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Obesity and Cancer—It's Causal and...Reversible?

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Obesity increases the risk of at least 13 types of cancer (1). By the year 2030, 1-in-2 U.S. adults will have obesity (2). Prospective cohort studies suggest that self-reported intentional weight loss reduces cancer risk, but uncertainty persists about whether such an association is causal (3). A randomized trial is required to obtain an unbiased estimate of causal effect.

The results of a large, randomized trial of the effects of a lifestyle intervention on cancer outcomes in patients with type 2 diabetes are reported in this issue of *Obesity*. The Look AHEAD (Action for Health in Diabetes) trial assigned 4,859 overweight or obese individuals with type 2 diabetes to an intensive lifestyle intervention (ILI) targeting a weight loss of 7% of body weight or to a diabetes support and education (DSE) group. The three key cancer outcomes included overall cancer incidence; obesity-related cancer incidence—pre-specified as one of the 13 cancers associated with obesity (1); and overall cancer mortality.

At 1-year, the between group (ILI vs. DSE) difference in weight loss was 7.9% (–8.6% vs –0.7%); after 12-years, this effect reduced to 1.9% (–6.5% vs –4.6%). After a median follow up of 11 years, incident cancer occurred in 332 participants in the ILI and 352 participants in the DSE group (hazard ratio, 0.93; 95% confidence interval, 0.80 to 1.08; P=0.32). Obesity-related incident cancer occurred in 158 participants in the ILI and 185 participants in the DSE group (hazard ratio, 0.84; 95% confidence interval, 0.68 to 1.04; P=0.10). Cancer-specific mortality occurred in 80 participants in the ILI and 85 participants in the DSE group (hazard ratio, 0.92; 95% confidence interval, 0.68 to 1.25; P=0.59).

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Recently, scientists and clinicians have called for a more accurate interpretation of clinical trial results, with evaluation of confidence intervals as estimates of a plausible range of effects that should be interpreted clinically (4). In this example, the ILI reduced the risk of obesity-related cancer incidence by 16%, a reduction that would be clinically valuable.

The effects of weight loss on cancer risk may differ by molecular tumor subtype, sex, age, race or ethnicity. The Look AHEAD trial was limited to individuals with type 2 diabetes. Future trials should be designed to test the effects of weight loss by specific cancer site and molecular subtype, in persons without diabetes, and in diverse sex, age, and race and ethnicities to determine if weight loss provides similar benefits across individual cancers and population subgroups.

Finally, future randomized studies that examine substantial and sustained weight loss (e.g., metabolic surgery and medications) will be critical to inform future cancer prevention and control policies. The findings from the Look AHEAD Research Group will inform the next generation of studies on obesity and cancer prevention and control. Interpreting the findings from this randomized trial in the context of current preclinical, observational, and experimental studies of biomarker endpoints, is consistent with the hypothesis that obesity has a causal, and plausibly reversible, effect on cancer risk (5).

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