Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 62, No. 10, 2013
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2013.06.027

Body Fat Distribution, Incident Cardiovascular Disease, Cancer, and All-Cause Mortality

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Objectives The aim of this study was to determine whether ectopic fat depots are prospectively associated with cardiovascular disease, cancer, and all-cause mortality.

Background The morbidity associated with excess body weight varies among individuals of similar body mass index. Ectopic fat depots may underlie this risk differential. However, prospective studies of directly measured fat are limited.

Methods Participants from the Framingham Heart Study (n = 3,086; 49% women; mean age of 50.2 years) underwent assessment of fat depots (visceral adipose tissue, pericardial adipose tissue, and periaortic adipose tissue) using multidetector computed tomography and were followed up longitudinally for a median of 5.0 years. Cox proportional hazards regression models were used to examine the association of each fat depot (per 1 SD increment) with the risk of incident cardiovascular disease, cancer, and all-cause mortality after adjustment for standard risk factors, including body mass index.

Results Overall, there were 90 cardiovascular events, 141 cancer events, and 71 deaths. After multivariable adjustment, visceral adipose tissue was associated with cardiovascular disease (hazard ratio: 1.44; 95% confidence interval: 1.08 to 1.92; p = 0.01) and cancer (hazard ratio: 1.43; 95% confidence interval: 1.12 to 1.84; p = 0.005). Addition of visceral adipose tissue to a multivariable model that included body mass index modestly improved cardiovascular risk prediction (net reclassification improvement of 16.3%). None of the fat depots were associated with all-cause mortality.

Conclusions Visceral adiposity is associated with incident cardiovascular disease and cancer after adjustment for clinical risk factors and generalized adiposity. These findings support the growing appreciation of a pathogenic role of ectopic fat. (J Am Coll Cardiol 2013;62:921–5) © 2013 by the American College of Cardiology Foundation

Visceral adipose tissue (VAT) has been cross-sectionally associated with cardiovascular disease (CVD) and cancer (1,2) and is correlated with smaller ectopic fat depots, including pericardial and periaortic fat, which surround the cardiovascular system and may exert local toxic effects (3). These smaller ectopic fat depots have been associated with cardiovascular risk factors and events (4,5). Despite the interest in ectopic fat, few studies have examined prospective outcomes (6–9). In addition, little is known about CVD risk prediction, which can be useful to assess the predictive utility of new measures for incident disease. The purpose of the current study was to examine the association of directly imaged fat measurements with incident CVD, cancer, and all-cause mortality.

Methods

Study sample. Participants were drawn from the Framingham Heart Study Offspring and Third Generation cohorts who underwent multidetector computed tomography (MDCT) from 2002 to 2005 (10). Of the 3,529 participants in the MDCT substudy, 3,394 had at least one evaluable fat depot measurement, 3,114 were free of CVD, 3,270 were free of cancer, and 3,086 had complete covariates.

The study protocol was approved by the institutional review boards of Boston University Medical Center and

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Manuscript received November 8, 2012; revised manuscript received May 28, 2013, accepted June 18, 2013.

Abbreviations and Acronyms

BMI = body mass index
CI = confidence interval
CVD = cardiovascular disease
HR = hazard ratio
MDCT = multidetector computed tomography
NRI = net reclassification index
SAT = subcutaneous adipose tissue
VAT = visceral adipose tissue

Massachusetts General Hospital. Participants provided written informed consent.

MDCT scan protocol and adipose tissue measurements. Participants underwent thoracic and abdominal MDCT using an 8-slice scanner. Details of MDCT protocols and measurement of fat volumes have been previously described (4,5,10). The estimated dose-length product as a measure of radiation exposure was approximately 300 mGy/cm. Figure 1 shows representative images of our 3 fat depots.

Outcome assessment. CVD events (myocardial infarction, angina pectoris, coronary insufficiency, cerebrovascular accident, transient ischemic attack, intermittent claudication, congestive heart failure, and CVD death) and cause of death were adjudicated by 3 investigators. Cancer events were validated using medical records (pathology reports). Nonmelanoma skin cancers were not included.

Risk factor assessment. Risk factors were measured at the seventh offspring (1998 to 2001) and first third-generation (2002 to 2005) examinations. Descriptions of the measurement of risk factors were previously reported (10).

Statistical analysis. Cox proportional hazards regression models were used to relate each adiposity measure to: 1) incident CVD: 2) incident cancer; and 3) all-cause mortality. Subjects with prevalent disease were excluded from the respective analyses. VAT, pericardial fat, and periaortic fat were the primary exposures. Multivariable models included age, sex, systolic blood pressure, hypertension treatment, diabetes, smoking status, total and high-density lipoprotein cholesterol, and body mass index (BMI). Hazard ratios (HRs) are presented per 1 SD increment of each adiposity measure.

For ectopic fat depots associated with CVD in multivariable models, we used several indices to determine the incremental predictive utility of the given fat depot for identifying individuals at risk for CVD. We assessed increment in the c-statistic to assess discrimination, net reclassification index (NRI) to assess risk reclassification, relative integrated discrimination index to assess risk reclassification, and calibration indices based on the Hosmer-Lemeshow goodness-of-fit test. For the NRI, we used the following categories based on the risk of CVD during our median follow-up of 5.0 years: 0 to 3.5%, 3.6 to 8.0%, 8.1 to 11.5%, and >11.5%. To compare risk prediction between different adiposity measures, we calculated the NRI for BMI, waist circumference, and VAT in multivariable models that did not include BMI (to allow for comparison). In secondary analyses, we examined the association of pericardial fat with myocardial infarction. We assessed effect modification by age (continuous) and sex.

All analyses were conducted with SAS version 9.2 (Cary, North Carolina). To account for 3 exposures, we used a p value of <0.017 (0.05/3) for our primary analyses.

Results

The mean age of the subjects was 50.2 years, and 49% were women. The mean BMI was in the overweight range (Table 1).

Cardiovascular disease. There were 90 CVD events, and the median follow-up time was 5.0 years (interquartile range: 3.9 to 6.0; maximum follow-up of 7.4 years). In multivariable-adjusted models, VAT was associated with incident CVD (HR: 1.44; p = 0.014) (Table 2) and remained associated with CVD when models were adjusted for waist circumference (HR: 1.47; 95% confidence interval [CI]: 1.09 to 1.98;

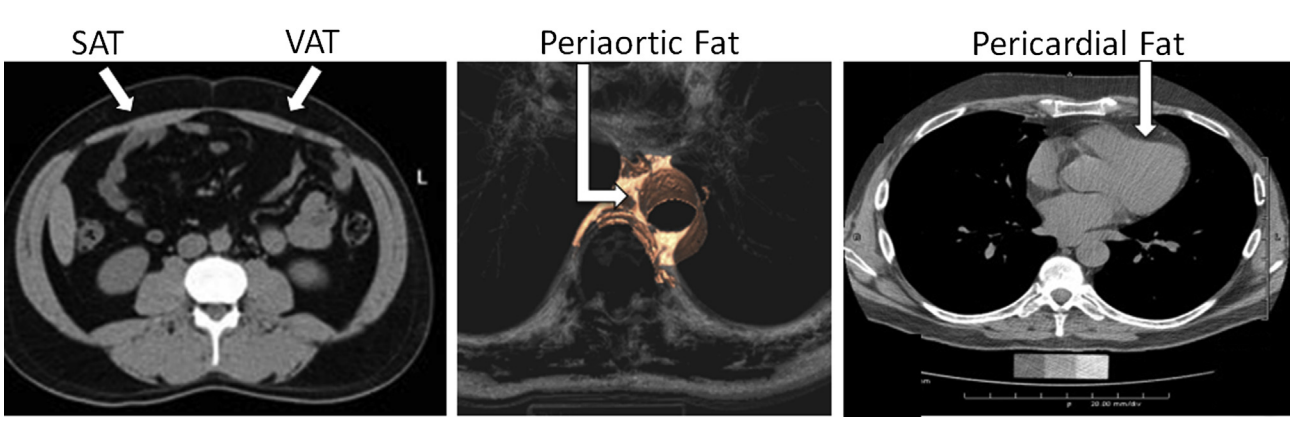

Figure 1 Multidetector Computed Tomography Images Demonstrating SAT, VAT, Periaortic Fat, and Pericardial Fat

Fat depots are defined by anatomic landmarks, and pixels of adipose tissue within a given fat depot are identified by their characteristic Hounsfield units. The middle panel (Periaortic Fat) is modified from Fox et al. (4). SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.