

EDITORIAL

Intentional Weight Loss and Cancer Risk: Never Too Late to Lose Weight

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Although the link between excess body weight and cancer risk is now well-established (1), important questions surrounding this relationship remain unanswered. For example, the impact of the duration and degree of overweight and obesity across the life span and the identification of (site-specific) susceptibility windows are important issues we currently do not fully understand. In addition, an important yet unresolved question is how intentional weight loss might influence cancer risk. In their article published in this issue of *JNCI Cancer Spectrum*, Luo and colleagues (2) used data from a large cohort of US women to study the association between intentional weight loss during a 3-year window following baseline and subsequent cancer risk. After adjustments for baseline body mass index and other relevant covariates, the authors report statistically significant reductions in the risk of obesity-related cancer (especially endometrial cancer) in women who intentionally lost more than 5% of their body weight, whereas unintentional weight loss or short-term weight gain showed no association. Because previous evidence on this topic has come from a small number of observational studies and from studies of patients undergoing bariatric surgery, this analysis based on prospective cohort data represents an important contribution to the field. Furthermore, it confers an important message for public health: among individuals who are overweight or obese, losing weight—even if reductions are small and regardless of age or the degree of excess weight—is beneficial for cancer risk.

A potential cancer preventive effect of intentional weight loss in overweight individuals is also supported by biological data. The biological mechanisms underlying the link between adiposity and cancer are not completely understood, but there is general consensus that dysregulated insulin signaling, inflammation, and sex hormone metabolism are likely to be relevant pathways (1). Importantly, there is evidence from randomized controlled trials and other intervention studies to suggest that intentional weight loss either through physical

activity or dietary modification can cause favorable changes in these pathways (3,4). In addition, there are now preclinical studies of the effect of weight loss achieved through calorie-restricted diets that have shown favorable effects on obesity-related biological pathways in target tissues (eg, colorectum) as well as on markers of cancer-related processes such as cellular proliferation and apoptosis (5). Overall, although more research is clearly needed in this area, these studies provide important evidence on the impact of intentional weight loss at the molecular level and can offer important clues to the underlying biology.

Measured or unmeasured confounding and reverse causation are among the main sources of bias in all observational studies. This is particularly challenging in studies with weight loss as exposure, because of its dynamic nature and various determinants. Achieving intentional weight loss of at least 5% of initial weight through lifestyle changes requires profound modifications in physical activity and/or dietary behaviors. Although the authors appropriately adjusted for physical activity levels before weight loss, though not for diet, the possibility remains that the observed inverse association between intentional weight loss and risks of cancer is at least partly due to lifestyle changes rather than weight loss per se. Randomized studies would be needed to more confidently rule out confounding by these behavioral factors. Future observational studies could also concurrently measure changes in levels of biomarkers that are modified by weight loss and are posited to lie on the pathway between obesity and cancer development. A major strength of the current study was separating those who intentionally lost weight from those who underwent weight loss because of potential subclinical disease processes. This is important to address the issue of reverse causation. Other than that, few people manage to maintain weight loss over the long term, which is crucial to uphold its health benefits (6). The authors correctly state that some women who lost weight

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between baseline and year 3 may have subsequently regained weight after the 3-year exposure period. It is plausible that sustained weight loss and maintenance of a healthy weight would be associated with more profound reductions in cancer risk. We and others have shown that duration of overweight and obesity is associated with cancer risk (7,8); therefore, truncating this duration likely reduces accumulation of further risk.

Placing this study by Luo et al. into a broader context, we can say with some confidence that intentional weight loss through changes in eating and physical activity is feasible and can reduce the risk of cancer. Although further studies are needed to confirm the remaining aspects of this relationship—for example, by conducting similar investigations in men (because the current analysis was restricted to postmenopausal women) and in larger study samples that can provide data on less common obesity-related cancers—the findings suggest that reducing weight has favorable effects on cancer risk at any age. Prospective cohorts should be encouraged to collect longitudinal data on weight change and on intentional weight loss to address the issue of weight loss and cancer development. Further evidence in this regard is important for both public health and obesity management in cancer prevention in that excess body weight is important to manage regardless of the age of the patient.

Notes

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