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An Analysis of Individual Body Fat Depots and Risk of Developing Cancer: Insights From the Dallas Heart Study

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Abstract

Objective: To examine the association between specific adipose tissue depots and the risk of incident cancer in the Dallas Heart Study.

Patients and Methods: Individuals without prevalent cancer in the Dallas Heart Study underwent quantification of adipose depots: visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue, and liver fat by magnetic resonance imaging, and subcutaneous lower-body fat (LBF) by dual-energy X-ray absorptiometry from January 1, 2000, through December 31, 2002, and were observed for the development of cancer for up to 12 years. Multivariable Cox proportional hazards modeling was performed to examine the association between fat depots and cancer.

Results: Of 2627 participants (median age, 43 years; 69% nonwhite race), 167 (6.4%) developed cancer. The most common primary sites of cancer were the breast (in women) and the prostate (in men). In multivariable models adjusted for age, sex, race, smoking, alcohol use, family history of malignancy, and body mass index, a 1-SD increase in VAT was not associated with increased risk of cancer (hazard ratio [HR], 0.94; 95% CI, 0.77-1.14). In contrast, each 1-SD increase in LBF was associated with a reduced incidence of cancer (HR, 0.69; 95% CI, 0.52-0.92) in the fully adjusted model.

Conclusions: In this study, adiposity-associated cancer risk was heterogeneous and varied by fat depot: VAT was not independently associated with incident cancer, and LBF seemed to protect against cancer development. Further studies of the adiposity-cancer relationship, including serial assessments, are needed to better elucidate this relationship.

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Obesity, as defined by a body mass index (BMI) of at least 30, is associated with an increased incidence of, and mortality from, cancer.[1,2] This association may be stronger for certain obesity-associated cancers, such as those of the breast, endometrium, colon, and kidneys.[3] However, BMI is not a completely representative measure of body fat risk because distinct fat depots, such as visceral adipose tissue (VAT), abdominal subcutaneous adipose tissue (SAT), and liver fat (LF), have been associated with differing effects on metabolic and cardiovascular disease risk.[4-8] The relation of these adipose depots with the risk of noncardiovascular chronic conditions, particularly cancer, is not well understood. Studies reporting the risk of cancer in patients who have undergone image-guided measurements of VAT are limited and have focused on predominantly white or elderly populations, with inconsistent results.[4,9] Although SAT has been shown to have a neutral association with cancer, LF and lower-body fat (LBF) have not been studied in this regard. We aimed to study the relationship between specific fat depots and the risk of incident cancer in relatively young, multiethnic participants in the Dallas Heart Study (DHS).

MATERIALS AND METHODS

Study Population

Details about the design of the DHS have been previously described.[10] Briefly, the DHS is a

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single-site, multiethnic, population-based probability sample of Dallas County (Texas) residents (aged 18-65 years), with deliberate oversampling of the black population. The present study population was drawn from 3072 participants who completed DHS phase 1 visits from January 1, 2000, through December 31, 2002, which included a computer-assisted survey, anthropometric and blood pressure measurements, laboratory testing, and imaging assessments. Participants without imaging assessment of VAT were excluded. Because cancer diagnoses were made through linkage to the state cancer registry, participants who had moved out of Texas before 2012 were censored at the date they were last known to be a Texas resident. Of the remaining participants, those with a history of or a present diagnosis of malignancy were also excluded. To account for cancers that may have been undetected at baseline, new cases of cancer diagnosed within 1 year after the DHS enrollment date were excluded from the analysis (blanking period). After these exclusions, 2627 participants were eligible for follow-up (Supplemental Figure, available online at http://www.mayoclinicproceedings.org). All the participants provided written informed consent, and the University of Texas Southwestern Medical Center institutional review board approved the protocol.

Demographic characteristics, lifestyle, and other risk factors were determined from a baseline questionnaire. The BMI was calculated as the weight in kilograms divided by the height in meters squared. Waist circumference (WC) and hip circumference (HC) were measured in centimeters, and waist-hip ratio (WHR) was calculated as the ratio of WC:HC. The hypertriglyceridemic waist phenotype was defined by a WC of at least 90 cm and with serum triglyceride levels of at least 177 mg/dL (to convert to mmol/L, multiply by 0.0113).[11] Hypertension was defined as blood pressure of at least 140/90 mm Hg or taking antihypertensive medication(s). Diabetes mellitus was defined as a fasting serum glucose level of at least 126 mg/dL (to convert to mmol/L, multiply by 0.0555), self-reported diabetes, or taking hypoglycemic medication. Smoking was defined as cigarette use within the previous 30 days or a lifetime history of having smoked at least 100 cigarettes. Alcohol use was determined in grams per week by self-report. Comorbid conditions were determined from self-report, medication history, and clinical assessment. Fasting blood samples were obtained from participants, collected in EDTA-containing tubes, and stored at −80°C. Samples were analyzed for high-sensitivity C-reactive protein, interleukin-6, adiponectin, leptin, and insulin levels.[5,8]

Body Fat Distribution Measurements

Participants were scanned using a 1.5-T magnetic resonance imaging (MRI) scanner (Intera; Philips Healthcare). Retroperitoneal, intraperitoneal, and SAT abdominal fat masses were quantified by a single MRI slice taken at the L2-L3 level using manual contours, as previously validated against cadaveric samples.[12] Areas were converted to mass using previously determined regression equations.[13] VAT was defined as the combination of retroperitoneal and intraperitoneal fat masses.[8] Participants also underwent ^{1}H-magnetic resonance spectroscopy for hepatic triglyceride quantification (LF) as previously described.[14] Participants were also scanned by dual-energy X-ray absorptiometry, which was performed using a Delphi W scanner (Hologic) with a fan beam to determine fat and lean mass.[15] Lower-body fat was quantified from the total fat mass from the lower extremities.

Cancer Outcomes

The DHS was systematically linked to the Texas Cancer Registry (TCR) to determine cancer cases in the cohort.[16] The TCR is a population-based registry of Texas that meets the quality data standards of the National Program of Cancer Registries (Centers for Disease Control and Prevention) and the North American Association of Central Cancer Registries. The Texas Cancer Incidence Reporting Act mandates that health care facilities, including hospitals, ambulatory surgical centers, and cancer treatment centers, report to the TCR. All cancer cases identified by the TCR were classified as prevalent or incident based on date of cancer diagnosis in relation to date of enrollment in the DHS. In cases with more than 1 known cancer, only the first cancer was included. Carcinoma in situ and skin cancers were not included. Cancers of the gastrointestinal tract in close proximity to visceral fat depots were classified as visceral cancers and

included colorectal, pancreatic, liver, gall bladder, esophageal, stomach, small intestinal, and anal cancers. Obesity-associated cancers were defined as per the National Cancer Institute Obesity and Cancer Fact Sheet and included breast and endometrial cancers in women, along with esophageal, pancreatic, gall bladder, colorectal, kidney, and thyroid cancer in men and women.[17]

Participants in the DHS undergo telephone calls from study coordinators along with regular data collection regarding place of residence and vital status. Thus, we were able to establish their residence and mortality at multiple points throughout the study period. Patients were observed until noncancer death, the date they were last known to be a Texas resident, incident cancer, or December 2012 (when the TCR was last queried).

Statistical Analyses

Baseline demographic, clinical, laboratory, and imaging variables are expressed as median (25th-75th percentile) or proportions as appropriate. Deaths due to noncancer causes were treated as competing events in time-to-event analyses according to the method of Fine and Gray.[18] Cumulative incidence curves for the relation of sex-specific quartiles of VAT to time to incident cancer were constructed using the method described by Prentice et al[19] and Gaynor et al[20] and were compared using the likelihood ratio test in a Cox model that accounts for competing risk. Cox proportional hazards models were used to examine the unadjusted and multivariable-adjusted associations between measures of adiposity and incident cancer and are reported as hazard ratios (HRs) and 95% CIs. Adipose measures were analyzed continuously per 1-SD increase and as sex-specific quartiles. VAT was the primary exposure. SAT, LF, LBF, and WC were secondary exposures. The primary outcome was any incident cancer. Secondary outcomes included the development of obesity- and visceral-associated cancers. Cox proportional hazards models were constructed such that the unadjusted model (model 1) was univariable in continuous analysis and sex specific in quartile analysis. Models were sequentially adjusted for age and race (and sex in the case of continuous analysis) (model 2); family history of cancer, smoking, and alcohol use (model 3); and BMI (model 4). Sensitivity analyses were performed by including cancers diagnosed within the 1-year blanking period, after excluding lung and esophageal cancers (associated with lower BMI), hematologic cancers, and breast and prostate cancers (associated with screening procedures) from the analysis. Because the association between ectopic fat depots and cancer may be mediated via obesity, we also analyzed the relation of BMI, WC, WHR, and hypertriglyceridemia-WC index with incident cancer. Two-sided $P<.05$ was considered statistically significant. All the analyses were performed using a

TABLE 1. Baseline Characteristics of 2627 Participants From the Dallas Heart Study[a,b]

Characteristic	Value
Clinical characteristics	
Age (y), median (IQR)	43 (36-51)
Male sex (No. [%])	1209 (46.0)
Race (No. [%])	
Black	1293 (49.2)
White	822 (31.3)
Hispanic	456 (17.4)
Other	56 (2.1)
Smoking (No. [%])	730 (27.8)
Alcohol use (No. [%])	1836 (70.0)
Diabetes mellitus (No. [%])	282 (10.7)
Hypertension (No. [%])	852 (32.4)
Hyperlipidemia (No. [%])	355 (13.5)
Physical activity (MET-min/wk), median (IQR)	145 (0-599)
Family history of cancer (No. [%])	583 (22.2)
Biochemical characteristics (median [IQR])	
High-sensitivity C-reactive protein (mg/L)	27 (12-63)
Interleukin-6 (pg/mL)	16.97 (0.0-35.76)
Adiponectin (μg/mL)	14.42 (9.60-21.43)
Leptin (ng/mL)	11.90 (5.2-25.3)
Insulin (μlU/mL)	12.2 (7.3-20.1)
Measures of adiposity (median [IQR])	
Body weight (kg)	82.10 (69.9-97.1)
Body mass index	29.07 (25.21-33.93)
Waist circumference (cm)	97 (87.0-108.5)
Waist-hip ratio	0.90 (0.84-0.96)
Abdominal subcutaneous adipose tissue (kg)	4.17 (2.79-6.26)
Liver fat (%)	3.60 (2.11-6.64)
Lower-body fat (kg)	8.69 (6.15-11.91)
Only women (n=1418) (No. [%])	
Postmenopausal state	488 (34.4)
Oral contraceptive use	1079 (76.1)
Hormone replacement therapy	180 (12.7)

[a]IQR = interquartile range; MET = metabolic equivalent of task.
[b]SI conversion factors: To convert high-sensitivity C-reactive protein values to nmol/L, multiply by 9.524; to convert insulin values to pmol/L, multiply by 6.945.

statistical software program (SAS version 9.2; SAS Institute Inc).

RESULTS

The study cohort consisted of 2627 individuals without cancer at inception. Characteristics of the overall cohort are presented in Table 1. One hundred sixty-seven individuals (6.4%) developed an incident cancer, of which 89 (53.0%) were female and 111 (66.0%) were nonwhite race. There were 129 noncancer deaths (4.9%) in the cohort during the study period.

Of the 167 patients who developed cancer, 69 (41.3%) had obesity-associated cancers and 25 (15.0%) had gastrointestinal or visceral cancers. The most common primary cancer sites in women and men were breast (24.6%) and prostate (19.8%), respectively. Further details regarding the primary site of cancer are presented in Table 2. These data are similar to the general distribution of cancers seen in the overall TCR registry.[21] Participants who developed cancer were more likely to be older and to have a family history of cancer and a higher prevalence of diabetes mellitus, hypertension, and hyperlipidemia compared with those who did not develop cancer. They were also more likely to have higher VAT levels and WC. No significant differences in serum biomarker levels were observed.

Relation With Adiposity Depots. VAT levels in participants with cancers at different sites are presented in Table 2. Characteristics of the cohort across sex-specific VAT quartiles are presented in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). The prevalence of hypertension, diabetes, and hyperlipidemia increased across the VAT quartiles, as did the age, BMI, WC, and WHR. Figure 1 shows the cumulative incidence curves for incident cancer by sex-specific quartiles of VAT; the cumulative rates of incident cancer at 12 years were 4.6% (95% CI, 2.8%-6.3%) for Q1, 3.6% (95% CI, 2.2%-5.1%) for Q2, 6.2% (95% CI, 4.3%-8.1%) for Q3, and 7.1% (95% CI, 5.1%-9.2%) for Q4 (P=.01).

Figure 2 shows the graded associations between continuous and categorical (sex-specific quartiles) measures of VAT, LBF, and incident cancer in unadjusted and fully adjusted models. In unadjusted models, each 1-SD increase in VAT was associated with a higher risk of cancer (HR, 1.20; 95% CI, 1.06-1.36) (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). However, this association attenuated with adjustment for age, race, and sex. The numbers of incident cancers in each quartile of VAT are presented in Supplemental Table 3 (available online at http://www.mayoclinicproceedings.org). In unadjusted models, there was a nonsignificant trend toward a lower risk of cancer related to LBF. In fully adjusted models, each 1-SD increase in LBF was associated with a significantly reduced incidence of cancer (HR, 0.69; 95% CI, 0.52- 0.92; P=.01) for LBF as a continuous measure, with a similar, graded decrease in risk across LBF quartiles (Figure 2). This association between LBF and cancer was revealed only on the addition of BMI to model 4 (Supplemental Table 4, available online at http://www.mayoclinicproceedings.org). No such association was observed for SAT and LF (Supplemental Table 5, available online at http://www.mayoclinicproceedings.org).

TABLE 2. Distribution of Incident Cancers by Primary Site, With VAT Levels

Type of cancer	Anatomical sites included	Incident cancers (No. [% of total])	VAT level (kg), median (IQR)
Breast	Breast	41 (24.6)	2.06 (1.55-2.51)
Prostate	Prostate	33 (19.8)	2.73 (1.99-3.27)
Lung	Lung	14 (8.4)	2.20 (1.11-2.75)
Genitourinary	Gynecologic, kidney, urinary bladder	24 (14.4)	2.43 (1.99-2.75)
Gastrointestinal	Esophagus, stomach, small intestine, colon, rectum, anus, liver, pancreas, gallbladder	25 (15.0)	2.77 (1.75-3.12)
Hematologic	Leukemia, lymphoma (Hodgkin and non-Hodgkin)	12 (7.2)	2.35 (1.76-2.88)
Others	Brain, thyroid, head and neck, not otherwise specified	18 (10.8)	2.01 (1.37-2.54)
Overall		167 (100)	2.34 (1.65-2.94)

IQR = interquartile range; VAT = visceral adipose tissue.

In an analysis stratified by sex and race, no association between VAT and cancer was observed in fully adjusted models (Supplemental Tables 6-9, available online at http://www.mayoclinicproceedings.org), although the number of events in each subgroup were limited. Mean VAT levels were higher in white patients (2.30 kg) than in nonwhite patients (2.09 kg) and in men (2.54 kg) than in women (1.83 kg). Similar to VAT, no significant association between WC, WHR, BMI categories, or hypertriglyceridemia-WC phenotype and incident cancer was seen in fully adjusted models (Supplemental Table 10, available online at http://www.mayoclinicproceedings.org). Sensitivity analyses performed including incident cancers diagnosed within 1 year of the baseline examination and after sequentially excluding lung cancers, esophageal cancers, and hematologic malignancies from the analysis and after excluding breast and prostate cancer cases from the analysis did not affect the results (Supplemental Tables 11-14, available online at http://www.mayoclinicproceedings.org). VAT was not associated with increased risk of visceral cancers or obesity-associated cancers in multivariable models (Table 3 and Supplemental Tables 15 and 16, available online at http://www.mayoclinicproceedings.org). On subgroup analysis for LBF by sex, the association was significant in women but not in men, but formal interaction testing did not show a statistically significant heterogeneity of effect (Supplemental Tables 17 and 18, available online at http://www.mayoclinicproceedings.org). Levels of LF were noted to be higher in Hispanic individuals, but subgroup analysis of LF in these racial groups did not show a relationship with incident cancer (Supplemental Tables 19 and 20, available online at http://www.mayoclinicproceedings.org).

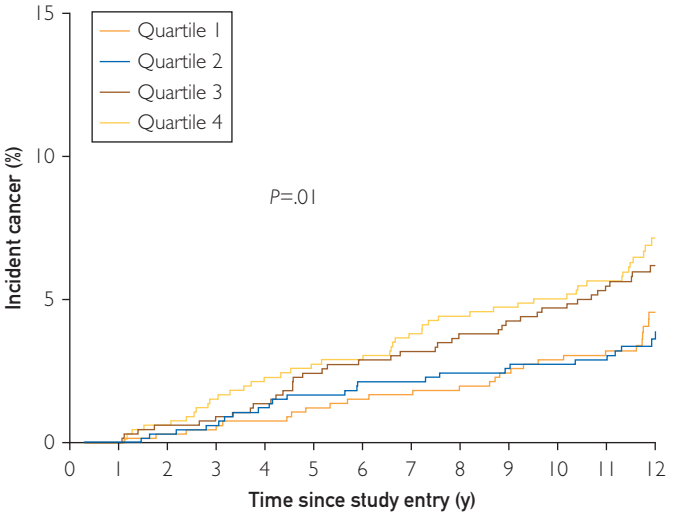

FIGURE 1. Cumulative incidence curves for the relation of sex-specific quartiles of visceral adipose tissue to time to incident cancer.

DISCUSSION

In this multiethnic cohort study, visceral adiposity as assessed by MRI was not associated with the development of incident cancer through follow-up as long as 12 years. We also did not observe an association between VAT and future development of gastrointestinal or obesity-associated cancers, although individual numbers of cancers were relatively small. A protective effect of LBF was observed in this study. This finding is novel and has not been demonstrated previously, and it is consistent with observed associations with cardiovascular disease[6] and type 2 diabetes[8] in which LBF is consistently protective. The lack of association between LBF and cancer in univariable analysis was likely due to reverse confounding such that adjustment for BMI (positively associated with cancer risk) revealed the inverse association of LBF. Further studies elucidating this relationship and its potential implications should be a priority. The other fat depots, SAT and LF, were not associated with cancer in this study.

There are clear data linking incident cancer with higher BMI,[2] but its association with regional fat depots remains less well studied. Britton et al[4] reported the positive association of VAT and incident cancer from the predominantly white Framingham cohort, with a stronger association in men. Murphy et al[9] reported a weak association between VAT and cancer in women and no association in men from an elderly population (mean age, 74 years). The present study population was much younger (mean age, 43 years), and only 6.4% of individuals in this cohort developed cancer compared with 24.5% in the

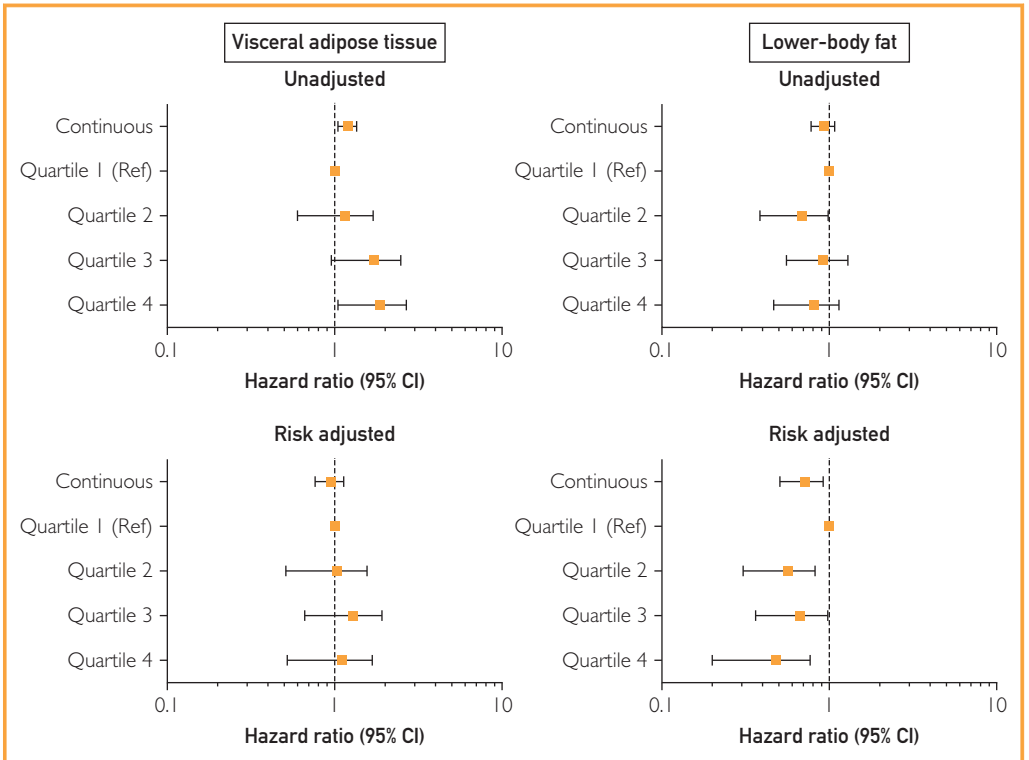

FIGURE 2. Forrest plots of the graded risk of incident cancer per 1-SD increase in visceral adipose tissue and lower-body fat before and after adjustment for sex, race, age, smoking, alcohol use, family history of cancer, and body mass index.

study by Murphy et al,[9] which is likely a function of the younger cohort. The lack of an age-independent association of VAT and cancer in the present study could potentially be explained by a lack of power brought about by this lower event rate. However, this study was similarly sized and had more events compared with the study by Britton et al.[4] Age and VAT are highly correlated,[22,23] and the unadjusted association between VAT and incident cancer in the present study became null after adjusting for age. The present study also had a similar proportion of obesity-associated cancers as the study by Murphy et al[9] (approximately 40%), making it unlikely that a differential cancer phenotype existed between the studies. In the present study, we observed that higher levels of LBF were associated with a lower risk of the future development of cancer, and this effect was independent of age. Because this study is the first to report a protective relationship between LBF and incident cancer, we are unable to compare these findings with those of previous studies.

Since the early 1980s, regional body fat distribution, as measured by WC or WHR, has been known to be more strongly correlated with cardiovascular outcomes than with BMI.[24,25] The emergence of imaging techniques such as computed tomography in the 1980s allowed for distinguishing VAT from subcutaneous adiposity,[26,27] which was associated with several metabolic abnormalities and increased risk of thrombosis.[28] From a mechanistic standpoint, paracrine release of cytokines from VAT may alter local nuclear transcription and gene regulation, inducing cell cycle and transcriptional changes leading to malignancy,[29] and systemic effects of adipose may induce various cancers via increased chronic inflammation and adipokine and sex hormone release.[30] Differential relations of VAT and cancer in men and women, seen in the present and previous studies, may partially be explained by levels of circulating sex

hormones, although we were unable to test this hypothesis in the current study. Furthermore, in the present study, we did not see a difference in levels of leptin, insulin, and inflammatory markers in individuals who did and did not develop cancer. Studies from the DHS also reported no association between adiponectin and leptin levels and cancer incidence.[16,31] This may also partially explain why we did not see an association between VAT and cancer in adjusted models. Lower-body fat has been shown to be a protective fat depot by virtue of being negatively correlated with metabolic and cardiovascular risk factors[15,32] and being inversely associated with incident type 2 diabetes[8] and cardiovascular disease.[6] It is hypothesized that LBF may act as a reservoir for ectopic fat and reduce its physiologic impact vis-à-vis its role as buffer for excess triglyceride stores. However, it is unclear whether the protective association of LBF on cancer is mediated through its role as a metabolic sink or whether deposition of fat in the lower-body compartment per se may decrease risk of cancer. Also, LBF may represent a protective reservoir for toxic lipophilic carcinogenic pollutants.

Strengths of the study include a multiethnic population cohort with precise imaging assessments of adipose depots and evaluation of novel fat depots not previously studied. Limitations include the observational design, which precludes the ability to ascribe causation. The cross-sectional nature of fat quantification also does not allow assessment of adiposity change on cancer outcomes. Because DHS participants who were diagnosed as having cancer outside of Texas may not have been captured through the TCR, we censored participants at the date they were last known to be a Texas resident to avoid ascertainment bias. The relatively small number of incident cancer cases also limits our ability to perform individual analyses for each cancer site and in sex and race subgroups. Finally, because the study did not include South or East Asians, we are unable to determine the impact of VAT on cancer in these racial groups.

CONCLUSION

We did not see an association between VAT and incident cancer in this study. In contrast, LBF was significantly and independently associated with lower cancer risk. Further studies that include serial adipose depot assessments in a large diverse population with close follow-up for cancer development are needed to better define the relationship between adiposity and cancer.

TABLE 3. Cox Proportional Hazards Models of Adiposity Depots and Incident Cancer

Adiposity measure	Hazard ratio (95% CI)[a]	
	Unadjusted model	Adjusted model[b]
All incident cancer		
Visceral adipose tissue	1.20 (1.06-1.36)	0.94 (0.77-1.14)
Subcutaneous adipose tissue	1.13 (0.97-1.31)	1.08 (0.78-1.51)
Liver fat	0.91 (0.79-1.06)	0.96 (0.93-1.01)
Lower-body fat	0.93 (0.79-1.09)	0.69 (0.52-0.92)
Obesity-associated cancer		
Visceral adipose tissue	1.08 (0.87-1.33)	1.13 (0.80-1.59)
Visceral/gastrointestinal cancer		
Visceral adipose tissue	1.47 (1.09-1.99)	1.21 (0.76-1.93)

[a]Data are per 1-SD increase in adiposity measure.
[b]Multivariable model adjusted for age, sex, race, smoking, alcohol use, family history of cancer, and body mass index.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **BMI** = body mass index; **DHS** = Dallas Heart Study; **HC** = hip circumference; **HR** = hazard ratio; **IQR** = interquartile range; **LBF** = lower-body fat; **LF** = liver fat; **MET** = metabolic equivalent of task; **SAT** = subcutaneous adipose tissue; **TCR** = Texas Cancer Registry; **VAT** = visceral adipose tissue; **WC** = waist circumference; **WHR** = waist-hip ratio

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