Next Steps in Understanding the Obesity Paradox in Cancer

Bette J. Caan and Candyce H. Kroenke

Although overweight and obesity, assessed by body mass index (BMI), are reliably related to an increased risk of cancer, data on the relationship between BMI and cancer prognosis are inconsistent. An emerging literature suggests that the relationship between BMI and cancer survival is U-shaped and that overweight, and in some cases mild obesity, may not increase risk and might even offer protection. This "obesity paradox" has been demonstrated in patients with lymphoma, leukemia, colorectal, endometrial, thyroid, and renal cancers. There is also substantial literature that demonstrates that weight gain after a cancer diagnosis does not lead to a poorer prognosis, especially small or moderate weight gains of less than 10% of initial body weight. In fact, weight loss (although we do not know about intentionality) appears to confer a higher mortality risk than does weight gain. Thus, just because obesity predicts a higher risk of incident cancer, we cannot infer that it is related to poorer outcomes once diagnosed.

Reasons provided to explain the obesity paradox in cancer include methodologic biases, such as reverse causality, confounding, detection bias, or collider bias. Yet others posit that the association reflects true benefits of a higher BMI, including extra nutritional reserves, greater muscle mass, a lower likelihood of dose-limiting toxicity, and less aggressive tumors, each of which may be independently associated with better prognosis.

Investigators need to better understand the underlying reasons for the obesity paradox to design effective interventions. One promising approach is to directly measure body composition (muscle and adiposity) rather than rely on BMI. Many studies have shown that BMI is not an accurate measure of muscle or adiposity, although it has often been used as a surrogate for fat mass. We argue that the use of BMI in cancer patients obscures examination of the independent relationships of muscle, adiposity, and cancer survival. Risks associated with muscle and adiposity may differ across cancers and by stage of cancer. A single approach to improving body composition phenotypes for cancer survivors is unlikely to be "one size fits all."

This issue focuses on some of the emerging literature suggesting an obesity paradox in cancer. Cespedes Feliciano and colleagues (1), Meyerhardt and colleagues (2), and Greenlee and colleagues (3) show that higher BMI and weight gain do not consistently predict poorer cancer outcomes. Mayeda and Glymour (4) show how to estimate the magnitude of bias in two settings (collider-stratification bias and heterogeneity of disease bias). Before dismissing unexpected associations between obesity and survival, simple simulation calculations can be used to evaluate the plausibility of large biases. The magnitude of bias may depend on the specific cancer. Shachar and colleagues (5) discuss the oncologist point of view in interpreting the literature. Finally, Kinsey and colleagues (6) show that muscle may play a particularly significant role in understanding the role of body size in cancer survival. We do not suggest that obesity is ideal for optimal cancer outcomes. Rather, we suggest that when BMI is used to measure body size, an obesity paradox can emerge because "overweight" patients often have higher levels of protective muscle. It is time to move beyond BMI and use body composition to help improve our understanding of how body size is related to cancer survival.

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

Disclosure of Potential Conflicts of Interest

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