The Obesity Paradox in Cancer—Moving Beyond BMI

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Abstract

Body mass index (BMI) and simple counts of weight are easy and available tools in the clinic and in research. Recent studies have shown that cancer patients with a low normal BMI (or those with weight loss) have worse outcomes than obese patients. These results suggest that obesity has a protective effect and has been termed the "obesity paradox." In this commentary, we discuss hypothetical explanations and take a step beyond BMI or simple weights alone to present other useful and more specific body composition metrics, such as muscle tissue mass, visceral fat mass, and subcutaneous fat mass. Body composition is highly variable between individuals with significant differences seen between various races and ages. Therefore, it is critical to consider that patients with the exact same BMI can have significantly different body compositions and different outcomes. We encourage further studies to examine body composition beyond BMI and to use other body composition metrics to develop individualized treatments and intervention strategies. *Cancer Epidemiol Biomarkers Prev; 26(1); 13–16. ©2017 AACR.*

See all the articles in this *CEBP Focus* section, "The Obesity Paradox in Cancer: Evidence and New Directions."

The usage of body mass index (BMI) to characterize the different body/obesity types has been commonplace for decades, yet limitations persist in its use. BMI is a calculated value [body weight (kg) divided by square height (m^2)] and exists as an easy and simple tool in the clinic and in research to differentiate and categorize patients as underweight (BMI < 18.5), normal weight (18.5–24.99), overweight (25–29.99), and obese (>30). In a large-scale British study (more than 5 million individuals; ref. 1), BMI was significantly associated with 17 of 22 cancers, among them liver, colon, and postmenopausal breast cancers. Although obesity in the general population is associated with an increased risk of death (2), there are conflicting reports about the relationship between obesity and mortality among individuals with cancer and several other chronic diseases (3–5). This phenomenon, known as the "obesity paradox," suggests a potential protective effect in overweight and mildly obese patients. Mortality curves for BMI for any population are usually U-shaped (with increased mortality at both ends), but the debate primarily lies as to where the nadir for mortality exists (6). Two studies in this issue evaluate the association of weight changes in a large cohort of patients with two common early-stage cancers: breast and colorectal. Cespedes Feliciano and colleagues concluded that weight loss and gain are equally common after breast cancer, and weight loss is a consistent marker of mortality risk (7). Meyerhardt and colleagues demonstrated that weight loss after a colorectal cancer diagnosis was associated with worse cancer-specific and overall mortality (8). The study by Greenlee and colleagues is a pooled analysis of 22 clinical trials from SWOG ($n = 11{,}724$) and showed that BMI ≥ 25 kg/m^2 was associated with better overall survival among men (HR = 0.82; $P = 0.003$), unlike in women (HR = 1.04; $P = 0.86$; ref. 9). Both methodologic and physiologic explanations exist for explaining this phenomenon and these results, but what is the clinician supposed to recommend patients today? Should we enter the clinic tomorrow and tell our patients to gain weight? Or stop encouraging them to keep within the "normal" range of BMI?

Many hypothetical explanations exist that help explain the obesity paradox. One of them is the collider stratification bias (a form of selection bias) that may, in part, explain the phenomenon (10, 11), but this unlikely fully accounts for the observed findings (12). The increased nutritional reserves provided by excess fat stores and higher lean body mass in obese patients (13) may provide an added advantage during periods of acute illness (14). In addition, it is plausible that lower BMI categories disproportionately include sicker patients and, in turn, are at a higher risk of mortality. The loss of weight could also be associated with smoking and related to other comorbidities, which can be another confounder (15). Weight loss among even the general older adult population is associated with frailty and an increased mortality risk (16, 17). Weight loss at a cancer diagnosis is often a marker of more aggressive cancer and/or advanced disease. Even in earlier stage patients, lower weights may be a marker of subclinical tumor activity. Changes in weight can be seen over 6 months prior to a cancer diagnosis, and appreciable subclinical impacts on lipid metabolism can start as early as 2 years before a diagnosis is made (18). Of note, the impact of cancer on body metabolism and cachexia varies greatly by tumor type and stage, and clearly, cancer can have a significant impact on weight, and the distinction between intentional and nonintentional weight loss is a major issue (19).

Although BMI and simple weight measurements are the easiest and most available clinical measures and have helped gain an enormous amount of knowledge regarding the relationship of obesity and cancer prevention as well as cardiovascular diseases (20), one major flaw and limitation of both are their inability to

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doi: 10.1158/1055-9965.EPI-16-0439

Table 1. Differences in body composition between various ethnic groups

		BMI[a] (kg/m^2) mean	Lean mass area (cm^2) mean (95% CI)	Visceral fat (cm^2) mean (95% CI)	Subcutaneous fat (cm^2) mean (95% CI)
White	$N = 785$	27.8	98 (95–100)	159 (153–165)	253 (243–264)
African American	$N = 407$	30.2	104 (101–108)	128 (120–136)	298 (283–313)
Latino	$N = 501$	29.4	99 (95–102)	164 (157–172)	264 (250–278)
South Asian	$N = 903$	25.8	93 (91–69)	134 (129–140)	237 (227–246)
Chinese American	$N = 251$	24	89 (85–94)	114 (104–125)	177 (160–195)

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Abbreviation: CI, confidence interval.
[a]BMI recorded from the all MASALA/MESA studies.

differentiate fat and muscle mass. Body composition and BMI differ considerably between different ethnic groups (see Table 1). While African Americans have higher BMI on average, they also have higher lean body mass (LBM) and subcutaneous fat with lower visceral fat, whereas Caucasians generally have higher visceral fat and lower subcutaneous and LBM. Of note, South Asians have almost "normal" average BMI but have a lower LBM and higher visceral fat than African Americans (21). Age is another factor associated with alterations in body composition, and with age, there is a decrease in muscle mass and strength, known as sarcopenia (22–24). The assumption that adults have an optimal weight range (corrected for height) is probably sound, but assuming that this is the same for all individuals regardless of ethnicity, age, and health status is challenging. Furthermore, nutritional status is also an important component, and BMI/weight is not always an adequate indicator of nutrition status (25).

In oncology, body composition has been shown to have a substantial impact on outcomes (26, 27). Many studies demonstrate an association between different indices and prognosis in different tumors. Table 2 highlights the multitude of body measures used in the literature, their measurement calculations, and some example findings in oncology. In a recent meta-analysis, sarcopenia (low muscle mass) derived from CT imaging was significantly associated with inferior survival across tumor types and disease stages (27). Assuming the impact of weight is the same regardless of the degree of adiposity or skeletal muscle ignores a growing body of evidence within oncology and elsewhere. Patients with lower muscle mass have higher rates of surgical complications (28), which may delay the preferable timing of adjuvant treatment initiation, a known factor for inferior outcomes (29). In addition, sarcopenic patients have higher rates of treatment toxicity (26, 30, 31) that, in turn, can cause dose delays and reductions, resulting in lower dose intensity and worse outcomes (32, 33). Also, recent evidence in a large cohort of patients with early-stage colorectal cancer demonstrated that decreased muscle mass and attenuation was significantly associated with markers of systemic inflammation, but neither have correlation with BMI. This highlights the significant interaction of body composition and the inflammation process that can impact metabolism, weight loss, and body resistance to tumor growth (34). Although body composition analysis is much more accurate in quantifying muscle mass and adiposity, it is not yet a standard component of clinical care in oncology or elsewhere.

In cancer, as well as other diseases, physical activity should be discussed alongside body composition, as physical activity has an important influence on the prevention of cancer (35) and survival after diagnosis (36). Physical activity can also increase muscle mass and augment metabolic and hormonal axes (37), as well as be used as an important intervention tool.

The evolving field of personalized medicine in oncology is playing an increasing role in cancer prevention, diagnosis, prognosis, and therapeutics (38). In the last decade, there has been

Table 2. Selected body measures and their association with cancer outcomes

Body measure	Method of calculation/measure	Examples for prognostic evidence
Weight at diagnosis	Weight scale (kg)	Breast cancer-worse OS (HR = 1.31; 95% CI, 1.17–1.46) for heavier vs. lighter (43)
BMI at diagnosis	Weight scale/meter weight (kg)/ height (m^2)	Contradicting evidence: - Better survival for higher BMI in men—SWOG trials (HR = 0.82; $P = 0.003$; ref. 9) - Worse survival in early breast cancer with higher BMI (HR = 1.48; 95% CI, 1.09–2.01; ref. 44)
Weight changes after diagnosis	Weight scale (kg)	Contradicting evidence in early breast cancer - Meta-analysis weight gain ≥10.0% associated with all-cause mortality (HR = 1.23; 95% CI, 1.09 –1.39; ref. 45) Breast cancer large cohort—weight loss ≥10% was associated with worse survival, all-cause mortality 2.63 (2.12–3.26; ref. 7) Colorectal cancer–specific mortality (HR = 3.20; 95% CI, 2.33–4.39; $P < 0.0001$; ref. 8)
Sarcopenia (low muscle mass)	DEXA/CT scan/MRI	Recent meta-analysis in different types and stages (HR = 1.44; 95% CI, 1.32–1.56; $P < 0.001$; ref. 27) HEAL—early breast cancer survivors—higher overall mortality in sarcopenic patients (HR = 2.86; 95 % CI, 1.67–4.89; ref. 46)
Muscle radiodensity [mean (HU)]	CT scan/MRI	Several studies low radiodensity associated with short survival (41, 42)
SAT	CT scan/MRI	Advanced prostate cancer- in multivariate analysis, SAT index was statistically significant predictors of OS ($P = 0.036$; ref. 47)
VAT	CT scan/MRI	Mainly reported VAT/SAT ratio-increasing ratio result in better OS (48) Higher VAT associated with worse survival (49, 50)
MAMC	Measuring tape (cm)	Better OS with normal MAMC (HR = 0.21; 95% CI, 0.09–0.5; ref. 51)

Abbreviations: CI, confidence interval; CT, computerized tomography; DEXA, dual-energy X-ray absorptiometry; HU, Hounsfield unit; MAMC, mid-arm muscle circumference; MRI, Magnetic Resonance Imaging; SAT, subcutaneous adipose tissue; SWOG, Southwest Oncology Group; VAT, visceral adipose tissue.

great progress in understanding tumor characteristics, including proliferation rate, mutation load, and type, and when utilized to guide cancer therapy, there is a potential for improved survival (39, 40). The impact of host factors remains underappreciated and poorly understood. Personalized medicine should go beyond only tumor genetics and pharmacogenomics but should also include a patient's body composition, physical function, and comorbidities. These factors can also greatly impact treatment decisions and drug dosing with an overall impact on outcomes. In the same way that treatments in oncology are rarely one size fits all, the "right" weight for a given individual is likely dependent on a multitude of factors and should also be individualized.

The studies in this issue highlight the importance of body measures in cancer and add to the growing literature in this emerging field. So what should clinicians be telling their patients regarding weight loss or weight gain after a cancer diagnosis? The answer is complex and not yet clear with many unresolved questions remaining. Is weight loss a sign for tumor activity, and if it is, can we even reverse that process? Will future randomized control trials with the goal of achieving the "right" BMI improve survival? Will it be the right BMI or the right body composition? Is it the amount of LBM or the ratio between the LBM to fat (adiposity/muscularity ratio)? Is it the size/quantity of muscle or as recent evidence has shown, the quality of muscle (radiodensity) that impacts survival (41, 42)? To date, we have more questions than answers, and we need to gear up with focused studies about the impact of body composition on different outcomes and step forward with intervention and prevention strategies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Grant Support

This work was supported, in part, by the UNC Oncology Clinical Translational Research Training Program (NCI 5K12CA120780-07; to G.R. Williams).

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Received May 31, 2016; revised July 13, 2016; accepted July 29, 2016; published online January 9, 2017.

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Cancer Epidemiology, Biomarkers & Prevention

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Cancer Epidemiol Biomarkers Prev 2017;26:13-16.