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The Plausibility of Obesity Paradox in Cancer

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Abstract

In contrast to the convincing evidence that obesity (measured by body mass index, BMI) increases the risk of many different types of cancer, there is an ambiguity in the role of obesity in survival among cancer patients. Some studies suggested that higher BMI decreased mortality risk in cancer patients, a phenomenon called the obesity paradox. The spurious positive association between BMI and cancer survival is likely to be explained by several methodological limitations including confounding, reverse causation, and collider stratification bias. Also, the inadequacy of BMI as a measure of body fatness in cancer patients commonly experiencing changes in body weight and body composition may have resulted in the paradox. Other factors contributing to the divergent results in literature are significant heterogeneity in study design and method (e.g., study population, follow-up length); time of BMI assessment (pre-, peri-, or post-diagnosis); and lack of consideration for variability in the strength and directions of associations by age, sex, race/ethnicity and cancer subtype. Robust but practical methods to accurately assess body fatness and body compositions and weight trajectories in cancer survivors are needed to advance this emerging field and develop weight guidelines to improve both the length and the quality of cancer survival.

Introduction

Body fatness, commonly assessed by body mass index (BMI) as overweight (BMI 25.0–29.9) and obese (BMI ≥30), has been linked to an increased risk of cancer. A report by the International Agency for Research on Cancer working group, which reviewed over 1,000 epidemiologic studies, concluded that excess body fatness causes cancer of the esophagus (adenocarcinoma), gastric cardia, liver, gallbladder, pancreas, colon and rectum, kidney, thyroid, female breast (postmenopausal), endometrium, ovary, multiple myeloma and meningioma (1). A recent umbrella review of meta-analyses also found strong evidence of positive associations between body fatness and those cancers (2,3). Taken together with plausible biological mechanisms such as systemic and tumor microenvironmental inflammation and immune mediated responses, insulin resistance, insulin-like growth factors

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(IGFs) and sex hormones pathways (4,5), the harmful effect of body fatness on cancer etiology is clear.

In addition, prospective cohort studies that followed their participants who were free of cancer at study baseline for causes of death consistently found that obese participants had a significantly increased risk of total cancer mortality as well as site-specific cancer mortality (6–9). Moreover, studies of breast cancer survivors also supported the hypothesis that obesity was associated with poor prognosis and worse survival in cancer patients. A meta-analysis of breast cancer survivor studies summarized that obesity assessed less than 12 months after cancer diagnosis and 12 months or more after cancer diagnosis was related to 23% and 21% increased risk of death, respectively, compared to normal weight (10). However, several emerging studies in some cancers such as colorectal cancer, renal cell carcinoma, and diffuse large B-cell lymphoma found no association or even suggested that obese cancer patients had a lower risk of mortality compared to normal weight cancer patients (11–14). A phenomenon known as the “obesity paradox” (i.e., obese people live longer) in individuals with cardiovascular disease, type 2 diabetes, and end-stage renal disease (15–18) was observed in cancer patients as well. Although the inconsistency in the current evidence on obesity and cancer survival is likely due to limitations and weaknesses in studies, sporadic observations on the positive association between BMI and survival in some cancers has been perceived as the paradox. Therefore, this review summarizes a number of hypothesized methodological explanations that may have caused spurious associations that led to the obesity paradox in some cancers. Also, other practical explanations that may provide insight into the plausibility of an obesity paradox in cancer are explored.

Methodological limitations in observational studies of obesity and cancer survival

Confounding

Confounding by unmeasured or poorly measured variables and failure to properly control for confounders are probably the most widely recognized limitations in analyses of risk factors for mortality. Classic examples of confounding in the obesity-mortality association studies are smoking and preexisting health conditions that cause weight loss (6,9). Because current smokers tended to have lower BMI but higher mortality risk than non-smokers, smoking is a strong confounder. A typical adjustment for smoking status or pack-years of smoking is not enough to avoid residual confounding (19). When a more drastic measure such as stratification or exclusion of ever smokers was taken, the obesity paradox in type 2 diabetes not only disappeared, but among never smokers, obesity was associated with increased mortality in individuals with type-2 diabetes (20). To investigate obesity in relation to mortality in cancer patients, many studies utilized data collected in clinical trials or retrospectively extracted from medical records (12,21). In such cases, smoking information is often not collected or poorly assessed. Studies also often failed to account for other potential confounders such as comorbidities, socioeconomic status, physical activity, and diet. The obesity paradox tended to be observed in studies with older adults than with

younger adults (20,22), in part due to a higher likelihood of residual confounding by smoking and comorbidities in studies with older individuals than younger individuals.

Reverse causation

Reverse causation could occur when weight loss is a consequence rather than a cause of cancer. For many cancers, weight loss often precedes clinical recognition of the disease and is associated with higher mortality. Cancer patients who have normal weight at the time of cancer diagnosis may have previously been overweight or obese prior to experiencing unintentional weight loss. Therefore, in studies of obesity and cancer survival, the normal weight group, often used as a reference group, is a mix of individuals with normal weight and those who have lost weight due to cancer and are thus at higher risk of mortality. A disproportionate number of weight-loss individuals in the reference group may attenuate the obesity-mortality association toward null or even make a spuriously lowered risk at higher levels of BMI (19). A comparison of findings in studies that examined pre- vs. post-cancer diagnosis BMI with mortality may demonstrate the possibility of reverse causation. Pre-diagnosis BMI assessed several years before cancer diagnosis (thus less likely to have reverse causality) was significantly associated with increased risk of mortality in cancer patients (23–31). In contrast, studies that examined BMI assessed at diagnosis or within 1 or 2 years of diagnosis found a null or inverse association with mortality (11,12,23,32–34).

Collider stratification bias

This is a form of selection bias that can occur in the study design or data analysis (19,35,36). When a study population or data analysis is stratified (i.e., conditioned) by a variable (i.e., collider) affected by exposure and outcome, a selection bias occurs, which can induce a false association or even reversed association between exposure and outcome (19,36,37). For example, obesity (i.e., exposure) is associated with cancer incidence (1) and cancer is an established risk factor for mortality (outcome). Obesity also directly influences mortality risk (9). Smoking is another factor that is related to risk for cancer as well as mortality. In this scenario, obese people may have developed cancer due to obesity or smoking whereas non-obese people developed cancer due to smoking in the absence of obesity. When the analysis is restricted to cancer patients (i.e., conditioned on cancer), obese cancer patients are less likely to be smokers, while nonobese cancer patients are more likely to be smokers. Because smoking is a stronger risk factor for cancer and mortality than obesity, obese cancer patients appear to have lower mortality risk than nonobese cancer patients (the obesity paradox). This collider stratification bias has been used to explain the obesity paradox in cardiovascular disease, other chronic diseases, and renal cell carcinoma (36,38,39). However, the collider bias may partially explain how the direction of a true association can be reversed and may not fully account for the obesity paradox (37,40).

Body fatness measured by BMI

BMI is the most commonly used measure of body fatness in studies and clinics. BMI is highly correlated with body fatness assessed by the hydrodensitometry or the dual-energy X-ray absorptiometry (DXA) (41–43). Higher BMI was associated with increased risks of cancer and other diseases in numerous studies (1,2,6–9,20). However, the performance of BMI to identify excess adiposity has a high specificity, but low sensitivity, suggesting the

underdetection of obesity, which attenuates an obesity-disease association (44). The validity of BMI is also low in older adults due to changes in body composition related to aging (41,45). In studies of cancer patients who tended to be old and experience changes in body weight as well as body composition due to cancer, a low sensitivity of BMI to identify obese patients and inability to differentiate fat and muscle mass significantly challenge its utility. Studies using computed tomography (CT) images showed that there was a high variability in fat mass and muscle mass within all strata of BMI in cancer patients (46–50). In a colorectal cancer survivor study that assessed fat mass and muscle mass using an abdominal CT scan taken within 4 months of diagnosis before chemotherapy or radiation, only 42% of cancer patients with BMI 20–<25 had a normal body composition (i.e., having adequate muscle mass and lower adipose tissue), whereas 59% of cancer patients with BMI 25–<30 had a normal body composition (50). When a specific body composition such as visceral fat mass and muscle mass was examined in relation to cancer survival, most studies found poor cancer survival with higher visceral fat mass and/or reduce muscle mass (50–57). However, studies of renal cell carcinoma patients reported inconsistent findings – some found higher visceral adipose tissue with lower mortality (58–61) whereas others found higher fat mass with poor survival (62,63). A study suggested that renal cell carcinoma developed in obese patients were more likely to be indolent than this in normal weight patients (34).

Challenges in summarizing current evidence on obesity and cancer survival

In combination with the methodological limitations discussed above, several other features in existing studies may have contributed to the inconsistent and contradicting findings in the current literature.

Heterogeneity in study design and method

There are significant heterogeneities across studies in many aspects, including study population, degree of control for confounding, and the length of follow-up. Some studies investigated the association between obesity and mortality in clinical trial participants whereas other studies used a retrospectively constructed cohort including all patients. Cancer patients who participated in clinical trials are those who met strict eligibility criteria for trials and their characteristics differed from non-participants (64). Moreover, many trials either did not collect or crudely assessed smoking, comorbidities, and weight history, which are critical in evaluating obesity-mortality in cancer patients. Characteristics of study population such as race/ethnicity, socioeconomic status, and prevalence of smoking, comorbidities and other potential confounders also differed across studies. Most studies, however, controlled for different sets of these risk factors, depending on the availability of their data that often lacked information on many confounders. In addition, the length of follow-up varies across studies, but most studies have a relatively short follow-up during which other risk factors such as cancer stage, comorbidities and adverse effect of treatment may have a stronger effect on survival than obesity does. It’s intriguing that the obesity paradox tends to be observed in studies with shorter follow-up than with longer follow-up (33,65–67).

The time of BMI ascertainment

The time of BMI ascertainment varied across studies. Some studies examined BMI reported several years before cancer diagnosis and found pre-diagnosis BMI was related to an increased risk of death in cancer patients (23–31). On the other hand, studies that used BMI assessed at diagnosis or several months to 1–2 years after cancer diagnosis found no association or lower mortality with higher BMI (11–13,23,32–34). Considering most cancers result in weight loss, and cancer treatments also lead to weight changes (either gain or loss), many cancer patients were likely to experience weight fluctuation during and after cancer treatment. Studies that examined weight changes within 1–2 years of cancer diagnosis consistently found that weight loss, but not weight gain, was associated with higher risk of mortality (68,69). Weight loss in cancer patients is mostly muscle loss due to sarcopenia and cachexia that are related to a higher mortality in cancer patients (46,70–72). Taken together with BMI's inability to assess body composition, a one-time measure of BMI does not reflect the cumulative effect of obesity on cancer survival. In addition, changes in BMI as well as confounding factors, such as smoking, comorbidities, physical activity, and diet during the follow-up, should be taken into account in analyses by periodically reassessing them (73).

Lack of stratified analysis

Despite large variations in obesity prevalence, body composition, and cancer rate and survival across racial/ethnic groups, studies did not evaluate the obesity-mortality association by race/ethnicity. Breast cancer survivors studies have suggested a differential effect of obesity on survival by race/ethnicity (74,75), but most cancer survivor studies did not examine the association by race/ethnicity. Some studies even failed to control for race/ethnicity in their analyses. Interestingly, the obesity-mortality association seems to differ by sex; the so-called obesity paradox was more likely to be observed in men than in women (21). However, due to a lack of report on sex-specific results, sex differences cannot be explored further. Another important characteristic to be considered is cancer subtypes. Accumulating evidence suggests that the risk factors, prognosis, and survival of cancer differ by its subtypes (76–78), but only few studies attempted to evaluate the obesity-mortality association by cancer subtypes. Breast cancer survivor studies showed a clear positive association between obesity and mortality in estrogen receptor-positive breast cancer patients but not in other subtypes such as triple-negative and human epidermal growth factor receptor 2-positive types (79,80). Lack of consideration for variability in the strength and direction of associations by various characteristics of participants or cancer may have contributed to the divergent results in the literature.

Quality of meta-analysis

Several meta-analyses were conducted to quantitatively summarize existing evidence on obesity and cancer survival (11,12,81,82). Two recent meta-analyses of renal cell carcinoma that used different inclusion criteria and statistical methods reported opposite results for the association between BMI and mortality (12,82). One meta-analysis (n=8 studies) found that compared to the lowest BMI group, highest BMI group (BMI cutoff in most included studies was 23 or 25) had a significantly lower total mortality and also observed a significant

heterogeneity in the summary estimate and a publication bias (12). On the other hand, the other dose-response meta-analysis (n=3 studies) found a U-shape association that the total mortality risk decreased in BMI <25 but increased linearly in BMI >25 (82). Although a well-conducted meta-analysis provides a concise summary of evidence, results of meta-analysis should be interpreted with caution (83). Meta-analyses are subject to search strategies, inclusion and exclusion criteria, and publication bias. A meta-analysis with the largest number of included studies does not mean a more robust study. A rigorous approach should be taken to conduct a meta-analysis, especially when there is a greater uncertainty in the topic area.

Moving forward

The inconsistencies in the current evidence on the effect of body fatness on cancer survival, which led to the obesity paradox, can be reduced by improving several study features, for example, proper control for confounders, minimizing potential biases, larger sample size, repeated measurements of weight over time, and clearly defined time frame for both BMI measurements and follow-up in future studies. Also, future studies need to examine the effect of obesity on cancer survival by cancer subtypes and in more defined sub-groups of age, sex, and race/ethnicity. Studies in African Americans, Hispanics, and Asians, whose body composition differs from whites and experience more disparities in cancer survival, are especially needed.

The critical challenge in investigating the obesity-mortality relation in cancer survivors is improving measures of overall body fatness and body composition. Although imaging methods provide more accurate and detailed data on body fatness and body composition, they also have methodological and practical limitations. Bioelectrical impedance analysis depends on individual’s hydration status and the presence of ascites, common in some cancer patients, which may bias the assessment. The dual-energy X-ray absorptiometry (DXA) measures bone mineral density as well as fat and fat free mass. However, correlations between DXA measured adiposity and cardiovascular risk factors were similar to those assessed by BMI or skinfold thickness (84) and whole body DXA may not be practical. Magnetic resonance imaging and CT can directly quantify adiposity in different compartments such as visceral adipose tissue, but they are expensive and not readily available in studies and clinics (85). Also, there is no standardized visceral adipose tissue assessment method used across studies. It is urgent to develop and validate robust but relatively simple and practical methods that utilize existing anthropometry measures, for example, a combination of BMI and % weight change (86), waist circumference, and thigh circumference as a measure of lower body muscle (87).

Furthermore, there is a significant gap in the literature about the role of body fatness on overall survivorship, including post-cancer morbidity and quality of life, which impact mortality. As more and more cancer survivors live longer after cancer (88), body weight management after cancer is important to maintain overall health and well-being of cancer survivors. Given that colorectal cancer survivors who were obese before cancer diagnosis had increased risk of second obesity-associated cancers compared to those with normal weight (24), body fatness is likely to affect the risk of new-onset of other obesity-related

health conditions such as diabetes, heart and renal diseases in cancer survivors. Future research on the effect of body fatness not only on mortality but also on post-cancer morbidity and quality of life in cancer survivors are warranted.

Conclusions

The obesity paradox observed in some cancers is mostly likely to be explained by methodological limitations in studies, including the low validity of BMI as a measure of body fatness in cancer survivors. However, no plausibility of the obesity paradox in cancer does not mean that we have a clear understanding on the role of body fatness at various stages in cancer prognosis and survival. We have just begun to look into the question of the optimal body composition and body weight for cancer survivors. Significant efforts are needed to move this emerging area forward.

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Abbreviations

BMI	Body mass index
DXA	dual-energy X-ray absorptiometry
CT	computed tomography

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Significance

This paper reviews a number of methodological explanations and limitations in studies, which provide insight into the plausibility of an obesity paradox in cancer.