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ORIGINAL REPORT

# Metabolic Dysfunction, Obesity, and Survival Among Patients With Early-Stage Colorectal Cancer

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## ABSTRACT

### Purpose

The effects of obesity and metabolic dysregulation on cancer survival are inconsistent. To identify high-risk subgroups of obese patients and to examine the joint association of metabolic syndrome (MetSyn) in combination with obesity, we categorized patients with early-stage (I to III) colorectal cancer (CRC) into four metabolic categories defined by the presence of MetSyn and/or obesity and examined associations with survival.

### Methods

We studied 2,446 patients diagnosed from 2006 to 2011 at Kaiser Permanente. We assumed MetSyn if patients had three or more of five components present at diagnosis: fasting glucose > 100 mg/dL or diabetes; elevated blood pressure (systolic ≥ 130 mm Hg, diastolic ≥ 85 mm Hg, or antihypertensives); HDL cholesterol < 40 mg/dL (men) or < 50 mg/dL (women); triglycerides ≥ 150 mg/dL or antilipids; and/or highest sex-specific quartile of visceral fat by computed tomography scan (in lieu of waist circumference). We then classified participants according to the presence (or absence) of MetSyn and obesity (BMI < 30 or ≥ 30 kg/m$^2$) and assessed associations with overall and CRC-related survival using Cox proportional hazards models adjusted for demographic, tumor, and treatment factors and muscle mass at diagnosis.

### Results

Over a median follow-up of 6 years, 601 patients died, 325 as a result of CRC. Mean (SD) age was 64 (11) years. Compared with the reference of nonobese patients without MetSyn (n = 1,225), for overall survival the hazard ratios (HR) and 95% CIs were 1.45 (1.12 to 1.82) for obese patients with MetSyn (n = 480); 1.09 (0.83 to 1.44) for the nonobese with MetSyn (n = 417), and 1.00 (0.80 to 1.26) for obese patients without MetSyn (n = 324). Obesity with MetSyn also predicted CRC-related survival: 1.49 (1.09 to 2.02). The hazard of death increased with the number of MetSyn components present, independent of obesity.

### Conclusion

Patients with early-stage CRC with obesity and MetSyn have worse survival, overall and CRC related.

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## INTRODUCTION

Colorectal cancer (CRC) is a leading cause of cancer death in the United States.[1] Overweight/obesity is an established risk factor for CRC, but its relationship to survival is inconsistent. Class II and III obesity are related to poor survival,[2,3] but overweight and mild obesity show protective and/or null associations.[3-8] These mixed findings reflect incomplete knowledge of the mechanisms underlying obesity's relationship to cancer survival and suggest the existence of high-risk subgroups of obese patients.

Obesity and metabolic dysfunction may act synergistically: obesity in combination with insulin resistance is characterized by chronic inflammation,[9] possibly leading to more aggressive tumors and worse prognosis.[10] By contrast, better insulin sensitivity among metabolically healthy obese individuals may contribute to lower insulin and insulin growth factor (IGF-1) levels.[9] It is unknown whether metabolically healthy obesity is an intermediate state on the road to

future dysfunction and worse survival or if it confers a survival advantage by providing metabolic reserves with which to withstand tumor progression, treatment demands, and accompanying alterations in nutrient intake and absorption.[11]

The metabolic syndrome (MetSyn) is a cluster of risk factors that predict cardiovascular disease: abdominal obesity; low HDL cholesterol (HDL-C); and elevated glucose, blood pressure, and triglycerides.[12] Although emerging evidence suggests MetSyn reduces cancer survival,[13-18] few studies have examined CRC survivors.[17,18] No prior study examines MetSyn in combination with obesity, important because metabolic dysfunction may help identify high-risk subgroups of obese patients. Furthermore, ours is the first study, to our knowledge, of MetSyn and obesity controlling for skeletal muscle mass at diagnosis. Muscle confounds the relationship of obesity to CRC survival: obese patients have more fat, hypothesized to have adverse effects on survival, but also greater muscularity, which is linked to improved CRC survival.[19-21]

Among 2,446 patients with early-stage CRC at Kaiser Permanente Northern California (KPNC), we examined whether four categories defined by the presence/absence of MetSyn and the presence/absence of obesity were associated with survival. We hypothesized that MetSyn and obesity would identify patients with poor survival, independent of prognostic factors including stage, treatment, and muscularity.

## METHODS

### Study Population

Our study population drew from all KPNC patients diagnosed from 2006 to 2011 with stage I to III invasive CRC who had a surgical resection (n = 3,978). We required an abdominal computed tomography (CT) scan around diagnosis (n = 3,276) of sufficient image quality to analyze and information about glucose, blood pressure, triglycerides, and HDL-C in the electronic medical record (EMR; n = 2,273). Patients included and excluded because of insufficient metabolic data were similar with respect to body mass index (BMI), race/ethnicity, and survival, but differed by sex (49% and 53% women), age (64 and 59 years), and stage (32% and 24% stage I). The study was approved by the KPNC Institutional Review Board.

### Body Composition and BMI

We selected the height and weight closest to diagnosis measured by KPNC medical assistants and computed BMI ($kg/m^2$), dichotomized as $<$ or $\geq$ 30 $kg/m^2$. We obtained at-diagnosis muscle and visceral fat from a CT scan taken before chemotherapy or radiation, if received. The median time from diagnosis to scan was 6 days (range, −2 to 4 months; 84% presurgical). A single trained researcher at the University of Alberta (J.X.) selected the third lumbar vertebra (L3) and analyzed the cross-sectional area of muscle and adipose in centimeters squared according to tissue-specific Hounsfield unit ranges with sliceOmatic Software 5.0 (Tomovision, Montreal, Canada).[22] Single-slice cross-sectional areas at L3 are strongly correlated with whole-body volumes of muscle and adipose tissue.[23-25] Because no established cut points align visceral adipose tissue (VAT) area with waist circumference cut points ($>$ 88 cm for women; $>$ 102 cm for men), we used the top sex-specific quartile of VAT to signify visceral adiposity (VAT $>$ 164 $cm^2$ for women; $>$ 280 $cm^2$ for men).

### Metabolic Categories

We included at-diagnosis laboratory, medication, and disease information beginning 24 months prediagnosis until $<$ 1 month postdiagnosis (presurgery) from the EMR. We defined MetSyn using the American Heart Association/National Heart, Lung, and Blood Institute criteria[26] as the presence of three or more of five components: high glucose (fasting glucose $>$ 100 mg/dL or diabetes diagnosis), high blood pressure (systolic $\geq$ 130 mm Hg or diastolic $\geq$ 85 mm Hg, hypertension diagnosis, or antihypertensives), low HDL-C ($<$ 40 mg/dL [men]; $<$ 50 mg/dL [women]), high triglycerides ($\geq$ 150 mg/dL or antilipids [eg, statins]), and/or visceral adiposity (in lieu of waist circumference).

For our main exposure, we categorized patients according to presence/absence of obesity (BMI $\geq$ 30 $kg/m^2$) and presence/absence of MetSyn. Patients with fewer than three MetSyn risk factors were designated "metabolically healthy." To evaluate the dose-response relationship of metabolic dysregulation with survival, we summed the MetSyn components (ranging from 0 [n = 344, no abnormalities] to 5 [all abnormal]). Scores of 4 (n = 291) and 5 (n = 36) were grouped because of small frequencies. Continuous sums were used in regression models to compute *P* values.

### Other Covariate Data and End Points

We reviewed the EMR and Cancer Registry for information on stage, tumor characteristics, surgical procedures, and treatment. We obtained data on deaths from the KPNC death file, comprising the California Department of Vital Statistics, US Social Security Administration, and healthcare utilization data. Deaths (including cause) were verified and searched for using state death certificates. Demographics (eg, age, race/ethnicity, and sex) and medical history (eg, smoking) were from the EMR.

### Statistical Analysis

We examined associations of our four categories defined by MetSyn and/or obesity with overall and CRC-related survival. We used Cox regression models to calculate hazard ratios (HRs) and 95% CIs. Potential confounding variables were considered for inclusion a priori on the basis of previous literature. On the basis of the results of a stepwise selection procedure ($P < .25$ for entry; $P < .15$ to remain), we adjusted for continuous age, sex, race/ethnicity (non-Hispanic white, black, Hispanic, or Asian/Pacific Islander), smoking (current, former, or never), tumor stage and grade, receipt of chemotherapy and/or radiation, cancer site (colon or rectum), and sex-specific tertile of muscle tissue. We also examined individual and mutually adjusted associations of individual MetSyn components with overall and CRC-related death. We assessed heterogeneity with cross-product terms for metabolic categories with stage, age, race/ethnicity, and cancer site.

For overall survival, we calculated person time from diagnosis date to death or censor date: December 30, 2015. CRC-related survival was from diagnosis until death, where CRC was a primary or contributing cause, or censored at death from other causes. We conducted proportionality tests with variable by log-time interactions and visual inspection of Kaplan-Meier plots. Tests of statistical significance were two sided ($\alpha = 0.05$).

In sensitivity analyses, we accounted for competing risks using the %PSHREG macro to fit the proportional subdistribution hazards model (Fine and Gray, 1999; Appendix Table A1, online only).[27-30] We also used the %CIF macro to apply Gray's test for the equality of cumulative incidence curves.[28,30] We assessed the robustness of our findings by excluding 401 (16%) of scans taken after surgery and redefining MetSyn without medications (eg, clinical/laboratory values only). We evaluated whether differing patterns of fat distribution by race/ethnicity influenced results by defining obesity for Asian/Pacific Islander patients as BMI $\geq$ 25 $kg/m^2$[22,31-33] and by defining visceral adiposity by race/ethnicity. Prior literature indicates patients with BMI $\geq$ 35 $kg/m^2$ have worse survival after CRC[2]; we also considered defining exposure categories with BMI $\geq$ 35 $kg/m^2$ as the obesity cut point.

## RESULTS

Table 1 shows patient characteristics (n = 2,446), overall and by metabolic categories. Patients were 49% women and 64% non-Hispanic white, 7% black, 11% Hispanic, and 17% Asian/Pacific Islander. Similar proportions had stage I, II, or III cancer at diagnosis; 72% had colon cancer (28% rectal cancer). Mean (SD) age at diagnosis was 64 (11) years. Obese patients had greater muscle mass than nonobese patients. Nonobese patients were more likely to be Asian/Pacific Islander. Metabolically healthy (fewer than three metabolic risk factors) obese patients were younger than other groups (mean [SD], 60 [11] years). Obese patients had a higher number of metabolic risk factors regardless of whether they met criteria for MetSyn: 58% of metabolically healthy obese patients approached the MetSyn cutoff with abnormal values for two risk factors versus 36% of metabolically healthy nonobese patients. Among obese patients with MetSyn, 46% had four or more abnormal metabolic risk factors, versus 26% of nonobese patients with MetSyn.

During a median of 6 years (range, 3 days to 10 years), we observed 601 deaths, 325 from CRC. Figure 1 shows Kaplan-Meier survivor functions by MetSyn. Patients with MetSyn at diagnosis had lower overall survival than metabolically healthy patients (log-rank $P = .046$). Similarly, cumulative incidence curves for CRC death suggested greater mortality among patients with MetSyn than metabolically healthy patients, but did not differ significantly ($P = .18$; Appendix Figures A1 and A2, online only). Tests of variable by log-time interactions ($P = .09$) suggested proportional hazards held.

Figure 2 shows Kaplan-Meier survivor functions and Table 2 shows multivariable-adjusted associations of our main exposure (four categories defined by MetSyn and/or obesity) with overall and CRC-related survival. Compared with metabolically healthy nonobese patients, obese patients with MetSyn had worse survival (HR [95% CI], 1.23 [1.03 to 1.56] for overall and 1.24

**Table 1.** Characteristics of Patients With Colorectal Cancer, Overall and by Metabolic Phenotype, Kaiser Permanente Northern California Health System 2006 to 2011

| Characteristic | Overall (N = 2,446) | Obese | | Nonobese | |
|---|---|---|---|---|---|
| | | Metabolically Dysregulated (n = 480) | Metabolically Healthy (n = 324) | Metabolically Dysregulated (n = 417) | Metabolically Healthy (n = 1,225) |
| Age, mean (SD), years | 64 (11) | 64 (9) | 60 (11) | 67 (9) | 64 (11) |
| BMI, mean (SD), kg/m$^2$ | 28.4 (6) | 35.7 (4.9) | 34.2 (4.3) | 26.3 (2.8) | 24.7 (3.1) |
| No. of risk factors, mean (SD) | 2.0 (1.3) | 3.5 (0.6) | 1.5 (0.7) | 3.3 (0.5) | 1.1 (0.8) |
| Muscle area, mean (SD), cm$^2$ | 141 (38) | 160 (40) | 157 (40) | 135 (33) | 131 (34) |
| Survival time, mean (SD), years | 5.8 (2.2) | 5.5 (2.3) | 5.9 (2.1) | 5.8 (2.3) | 5.9 (2.1) |
| Female | 1,195 (49) | 232 (48) | 165 (51) | 175 (42) | 623 (51) |
| Race | | | | | |
| Non-Hispanic white | 1,567 (64) | 336 (70) | 218 (67) | 223 (53) | 790 (64) |
| Black | 165 (7) | 31 (6) | 44 (14) | 25 (6) | 65 (5) |
| Hispanic | 269 (11) | 72 (15) | 38 (12) | 63 (15) | 96 (8) |
| Asian/Pacific Islander | 425 (17) | 34 (7) | 22 (7) | 103 (25) | 266 (22) |
| Other | 20 (1) | 7 (1) | 2 (1) | 3 (1) | 8 (1) |
| Smoking history | | | | | |
| Current | 285 (12) | 47 (10) | 46 (14) | 41 (10) | 151 (12) |
| Former | 1,037 (42) | 221 (46) | 137 (42) | 191 (46) | 488 (40) |
| Never | 1,124 (46) | 212 (44) | 141 (44) | 185 (44) | 586 (48) |
| Stage | | | | | |
| 1 | 776 (32) | 159 (33) | 111 (34) | 126 (30) | 380 (31) |
| 2 | 757 (31) | 125 (26) | 79 (24) | 157 (38) | 396 (32) |
| 3 | 913 (37) | 196 (41) | 134 (41) | 134 (32) | 449 (37) |
| Grade | | | | | |
| 1 | 169 (7) | 32 (7) | 24 (7) | 39 (9) | 74 (6) |
| 2 | 1,842 (75) | 373 (78) | 231 (71) | 315 (76) | 923 (75) |
| 3 | 311 (13) | 57 (12) | 41 (13) | 40 (10) | 173 (14) |
| Unknown | 124 (5) | 18 (4) | 28 (9) | 23 (6) | 55 (4) |
| Treatment | | | | | |
| Chemotherapy | 1,054 (43) | 198 (41) | 156 (48) | 159 (38) | 541 (44) |
| Radiation | 364 (15) | 49 (10) | 55 (17) | 64 (15) | 196 (16) |
| Colon cancer | 1,752 (72) | 369 (77) | 237 (73) | 283 (68) | 863 (70) |
| Metabolic risk factors | | | | | |
| Visceral adiposity | 620 (25) | 377 (79) | 84 (26) | 114 (27) | 45 (4) |
| High glucose/diabetes | 1,317 (54) | 405 (84) | 126 (39) | 367 (88) | 419 (34) |
| High triglycerides | 1,507 (62) | 432 (90) | 135 (42) | 399 (96) | 541 (44) |
| Low HDL cholesterol | 932 (38) | 322 (67) | 82 (25) | 306 (73) | 222 (18) |
| High blood pressure | 526 (22) | 154 (32) | 45 (14) | 178 (43) | 149 (12) |

NOTE. Data presented as No. (%) unless otherwise noted. Percentages may not add to 100% because of rounding. No. of risk factors refers to the number of abnormal values for metabolic syndrome components present at diagnosis among a possible five, consisting of elevated glucose, elevated blood pressure, low HDL, elevated triglycerides, and/or visceral adiposity. Visceral adiposity is the top sex-specific quartile of visceral adipose tissue as derived from computed tomography scan. Metabolically healthy subjects do not meet metabolic syndrome criteria (ie, fewer than three factors meeting risk cutoffs).
Abbreviations: BMI, body mass index; SD, standard deviation.

  

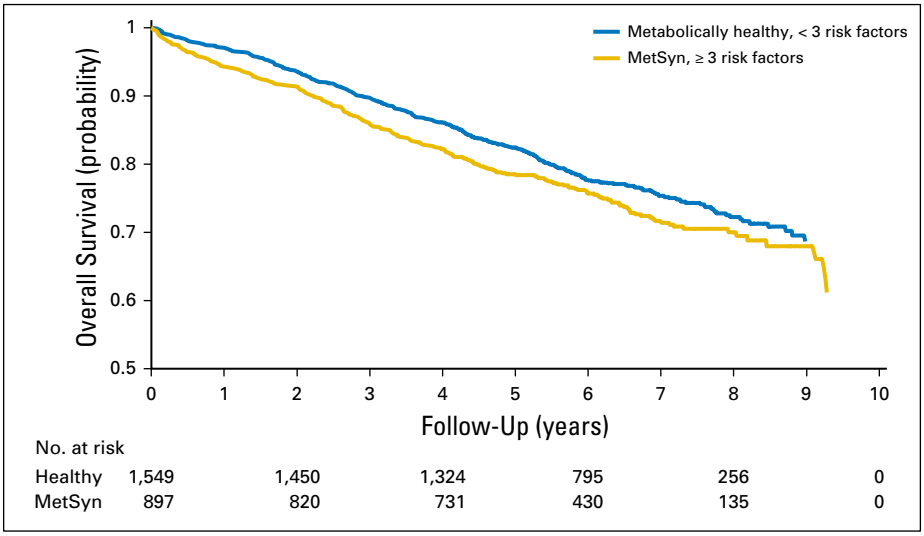


**Fig 1.** Kaplan-Meier unadjusted survivor functions: overall survival by metabolic syndrome after a diagnosis of early-stage colorectal cancer (n = 2,446). Log-rank $P = .046$. Metabolically healthy, fewer than three metabolic risk factors at diagnosis. MetSyn, metabolic syndrome at diagnosis (three or more metabolic risk factors).

[0.94 to 1.64] for CRC-related death). However, after adjustment for the sex-specific tertile of muscle mass, associations were stronger (1.45 [1.12 to 1.82] for overall and 1.49 [1.09 to 2.02] for CRC-related death). Although we observed a trend toward worse survival among nonobese patients with MetSyn and metabolically healthy obese patients, neither reached statistical significance.

Table 3 examines MetSyn components with survival: elevated triglycerides and low HDL-C were associated with worse overall survival (HR [95% CI], 1.23 [1.03 to 1.46] and 1.23 [1.04 to 1.45], respectively), whereas visceral adiposity was associated with worse overall (1.28 [1.03 to 1.59]) and CRC-related survival (1.36 [1.01 to 1.85]). When all metabolic risk factors were mutually adjusted, only low HDL-C and visceral adiposity remained associated with overall survival. Neither blood pressure nor glucose was associated with survival.

Because 75% of metabolically healthy nonobese patients had at least one metabolic risk factor, we evaluated the dose-response relationship of severity of metabolic risk with survival. Overall and CRC-related survival decreased with the presence of additional metabolic risk factors independent of BMI category at diagnosis (Fig 3). There was no difference in survival comparing patients with zero or one risk factor; those with two risk factors had borderline decreased survival, and patients with three or more risk factors had significantly decreased overall survival. Dose-response trends for overall and CRC-related survival were significant (HR [95% CI], 1.11 [1.03 to 1.19]; $P = .01$; and 1.14 [1.01 to 1.23]; $P = .03$, respectively, for each additional metabolic risk factor at diagnosis). There was no evidence of heterogeneity among subgroups defined by sex, age, cancer site, or stage.

Sensitivity analyses did not substantially alter conclusions: accounting for competing risks (Appendix Table A1), excluding

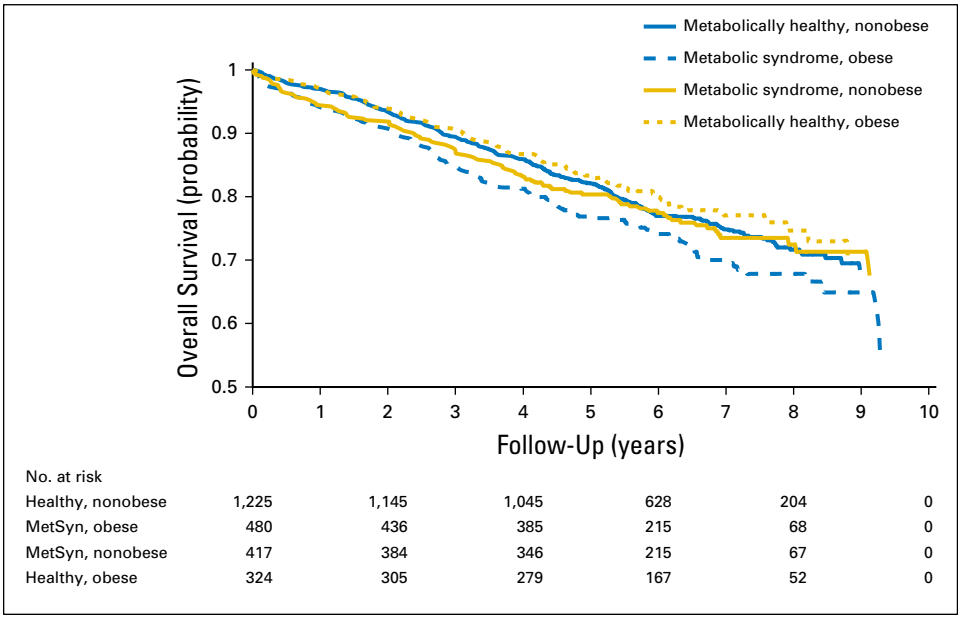


**Fig 2.** Kaplan-Meier unadjusted survivor functions: overall survival by metabolic syndrome and obesity after a diagnosis of early-stage colorectal cancer (n = 2,446). Log-rank $P$ value = .07. Metabolically healthy, fewer than three metabolic risk factors at diagnosis. MetSyn, metabolic syndrome at diagnosis (three or more metabolic risk factors).

**Table 2.** Associations of Metabolic Dysregulation and Obesity With Overall and Colorectal Cancer–Specific Survival

| Survival | Obese | | Nonobese | |
|---|---|---|---|---|
| | Metabolically Dysregulated (n = 480) | Metabolically Healthy (n = 324) | Metabolically Dysregulated (n = 417) | Metabolically Healthy (n = 1,225) |
| Events, No. | 136 | 70 | 102 | 293 |
| Overall survival | | | | |
| Multivariable adjusted | 1.23 (1.03 to 1.56) | 0.97 (0.75 to 1.27) | 1.00 (0.80 to 1.25) | Reference |
| Muscle adjusted | 1.45 (1.12 to 1.82) | 1.09 (0.83 to 1.44) | 1.00 (0.80 to 1.26) | Reference |
| Colorectal cancer survival | | | | |
| Events, No. | 74 | 42 | 55 | 154 |
| Multivariable adjusted | 1.24 (0.94 to 1.64) | 1.03 (0.73 to 1.86) | 1.10 (0.81 to 1.51) | Reference |
| Muscle adjusted | 1.49 (1.09 to 2.02) | 1.20 (0.83 to 1.73) | 1.12 (0.82 to 1.52) | Reference |

NOTE. Data presented as hazard ratio (95% CI) unless otherwise noted. Cox regression models adjust for race/ethnicity (black, Hispanic, Asian/Pacific Islander or non-Hispanic white [reference]), sex (female *v* male [reference]), diagnosis age in years, smoking history (current, former, or never [reference]), tumor stage (II, III, or I [reference]) and grade (II, III, IV, unknown, or I [reference]), receipt of chemotherapy and/or radiation, cancer site (colon or rectal), sex-specific tertile of muscle tissue at diagnosis. Metabolically dysregulated indicates the presence of three or more of the risk factor components of the metabolic syndrome (high glucose, high blood pressure, low HDL, high triglycerides, and/or visceral adiposity [the top sex-specific quartile of visceral adipose tissue as derived from computed tomography scan]). Metabolically healthy is the presence of fewer than three of the risk factor components. The reference group is nonobese (body mass index $< 30$ kg/m$^2$) patients with colorectal cancer who are metabolically healthy (ie, fewer than three risk factors).

scans after surgery or defining visceral adiposity within racial/ethnic groups or using BMI $\geq 25$ kg/m$^2$ for Asian/Pacific Islanders resulted in similar overall and subgroup results. Defining MetSyn without medication data slightly strengthened the HR (95% CI) comparing obese patients with MetSyn to nonobese, metabolically healthy patients from 1.45 (1.12 to 1.82) to 1.51 (1.18 to 1.93). Defining metabolic categories according to BMI $\geq 35$ kg/m$^2$ rather than $\geq 30$ kg/m$^2$ strengthened that HR to 2.03 (1.53 to 2.68).

## DISCUSSION

In this study of 2,446 patients with early-stage CRC, the combination of obesity and MetSyn was associated with the worst survival, overall and CRC-related. Nonobese patients without MetSyn had the best survival. The hazard of death increased in a dose-response fashion with additional metabolic risk factors, independent of BMI, suggesting each degree of metabolic dysregulation incrementally worsens outcomes.

To our knowledge, this is the first study examining whether patients defined by their obesity and MetSyn status have decreased survival after CRC diagnosis controlling for cancer stage and treatment and, importantly, skeletal muscle. We previously examined at-diagnosis BMI and postdiagnosis weight change in this cohort and found the hazard of death does not increase until BMI $\geq 35$ kg/m$^2$, and postdiagnostic weight loss is adversely associated with survival regardless of at-diagnosis BMI.[3,34] However, BMI cannot distinguish between fat and lean mass, which exert differing influences on metabolic dysregulation[35] and cancer survival.[36,37] In the current study, adjustment for muscularity strengthened associations. This is likely because sarcopenia and muscle loss, independent of adiposity, are associated with worse CRC prognosis.[19-21] Comparing metabolic categories with the same muscularity highlights the detrimental effects of excess adiposity and metabolic dysregulation previously masked by the benefits of additional muscle present in obese patients.

Few studies are directly comparable, but our findings are consistent with a 2013 meta-analysis reporting an association of MetSyn with decreased CRC-related survival in men (HR [95% CI], 1.36 [1.25 to 1.48]) and women (1.16 [1.03 to 1.30]).[17] Multiple processes could explain reduced survival among obese patients with MetSyn. Inflammation may represent a unifying

**Table 3.** Associations of Metabolic Syndrome and Components With Overall and Colorectal Cancer–Specific Survival

| Event | High Triglycerides | High Blood Pressure | Low HDL Cholesterol | High Glucose or Diabetes | Visceral Adiposity |
|---|---|---|---|---|---|
| Overall death, 601 events | | | | | |
| Multivariable adjusted | 1.23 (1.03 to 1.46) | 0.84 (0.68 to 1.03) | 1.24 (1.05 to 1.46) | 1.07 (0.90 to 1.26) | 1.25 (1.00 to 1.56) |
| Muscle adjusted | 1.23 (1.03 to 1.47) | 0.85 (0.69 to 1.04) | 1.23 (1.04 to 1.45) | 1.07 (0.90 to 1.27) | 1.28 (1.03 to 1.59) |
| Mutually adjusted | 1.18 (0.98 to 1.41) | 0.84 (0.68 to 1.03) | 1.18 (1.00 to 1.40) | 1.01 (0.85 to 1.20) | 1.25 (1.00 to 1.56) |
| Colorectal cancer death, 325 events | | | | | |
| Multivariable adjusted | 1.17 (0.92 to 1.49) | 0.96 (0.73 to 1.26) | 1.20 (0.95 to 1.50) | 1.03 (0.81 to 1.29) | 1.32 (0.97 to 1.78) |
| Muscle adjusted | 1.18 (0.93 to 1.50) | 0.97 (0.74 to 1.27) | 1.18 (0.94 to 1.49) | 1.03 (0.82 to 1.30) | 1.36 (1.01 to 1.85) |
| Mutually adjusted | 1.14 (0.88 to 1.46) | 0.96 (0.73 to 1.26) | 1.15 (0.91 to 1.45) | 0.98 (0.77 to 1.24) | 1.34 (0.99 to 1.82) |

NOTE. Data presented as hazard ratio (95% CI). All hazard ratios in the multivariable-adjusted row are derived from separate Cox regression models for each metabolic syndrome component and adjusted for race/ethnicity, sex, diagnosis age, smoking history, tumor stage and grade, receipt of chemotherapy and/or radiation, cancer site, sex-specific tertile of muscle tissue, and body mass index category at diagnosis. By contrast, in the mutually adjusted row, each metabolic risk factor is adjusted for all others in the row as well as for the covariates listed above. Visceral adiposity is the top sex-specific quartile of visceral adipose tissue as derived from computed tomography scan.

  

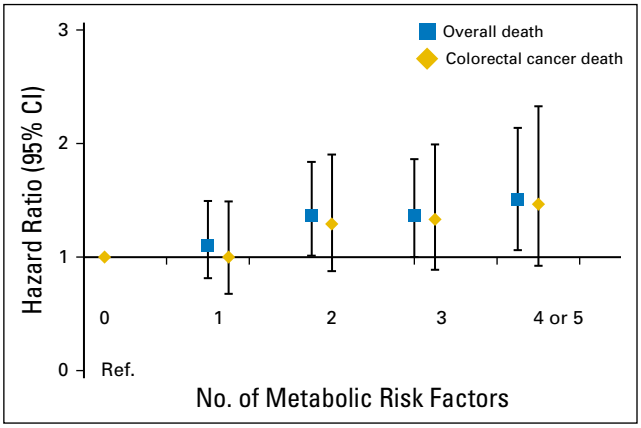


**Fig 3.** Degree of metabolic dysregulation at diagnosis and overall and colorectal cancer (CRC) –specific survival (n = 2,446). Each additional metabolic syndrome component present at diagnosis increased hazard of death by 11% (hazard ratio [HR], 1.11; 95% CI, 1.03 to 1.19; $P = .01$) for overall survival and 14% (HR, 1.14; 95% CI, 1.01 to 1.23; $P = .03$) for CRC-related survival. Cox regression models adjusted for age at diagnosis, sex, race/ethnicity, smoking history, tumor site, stage and grade, chemotherapy and/or radiation, sex-specific tertile of muscle tissue, and body mass index category at diagnosis. Number of risk factors indicates the number of abnormal metabolic syndrome components present at diagnosis (ie, high glucose, high blood pressure, low HDL, high triglyceride level, and/or visceral adiposity). The reference group had 0 metabolic risk factors (n = 344; total deaths = 63; CRC deaths = 40). Risk factor = 1 (n = 562; total deaths = 131; CRC deaths = 68); risk factor = 2 (n = 643; total deaths = 169; CRC deaths = 88); risk factor = 3 (n = 570; total deaths = 147; CRC deaths = 80); risk factor = 4 or 5 (n = 327; total deaths = 91; CRC deaths = 49).

mechanism: greater visceral adiposity may increase cytokines from adipocytes and infiltrating immune cells, creating an environment of low-grade inflammation favorable for proliferating tumor cells. Inflammation might also contribute to dysregulated growth signals (eg, IGF-1 and insulin). Insulin resistance, a signature characteristic of MetSyn, has been associated with worse outcomes in CRC[38] and other cancers.[39] Furthermore, increasing insulin can increase IGF bioavailability (decreased levels of IGF-binding proteins and increased IGF-1 synthesis). Both insulin and IGF-1 can activate the phosphatidylinositol 3′-kinase and mitogen-activated protein kinase pathways.[40] IGF-1 signaling has also been associated with progression in other cancers, including breast, pancreatic, and esophageal.[41]

Despite multiple pathways through which MetSyn might influence prognosis, not all prior studies found that MetSyn decreases CRC survival. Furthermore, individual MetSyn components exhibit adverse and protective relationships, depending on how they are defined and measured. For example, a study of approximately 36,000 patients in the SEER-Medicare linked database found no association of MetSyn with survival.[42] The authors attributed results to the paradoxical associations with individual components; elevated glucose and hypertension decreased survival, whereas dyslipidemia improved survival, particularly among patients with early-stage disease. By contrast, we observed worse survival with low HDL-C, high triglycerides, and visceral adiposity and null results for blood pressure and glucose/diabetes. Low HDL-C is inconsistently associated with CRC risk, and patients with CRC with distant metastases have higher ratios of LDL cholesterol/HDL-C than those without, but in previous studies low HDL-C was not an independent prognostic factor.[43,44]

A potential explanation for the null associations with the glucose/diabetes and blood pressure components could be measurement error: 50% of patients with abnormal blood pressure in our study were prescribed antihypertensives, whereas others met MetSyn criteria on the basis of single blood pressure measurements close to diagnosis. Furthermore, medications themselves may influence progression or survival: the capacity of metformin to inhibit tumor growth and proliferation[45] is currently being tested.[46-48] Similarly, statins are being explored to improve CRC survival[49] because they may inhibit inflammation and angiogenesis and selectively promote tumor cell apoptosis.[50,51] However, we repeated analyses without medication data, and results were nearly identical. Thus, medications alone are not driving results.

There was no significant decrease in survival among metabolically healthy obese patients or nonobese patients with MetSyn. Although not as severe as MetSyn and obesity combined, these patients exhibited greater metabolic dysregulation than the healthy reference group: among nonobese patients, those with MetSyn had higher BMI (26.3 *v* 24.7 kg/m$^2$) and were more likely to be Asian/Pacific Islanders (and thus experience poor outcomes at lower BMI). Metabolically healthy obesity may be a transient state[52] along a trajectory toward further dysregulation and decreased survival. Consistent with this, although metabolically healthy obese patients were younger, more than half already had two abnormal values for metabolic factors, approaching the MetSyn cut point. As metabolically healthy obese patients age, they may develop additional risk factors that influence long-term CRC prognosis.

With respect to near-term survival, obesity alone does not identify high-risk patients.[3] Rather, the subset of obese patients with MetSyn is at highest risk. Within this group, those with a BMI $\geq$ 35 kg/m$^2$ and MetSyn had nearly twice the hazard of death as patients with BMI $<$ 35 kg/m$^2$ without MetSyn. Thus, even among the obese, metabolic dysregulation further distinguishes high-risk patients. MetSyn in conjunction with obesity may be the best indicator of severity of metabolic dysfunction, including systemic inflammation; from this perspective, it is not surprising to find stronger associations among patients who exhibit a cluster of symptoms rather than with individual MetSyn components.

Including all qualifying patients with CRC and using abdominal CT scans to define visceral adiposity and control for muscularity were unique strengths of this study. That MetSyn information was collected opportunistically through the EMR was a limitation; because patients excluded for lack of metabolic data are likely healthier, the harms of MetSyn may be underestimated. Furthermore, we could not evaluate the effect of optimizing treatment of MetSyn on survival. The EMR lacked information on diet and activity; stratifying by obesity and adjusting for muscularity likely mitigates the influence of energy balance behaviors, but in observational research we cannot exclude residual confounding. We also had limited power for analyses by race/ethnicity. KPNC is representative of Northern California's population except at extreme tails of the income distribution; however, if culture or environment (eg, dietary patterns or access to health care) modify the relationship of obesity or MetSyn to cancer survival, that would limit generalizability (eg, to insured populations or similar regions). Finally, although the difference between unadjusted cumulative incidence curves was nonsignificant (Appendix Figure A2), in multivariable-adjusted analyses accounting for competing risks, the combination of

obesity and MetSyn was significantly associated with worse survival (HR [95% CI], 1.44 [1.13 to 1.75]; Appendix Table A1).

In conclusion, the combination of MetSyn and obesity may decrease survival among patients with CRC, whereas obesity or MetSyn alone do not. However, even metabolically healthy patients have some degree of metabolic dysregulation, and the hazard of death increases with additional metabolic risk factors present at diagnosis. Whether optimizing clinical management of MetSyn will improve survival in early-stage CRC remains an area for future research.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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## REFERENCES


1. Siegel RL, Miller KD, Jemal A: Cancer statistics, 2016. CA Cancer J Clin 66:7-30, 2016
2. Sinicrope FA, Foster NR, Yothers G, et al: Body mass index at diagnosis and survival among colon cancer patients enrolled in clinical trials of adjuvant chemotherapy. Cancer 119:1528-1536, 2013
3. Kroenke CH, Neugebauer R, Meyerhardt J, et al: Analysis of body mass index and mortality in patients with colorectal cancer using causal diagrams. JAMA Oncol 10.1001/jamaoncol.2016.0732 [epub ahead of print on May 19, 2016
4. Baade PD, Meng X, Youl PH, et al: The impact of body mass index and physical activity on mortality among patients with colorectal cancer in Queensland, Australia. Cancer Epidemiol Biomarkers Prev 20:1410-1420, 2011
5. Campbell PT, Newton CC, Dehal AN, et al: Impact of body mass index on survival after colorectal cancer diagnosis: The Cancer Prevention Study-II Nutrition Cohort. J Clin Oncol 30:42-52, 2012
6. Kuiper JG, Phipps AI, Neuhouser ML, et al: Recreational physical activity, body mass index, and survival in women with colorectal cancer. Cancer Causes Control 23:1939-1948, 2012
7. Meyerhardt JA, Niedzwiecki D, Hollis D, et al: Impact of body mass index and weight change after treatment on cancer recurrence and survival in patients with stage III colon cancer: Findings from Cancer and Leukemia Group B 89803. J Clin Oncol 26:4109-4115, 2008
8. Schlesinger S, Siegert S, Koch M, et al: Postdiagnosis body mass index and risk of mortality in colorectal cancer survivors: A prospective study and meta-analysis. Cancer Causes Control 25: 1407-1418, 2014
9. Moore LL, Chadid S, Singer MR, et al: Metabolic health reduces risk of obesity-related cancer in Framingham Study adults. Cancer Epidemiol Biomarkers Prev 23:2057-2065, 2014
10. Khandekar MJ, Cohen P, Spiegelman BM: Molecular mechanisms of cancer development in obesity. Nat Rev Cancer 11:886-895, 2011
11. Azvolinsky A: Cancer prognosis: Role of BMI and fat tissue. J Natl Cancer Inst 106:dju177, 2014
12. Grundy SM, Brewer HB Jr, Cleeman JI, et al: Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 109:433-438, 2004
13. Trevisan M, Liu J, Bahsas FB, et al: Syndrome X and mortality: A population-based study. Am J Epidemiol 148:958-966, 1998
14. Oh C-M, Jun JK, Suh M: Risk of cancer mortality according to the metabolic health status and degree of obesity. Asian Pac J Cancer Prev 15: 10027-10031, 2014
15. Lee JS, Cho SI, Park HS: Metabolic syndrome and cancer-related mortality among Korean men and women. Ann Oncol 21:640-645, 2010
16. Jaggers JR, Sui X, Hooker SP, et al: Metabolic syndrome and risk of cancer mortality in men. Eur J Cancer 45:1831-1838, 2009
17. Esposito K, Chiodini P, Capuano A, et al: Colorectal cancer association with metabolic syndrome and its components: A systematic review with meta-analysis. Endocrine 44:634-647, 2013
18. Colangelo LA, Gapstur SM, Gann PH, et al: Colorectal cancer mortality and factors related to the insulin resistance syndrome. Cancer Epidemiol Biomarkers Prev 11:385-391, 2002
19. Blauwhoff-Buskermolen S, Versteeg KS, de van der Schueren MA, et al: Loss of muscle mass during chemotherapy is predictive for poor survival of patients with metastatic colorectal cancer. J Clin Oncol 34:1339-1344, 2016
20. van Vledder MG, Levolger S, Ayez N, et al: Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg 99:550-557, 2012
21. Miyamoto Y, Baba Y, Sakamoto Y, et al: Sarcopenia is a negative prognostic factor after curative resection of colorectal cancer. Ann Surg Oncol 22: 2663-2668, 2015
22. Prado C, Cushen S, Orsso C, et al: Sarcopenia and cachexia in the era of obesity: Clinical and nutritional impact. Proc Nutr Soc:75:188-198, 2016
23. Shen W, Punyanitya M, Wang Z, et al: Total body skeletal muscle and adipose tissue volumes: Estimation from a single abdominal cross-sectional image. J Appl Physiol (1985) 97:2333-2338, 2004
24. Mourtzakis M, Prado CM, Lieffers JR, et al: A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 33:997-1006, 2008
25. Prado CM, Birdsell LA, Baracos VE: The emerging role of computerized tomography in assessing cancer cachexia. Curr Opin Support Palliat Care 3:269-275, 2009
26. Grundy SM, Cleeman JI, Daniels SR, et al: Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. Cardiol Rev 13:322-327, 2005
27. Fine JP, Gray RJ: A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496-509, 1999
28. Gray RJ: A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 16:1141-1154, 1988
29. Kohl M, Heinz G: PSHREG: A SAS macro for proportional and nonproportional subdistribution hazards regression. Comput Methods Programs Biomed 118.2:218-233, 2015
30. Lin G, So Y, Johnston G: Analyzing survival data with competing risks using SAS software. SAS Global Forum, 2012. http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.306.7517&rep=rep1&type=pdf
31. Hsu WC, Araneta MRG, Kanaya AM, et al: BMI cut points to identify at-risk Asian Americans for type 2 diabetes screening. Diabetes Care 38:150-158, 2015
32. WHO Expert Consultation: Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363: 157-163, 2004 [Erratum: Lancet 363:902, 2004]
33. World Health Organization, International Association for the Study of Obesity, International Obesity Task Force: Assessment/diagnosis, in: The Asia-Pacific perspective: Redefining obesity and its treatment. Sydney, Australia. Health Communications Australia 2000, pp 15-21
34. Meyerhardt JA, Kroenke CH, Prado CM, et al: Association of weight change after colorectal cancer diagnosis and outcomes in the Kaiser Permanente Northern California Population. Cancer Epidemiol Biomarkers Prev (in press)
35. Lee J, Hong YP, Shin HJ, et al: Associations of sarcopenia and sarcopenic obesity with metabolic syndrome considering both muscle mass and muscle strength. J Prev Med Public Health 49:35-44, 2016
36. Prado CM, Gonzalez MC, Heymsfield SB: Body composition phenotypes and obesity paradox. Curr Opin Clin Nutr Metab Care 18:535-551, 2015
37. Gonzalez MC, Pastore CA, Orlandi SP, et al: Obesity paradox in cancer: New insights provided by body composition. Am J Clin Nutr 99:999-1005, 2014
38. Trevisan M, Liu J, Muti P, et al: Markers of insulin resistance and colorectal cancer mortality. Cancer Epidemiol Biomarkers Prev 10:937-941, 2001
39. Perseghin G, Calori G, Lattuada G, et al: Insulin resistance/hyperinsulinemia and cancer mortality: The Cremona study at the 15th year of follow-up. Acta Diabetol 49:421-428, 2012


  

**40.** Gallagher EJ, LeRoith D: The proliferating role of insulin and insulin-like growth factors in cancer. Trends Endocrinol Metab 21:610-618, 2010

**41.** Renehan AG, Frystyk J, Flyvbjerg A: Obesity and cancer risk: The role of the insulin-IGF axis. Trends Endocrinol Metab 17:328-336, 2006

**42.** Yang Y, Mauldin PD, Ebeling M, et al: Effect of metabolic syndrome and its components on recurrence and survival in colon cancer patients. Cancer 119:1512-1520, 2013

**43.** Gallagher EJ, LeRoith D: Epidemiology and molecular mechanisms tying obesity, diabetes, and the metabolic syndrome with cancer. Diabetes Care 36:S233-S239, 2013 (suppl 2)

**44.** Muc-Wierzgoń M, Nowakowska-Zajdel E, Dzięgielewska-Gęsiak S, et al: Specific metabolic biomarkers as risk and prognostic factors in colorectal cancer. World J Gastroenterol 20:9759-9774, 2014

**45.** Mei ZB, Zhang ZJ, Liu CY, et al: Survival benefits of metformin for colorectal cancer patients with diabetes: A systematic review and meta-analysis. PLoS One 9:e91818, 2014 [Erratum: PLoS One 9:e103652, 2014]

**46.** Kalinsky K, Crew KD, Refice S, et al: Presurgical trial of metformin in overweight and obese patients with newly diagnosed breast cancer. Cancer Invest 32:150-157, 2014

**47.** Kim J, Lim W, Kim EK, et al: Phase II randomized trial of neoadjuvant metformin plus letrozole versus placebo plus letrozole for estrogen receptor positive postmenopausal breast cancer (METEOR). BMC Cancer 14:170, 2014

**48.** Ko KP, Ma SH, Yang JJ, et al: Metformin intervention in obese non-diabetic patients with breast cancer: Phase II randomized, double-blind, placebo-controlled trial. Breast Cancer Res Treat 153: 361-370, 2015

**49.** Boman BM, Bandos H, Wickerham DL, et al: Statin polyp prevention trial in patients with resected colon cancer: NSABP protocol P-5. J Clin Oncol 30, 2012 (suppl; abstr TPS1615)

**50.** Ling Y, Yang L, Huang H, et al: Prognostic significance of statin use in colorectal cancer: A systematic review and meta-analysis. Medicine (Baltimore) 94:e908, 2015

**51.** Zhong S, Zhang X, Chen L, et al: Statin use and mortality in cancer patients: Systematic review and meta-analysis of observational studies. Cancer Treat Rev 41:554-567, 2015

**52.** Bell JA, Hamer M, Sabia S, et al: The natural course of healthy obesity over 20 years. J Am Coll Cardiol 65:101-102, 2015

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Metabolic Dysfunction, Obesity, and Survival Among Patients With Early-Stage Colorectal Cancer**

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## *Appendix*

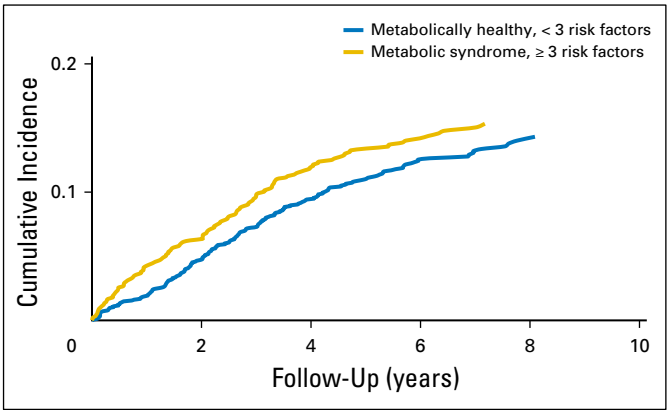


**Fig A1.** Cumulative incidence of colorectal cancer death by metabolic syndrome.

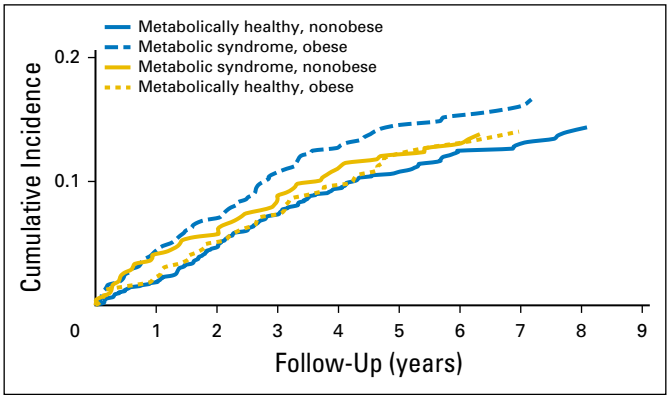


**Fig A2.** Cumulative incidence of colorectal cancer death by metabolic syndrome and obesity.

**Table A1.** Accounting for Competing Risks Using Fine and Gray Proportional Subdistribution Hazards Regression: Associations of Metabolic Dysregulation and Obesity With Colorectal Cancer–Specific Mortality

| Event | Obese | | Nonobese | |
|---|---|---|---|---|
| | Metabolically Dysregulated (n = 480) | Metabolically Healthy (n = 324) | Metabolically Dysregulated (n = 417) | Metabolically Healthy (n = 1,225) |
| Events, No. | 74 | 42 | 55 | 154 |
| Colorectal cancer death, adjusting for competing risks | | | | |
| Multivariable adjusted | 1.22 (0.94 to 1.50) | 1.04 (0.69 to 1.39) | 1.10 (0.78 to 1.42) | Reference |
| Muscle adjusted | 1.44 (1.13 to 1.75) | 1.21 (0.83 to 1.58) | 1.11 (0.79 to 1.43) | Reference |

NOTE. Data presented as hazard ratio (95% CI). Models use the %PSHREG macro[29] to estimate the proportional subdistribution hazards model proposed by Fine and Gray,[27] which accounts for competing risks. Models adjust for race/ethnicity (black, Hispanic, Asian/Pacific Islander, or non-Hispanic white [reference]), sex (female *v* male [reference]), diagnosis age in years, smoking history (current, former, or never [reference]), tumor stage (II, III, or I [reference]) and grade (II, III, IV, unknown, or I [reference]), receipt of chemotherapy and/or radiation, cancer site (colon or rectal), sex-specific tertile of muscle tissue at diagnosis. Metabolically dysregulated indicates the presence of three or more of the risk factor components of the metabolic syndrome (high glucose, high blood pressure, low HDL, high triglycerides, and/or visceral adiposity [the top sex-specific quartile of visceral adipose tissue as derived from computed tomography scan]). Metabolically healthy is the presence of fewer than three of the risk factor components. The reference group is nonobese (body mass index $< 30$ kg/m$^2$) patients with colorectal cancer who are metabolically healthy.