Associations of Abdominal Skeletal Muscle Mass, Fat Mass, and Mortality among Men and Women with Stage I–III Colorectal Cancer

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ABSTRACT

Background: The associations of abdominal skeletal muscle mass index (SMI), visceral and subcutaneous adipose tissue (VAT and SAT, respectively), and mortality among patients with stage I–III colorectal cancer may differ for men and women, but only few studies stratified their data into men and women. We investigated associations of abdominal SMI, VAT, and SAT with overall mortality among men and among women with stage I–III colorectal cancer.

Methods: SMI, VAT, and SAT were assessed from abdominal CT images for 1,998 patients with stage I–III colorectal cancer diagnosed between 2006 and 2015. Restricted cubic splines (RCS) were used to investigate associations of SMI, VAT, and SAT with overall mortality.

Results: Average age of the participants was 67.9 ± 10.6 years and 58% were men. During a median follow-up of 4.3 years, 546 (27%) patients died. Among men, the association of SMI and mortality was statistically significant in a nonlinear way in the RCS analyses, with lower SMI levels associated with higher mortality. SMI was not associated with mortality among women. SAT was associated with mortality in a nonlinear way for men and for women, with lower SAT levels being associated with higher mortality. VAT was not significantly associated with mortality in men or women.

Conclusion: Associations of abdominal skeletal muscle mass with mortality among patients with colorectal cancer were not the same for men and for women.

Impact: This study stresses the importance for more attention on sex-related differences in body composition and cancer outcomes.

Introduction

Colorectal cancer is one of the most common malignancies worldwide, with over 1.8 million new cases in 2018 (1). Various studies have investigated associations of abdominal skeletal muscle mass, amount of visceral adipose tissue (VAT) or subcutaneous adipose tissue (SAT), and mortality among patients with colorectal cancer (2–18), but up till now, the results are inconsistent. This inconsistency has several reasons. First, studies included a mix of patients with stage I–III and stage IV colorectal cancer. Five-year survival rate of patients with stage I–III colorectal cancer is generally above 70%, whereas in patients with stage IV colorectal cancer, this is generally less than 15% (19). Severe weight loss and muscle wasting (cachexia) are highly prevalent among patients with stage IV cancer, due to metabolic alterations induced by the tumor (20). Among patients with stage I–III cancer, cachexia is less common; thus, low skeletal muscle mass is more likely to be related to aging and/or a sedentary lifestyle. Analyses on body composition and mortality should therefore not include combined populations of stage I–III and stage IV patients.

A second possible explanation for the inconsistent results is the use of inappropriate cutoff values to identify patients with a low or high abdominal muscle or fat mass. When it comes to patients with stage I–III colorectal cancer, five studies investigated the association of low abdominal skeletal muscle mass and mortality all using different cutoff values for low skeletal muscle mass: the used cutoffs ranged from <31.6 to <46.6 cm^2/m^2 for women and <43 to <54.3 cm^2/m^2 for men (9–12, 17). An Asian ($n = 220$), a Canadian ($n = 968$), and a large U.S. study ($n = 3{,}262$; refs. 10, 12, 17) reported a significant association between low abdominal skeletal muscle mass and higher mortality, while in two European studies ($n = 816$ and $n = 339$; refs. 9, 11), low abdominal skeletal muscle mass was not associated with higher mortality. Both European studies used cutoff levels for low skeletal muscle as defined by U.S. or Canadian cohorts (12, 14). As noted by others (21, 22), the cutoff levels for low abdominal skeletal muscle as defined in U.S./Canadian populations might not be appropriate for European populations.

VAT is known to be associated with chronic, low-grade inflammation, and a higher risk of worse cardiovascular outcomes (23, 24). So far there is no convincing evidence that VAT is also associated with mortality among patients with stage I–III colorectal cancer (11, 12, 15–18). A relatively small study ($n = 62$; ref. 15) reported a statistically significant association of high VAT with increased overall mortality among patients receiving adjuvant chemotherapy. Four other studies observed no clear associations between low or high VAT

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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Cancer Epidemiol Biomarkers Prev 2020;29:956–65

doi: 10.1158/1055-9965.EPI-19-1134

and mortality (11, 12, 16, 17). One study determined a cutoff value for high VAT using optimal stratification (17), two studies used tertiles (11, 12), and one study applied a median split (16) to categorize VAT. All these categorizations are relatively crude, and these four studies may have failed to detect an association as a result of these crude categorizations. A sixth study used cubic splines to investigate the association of VAT and mortality (18) and observed a nonlinear association between VAT and mortality.

Compared with VAT, SAT contains a lower number of inflammatory and immune cells and is considered to be a less active fat tissue then VAT (25). Three studies (11, 12, 18) reported on the association of abdominal SAT and mortality among patients with stage I–III colorectal cancer exclusively. Two studies did not observe significant associations while using tertiles to categorize SAT. Again, Brown and colleagues (18) observed a nonlinear association between SAT and mortality using restricted cubic splines. This shows that dose–response analyses using restricted cubic spline (RCS) functions (26) could help identify possible linear or nonlinear associations of VAT and SAT with mortality that might be missed when categorizing muscle or adipose tissue variables.

Another possible explanation for inconsistent results on associations of body composition and survival could be that not all studies stratified their data into men and women. Body composition differs between men and women, with men generally having more VAT and higher muscle mass, and women generally having more SAT and lower muscle mass (27). Age-related changes in skeletal muscle structure, function, and metabolism differ between men and women, possibly mediated by sex hormones (28). Sex differences in body fat distribution might account for differences in inflammatory markers between men and women (29). Currently, there is a gap in literature on whether these sex-based differences in body composition have an impact on the association between body composition and mortality in patients with cancer. Of the previous studies among patients with stage I–III colorectal cancer (9–12, 15–18), only two studies (both in the same dataset: men $n = 1{,}634$, women $n = 1{,}628$; refs. 12, 18) stratified their data by sex. The stratified analyses suggest that associations of abdominal skeletal muscle mass, VAT, and SAT with mortality differ between men and women.

The aim of this study was to investigate the associations of abdominal skeletal muscle mass, VAT, and SAT with overall mortality among men and among women with stage I–III colorectal cancer.

Materials and Methods

Population

For this study, data of two ongoing prospective cohort studies among patients with colorectal cancer, the COLON (30) and EnCoRe (31) study, were combined with registry-based data, as described previously (32). Briefly, for the COLON study, participants were recruited between August 2010 and January 2016; for the EnCoRe

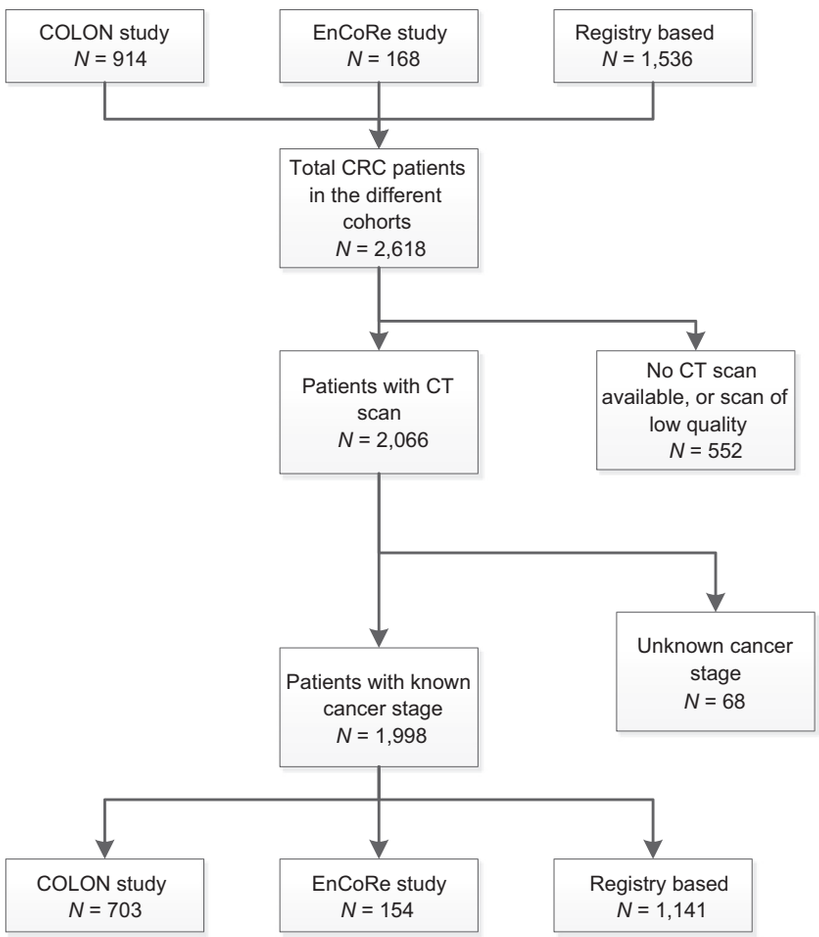


Figure 1.
Flowchart for inclusion of patients with stage I–III colorectal cancer in an observational study on body composition and mortality.

study, participants were recruited between April 2012 and September 2015; and for the registry-based data, the Netherlands Cancer Registry was used to select all patients with stage I–III colorectal cancer diagnosed between 2007 and 2010 in three hospitals. Patients had to be diagnosed with stage I–III colorectal cancer to be eligible for the current analysis. Additional exclusion criteria for the present analyses were missing CT image, CT images of poor quality, or missing data on stage of disease (see **Fig. 1**). Only pretreatment CT images assessed within 3 months of diagnosis were considered representative for body composition at diagnosis. Patients with a CT image assessed after treatment or outside this time period were excluded from analyses.

The study was performed in accordance with the Declaration of Helsinki. The COLON study (ClinicalTrials.gov Identifier: NCT03191110) was approved by the Committee on Research involving Human Subjects, region Arnhem-Nijmegen, the Netherlands. The EnCoRe study (Netherlands Trial register number 7099) was approved by the Medical Ethics Committee of the University Hospital Maastricht and Maastricht University (Maastricht, the Netherlands). All participants of the COLON and EnCoRe study provided written informed consent. According to the Central Committee on Research involving Human Subjects (CCMO), studies using the data of the Netherlands Cancer Registry do not require approval from an ethics committee in the Netherlands. The study was approved by the Privacy Review Board of the Netherlands Cancer Registry. In addition, the ethical committees of the three participating hospitals gave permission to use additional data from CT images.

Table 1. Baseline characteristics of patients with stage I–III colorectal cancer in an observational study on body composition and mortality.

	Total population (n = 1,998)	**Women (n = 832) (42%)**	**Men (n = 1166) (58%)**
Demographic characteristics			
Age [y, mean (SD)]	67.9 (10.6)	67.8 (11.6)	68.0 (9.8)
Follow-up time [months, median (IQR range)]	51 (28–79)	54 (29–82)	49 (27–77)
Deceased patients [*n* (%)]	546 (27)	223 (27)	323 (28)
Study [*n* (%)]			
Prospective	857 (43)	323 (39)	534 (46)
Registry-based	1,141 (57)	509 (61)	632 (54)
Clinical characteristics			
Cancer stage [*n* (%)]			
I	478 (24)	203 (24)	275 (23)
II	691 (35)	281 (34)	410 (35)
III	829 (42)	348 (42)	481 (41)
Tumor location [*n* (%)][a]			
Colon	1,303 (67)	595 (74)	708 (62)
Rectal	648 (33)	214 (27)	434 (38)
Number of comorbidities [*n* (%)][b]			
0	622 (33)	288 (37)	334 (30)
1	474 (25)	209 (27)	265 (24)
≥2	796 (42)	292 (37)	505 (43)
Neoadjuvant or adjuvant treatment			
Radiotherapy [*n* (%)][c]			
No	1,395 (74)	616 (74)	779 (71)
Yes	488 (26)	173 (21)	315 (29)
Chemotherapy [*n* (%)][d]			
No	1,401 (73)	581 (72)	820 (74)
Yes	510 (27)	221 (28)	289 (26)
Body composition			
BMI [kg/m^2, n (%)][e]			
<20	67 (4)	44 (6)	23 (2)
20–24.9	629 (37)	278 (40)	351 (30)
25–29.9	728 (42)	254 (31)	474 (47)
≥30	295 (17)	124 (15)	171 (17)
Visceral adipose tissue [cm^2, median (IQR range)]	145 (76–219)	93 (47–150)	186 (117–260)
Subcutaneous adipose tissue [cm^2, median (IQR range)]	156 (112–215)	189 (137–256)	136 (105–183)
Skeletal muscle index [cm^2/m^2, mean (SD)]	46.8 (8.8)	40.4 (5.9)	51.3 (7.7)
Skeletal muscle radiodensity [HU, mean (SD)]	34.2 (9.3)	32.0 (10.0)	35.7 (8.5)

Abbreviations: BMI, body mass index; HU, Hounsfield unit.
[a]Tumor location data of 47 patients missing.
[b]Comorbidity data of 106 patients missing.
[c]Radiotherapy data of 115 patients missing.
[d]Chemotherapy data of 87 patients missing.
[e]BMI data of 279 patients missing.

Body composition

Skeletal muscle, VAT, and SAT cross-sectional areas were quantified on CT images at the level of the third lumbar vertebrae with the use of Slice-O-Matic software version 5.0 (Tomovision). Standard radiodensity thresholds, measured in Hounsfield units (HU), were used to quantify the cross-sectional areas of VAT, SAT, and skeletal muscle. Threshold values were between −150 and −50 HU for VAT, between −190 and −30 HU for SAT, and between −29 and +150 HU for skeletal muscle (33, 34). The skeletal muscle cross-sectional area (cm^2) was adjusted for height (cm^2/m^2) to calculate the skeletal muscle index (SMI). Skeletal muscle radiodensity (32) was assessed as the mean radiographic density of the total skeletal muscle cross-sectional area. Total adipose tissue (TAT) was calculated as the sum of VAT and SAT.

Medical history and mortality

For both the COLON and EnCoRe study, data on age, sex, type of cancer, stage of disease, comorbidities, and date of surgery were collected from medical records. For the registry-based dataset, these data were retrieved from the Netherlands Cancer Registry. Mortality data (i.e., vital status and date of death) were retrieved from the Municipal Personal Records Database.

Statistical analyses

Demographic and clinical characteristics are presented as median and interquartile range (IQR) for continuous variables that were not normally distributed (SMI, VAT, SAT, and follow-up time). Mean and SD are presented for continuous variables that followed a normal distribution. Frequency and percentages are presented for categorical variables.

RCS analyses (26) were used to investigate associations of SMI, VAT, and SAT with mortality, and to assess whether associations were non-linear. Knots were places at the 5th, 50th, and 95th percentiles of SMI, VAT, or SAT. HRs for the RCS analyses were calculated using the median as the reference. All analyses were stratified into men and women. On the basis of literature, the RCS analyses for abdominal SMI, VAT, and SAT were adjusted for age and stage of the disease. Other variables, that is, tumor location (colon or rectum), number of comorbidities (0, 1, or ≥2), neoadjuvant and/or adjuvant treatment (chemotherapy yes or no, radiotherapy yes or no), cohort (COLON or EnCoRe or registry-based), height (continuous, in the VAT and SAT analyses), skeletal muscle radiodensity (continuous), SMI (continuous, in the VAT and SAT analyses), VAT (continuous, in the SMI and SAT analyses), SAT (continuous, in the SMI and VAT analyses), and TAT (continuous, in the SMI analyses) were included in the final models if they changed the HR for mortality in any of the models with at least 10% when the potential confounder was individually added to the model. On the basis of these analyses, skeletal muscle radiodensity, SMI, chemotherapy, and radiotherapy were identified as confounding variables. Additional to the RCS plots, HRs with 95% confidence intervals for specific SMI, VAT, and SAT values were calculated using the RCS analyses.

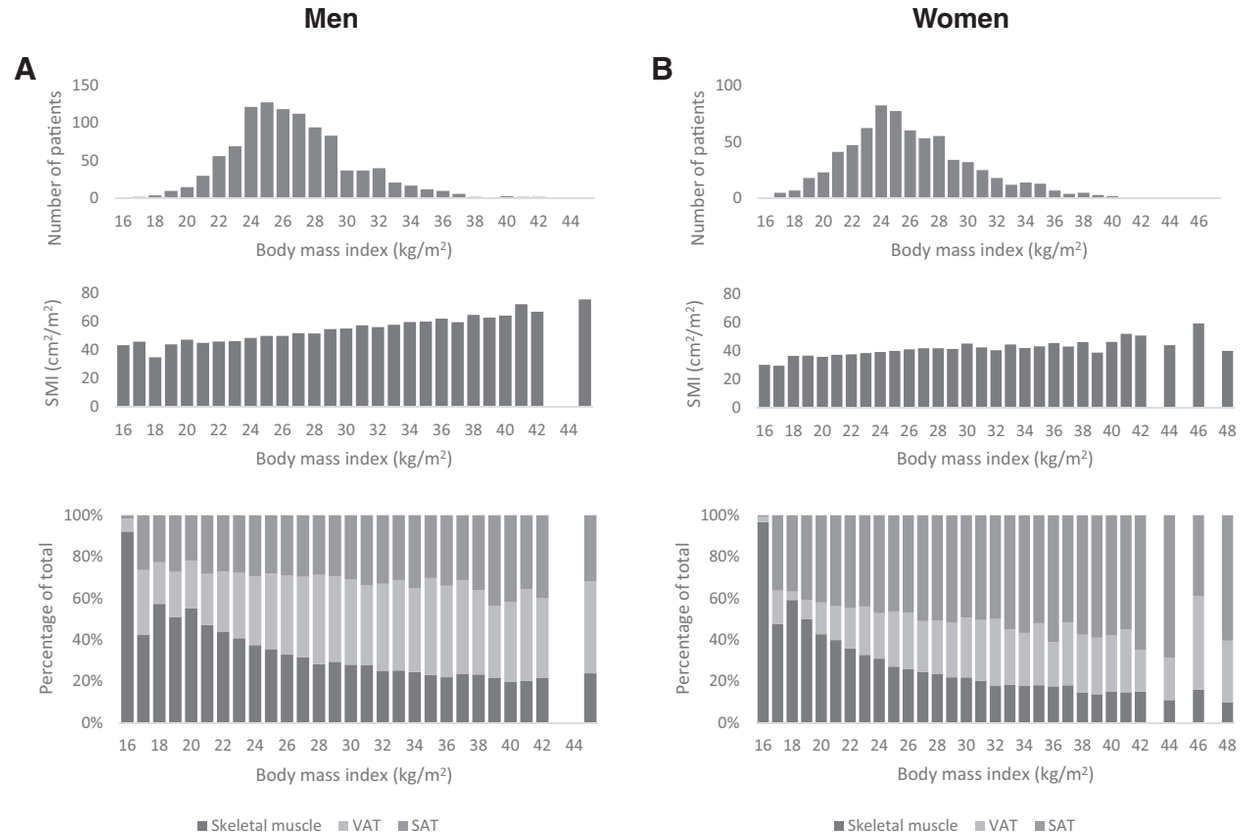


Figure 2.

Top, number of patients per BMI category. Middle, mean absolute values of skeletal muscle index (SMI) per BMI category among men (**A**) and women (**B**). Bottom, mean relative distribution of skeletal muscle, VAT, and SAT by BMI categories among men (**A**) and women (**B**).

A sensitivity analysis was performed excluding all patients who died within 30 days of surgery, as those patients most likely died due to postoperative complications.

Overall mortality was defined as number of days between date of the CT image and date of death or January 31, 2017. Patients still alive on this date were censored in the survival analyses.

Level of significance was set at 0.05. Analyses were performed using IBM SPSS Statistics software (version 23.0, SPSS Inc.) and SAS software (version 9.4, SAS Institute Inc).

Results

In total, 2,618 eligible patients with colorectal cancer were identified; 552 of them were excluded because no suitable CT image was available, and 68 were excluded due to missing stage of disease data (**Fig. 1**). The final dataset consisted of 1,998 patients; 703 of them were participants from the COLON study, 154 were participants from the EnCoRe study, and 1,141 came from the registry-based dataset (Supplementary Table S2 describes baseline characteristics of the separate cohorts).

Table 1 shows the demographic and clinical characteristics for the total study population. The average age of the included patients was 67.9 ± 10.6 years, 58% of the patients were men, and 33% of the patients were diagnosed with rectal cancer. The majority of the patients were diagnosed with stage III of the disease (42%). Forty-two percent of the population was overweight (BMI 25–30 kg/m^2), and 17% was obese (BMI ≥30 kg/m^2). On average, men had more VAT and SMI and less SAT than women. The median follow-up time was 51 months and during this period, 546 (27%) patients died.

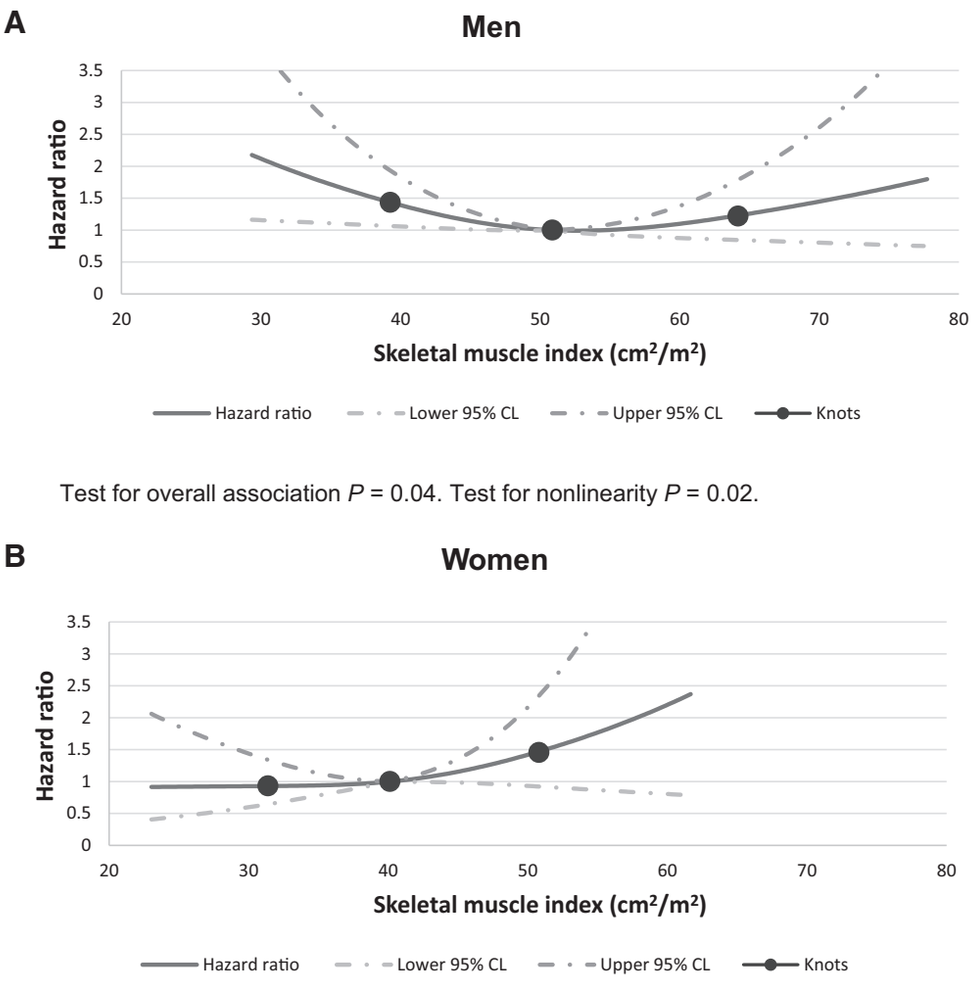


Figure 3.

The association of SMI and mortality among patients with colorectal cancer stratified into men (**A**) and women (**B**), adjusted for age and stage of disease, radiotherapy, chemotherapy, and skeletal muscle density with three knots located at the 5th, 50th (reference), and 95th percentiles of the distribution ofSMI.

Table 2. Estimated hazard ratios for specific SMI, VAT, and SAT values and mortality, with median values as the reference category (i.e., for skeletal muscle index: men 50.8 cm^2/m^2, women 40.2 cm^2/m^2; for visceral adipose tissue: men 185.6 cm^2, women 93.3 cm^2; for subcutaneous adipose tissue: men 136.4 cm^2, women 188.3 cm^2).

Men		Women	
	HR (95% CI)		HR (95% CI)
SMI (cm^2/m^2)[a]		SMI (cm^2/m^2)[a]	
40	1.39 (1.06–1.83)	30	0.93 (0.60–1.44)
45	1.15 (1.01–1.30)	35	0.94 (0.78–1.13)
50	1.01 (1.00–1.02)	40	1.00 (0.99–1.00)
55	1.00 (0.92–1.09)	45	1.15 (0.98–1.36)
60	1.10 (0.88–1.38)	50	1.42 (0.93–2.16)
VAT (cm^2)[b]		VAT (cm^2)[b]	
100	1.16 (0.97–1.38)	50	1.05 (0.85–1.30)
150	1.05 (0.99–1.11)	100	1.00 (0.97–1.02)
200	0.99 (0.97–1.01)	150	1.00 (0.87–1.16)
250	0.99 (0.92–1.08)	200	1.06 (0.81–1.38)
300	1.04 (0.88–1.23)	250	1.14 (0.72–1.80)
SAT (cm^2)[b]		SAT (cm^2)[b]	
50	2.12 (1.49–3.01)	100	1.44 (1.09–1.90)
100	1.31 (1.16–1.48)	150	1.14 (1.03–1.26)
150	0.94 (0.91–0.97)	200	0.98 (0.95–1.00)
200	0.85 (0.74–0.97)	250	0.94 (0.84–1.04)
250	0.89 (0.63–1.17)	300	0.98 (0.81–1.18)

[a]Adjusted for age and stage of disease, radiotherapy, chemotherapy, and skeletal muscle density.
[b]Adjusted for age and stage of disease, radiotherapy, chemotherapy, skeletal muscle density, and SMI.

Baseline characteristics were similar for included and excluded patients. Of the excluded patients, 59% were men, mean age was 70.6 years, 36% had rectal cancer, and of the excluded patients with stage of disease data available (68%), 26% had stage I disease, 35% stage II, and 40% stage III colorectal cancer.

Distribution of abdominal skeletal muscle, VAT, and SAT by BMI categories among men and women are shown in **Fig. 2**. These figures illustrate that among men, VAT tended to increase with increasing BMI, while for women, SAT tended to increase with increasing BMI. Moreover, the figure shows that with increasing BMI, absolute SMI increased, but more so among men than among women.

In the RCS analyses, SMI was associated with mortality in a nonlinear way among men ($P = 0.04$), but no significant association between SMI and mortality was observed for women ($P = 0.21$; **Fig. 3A** and **B**). **Table 2** shows estimated HRs for specific SMI values and illustrates that among men, lower levels of SMI were significantly associated with higher mortality but that among women, no statistically significant associations are apparent.

For VAT, the RCS analyses showed that VAT was not significantly associated with mortality either in men ($P = 0.21$), or in women ($P = 0.79$; **Fig. 4A** and **B**).

The RCS analyses for SAT showed that among men and among women, SAT was associated in a nonlinear way with mortality ($P < 0.01$ and $P = 0.02$, respectively; **Fig. 5A** and **B**). **Table 2** shows that SAT levels below the median were associated with higher mortality in both men and women.

Sensitivity analyses excluding all patients who died within 30 days postsurgery ($n = 41$) did not substantially alter the shape of any of the splines (Supplementary Figs. S1–S3; Supplementary Table S1). However, the results for the analyses for SMI among men no longer reached statistical significance ($P = 0.10$).

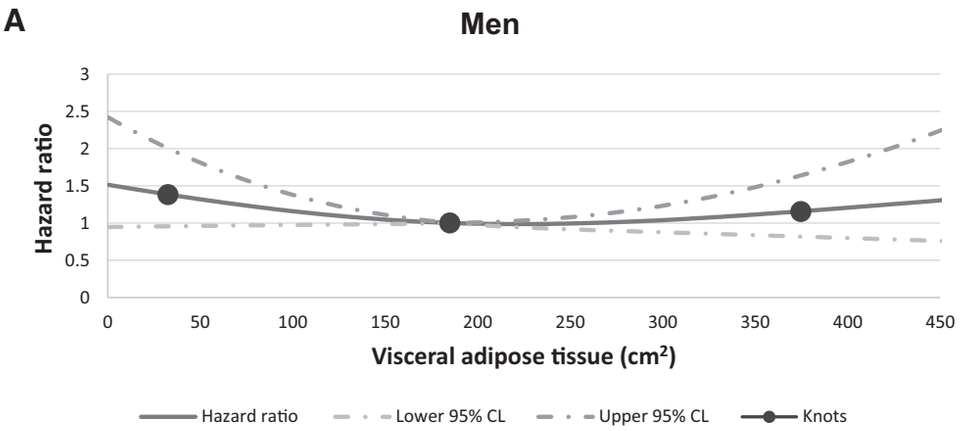
Discussion

In this study, lower abdominal SMI levels were associated with higher overall mortality among men, but not among women. Lower abdominal SAT levels were associated with higher overall mortality among men and among women. VAT was not associated with overall mortality among men or women.

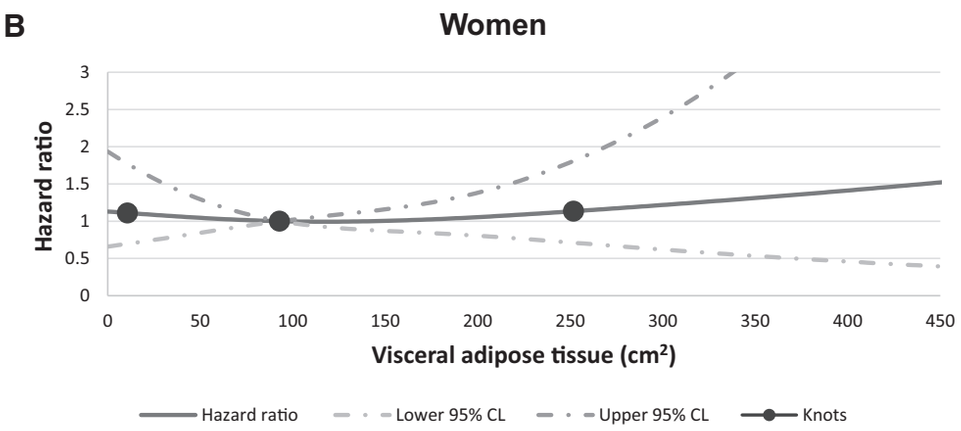
Our findings that lower abdominal SMI levels were associated with higher mortality among men, but not among women, are in agreement with findings in a U.S. cohort of patients with stage I–III colorectal cancer (12). The splines presented in that paper also show no association between abdominal SMI and mortality among women (*P* for overall significance of the spline = 0.72), and a significant association among men (*P* for overall significance of the spline = 0.05). In both the current and the U.S. study, the HR did not increase among women with lower SMI level. Interestingly, in the current study, higher levels of SMI among women were associated with increased risk of mortality, although this was not statistically significant. Because higher SMI levels in general are correlated with higher levels of adipose tissue, one could hypothesize that the higher HR is actually a result of having more adipose tissue. However, adjustment for TAT (or VAT or SAT) did not change this HR and for that reason TAT, VAT, or SAT were not included as possible confounding factors in those analyses. Therefore, the potential higher risk of mortality among women with higher SMI was not explained by having more adipose tissue.

Other studies may have decided not to stratify by sex, because they were too small (9–11). Other cohorts of (healthy) elderly populations found differences between men and women in associations of body composition and mortality although data were not fully consistent (35). Sex-related differences in inflammation levels seen with muscle wasting (36) may be part of the mechanism of why there are sex-related differences in the association of skeletal muscle mass with mortality. In addition, age-related changes in muscle mass have been hypothesized to differ between men and women (28), which could shed further light on why associations with mortality could differ between men and women, but the exact mechanisms remain to be fully elucidated. Our findings stress the importance of the recent increase of attention for sex-related differences in biomedical research (37).

We showed that lower abdominal SAT levels were associated with higher mortality among men and among women with stage I–III colorectal cancer. This is in agreement with a recent study among patients with stage I–III colorectal cancer where splines were used to investigate the association of abdominal SAT and mortality (18). Notably, however, having higher levels of SAT was associated with lower risk of mortality in that study, which is something that we did not observe in our data. A possible explanation for this discrepancy can be that we chose to use the median as reference value in our splines, while the other study elected to use a SAT level of 50 cm^2 as reference value (18). Moreover, the variation in SAT levels in our study was lower in our cohort than in the published study: in our study, 95% of the men had a SAT level below 272.1 cm^2 and 95% of the women had a SAT level below 398.4 cm^2 while a substantial number of participants had SAT levels above 400 cm^2 in the other published study. This lower range of SAT values in our study is the result of a lower average BMI in the population in the Netherlands, relative to the BMI distribution in



Test for overall association $P = 0.21$. Test for nonlinearity $P = 0.10$.



Test for overall association $P = 0.79$. Test for nonlinearity $P = 0.52$.

Figure 4.
The association of VAT and mortality among patients with colorectal cancer stratified into men (**A**) and women (**B**), adjusted for age and stage of disease, radiotherapy, chemotherapy, skeletal muscle density, and skeletal muscle index with three knots located at the 5th, 50th (reference), and 95th percentiles of the distribution of VAT.

the United States (38). As a result, we had less statistical power to detect associations, especially for SAT values, in the upper/high range.

Our results for abdominal SAT are not in agreement with analyses in a cohort of patients with colorectal cancer from the United States (12). In that analysis, no associations were observed for abdominal SAT and mortality. We hypothesize that this inconsistency is the result of methodologic differences in the statistical analysis between those results and the results presented in the current article. The U.S. study (12) only reported on risk associated with high SAT (highest tertile) versus lower SAT (reference group consisting of participants in the lowest two tertiles). This categorization may not have been optimal to detect a potential increased risk of mortality with lower levels of SAT. This underlines the importance of using splines to explore the potential associations of features of body composition and mortality (39). Studies among other cancer populations have also reported a statistically significant association between low abdominal SAT versus normal/high abdominal SAT and higher mortality (13, 40, 41). The potential mechanism of why low SAT may be associated with increased risk of mortality remains to be established, but low SAT areas may be a sign of minimal metabolic reserves, which may explain why these patients have a higher mortality (42).

VAT was not significantly associated with worse survival in our population, which is consistent with three other studies (11, 12, 16), but not with two other studies (15, 18). As mentioned before, one of those earlier studies used splines to investigate the association of VAT and mortality. That study observed that among women, higher levels of VAT were associated with higher mortality relative to a reference value of 50 cm^2, and that among men, having VAT levels of ∼100–300 cm^2 was associated with lower mortality compared with the reference value of 50 cm^2. As also argued in the earlier paragraph on the SAT findings, an important factor to consider is what was chosen as the reference group. In our analyses, we chose the median value as reference value, while in the other study a (very low) VAT level of 50 cm^2 was chosen as reference value. Moreover, the range of values in VAT is smaller in our cohort than in the cohort from the United States. From the splines reported in that article, it is apparent that the increased risk of mortality with increasing VAT levels reached statistical significance when levels of VAT were above approximately 200 cm^2. In our dataset, only a limited number of women had VAT levels above that value, and thus our statistical power to observe associations was limited. In addition, contrary to the other study, we adjusted our analyses for VAT for skeletal muscle radiodensity. This adjustment attenuated our

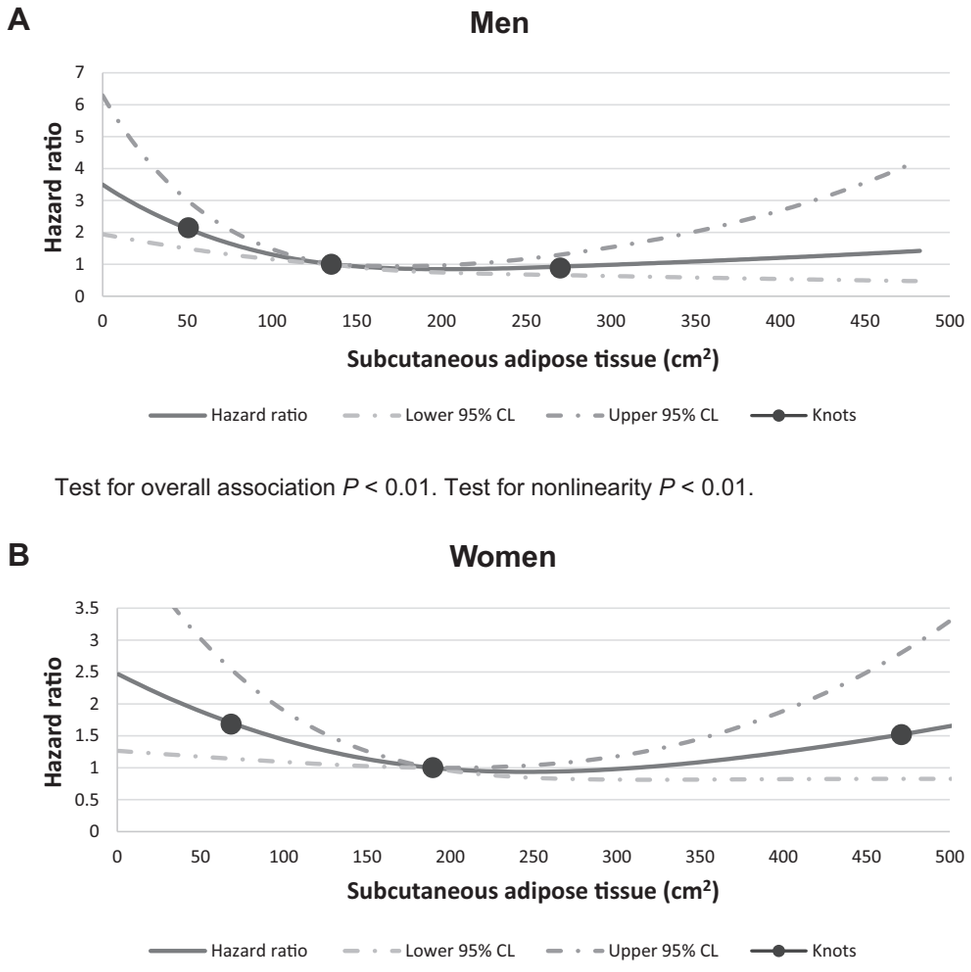


Figure 5.

The association of subcutaneous adipose tissue and mortality among patients with colorectal cancer stratified into men (**A**) and women (**B**), adjusted for age and stage of disease, radiotherapy, chemotherapy, skeletal muscle density, and SMI with three knots located at the 5th, 50th (reference), and 95th percentiles of the distribution of SAT.

HR with more than 10%, while the other study chose not to adjust for it. Thus, this discrepancy can partly explain the different findings. Although more research on this topic is warranted, a conclusion could be that the increased risk of higher levels of VAT is evident mostly among very high levels of VAT, and this is most relevant for populations with extremely high BMI.

This study has some limitations. Almost one quarter of the patients in the original dataset had to be excluded, mostly due to unavailable or unusable CT images. Nevertheless, sex, age, and stage distribution were largely similar for in- and excluded patients, so we are confident that excluding these patients did not affect our findings substantially. This study consisted of data from three independent studies. The size of the separate studies was too small to conduct separate analysis for the different studies. However, Supplementary Table S2 shows that characteristics are generally similar across cohorts, thus we are confident that results are similar across cohorts and across the total cohort. As in any observational study, we might miss data of unknown confounders which could influence the observed associations and lead to residual confounding.

Strengths of this study were the large study population and the use of CT images to assess body composition. Furthermore, this is the largest European study with information on body composition, clinical factors, and personal factors thus far. Although earlier large-scale studies in U.S./Canadian populations have been performed, the differences in body composition (related to a generally lower BMI in Europe; ref. 38) underline the necessity to study these associations in European populations. Further studies, including even more diverse populations, for example Asian or African cohorts, could shed further light on associations between body composition and colorectal cancer prognosis.

In conclusion, in this large-scale study among patients with stage I–III colorectal cancer, lower abdominal SMI levels were associated with higher mortality among men, but not among women. Lower abdominal SAT levels were associated with higher

overall mortality in both men and women. An association between VAT and mortality was not observed. Our results show the utility and importance of using splines to explore relationships of features of body composition and mortality. Furthermore, our findings underline the importance for more attention to sex-related differences in body composition and cancer outcomes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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Acknowledgments

The authors would like to thank all participants, the involved coworkers in the participating hospitals, and the COLON investigators at Wageningen University & Research. The COLON study was financially supported by: Wereld Kanker Onderzoek Fonds (WKOF) and World Cancer Research Fund International (WCRF International; principal investigator: E. Kampman) as well as by funds from grant 2014/1179 as part of the World Cancer Research Fund International Regular Grant Programme (principal investigator: E. Kampman and R.M. Winkels); Alpe d'Huzes/Dutch Cancer Society [UM 2012-5653 (principal investigator: M.P. Weijenberg), UW 2013-5927 (principal investigator: F.J.B van Duijnhoven), UW 2015-7946 (principal investigator: F.J.B van Duijnhoven)]; ERA-NET on Translational Cancer Research [TRANSCAN: Dutch Cancer Society (UW2013-6397, UW2014-6877 (principal investigator for both: E. Kampman) and the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands (principal investigator: E. Kampman)]. The EnCoRe study was supported by a grant from the Stichting Alpe d'HuZes within the research program 'Leven met kanker' of the Dutch Cancer Society [grant no. UM-2010-4867 (principal investigator: M.P. Weijenberg)] and by a grant from 'Kankeronderzoekfonds Limburg' as part of Health Foundation Limburg [grant no. 00005739 (principal investigator: M.P. Weijenberg)].

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Received September 16, 2019; revised December 12, 2019; accepted February 25, 2020; published first March 4, 2020.

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