Association of Abdominal Visceral Adiposity and Total Fat Mass with Cancer Incidence and Mortality in White and Black Adults

Peter T. Katzmarzyk[1], Justin C. Brown[1,2,3], Shengping Yang[1], Emily F. Mire[1], Xiao-Cheng Wu[2,3,4], Lucio Miele[2,3], Augusto C. Ochoa[2,3], and Jovanny Zabaleta[2,3]

ABSTRACT

Background: Race modifies the association between anthropometric measures of obesity and cancer risk. However, the degree to which abdominal visceral adipose tissue (VAT) and total fat mass (FM) are associated with cancer risk is not known.

Methods: The sample included 3,017 White and 1,347 Black adults who were assessed between 1995 and 2016 and followed for outcome assessment through 2017. Abdominal VAT and FM were measured using imaging techniques. The co-primary endpoints were diagnosis of histologically confirmed invasive cancer (excluding nonmelanoma skin cancer) or death from cancer. Multivariable Cox proportional hazards models quantified the HR of incident cancer and cancer mortality.

Results: There were 353 incident cancer cases and 75 cancer deaths in an average of 12.9 years of follow-up. Both VAT [HR, 1.21; 95% confidence interval (CI), 1.09–1.36] and FM (HR, 1.25; 95% CI, 1.10–1.43) were significantly associated with incident cancer, while VAT (HR, 1.28; 95% CI, 1.01–1.61) was significantly associated with cancer mortality after adjustment for several covariates. VAT remained significantly associated with cancer incidence (HR, 1.22; 95% CI, 1.03–1.46) after additional inclusion of FM in the multivariable model, but not vice versa. There were no significant sex- or race-interactions.

Conclusions: VAT was associated with risk of cancer and cancer mortality in this cohort, and the associations did not differ by sex or race. The association between VAT and incident cancer was largely independent of total FM.

Impact: Our results suggest that utility of anthropometry in assessing obesity-related cancer risk may need to be further refined by including more direct measures of adiposity.

Introduction

Obesity increases the risk of several cancers as well as the risk of cancer mortality (1, 2). To date, 13 obesity-related cancers have been identified which show sufficient evidence of association in humans (2). Furthermore, Black Americans have the highest mortality rates for obesity-related cancers and for developing major cancers (3). A recent study from the National Health and Nutrition Examination Survey reported that Black Americans were 2.1 times as likely to have an obesity-related cancer compared with White Americans (4). In Louisiana, the incidence rates for obesity-related cancer is 13.3% higher in Blacks than Whites based on 2013 to 2017 data (5). On the other hand, we recently reported that race modified the association of body mass index (BMI) with cancer incidence; in White men, a BMI of 35 kg/m^2 was associated with a HR of 1.83 [95% confidence interval (CI), 1.58–2.12] compared with a BMI of 22 kg/m^2, whereas in Black men, the HR was 0.89 (95% CI, 0.72–1.11; ref. 6). Among women, race did not modify the association of BMI with cancer incidence. In a similar vein, results from our cohort also showed that obesity increased risk of cancer death in White men and women, reduced risk of cancer death in Black men, and did not influence the risk of cancer death in Black women (7). More studies are required to further delineate the risk of obesity-related cancers in across race/ethnic groups.

Beyond total adiposity, abdominal visceral adipose tissue (VAT) is considered to be a marker of metabolic dysfunction, and is associated with an increased risk of cardiometabolic disease (8) and premature mortality (9, 10). Several studies have demonstrated that White Americans have higher levels of VAT compared with Black Americans, even after adjustment for levels of total adiposity (11–14). Further, for a given BMI or waist circumference, Black adults have lower levels of VAT compared with White adults (15). The degree to which VAT or fat mass (FM) are associated with cancer risk in White and Black adults is not known. Therefore, the purpose of this study was to examine the association between abdominal VAT, FM, and cancer incidence and mortality in a biracial cohort.

Materials and Methods

Sample

The Pennington Center Longitudinal Study (PCLS) is a prospective cohort study of the effects of obesity and lifestyle factors on the development of chronic diseases and premature mortality (ClinicalTrials.gov: NCT00959270). The sample includes participants in clinical studies conducted at the Pennington Biomedical Research Center. These studies included physical activity and dietary interventions, weight loss, and other metabolic studies. All data for these analyses

[1]Pennington Biomedical Research Center, Baton Rouge, Louisiana. [2]LSU Health Sciences Center New Orleans School of Medicine, New Orleans, Louisiana. [3]Stanley S. Scott Cancer Center, Louisiana State University Health Sciences Center, New Orleans, Louisiana. [4]Louisiana State University Health Science Center School of Public Health/Louisiana Tumor Registry, New Orleans, Louisiana.

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

Corresponding Author: Peter T. Katzmarzyk, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808. Phone: 225-763-2536; E-mail: Peter.Katzmarzyk@pbrc.edu

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were obtained from cross-sectional studies and from baseline exams in intervention studies. All procedures were approved by the Pennington Biomedical Research Center Institutional Review Board and participants provided written informed consent.

The full PCLS sample currently includes 19,910 participants. The full sample of participants with baseline measures of abdominal VAT in the PCLS included 4,856 adults. After exclusion of participants ≥90 years of age ($n = 174$), with <1 year of follow-up ($n = 152$), with a history of cancer at baseline ($n = 38$), or a reported race other than Black or White ($n = 128$), the analytical sample included 4,364 adults (3,017 White; 1,347 Black; See Supplementary Fig. S1). Compared with the 15,546 participants from the full cohort who were excluded from the analysis, the analytical sample of 4,364 participants was significantly older (45.0 vs. 42.3 years), taller (168.5 vs. 168.2 cm), weighed less (87.5 vs. 88.2 kg), and had a lower BMI (30.8 vs. 31.2 kg/m^2). Although these differences were statistically significant ($P < 0.05$), they are small from a clinical perspective. The subsample of participants who additionally had measurements of dual-energy x-ray absorptiometry (DXA)-measured FM was 3,842. Participants were assessed at baseline between 1995 and 2016 and followed for outcome assessment through 2017.

Primary exposures

The co-primary exposures were abdominal VAT and total body FM. Abdominal VAT was measured by either CT at the L4–L5 vertebral level (cm^2; $n = 1,038$) as previously described (13) or by DXA ($n = 3,326$). Two types of DXA scanners were used to estimate VAT. A Hologic whole-body scanner (QDR4500, $n = 3,047$; Bedford, MA) was used to estimate VAT using APEX software (Version 4.0) as previously described (16, 17). The software estimates abdominal VAT within a 5-cm abdominal region, with the bottom edge located 1 cm above the iliac crest. VAT is estimated by measuring total FM and subtracting subcutaneous fat between the skin line and outer abdominal wall (17). A General Electric iDXA whole body scanner ($n = 279$; GE Medical Systems, Milwaukee, Wisconsin) was used to estimate VAT using enCORE software (Version 13.6). The abdominal region is automatically defined between the top of the iliac crest to a point 20% of the distance from the top of the iliac crest to the base of the skull. Abdominal subcutaneous fat and VAT are estimated within this region of interest using automated software (18). Both the CT and iDXA VAT estimates were converted to Hologic estimates of VAT using regression procedures (CT: $y = 0.88x + 18.3$, $R^2 = 0.84$; SEE = 24.7; $n = 101$; iDXA: $y = 0.06x + 29.5$, $R^2 = 0.93$, SEE = 10.8; $n = 32$) and combined for analysis.

Total body FM (in kg) was estimated by DXA using a Hologic whole-body scanner (QDR4500, $n = 3,048$ or QDR2000; $n = 514$; Bedford, MA) as previously described (13) or a General Electric iDXA whole body scanner ($n = 280$; GE Medical Systems, Milwaukee, Wisconsin). The iDXA values were converted to Hologic QDR4500 values using regression procedures in a sample of 32 participants who had both measures ($y = 0.90x - 0.57$, $R^2 = 0.97$; SEE = 1.34), and data were combined for analysis.

Covariates

Information on covariates was collected from participants at baseline. Age was computed from birth and enrollment dates and was coded as a continuous variable. Participants were asked to self-report their race with a single selection, and those coded as Black or White were retained for the current analysis. Smoking status was self-reported at baseline and was coded in the categories of never, former, current. Anthropometric measurements (weight, height, waist circumference) were obtained using standard procedures as described elsewhere (19), and BMI was computed [weight (kg)/height (m)^2]. The year of the baseline was included as a covariate to account for potential temporal trends.

Outcomes

The co-primary endpoints for this analysis were incident cancer or death attributable to cancer. The secondary endpoints included incident obesity-related cancer and death from obesity-related cancer.

Histologically confirmed cases of invasive cancer (excluding nonmelanoma skin cancer) were adjudicated by a blinded tumor registrar through the Louisiana Tumor Registry (LTR). The LTR is a population-based registry funded by the Surveillance, Epidemiology and End Results Program (NCI) and the National Program of Cancer Registries (Centers for Disease Control and Prevention; ref. 20). The LTR collects and adjudicates incident cancer data for 100% of Louisiana's population (21). A secondary endpoint included time from baseline to a diagnosis of an obesity-related cancer. Obesity-related cancers included the 13 malignancies identified by the International Agency for Research on Cancer as being convincingly related to obesity, including renal cell kidney, colon and rectum, gastric cardia, esophageal adenocarcinoma, pancreas, gallbladder, liver, postmenopausal breast, uterine, ovarian, thyroid, meningioma, and multiple myeloma (2). Participants were followed through December 31, 2017. Postmenopausal breast cancer was defined as a breast cancer diagnosed in a woman ≥51 years of age, or who indicated that she was postmenopausal at the baseline visit.

Cancer deaths were identified by linking the PCLS data to the National Death Index. Deaths were included if cancer was documented as an underlying or contributing cause of death on the death certificate. All participants were followed for death through December 31, 2017.

Statistical analysis

Differences between groups at baseline were assessed using ANOVA and TUKEY *post hoc* multiple comparisons. Multivariable adjusted Cox proportional hazards survival models quantified the cause-specific HR of incident cancer and cancer mortality with 95% CI. We present the results from two models where HRs are expressed per standard deviation of VAT (70.9 cm^2) or FM (12.4 kg). Model 1 included age, sex, race, and exam year as covariates; Model 2 additionally included smoking status and the other primary exposure variable (i.e., either VAT or FM). Analyses were performed on the combined sample of White and Black participants. Race and sex interaction terms were included in the models. However, when they were not statistically significant, race- or sex-stratified analyses were not performed, and the interaction terms were removed from the models prior to presenting the main effects of VAT and FM. We conducted a sensitivity analysis by using only those participants who were measured with the Hologic DXA scanner ($n = 3,047$). To assess potential nonlinear relationships with cancer incidence/mortality, VAT area and FM were also modeled using B-splines, to provide visual depictions of associations (22). We additionally modeled the association between adiposity and all-cause mortality.

The proportional hazards assumption was confirmed by visual inspection of log–log plots and statistical testing in a generalized linear model of the scaled Schoenfeld residuals on time (23).

Data availability

The data used in this study are available upon reasonable request from the corresponding author.

Table 1. Characteristics of participants from the PCLS.

	Overall cohort	Men		Women	
		White	Black	White	Black
N	4,364	1,303	348	1,714	999
Age, y	45.1 (15.0)	45.3 (16.0)[a]	38.1 (14.8)[b]	48.3 (14.4)[c]	41.6 (13.3)[d]
Height, cm	168.5 (9.4)	177.4 (6.6)[a]	177.2 (6.8)[a]	163.0 (6.4)[b]	163.3 (6.1)[b]
Weight, kg	87.5 (19.2)	94.6 (17.7)[a]	93.8 (17.9)[a]	80.7 (18.6)[b]	87.8 (18.4)[c]
BMI, kg/m^2	30.8 (6.3)	30.1 (5.3)[a]	29.9 (5.4)[a]	30.4 (6.7)[a]	32.9 (6.6)[b]
VAT, cm^2	130.4 (70.9)	152.5 (77.3)[a]	100.8 (60.6)[b]	131.5 (69.8)[c]	110.1 (56.2)[b]
FM, kg*	30.6 (12.4)	26.4 (10.9)[a]	22.6 (10.5)[b]	32.9 (12.4)[c]	35.2 (11.6)[d]
Smoking history, *n* (%)					
Never	2,921 (78.2)	815 (73.1)	223 (75.1)	1,092 (76.7)	791 (88.2)
Former	621 (16.6)	263 (23.6)	46 (15.5)	249 (17.5)	63 (7.0)
Current	191 (5.1)	37 (3.3)	28 (9.4)	83 (5.8)	43 (4.8)
Cancer cases, *n* (%)	353 (8.1)	144 (11.1)	24 (6.9)	124 (7.2)	61 (6.1)
Obesity-related cancer cases, *n* (%)	159 (3.6)	30 (2.3)	4 (1.2)	78 (4.6)	47 (4.7)
Cancer death, *n* (%)	75 (1.7)	32 (2.5)	2 (0.6)	33 (1.9)	8 (0.8)
Obesity-related cancer deaths, *n* (%)	39 (0.9)	12 (0.9)	1 (0.3)	20 (1.2)	6 (0.6)

Note: Participants with known history of cancer were excluded. Results for continuous variables are presented as mean (SD). Groups with a different superscript letter have significantly different means ($P < 0.05$; Tukey *post hoc* pairwise comparisons).
*$N = 3,842$.

Results

Table 1 presents the baseline characteristics of the biracial sample. The sample was 31% Black race and 62% women. The average age in the cohort was 45.1 years (SD 15.0) while the average BMI was 30.8 (SD 6.3) kg/m^2. There were significant differences among the four race-by-sex groups in several characteristics. Notably, White men and women had higher levels of VAT compared with Black men and women, respectively. Of 4,363 participants, there were 353 incident cancer cases (159 obesity-related cancers; 45%) identified during an average of 12.9 years of follow-up through the LTR, and 75 cancer deaths (39 obesity-related cancer deaths; 52%) in 12.9 years of follow-up through the National Death Index. The distribution of causes of cancer and cancer mortality are presented in Supplementary Table S1.

Cancer incidence

The interactions of race*VAT ($P = 0.67$) and sex*VAT ($P = 0.41$), race*FM ($P = 0.31$) and sex*FM ($P = 0.18$) were not statistically significant in models predicting cancer incidence (**Table 2**); therefore, the sample was analyzed as a whole and interaction terms were removed. In model 1, both VAT (HR, 1.21; 95% CI, 1.09–1.36) and FM (HR, 1.25; 95% CI, 1.10–1.43) were significantly associated with incident cancer. However, after the inclusion of smoking status and the other primary outcome, only VAT remained significantly associated with cancer incidence (HR, 1.22; 95% CI, 1.03–1.46).

Figure 1 presents the results of the B-splines analyses. In model 1, the association between VAT and incident cancer is primarily linear; however, the association between FM and incident cancer has a nonlinear relationship ($P = 0.04$). In model 2, a similar linear association was observed for VAT; however, the linear and nonlinear components of the association with FM was no longer significant.

Cancer mortality

The interactions of race*VAT ($P = 0.23$) and sex*VAT ($P = 0.96$), race*FM ($P = 0.49$) and sex*FM ($P = 0.88$) were not statistically significant in models predicting cancer mortality, therefore the sample was analyzed as a whole (**Table 2**). In model 1, only VAT (HR, 1.27; 95% CI, 1.01–1.61) was significantly associated with cancer mortality. No other associations were statistically significant.

Figure 2 presents the results of the B-splines analyses. In model 1, the association between VAT and cancer mortality is primarily linear; however, the association between FM and incident cancer mortality was not significant. In model 2, none of the associations with adiposity were significant.

Table 2. HRs and 95% CIs for cancer incidence and mortality associated with abdominal VAT and total body fat.[a]

	Model 1[b]			Model 2[c]		
	HR (95% CI)	Race interaction	Sex interaction	HR (95% CI)	Race interaction	Sex interaction
Cancer incidence						
VAT	**1.21 (1.09–1.36)**	$P = 0.67$	$P = 0.41$	**1.22 (1.03–1.46)**	$P = 0.92$	$P = 0.24$
FM	**1.25 (1.10–1.43)**	$P = 0.31$	$P = 0.18$	1.08 (0.89–1.31)	$P = 0.14$	$P = 0.27$
Cancer mortality						
VAT	**1.27 (1.01–1.61)**	$P = 0.23$	$P = 0.96$	1.12 (0.77–1.63)	$P = 0.37$	$P = 0.95$
FM	1.18 (0.87–1.59)	$P = 0.49$	$P = 0.88$	1.10 (0.71–1.70)	$P = 0.56$	$P = 0.87$

[a]HR per SD increment in each exposure.
[b]Model 1 includes age, sex, race, and exam year as covariates.
[c]Model 2 includes age, sex, race, exam year, smoking status and the other primary exposure as covariates.

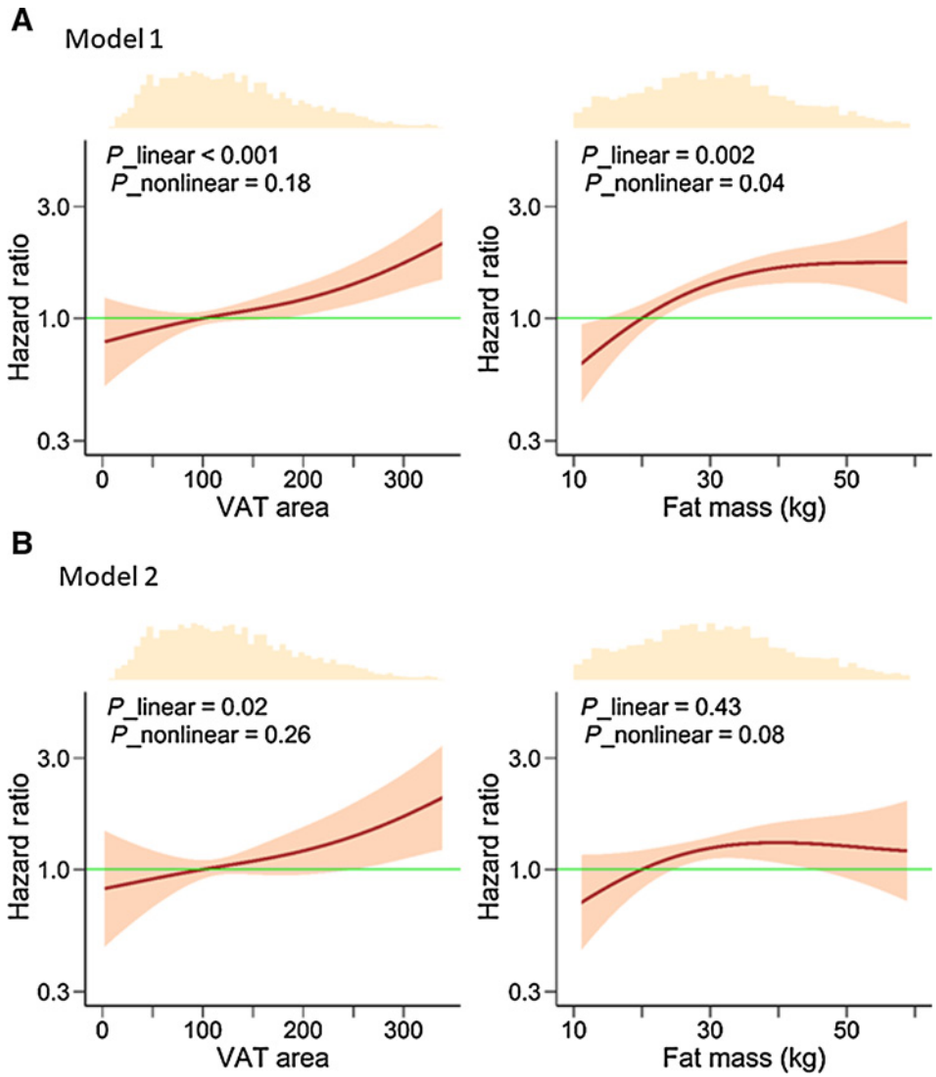

Figure 1.
HRs for incident cancer across levels of VAT and FM derived from multivariable cubic splines analysis. Model 1 (**A**) includes age, sex, race, and exam year as covariates, and Model 2 (**B**) includes these covariates in addition to smoking status and the other primary exposure (i.e., FM or VAT). Shaded regions indicate 95% confidence bands and the histogram atop the figures indicate the distribution of the exposure variable in the sample.

Obesity-related cancer

The results for obesity-related cancers are presented in Supplementary Table S2. None of the sex or race interactions were significant, therefore the sample was analyzed as a whole. In model 1, both VAT (HR, 1.26; 95% CI, 1.06–1.48) and FM (HR, 1.25; 95% CI, 1.04–1.52) were significantly associated with incident cancer. None of the other associations were statistically significant.

All-cause mortality

There were a total of 256 total deaths over the follow-up period. We provide the results for the relationship between adiposity and all-cause mortality in Supplementary Table S3. There was no association between FM and all-cause mortality. There was no association between VAT and all-cause mortality in the overall sample, however there was a significant VAT*sex interaction ($P = 0.04$). In model 1 the association was significant in women (HR, 1.28; 95% CI, 1.06–1.54) but not in men (HR, 0.97; 95% CI, 0.80–1.17). Similarly, in model 2 the association was stronger in women (HR, 1.18; 95% CI, 0.92–1.52) than in men (HR, 0.89; 95% CI, 0.69–1.15).

Sensitivity analysis

We conducted a sensitivity analysis using data from participants measured with the Hologic DXA scanner ($n = 3{,}047$). The results of the sensitivity analysis are presented in Supplementary Table S4. The results are largely the same as those from the primary analysis; VAT and FM were both associated with cancer incidence, and VAT remained associated after inclusion of FM in the model. For mortality, the same trend was evident but VAT was no longer a significant predictor in model 1.

Discussion

The results of this study demonstrate a positive association between VAT and both incident cancer and cancer mortality, and that the risk of cancer associated with VAT does not appear to differ between White and Black adults. FM was also positively associated with incident cancer, but not cancer mortality. In a model that included both primary exposures, VAT was independently associated with cancer incidence but not mortality, while FM was not associated with either

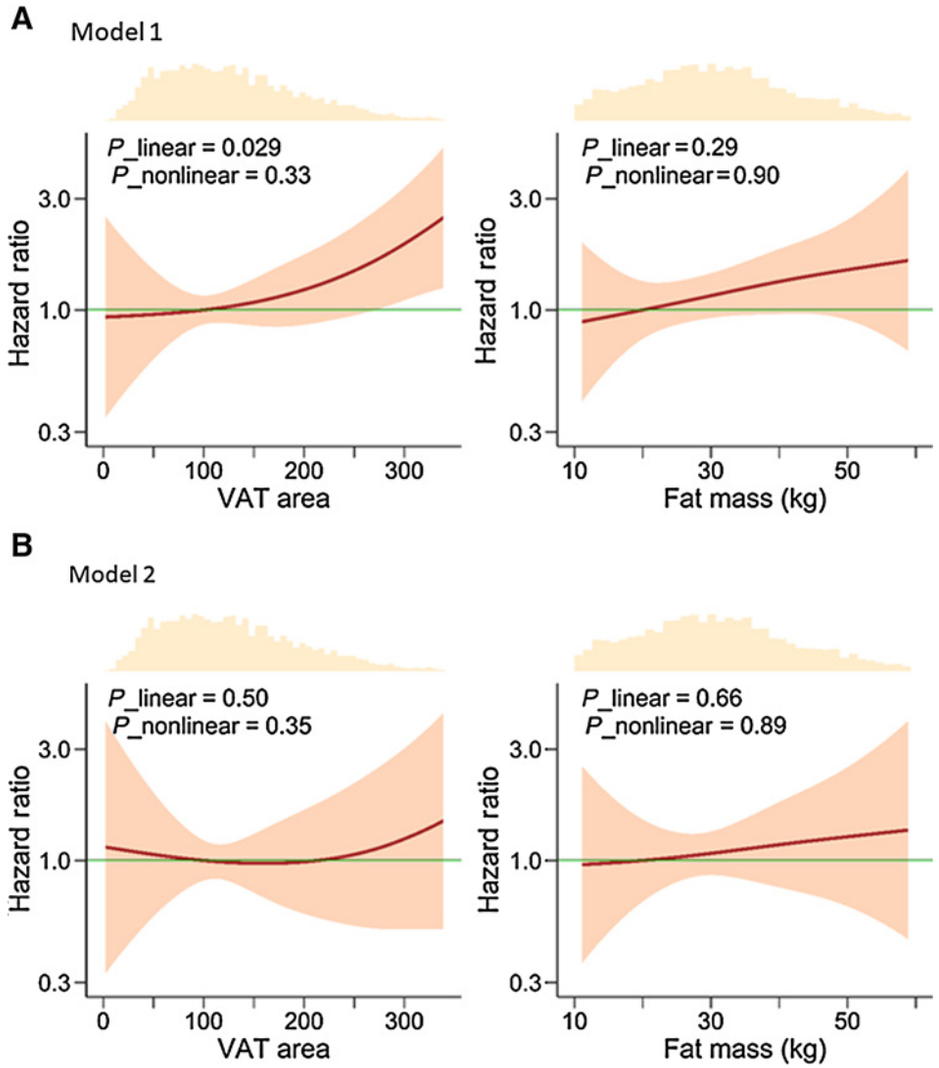

Figure 2.
HRs for cancer mortality across levels of VAT and FM derived from multivariable cubic splines analysis. Model 1 (**A**) includes age, sex, race, and exam year as covariates, and Model 2 (**B**) includes these covariates in addition to smoking status and the other primary exposure (i.e., FM or VAT). Shaded regions indicate 95% confidence bands and the histogram atop the figures indicate the distribution of the exposure variable in the sample.

incidence or mortality. The results of the cubic splines analysis revealed that the associations were largely linear, with the exception of FM and incident cancer, which tended to show a curvilinear association. These results build upon those from previous studies that have documented positive associations between VAT and risk of all-cause mortality (9, 10, 24), and differ from one study that did not result in a positive association (25). Some studies have documented race differences in the association between generalized obesity (i.e., BMI) and all-cause mortality whereby Black women do not experience the increased obesity-related mortality risks observed among White adults (26–28), but little is known about race differences in the association between VAT and mortality.

Studies of the association between VAT and cancer are beginning to appear in the literature. For example, VAT was associated with increased cancer incidence in the Framingham Heart Study Cohort (HR per SD of VAT = 1.43; 95% CI, 1.12–1.84; ref. 25). A dose–response meta-analysis of 6 studies reported a linear association between VAT and colorectal adenomas such that there was a 13% elevated odds of having adenomas for each 25 cm^2 higher VAT area (29). With respect to cancer survival, a recent review of 22 studies found negative associations between VAT and survival among patients with colorectal (four of six studies) and pancreatic (three of five studies) cancers, and positive associations between VAT and survival among patients with renal cell carcinoma (four of five studies; ref. 30). These results highlight the heterogeneity of cancer etiology and factors associated with incidence and survival. There is a need for further studies of the association between VAT and cancer risk.

The results presented here can be placed within the context of obesity and health disparities. Previous results from several studies have demonstrated that Black adults have lower levels of VAT compared with White adults (11–14) and these differences are also evident in childhood (31). Furthermore, Black adults have lower levels of VAT for a given BMI or waist circumference compared with White adults (15), suggesting that the clinical utility of anthropometry in identifying adiposity and obesity-related health risk may differ by race.

There is little information available about race differences in the association between obesity and cancer. A recent meta-analysis involving 6.3 million participants found that obesity was associated with worse survival outcomes among patients with cancer, independent of race, with several types of cancer being exceptions with an inverse association (32). Recent studies from the PCLS have demonstrated that BMI is positively associated with incident cancer and cancer mortality,

but the effects are race- and sex-specific: BMI was positively associated with incident cancer in White men and women and Black women, but not in Black men (6); BMI was positively associated with cancer mortality in White men and women, and a reduced risk of cancer death in Black men, but did not influence the risk of cancer death in Black women (7). Taken together, these results suggest that utility of anthropometry in assessing obesity-related cancer risk may need to be further refined. It may be prudent to rely on more precise measures of adiposity such as those obtained from DXA to inform obesity-related cancer risk.

The potential mechanisms linking adiposity and cancer risk are being investigated (33–35); however, the precise triggers, pathways and metabolic changes that facilitate tumor development and proliferation remain elusive. Overweight and obesity are characterized by nutrient (and energy) excess, which could activate cellular growth factor signaling pathways and increase the risk for tumor formation, progression, and recurrence (33). The positive energy balance underlying weight gain and obesity induces systemic changes in the insulin–IGF-1 axis, sex hormones, and adipocyte-derived cytokines, which in turn may increase the risk for cancer development (34). In particular, high levels of VAT may be a marker of dysfunctional adipose tissue (8), which in turn contributes directly to increased insulin resistance, systemic inflammation and altered sex hormone profiles. Furthermore, dysfunctional adipose tissue is a source of several extracellular matrix proteins, cancer stem cells, cancer-associated adipocytes and adipocyte progenitors (34).

The strengths and limitations of this study warrant discussion. A marked strength of the study is the diverse sample of participants (62% women, 31% Black race) and the rigorous adjudication of outcomes. Another strength is the long period of follow-up and attempt to control for reverse causation by removing participants with a history of cancer at baseline, and exclusion of outcomes that occurred in the first year of follow-up. Furthermore, this study adds to the existing literature by using "gold standard" assessment methods including CT and DXA for the assessment of VAT and overall adiposity. We chose to use VAT measured at the L4L5 vertebral level from the CT; however, this measurement may not be comparable with other studies that used different landmarks such as L2-L3 or L3-L4. While the use of CT to measure abdominal VAT is well-accepted, DXA has also been validated for this purpose (17). In our laboratory, replicate measures of VAT using the Hologic produced a standard error of single determination of 8.1% for measurements obtained 14 days apart (16). Data from a CT scanner and two DXA scanners were combined using regression procedures based on data from individuals measured on more than one scanner on the same day. The concordance between measurements from the different scanners was high ($r>0.90$), but the degree to which variation among the scanners contributed to error in our predictions is not known. This error would have contributed to influencing our point estimates towards the null; thus, our results should be interpreted as conservative. Our sensitivity analysis using data only from the Hologic scanner (Supplementary Table S4) demonstrates similar results as those obtained from the primary analysis.

Unfortunately, our sample size was too small to examine associations between VAT and site-specific cancers, and the small sample sizes in some subgroups warrant caution in interpreting the results. Further, we were unable to adjust for several important covariates, such as family history of cancer, socio-economic status, and lifestyle variables such as diet and physical activity; it was also impossible to control for residual confounding, which is an issue in all observational studies. Our sample was comprised of participants from a variety of cross-sectional studies and longitudinal interventions. All outcomes were measured prior to the initiation of any intervention. While it is unknown how participation in interventions may have impacted the outcomes, we believe this would bias our point estimates towards the null (36). The sample included White and Black adults who were volunteers for research studies, and therefore may not be representative of the general population, However, the racial distribution in our sample (69% White, 31% Black) was similar to that of the Louisiana population (57% White, 31% Black, 13% other/mixed race; ref. 37).

In conclusion, this study found statistically significant associations between imaging-derived measures of adiposity and risk of incident cancer and cancer mortality in this cohort. The associations did not differ by sex or race; however, the sample size was small, especially in some subgroups, therefore caution should be used in interpreting the results. Given that previous studies have demonstrated race differences in VAT, and that associations between anthropometry and cancer may vary by race, these results have important implications for the identification of obesity-related cancer risk using common anthropometric measurements such as BMI or waist circumference. Future studies should further explore the utility of incorporating more direct measures of adiposity in risk stratification models.

Authors' Disclosures

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Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Authors' Contributions

P.T. Katzmarzyk: Conceptualization, resources, formal analysis, funding acquisition, writing–original draft. **J.C. Brown:** Conceptualization, writing–review and editing. **S. Yang:** Formal analysis, writing–review and editing. **E.F. Mire:** Formal analysis, writing–review and editing. **X.C. Wu:** Conceptualization, supervision, writing–review and editing. **L. Miele:** Funding acquisition, writing–review and editing. **A.C. Ochoa:** Funding acquisition, writing–review and editing. **J. Zabaleta:** Funding acquisition, writing–review and editing.

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