Point–Counterpoint Review

Cancer Research

*Counterpoint*

# The Importance of Body Composition in Explaining the Overweight Paradox in Cancer

*See Point and Reply by Park, et al., p. 1898 and p. 1913*

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## Abstract

Despite a greater risk of cancer associated with higher BMI, overweight (BMI 25–<30 kg/m$^2$) and class I obese (BMI 30–<35 kg/m$^2$) patients often have a paradoxically lower risk of overall mortality after a cancer diagnosis, a phenomenon called the "obesity paradox." Only when patients exceed a BMI ≥35 kg/m$^2$ are elevations in mortality risk consistently noted. This paradox has been dismissed as the result of methodologic bias, which we will describe and debate here. However, even if such bias influences associations, there is growing evidence that body composition may in part explain the paradox. This phenomenon may more accurately be described as a BMI paradox. That is, BMI is a poor proxy for adiposity and does not distinguish muscle from adipose tissue, nor describe adipose tissue distribution. Low muscle mass is associated with higher risk of recurrence, overall and cancer-specific mortality, surgical complications, and treatment-related toxicities. Patients with who are overweight or obese have on average higher levels of muscle than their normal-weight counterparts. Also, there is some evidence that patients with moderate levels of subcutaneous adipose tissue may have lower mortality. More research utilizing body composition is needed to clarify the effects of adiposity on cancer mortality. *Cancer Res; 78(8); 1906–12.* ©2018 AACR.



## BMI and Survival

Overweight (body mass index, BMI: 25–<30 kg/m$^2$) and obesity (≥30 kg/m$^2$) are established cancer risk factors. They are associated with a host of metabolic and endocrine changes implicated in cancer development including insulin resistance, systemic inflammation, and alterations in hormone levels and growth factors. Many of these pathways are also implicated in cancer progression, suggesting that overweight and obese patients should have a higher risk of cancer mortality. Yet, in many cancers, including lymphoma (1), leukemia (2), colorectal (3), gastric (4, 5), and renal (3, 6), cancers, a higher BMI at diagnosis has not been associated with a higher mortality risk, or it has exhibited a protective association, leading to an apparent "obesity paradox." In other cancer sites such as in postmenopausal breast cancer (7), there is often a J-shaped relationship of BMI and mortality; obese patients have a higher risk of death compared with normal-weight patients, but the elevation in risk does not approach the magnitude of risk observed in underweight patients. Further, in studies with large sample sizes that distinguish classes of obesity, this increased risk often does not emerge until patients exceed a BMI ≥35 kg/m$^2$ (i.e., class II+ obesity; ref. 8). In a recent pooled analysis of clinical treatment trials, there was no cancer or treatment combination in which overweight (BMI ≥25 kg/m$^2$) patients had a higher risk of death compared with normal-weight patients (overall mean HR 0.96; $P = 0.06$). This was true across tumor sites (breast, prostate, bladder, ovarian, lung, kidney, colorectal, and hematologic) and stages (both nonmetastatic and metastatic). In fact, a statistically significant survival advantage among those with BMI ≥25 kg/m$^2$ was frequently observed; these results were consistent when patients with advanced stages of cancer were examined separately (9).

## BMI Paradox, Not an Obesity Paradox

One explanation for this phenomenon is that BMI is an imprecise measure of body composition [the amount and distribution of muscle and specific adipose tissue compartments (visceral, subcutaneous, and intramuscular), and other components of weight such as water, bone and organs; refs. 10–18]. Its use often results in misclassification of level of adipose tissue (19, 20). A "normal" BMI can mask excess adiposity, whereas patients with a BMI ≥25 kg/m$^2$ do not always have levels of adiposity sufficient to increase mortality risk. Patients with BMI of 25 to 35 kg/m$^2$ do not necessarily show poorer cancer outcomes due to excess adiposity (19, 21, 22). Critically, BMI does not measure muscle, an important predictor of cancer morality. Skeletal muscle is the largest organ in the body, and secretes cytokines and other peptides (known as myokines) that have autocrine, paracrine, or endocrine actions (23). Like adipose tissue, skeletal muscle has a role in regulating whole body metabolism, inflammation, and insulin resistance and is an important prognostic factor; for example, a recent meta-analysis of 7,843 patients with solid tumors found lower muscle mass was associated with a 44% higher risk of death [HR 1.44; 95% confidence interval (CI), 1.32–1.56; ref. 24]. Given the wide range of muscularity among

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patients with identical BMI, illustrated in Figure 1 and in other studies (20, 22, 25), it is unsurprising that studies using precise measures of body composition obtained from biomedical imaging often present different patterns of association with cancer mortality than those using BMI alone (19, 20).

Figure 1 demonstrates that two patients with the same BMI in the overweight range can have different body composition phenotypes. The patient on the left has low muscle and high levels of visceral adipose tissue. In contrast, the patient on the right has sufficient muscle mass and lower levels of visceral adiposity. Measured by BMI, these two patients fall into identical risk strata, likely resulting in a mixture of effects on the associations of muscle and visceral adiposity, with mortality differing substantially. However, if body composition measures are used, these same two patients fall into different risk strata; the patient with low muscle and high visceral adiposity may have a higher risk of death than the patient with high muscle and low visceral adiposity.

## Explanations of the Obesity Paradox

### Methodologic biases

Beyond the misclassification of patients with cancer regarding muscle and adiposity levels associated with poorer survival, researchers have raised various methodological problems that could explain the "obesity paradox": sampling selection bias, residual or unmeasured confounding, reverse causation, or collider bias (26–28).

***Sample selection bias.*** First, many studies of BMI and death from any cause are conducted in samples recruited after diagnosis, causing concerns that only the healthiest may enroll. Such sampling selection bias could produce an obesity paradox if the sickest overweight patients are less likely to enroll than the sickest normal-weight patients or they die prior to enrollment. For example, in the Life After Cancer Epidemiology Study where women were recruited on average 2 years post diagnosis, enrolled women were more likely to have the less aggressive luminal A tumor than the more aggressive basal subtype (29). However, data from the Breast-Sarcopenia, Cancer and Near-term Survival (B-SCANS) cohort of patients with nonmetastatic breast cancer and the Colorectal-Sarcopenia, Cancer and Near-term Survival (C-SCANS) cohort of patients with nonmetastatic colorectal cancer derived from electronic medical records, where we include the entire population at risk, demonstrate that the overweight and even mildly obese still have a reduced risk of disease-specific or death from any cause (30) compared to the normal weight.

***Residual confounding.*** A second methodologic concern is that of residual or unmeasured confounding: bias that distorts risk estimates despite the investigator's best efforts to eliminate confounding through the inclusion of measured covariates. For example, many studies control for current smoking, but do not have detailed information on smoking duration or intensity or former smoking, and this may confound the associations of BMI with both overall and cancer-specific mortality as smoking is strongly associated both with lower BMI and higher risk of death from cancer as well as other causes (31).

***Reverse causality.*** A third methodologic concern, and perhaps the most important source of possible bias, is reverse causality: underweight or normal-weight patients may have more severe disease, greater disease-related weight loss, and higher mortality compared with overweight patients, thus giving rise to an obesity paradox (32).

To dispel these concerns, we present two analyses in Table 1, evaluating the association of BMI at diagnosis of colorectal cancer with overall mortality using data from the C-SCANS cohort. To address confounding by smoking, we conducted separate analyses among "ever smokers" and "never smokers." Other researchers have observed a U-shaped relationship between BMI and mortality in ever smokers, consistent with

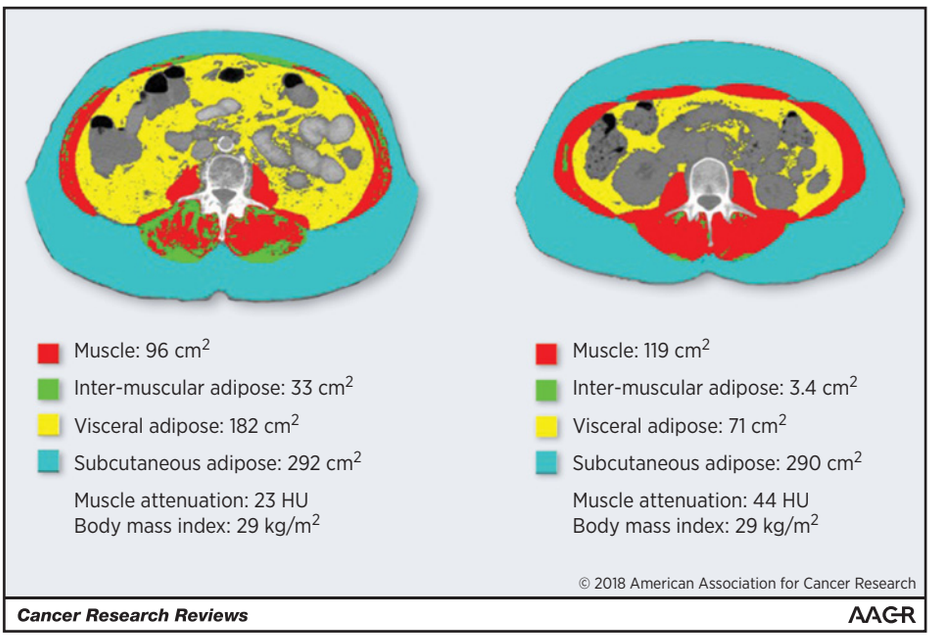


**Figure 1.**
Two female patients with identical overweight BMI (29 kg/m$^2$) and different body compositions.

the obesity paradox, but the expected, linear relationship when analyses are restricted to never smokers (31). When we stratify by smoking status in C-SCANS, we find similar associations between BMI and overall mortality in both the ever and the never smokers, and no evidence of statistical interaction ($P_{interaction} = 0.33$). For example, among ever smokers, overweight patients have a 24% lower mortality risk (HR 0.76; 95% CI, 0.60–0.95) relative to normal-weight patients. Among never smokers, overweight patients have a 13% lower mortality risk compared with normal-weight patients. Although confidence intervals are wide, results are consistent with a nonsignificant, protective effect (HR 0.87; 95% CI, 0.65–1.17).

To address reverse causality, we compare effects in the whole sample to a subsample where we removed patients who lost weight in the 5 years prior to colorectal cancer diagnosis. Specifically, we removed from the analysis patients who moved downward at least one BMI category prior to diagnosis, that is, who were previously obese (>30 kg/m$^2$) but became either overweight (25–30 kg/m$^2$) or normal-weight (18.5–25 kg/m$^2$) by the time of diagnosis, or who were previously overweight (25–30 kg/m$^2$) but became normal-weight (18.5–25 kg/m$^2$) by the time of diagnosis. With a median follow-up of 5.8 years, in the whole cohort ($n = 3175$), being overweight (BMI 25–30 kg/m$^2$) is associated with a 19% lower risk of death (HR 0.81; 95% CI, 0.67–0.96). When we remove from the analysis those patients who moved downward at least one BMI category, we note similar findings. However, as we observed when restricting to never smokers, confidence intervals were wide, and associations were no longer statistically significant (HR 0.89; 95% CI, 0.71–1.12).

Despite nonsignificant findings in both scenarios illustrated in Table 1, due in part to loss of power from the reduced sample size, hazard ratios still suggest a protective, rather than an adverse effect of overweight. Furthermore, in the C-SCANS cohort, we note that overweight versus normal-weight patients have a lower mortality risk regardless of stage, including a protective association in stage I patients who we would not expect to die from their cancer (33).

***Collider bias.*** A fourth concern is collider bias (27). In the presence of an unmeasured risk factor for colorectal cancer, selecting a population based on a colorectal cancer diagnosis (i.e., conditioning on diagnosis by restricting analyses to patients with existing colorectal cancer) could introduce a spurious association between an exposure (e.g., at-diagnosis BMI) and an outcome (e.g., death) that could reverse the direction of association, making a harmful exposure appear protective (26); that is, collider bias may occur if overweight/obesity leads to higher disease incidence, but unmeasured genetic or other risk factors occurring disproportionately in normal-weight patients are more strongly related to mortality than is overweight/obesity.

One potentially important risk factor that could lead to collider bias is tumor indolence. There is evidence to support the hypothesis that obese patients may have tumors with more indolent molecular characteristics, leading to less aggressive cancers with better survival (also referred to as disease heterogeneity bias). For example, obesity is associated with slow-growing renal tumors with low levels of fatty acid synthase gene expression (34). Similarly, in endometrial cancer, obese patients are less likely to have the unfavorable type 2 carcinomas, but even among those with type 1 carcinomas, higher BMI was associated with more favorable pathologic characteristics including lower grade and less depth of invasion (35). However, although obesity has been associated more strongly with the incidence of the less aggressive, ER+ breast tumors (36–39), it has also been associated with more aggressive, ER− breast tumors (40), In "case-only" studies restricted to patients with existing breast cancer, BMI >35 kg/m$^2$ is associated with more proliferative tumors (41) and with increased risk of late recurrence even among women with ER+ tumors (42).

Based on assumptions about the structure of the relationships between BMI history and cancer incidence and mortality considered in articles describing concerns about collider bias, spuriousness may be avoided with adjustment for pre-diagnosis BMI. Although most studies do not have this information, adjustment for this variable in our previous analysis in C-SCANS had no impact on our findings; overweight patients consistently had the lowest risk of colorectal cancer-specific and overall mortality (30). Furthermore, Glymour and colleagues (43) evaluated conditions under which collider bias would be a concern and they noted that the magnitude of an association of some unmeasured factor and mortality would have to be very large to explain the association we noted in our analysis.

## Clinical and biological arguments for the obesity paradox

***Muscle reserves ensure superior outcomes.*** Substantial evidence shows that low muscle is an important risk factor for mortality; low muscle mass is associated with higher risks of recurrence, overall and cancer-specific mortality, surgical complications, and treatment-related toxicities.

The restricted cubic spline displayed in Figure 2A demonstrates that the lowest risk of mortality is between a BMI of 25 to <30 kg/m$^2$, the category of BMI at which patients are least likely to have low levels of muscle but also do not have excessive levels of adiposity. When body composition phenotypes are

**Table 1.** Association of BMI and mortality in nonmetastatic colorectal cancer by smoking status and in the strata of patients with stable weight prior to diagnosis

| | Normal weight (18.5–<25) HR (95% CI) | Overweight (25–<30) HR (95% CI) | Obese (≥30) HR (95% CI) |
|---|---|---|---|
| Full cohort ($N = 3,175$) | Reference | 0.81 (0.67–0.96) | 1.08 (0.90–1.29) |
| To address residual confounding: | | | |
| Ever smokers ($N = 1,691$) | Reference | 0.76 (0.60–0.95) | 1.07 (0.85–1.34) |
| Never smokers ($N = 1,481$) | Reference | 0.87 (0.65–1.17) | 1.03 (0.76–1.41) |
| To address reverse causality: | | | |
| Weight stable/gain[a](those with major weight loss dropped) $N = 2,589$ | Reference | 0.89 (0.71–1.12) | 1.11 (0.89–1.38) |

[a]Excluded are those who dropped a BMI category: from overweight/obese to normal or from obese to overweight.

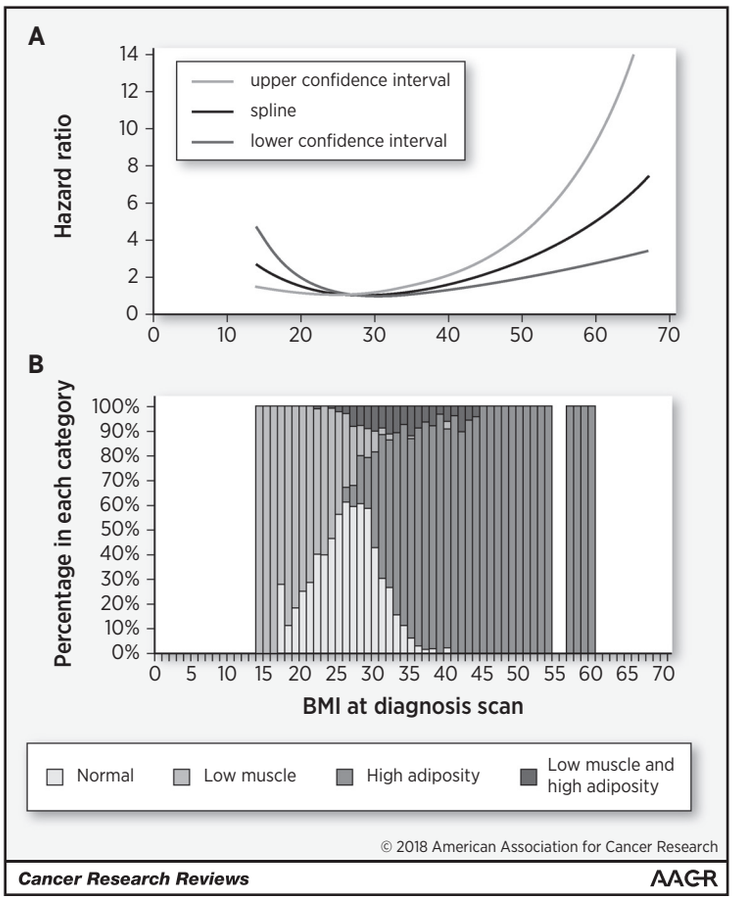


**Figure 2.**

**A** and **B,** Adapted from Caan and colleagues (34). Cubic spline for BMI has four knots and a reference value of BMI = 27; adjusted for age, sex, race, stage, grade, site, treatment, prediagnosis BMI, smoking, and physical activity; $P < 0.001$ (test for nonlinearity; **A**); and accompanying histogram of body composition phenotypes by BMI (**B**).

plotted against BMI (Fig. 2B), a large percentage of patients (59.5%) with a BMI in the normal weight range 18 to 25 kg/m$^2$ are at higher risk of mortality due to low muscle. As expected, a large percentage of patients at a BMI $\geq$35 kg/m$^2$ are at higher risk of mortality due to high adiposity. Interestingly, the highest percentage of patients classified as "normal," that is, they have both adequate muscle mass (middle or high tertile) and low or modest (low or middle tertile) adiposity (58.6%), fall into the overweight (BMI 25 to <30 kg/m$^2$) range, potentially explaining why overweight is associated with the lowest risk of mortality.

***Moderate subcutaneous fat may provide protective nutritional reserves.*** More controversial is whether a moderate level of adiposity, consistent with a BMI in the overweight range, is beneficial for survival among patients with cancer. Total adipose tissue (TAT) is comprised of subcutaneous (SAT), visceral (VAT), and intra/intermuscular (IMAT) adipose tissue. Complicating the understanding of adiposity's role in cancer outcomes, associations and mechanisms of SAT, VAT, IMAT, and cancer outcomes differ, with SAT most often inversely associated or associated in a U-shaped fashion with mortality (44–46), whereas higher VAT (45, 47, 48) and IMAT levels often predict worse outcomes. However, in most patients, SAT is by far the largest contributor to TAT and may substantially influence associations of TAT and outcomes.

VAT has been related to higher inflammation (49) and an adverse cardiometabolic risk profile including higher insulin resistance (50), impaired glucose, low HDL-cholesterol, and high triglyceride levels (51–54). These conditions may directly promote tumor progression or predict a higher risk of comorbid conditions, such as diabetes (55) and coronary heart disease (56, 57), which can further jeopardize cancer survival (58, 59). Despite this, some studies show better survival with modest levels of VAT (48, 60).

By contrast to most studies of VAT, cardiometabolic risk profiles for SAT have often been relatively benign (51, 54, 61–63). More importantly, the apparent benefits of SAT in cancer populations may be due to better nutritional status (64). A moderate amount of SAT may enable patients to survive weight losses that can occur with tumor progression and treatment. Two other studies suggest that SAT may confer survival benefits. In the first study, which included 1,473 patients with gastrointestinal and respiratory cancer and 273 patients with metastatic renal cell carcinoma (stages I–IV), Ebadi and colleagues found that patients with higher SAT levels (SAT index $\geq$50.0 cm$^2$/m$^2$ in males and $\geq$42.0 cm$^2$/m$^2$ in females) had the longest survival. This differentiated risk in patients with low skeletal muscle; Ebadi and colleagues found substantially longer survival observed in patients with higher levels of SAT, suggesting potential benefit in carrying extra weight when coping with advanced cancer. In the second study, which included 120 patients with metastatic castration-resistant

prostate cancer, those with higher SAT (SAT index >median value vs. <median value) had significantly longer overall survival (65). Thus, some evidence suggests that moderate SAT levels are related to better survival and that these associations may also underpin the overweight paradox. However, more research is needed to confirm whether and how moderate adiposity protects against mortality.

Of note, much of the research summarized in the sections above uses single-slice images from computed tomography scans to assess body composition. These scans are readily available in clinical practice for many cancers and provide precise estimates of muscle and adipose tissue that are highly correlated (0.90) with whole-body volumes of muscle and adipose tissue (66). However, though the use of CT scans can facilitate integration into clinical practice with little added cost and no additional ionizing radiation to the patient, such assessment does not provide insights into muscle function, physical function, or tissue biology, which may be important to understanding the role of body composition in cancer survival.

## Implications

We argue that the association of higher BMI with lower mortality among patients with cancer should be termed a BMI paradox, rather than an obesity paradox. BMI is a poor proxy for adiposity. Excess adiposity in many cancers (reliably identified by a BMI $\geq$35 kg/m$^2$) may be associated with higher risk of overall mortality, apparent in our own B-SCANS and C-SCANS data. However, higher adiposity may not always be related to worse outcomes. Muscle, an important predictor of mortality, is also not accurately measured by BMI. Thus, the apparent paradox is due to the fact that a large majority of patients with a BMI of 25 to <30 kg/m$^2$ have the necessary protective muscle reserves but have not yet reached adiposity levels high enough to increase mortality. In our own studies, we have not fully examined if moderate adiposity may be protective and whether subcutaneous adipose tissue, specifically, may offer some benefit in nonmetastatic cancer. This is an important area of future research.

Thus, we refute the notion that the primary reason for the observed association between overweight and lower mortality in cancer is methodologic bias. We have demonstrated that confounding by smoking, reverse causality, and/or collider bias are unlikely to fully account for the observation.

In conclusion, the best evidence supports a survival advantage due to higher muscle reserves in overweight patients with cancer.

## Future Directions

A new focus on the role of muscle in addition to adiposity as an important contributor to body size and to cancer survival is warranted and should be a research priority.

Measures of body composition beyond BMI should be integrated into clinical practice whenever possible and maintenance of muscle mass should be a treatment goal throughout the cancer process; interventions that incorporate strength training and adequate protein intake are recommended. Exercise (67–70), especially resistance training (71, 72), builds muscle mass and reduces intra-abdominal adipose tissue in patients with cancer. These improvements in body composition translate to improved quality of life and physical function (22, 73–75), and may improve chemotherapy completion (75, 76) and reduce long-term treatment side effects (77). Based on strong observational evidence, ongoing randomized controlled trials are testing whether exercise prolongs recurrence-free survival (78). In patients with cancer, preservation of muscle mass should be a key component of any intentional weight loss program, for example, including an exercise component to preserve muscle in studies focused on caloric restriction. In the era of precision medicine, our goal should be to target interventions based on individual body composition phenotypes to optimize survival outcomes.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Authors' Contributions

**Conception and design:** B.J. Caan, E.M. Cespedes Feliciano, C. H. Kroenke
**Development of methodology:** B.J. Caan, E.M. Cespedes Feliciano
**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** B.J. Caan, E.M. Cespedes Feliciano, C. H. Kroenke
**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** B.J. Caan, E.M. Cespedes Feliciano
**Writing, review, and/or revision of the manuscript:** B.J. Caan, E.M. Cespedes Feliciano, C. H. Kroenke

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