Sensitivity analysis that adjusted for physical activity did not substantively alter the shape or magnitude of the above-described effect estimates (Supplementary Figure 3, available online). The exclusion of 61 (1.9%) patients with underweight BMI (< 18.5 kg/m²) did not substantively alter the shape or magnitude of the above-described effect estimates.

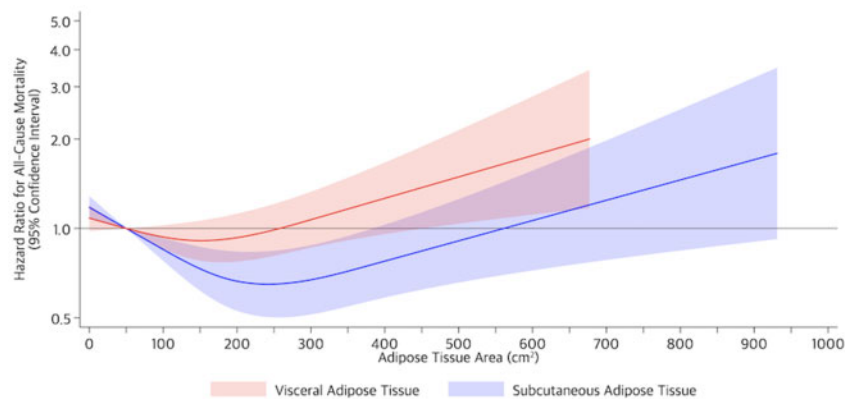


Figure 1. Risk of all-cause mortality on the relative hazard scale in 3262 patients with colorectal cancer. Shaded regions indicate 95% confidence bands for risk of mortality as a function of visceral (red) and subcutaneous (blue) adipose tissue area. Estimates are adjusted for age, sex, race and ethnicity, cancer site, cancer stage, chemotherapy, radiation therapy, smoking history, Charlson comorbidity index, height, muscle area, subcutaneous adipose tissue area (for visceral adipose tissue area models), and visceral adipose tissue area (for subcutaneous adipose tissue area models).

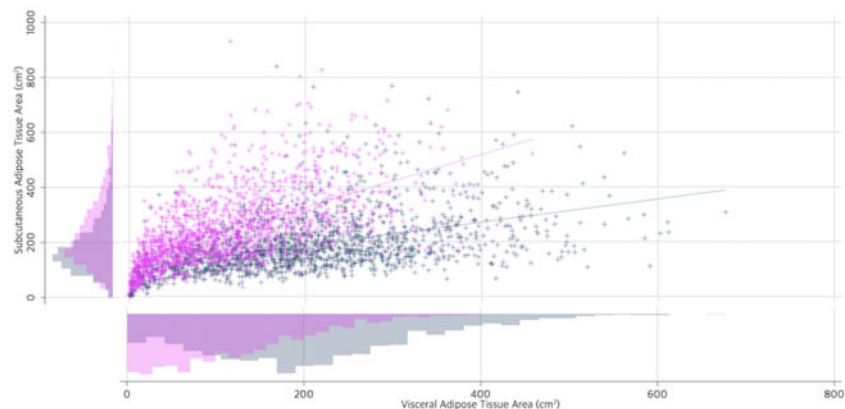


Figure 2. Distribution and correlation between visceral adipose tissue area and subcutaneous adipose tissue area among 3262 men (navy blue) and women (magenta) with colorectal cancer.

Patient Sex Modified the Prognostic Effects of Adipose Tissue Distribution on Mortality

Analyses stratified by patient sex demonstrated that men had more visceral adipose tissue (+91.3 cm², 95% CI = 84.4 to 98.2 cm², $P < .001$) and less subcutaneous adipose tissue (−50.4 cm², 95% CI = −58.5 to −42.3 cm², $P < .001$) than women. The correlation between visceral and subcutaneous adipose tissue was moderate among men ($r = 0.47$, 95% CI = 0.43 to 0.50, $P < .001$) and women ($r = 0.61$, 95% CI = 0.57 to 0.63, $P < .001$; **Figure 2**).

Patient sex modified the prognostic association of visceral adipose tissue and all-cause mortality ($P_{\text{interaction}} = .049$). Among men, visceral adiposity was associated with mortality in a J-shaped pattern (nonlinear $P = .003$), whereas among women, visceral adiposity was associated with mortality in a linear pattern (linear $P = .008$; **Figure 3**). Patient sex modified the prognostic association of subcutaneous adipose tissue and all-cause mortality ($P_{\text{interaction}} = .04$). Among men, subcutaneous adiposity was associated with mortality in an L-shaped pattern (nonlinear $P = .01$), whereas among women, subcutaneous adiposity was associated with mortality in a J-shaped pattern (nonlinear $P < .001$). Patient sex did not modify the prognostic association between visceral adipose tissue ($P_{\text{interaction}} = .44$) or subcutaneous adipose tissue ($P_{\text{interaction}} = .39$) with colorectal

cancer-specific mortality (**Supplementary Figure 4**, available online). Sensitivity analysis that adjusted for physical activity did not substantively alter the shape or magnitude of the above-described effect estimates (**Supplementary Figure 5**, available online). The exclusion of 61 (1.9%) patients with underweight BMI (<18.5 kg/m²) at colorectal cancer diagnosis did not substantively alter the shape or magnitude of the above-described effect estimates.

Age, cancer site, cancer stage, smoking history, and muscle area did not modify the prognostic associations of visceral and subcutaneous adipose tissue with mortality (results not shown).

Discussion

In this population-based cohort study of 3262 patients with stage I–III colorectal cancer, abdominal adipose tissue quantity and distribution were prognostic of all-cause mortality. The shapes of these associations were generally nonlinear and modified by patient sex. Among men, larger quantities of abdominal subcutaneous adipose tissue were associated with a higher risk of mortality, whereas among women, larger quantities of abdominal visceral adipose tissue were associated with an increased risk of mortality. Conversely, among men, moderate

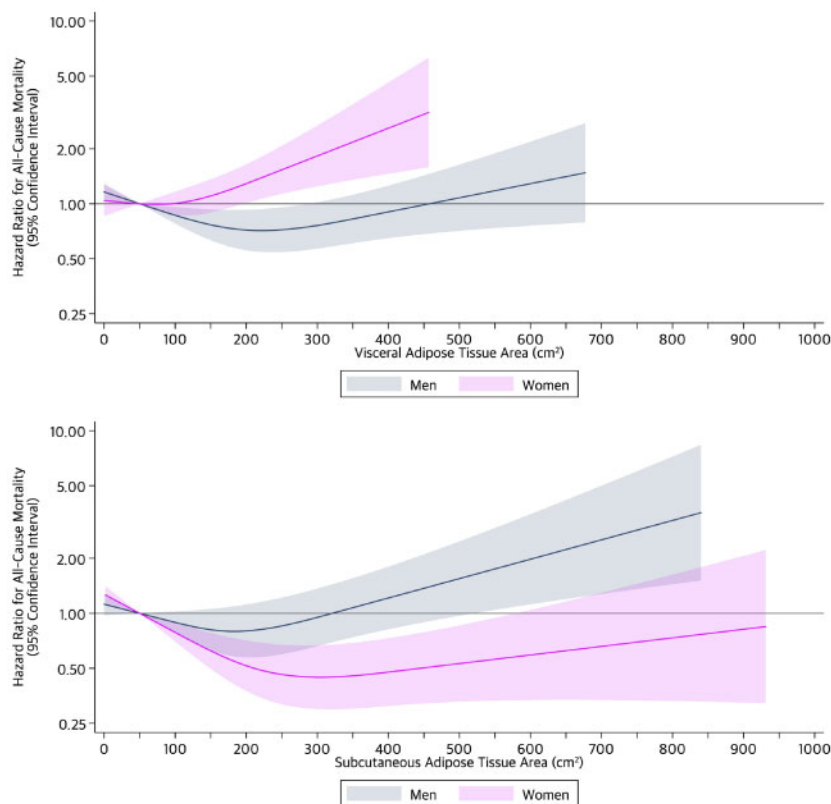


Figure 3. Risk of all-cause mortality by sex and adipose tissue compartment on the relative hazard scale in 3262 patients with colorectal cancer. Shaded regions indicate 95% confidence bands for risk of mortality as a function of visceral (top) and subcutaneous (bottom) adipose tissue area among men (navy blue) and women (magenta). Estimates are adjusted for age, race and ethnicity, cancer site, cancer stage, chemotherapy, radiation therapy, smoking history, Charlson comorbidity index, height, muscle area, subcutaneous adipose tissue area (for visceral adipose tissue area models), and visceral adipose tissue area (for subcutaneous adipose tissue area models).

quantities of visceral adipose tissue were associated with a lower risk of mortality, whereas among women, moderate quantities of subcutaneous adipose tissue were associated with a lower risk of mortality.

Previous studies have modeled adipose tissue using categories, which has led to inconsistent findings. In a retrospective cohort study of 62 patients with stage I–III colorectal cancer, a visceral adipose tissue area greater than 130 cm² was associated with a statistically significantly higher risk of all-cause mortality (hazard ratio [HR] = 7.0, 95% CI = 2.0 to 24.6) (12). In another study of 219 patients with stage I–III colorectal cancer, visceral adipose tissue in the higher 50th percentile was associated with statistically significantly higher risk of disease recurrence and mortality in patients with stage II disease (HR = 2.72, 95% CI = 1.21 to 6.10) and a pattern of lower risk of disease recurrence and mortality in patients with stage III disease, but this did not reach statistical significance (HR = 0.50, 95% CI = 0.23 to 1.06) (13). The large sample size of the current study, combined with the application of restricted cubic splines, afforded us greater statistical power and model flexibility to characterize the associations of abdominal adipose tissue with mortality. Unlike the prior study (13), no effect modification by cancer stage was identified in the current study. The prognostic associations of adiposity were independent of muscle area, which has been previously reported as a predictor of mortality in cancer patients (18). Notably, moderate amounts of visceral adiposity among men and moderate amounts of subcutaneous adiposity among women were not associated with mortality; the nadir risks of

mortality for visceral adiposity in men were 200–250 cm² and for subcutaneous adiposity in women were 275–325 cm².

Prior studies that investigated the association between BMI and mortality reported effect modification by patient sex for early-stage colon cancer ($P_{\text{interaction}} = .034$) (2) and metastatic colorectal cancer ($P_{\text{interaction}} < .001$) (26). The underlying biological mechanism of effect modification by patient sex is hypothesized to relate to adipose tissue distribution and resultant metabolic perturbations (9,10). Biopsy studies of patients with colorectal cancer demonstrated that visceral adipose tissue exhibits altered inflammatory, lymphocytic, and fatty acid secretory properties compared with subcutaneous adipose tissue (5–7). In the current study, correlational analyses between these tissues demonstrated that patients with higher areas of subcutaneous adipose tissue did not necessarily also have higher areas of visceral adipose tissue. This counters the hypothesis that patients who have poor outcomes are those who have both excess visceral adipose tissue and excess subcutaneous adipose tissue when measured at the third lumbar vertebra.

Our data are consistent with the hypothesis that dysregulated deposition of adiposity is prognostic of mortality: Men who preferentially store excess adiposity subcutaneously and women who preferentially store excess adiposity viscerally are at a statistically significantly higher risk of mortality than their counterparts who store adiposity in the regions expected for their sex. Sex steroid hormones are the principal factor that influences adipose tissue deposition (29). Testosterone suppression in healthy young men increases subcutaneous adipose

tissue deposition (30), whereas ovarian hormone suppression in healthy premenopausal women increases visceral adipose tissue deposition (31). Similarly, the decline in estrogen that naturally occurs during menopause in women is associated with increases in visceral adipose tissue deposition (32). Sex steroid hormones that regulate adipose tissue deposition, including estradiol and testosterone, are associated with cancer risk and prognosis (33,34).

Study limitations include the observational design and the potential for residual confounding. Because this study relied on routine clinically acquired data, measures of socioeconomic status, diet, or menopausal status were not available. The inclusion of these variables may modestly influence our effect size estimates, but it is unlikely that the overall shape of these prognostic associations would substantively change. Body composition was measured at the third lumbar vertebra at a solitary time point. Although the third lumbar vertebra is strongly correlated with visceral and subcutaneous adipose tissue volumes (20), anatomic differences in the distribution of adiposity between men and women may have an influence on our findings (35); nevertheless our data demonstrate that the third lumbar vertebra is prognostic in both sexes. We did not have complete measures of body mass or composition before the diagnosis of cancer; therefore, we cannot rule out the possibility that some patients may have experienced tumor-induced changes in adiposity. However, we did not identify any interactions with clinical cancer stage.

There are several strengths of this study. The main strengths are the large sample size and population-based, racially and ethnically diverse sample. The large sample size offered sufficient statistical power to evaluate associations by sex-specific subgroups. The use of clinically acquired CT images, coupled with recently developed semi- and fully automated radiologic techniques to quantify adiposity using clinical imaging, make the integration of body composition measures into clinical practice cost effective and offers the opportunity to personalize oncology care.

In conclusion, abdominal visceral and subcutaneous adipose tissue quantity was prognostic of all-cause mortality in patients with stage I-III colorectal cancer, and the strength and shape of these prognostic associations varied by patient sex. Measurements of body composition using CT can be seamlessly integrated into clinical care and used to identify those at risk for poor outcome.

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Notes

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