JACC: CARDIOONCOLOGY VOL. 4, NO. 1, 2022

EDITORIAL COMMENT

Toward a More Precise Understanding of Obesity and Cancer and Cardiovascular Disease Risk*

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Epidemiologic studies have investigated obesity predominantly through the use of body mass index (BMI), without considering measures of excess fat deposition, driven by the ready accessibility of BMI. Although BMI is an imprecise and potentially ambiguous measure for obesity, many studies have demonstrated associations between increased BMI and risk for cancer.[1] However, more precise methods of assessing adiposity (Table 1) may offer improvements in the precision of risk estimates. One example is measurement of abdominal adiposity via waist circumference (WC), which has been associated with an elevated risk for breast cancer even after controlling for BMI.[2] Further improvement in assessment of obesity as an etiologic risk factor may be gained through phenotyping of anatomical locations of fat depots within the abdomen because of disparate physiological impact according to location. For example, in the abdomen, visceral adipose tissue (VAT) is more strongly associated with systemic inflammation compared with subcutaneous (SQ) adipose tissue.[3] Thus, variation in definitions of obesity and incomplete phenotyping of body composition may lead to discordant results when attempting to characterize the association of obesity with incident cancer, potentially explaining differences in prior studies.

Deeper phenotyping of adiposity has also improved understanding of the etiologic impact of obesity on cardiovascular disease (CVD) outcomes.[4] It has been appreciated for some time that abdominal adiposity is a risk factor for CVD above and beyond BMI. In particular, VAT is particularly detrimental because of its role in systemic inflammation.[5] Thus, an expanded understanding of the physiological impact of obesity may lend itself to an investigation of cardiometabolic pathways through which adiposity influences both cancer and CVD, such as inflammation, insulin resistance, and adipokine production. Importantly, these represent shared risk factors, suggesting common biologic pathways between cancer and CVD.[5,6] A deeper understanding of these mechanistic underpinnings may provide insights toward preventive approaches to simultaneously reduce the risk for both.[7]

In this issue of *JACC: CardioOncology*, Liu et al[8] investigated obesity, central adiposity, and adipose depots in relation to cancer incidence in 2 prospective community-based cohorts: the FHS (Framingham Heart Study) and the PREVEND (Prevention of Renal and Vascular End-Stage Disease) study. Central adiposity was investigated through WC and adipose depots via detailed assessment of VAT, pericardial adipose tissue, and SQ adipose tissue with multidetector computed tomography. Biomarkers linked to putative mechanistic pathways underlying the pathophysiology of a variety of cancer sites, including gynecologic, breast, and colorectal cancer, were examined. Particular strengths of the study included an inception cohort design that ensured

*Editorials published in *JACC: CardioOncology* reflect the views of the authors and do not necessarily represent the views of *JACC: CardioOncology* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2022.02.004

TABLE 1 Techniques Commonly Used to Estimate Body Composition and Adipose Deposits

Method of Assessment	Brief Description	Advantages	Disadvantages
Anthropometric measures	Various measures including body mass index, skinfold thickness, waist circumference, arm circumference, predicted fat mass	• Low cost • Readily available data in many cases	• Limited accuracy • Unclear if same thresholds apply across different races and ethnicities
Bioelectrical impedance	Weak electric current is used to calculate impedance of the body, with differences in values for total body water and body fat	• Low cost • Relatively accurate estimates	• Limited accuracy
Dual-energy X-ray absorptiometry	X-rays are differentially attenuated with bone mineral content, fat and lean mass	• High accuracy • Low cost • Widely available • Total body assessment possible	• Radiation exposure (low) • Manual measurement required
Ultrasound	Echo reflections of multiple imaging planes are used to assess adipose tissue thickness	• Relatively low cost • High accuracy	• Interscan variability and scans can be user dependent • Lack of volumetric data
Computed tomography	Cross-sectional imaging with volumetric reconstruction to measure abdominal adipose tissue, pericardium, epicardium, pancreas, liver, kidney, and skeletal muscle on the basis of preestablished Hounsfield units	• High accuracy • Clinically available at most sites • Rapid scan time • Total volume datasets • Semiautomatic quantification with commercial software	• Radiation exposure • Higher cost than other modalities
Magnetic resonance imaging	Cross-sectional imaging with volumetric reconstruction on the basis of different magnetic properties of water vs fat focusing on abdominal adipose tissue (subcutaneous separately from visceral adipose tissue), pericardium, epicardium, pancreas, liver, kidney, and skeletal muscle	• Highest accuracy • Total volume datasets • Allows complete separation of adipose and lean tissues into fat-only (adipose) and water-only (lean) images • Whole-body scans possible	• Higher cost than other modalities • Limited access at some locations • Specially trained personnel are required • Longer scan times relative to other modalities

Adapted and modified with permission from Neeland IJ, Yokoo T, Leinhard OD, Lavie CJ. 21st century advances in multimodality imaging of obesity for care of the cardiovascular patient. *J Am Coll Cardiol Img.* 2021;14(2):482-494.

ascertainment of adiposity measures before cancer, thereby reducing the risk for reverse causation, which has been a concern with prior cross-sectional or retrospective studies. Differential adipose deposits were measured directly rather than using only BMI or WC or estimating body composition from derived anthropometric equations. Additionally, all cancers were histologically confirmed, and results were stratified by site-specific cancer, increasing accuracy of the results.

Of particular interest is the observed heterogeneity in risk for site-specific cancers, underscoring the argument that not all cancers are the same and that targeted interventions need to be personalized. Not all cancer sites were associated with obesity or central adiposity, and some differed in directionality of association. However, for cancers overall, an elevated risk was observed in relation to higher WC. VAT and pericardial fat increased the risks for cancer overall as well as lung cancer and melanoma; these findings are consistent with previous data from the FHS, although the prior study did not stratify cancer by site.[9] This was contrasted with SQ adipose tissue, in which there was no association of risk with any cancer and a decreased risk for gynecologic cancers.

The investigators illustrated the parallel results for incremental risk for any cancer or any CVD (myocardial infarction, stroke, heart failure) with each quartile increase in WC. From the cumulative incidence curves, it appears that WC may be slightly better than BMI at discriminating the risks for cancer and CVD. Overall, this finding of elevated risk for both cancer and CVD again accentuates the overlap in risk factors between the 2 disease processes. CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcome Study) was a prime example of the common-pathway hypothesis, in which participants with prior myocardial infarction and systemic inflammation were randomized to canakinumab, an anti-inflammatory agent targeting the interleukin-1β innate immunity pathway, compared with placebo.[10] Those who received canakinumab had a significantly decreased rate of recurrent cardiovascular events. Intriguingly, canakinumab also appeared to decrease the risk for incident lung cancer and lung cancer mortality.[11] Hence, findings by Liu et al[8] of increased risk for lung, gastrointestinal or colorectal, and gynecologic cancers in relation to elevated C-reactive protein are aligned with the results of CANTOS. The evidence suggests that a combination of adiposity measures

JACC: CARDIOONCOLOGY, VOL. 4, NO. 1, 2022
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and systemic inflammation markers is synergistic for risk stratification and may improve the identification of obese individuals at highest risk for cancer and CVD, potentially for future targeted intervention studies.

Investigations of sex-specific risks for CVD and cancer in relation to adiposity have been inconsistent.[12] The present study revealed no interactions or synergistic effect between sex and BMI, while an interaction was observed between sex and WC. A stronger association of WC with cancer in men is provocative and is aligned with a Swedish study of 27,007 adults demonstrating that the elevated risk for cardiac events in relation to elevated waist/hip ratio was limited to men.[12] The lack of elevated risk among women, in contrast, argues against a role of estrogen as a mechanism by which adiposity may increase cancer risk, as has been proposed for breast cancer. It should be noted that in the present study, no distinction was made between pre- and postmenopausal breast cancer, which have differing risks in relation to obesity, thought to be due to the difference between the levels of ovarian and adipose production of endogenous estrogen in those groups.

Future studies are needed to confirm systemic inflammation as a mediator of the relationship between site-specific adipose depots and cancer development. In women, further evaluation of whether there is effect modification by menopausal status and a role of estrogen as a mediator for risk is also critical. Last, whether obesity holds the same implications for cancer risk across differing race or ethnic groups needs clarification, as disparities exist for prevalence and trends in obesity and adiposity by race and ethnicity.[13]

The relationship between obesity with cancer and CVD risk highlighted in this analysis underscores the importance of focusing on overall health in the general population to reduce both incidence of cancer and heart disease. Cancer control has been historically focused on tobacco cessation and limits to alcohol intake, as well as access to screening and genetic testing. Proper nutrition, reduction of obesity, and adiposity are universal concerns and require equal attention from all aspects of society, not only from health care providers, but also in collaboration with the food industry, government, and public health researchers.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS adiposity, body composition, cardio-oncology, cardiometabolic, obesity