Bariatric Surgery and Cancer Risk
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Approximately 42% of adults in the US have obesity, with a body mass index of 30 or greater. Obesity has been shown to be associated with multiple types of cancer (including postmenopausal breast, endometrial or uterine, ovarian, esophageal adenocarcinoma, gallbladder, gastric cardia, colorectal, renal cell, liver, pancreas, thyroid, meningioma, multiple myeloma) and these are referred to as obesity-associated cancers. Obesity promotes and accelerates cancer by multiple mechanisms, including increases in circulating adipokines, insulin and insulin growth factor, circulating estrogen, inflammatory cytokines, changes in microbiota, and epigenetic changes.

Despite this knowledge, definitive data on the effect of intentional weight loss through interventional studies and cancer risk reduction are lacking. The reasons for this knowledge gap include the difficulty in achieving sustained weight loss through diet and exercise, the large number of patients needed to observe changes in cancer incidence and mortality, and the long length of follow-up required to assess cancer risk reduction. Bariatric surgery results in significant (25%-30%) and durable weight loss and thus provides a unique opportunity to assess the relationship between large intentional weight loss and cancer risk, including both incident cases and mortality.

In this issue of JAMA, Aminian et al4 present data from an observational, matched cohort study designed to address the question of whether bariatric surgery is associated with decreased risk of incident cancer cases and cancer mortality. The authors included 5053 patients who underwent the 2 most common modern bariatric procedures (Roux-en-Y gastric bypass or sleeve gastrectomy) and compared them with 25265 patients in a propensity-matched control group from 2 hospitals within a single health system. Similar to most bariatric surgery studies, the patients were young (median age of 46 years) with an average body mass index of 45, and mostly female (77%) and White (73%).

During a median follow-up of 6.1 years, 96 patients in the bariatric surgery group and 780 patients in the nonsurgical control group had an incident obesity-associated cancer (incidence rate of 3.0 events vs 4.6 events, respectively, per 1000 person-years). At 10 years, there was a significant reduction in the cumulative incidence of obesity-associated cancer in the bariatric surgery group (2.9%) compared with the nonsurgical control group (4.9%) (absolute risk difference, 2.0% [95% CI, 1.2%-2.7%]; adjusted hazard ratio [HR], 0.68 [95% CI, 0.53-0.87]). Bariatric surgery also was associated with a significantly lower cumulative incidence of all types of cancer at 10 years. In addition, there was a significant reduction in cancer-related mortality at 10 years (0.8% in the bariatric surgery group vs 1.4% in the nonsurgical control group).4 This report by Aminian et al is not the first observational study to demonstrate this association, but it does lend even more support to the finding that people who undergo bariatric surgery may experience a decreased risk of cancer. The study also raises several important questions that need to be addressed, the answers to which will help guide future work.

A growing body of data, including both observational cohort studies and randomized clinical trials, demonstrates durable and important improvements in type 2 diabetes and cardiovascular risk after bariatric surgery.5,6 So far, only observational data have been published with respect to cancer risk outcomes, and the results of these studies are fairly consistent but not yet definitive. Prior data from 8 observational studies that involved more than 600 000 patients suggest that bariatric surgery was associated with a reduced risk of all types of cancer (pooled odds ratio, 0.72 [95% CI, 0.59-0.87]) and a reduced risk of obesity-associated cancer (pooled odds ratio, 0.55 [95% CI, 0.31-0.96]), including breast cancer.7

In a large, multisite cohort study that included 22198 patients with severe obesity who underwent bariatric surgery, compared with 66 427 nonsurgical controls, bariatric surgery was associated with a lower risk of any incident cancer type (HR, 0.67 [95% CI, 0.60-0.74]; 488 incident cases over 87 071 person-years in the bariatric surgery group vs 2055 incident cases over 228 010 person-years in the nonsurgical group) and a larger reduction in obesity-associated cancer, such as postmenopausal breast cancer (HR, 0.58 [95% CI, 0.44-0.77]), endometrial cancer (HR, 0.50 [95% CI, 0.37-0.67]), and colon cancer (HR, 0.59 [95% CI, 0.36-0.97]).8 Another study involving 17 998 patients who had undergone bariatric surgery compared with 53 899 controls showed that bariatric surgery was associated with a reduced risk of both premenopausal breast cancer (0.36% vs 0.44%, respectively; HR, 0.72 [95% CI, 0.54-0.94]) and postmenopausal breast cancer (0.38% vs 0.61%; HR, 0.55 [95% CI, 0.42-0.72]), although the reduction in risk was most pronounced among women with postmenopausal estrogen receptor–positive breast cancer who underwent bariatric surgery compared with women who did not undergo bariatric surgery.9

However, the picture becomes more complicated when looking at the details, such as site-specific cancer studies for which some data suggest that the risk of colorectal cancer decreased after bariatric surgery10 and other data suggest that the risk increased after bariatric surgery, specifically following gastric bypass.11 It is also unclear why these studies (by Aminian et al4 and some of the other reports) show a reduction in both obesity-associated cancer and non–obesity-associated cancer (all cancer types) in the bariatric surgery groups compared with the control groups. There is less biological plausi-
bility for the effect of weight loss on non-obesity-associated cancer types and also a lack of specificity for the potential effects of the surgical weight loss intervention on obesity-associated conditions, in particular.

Although the current study by Aminian et al\(^4\) demonstrates an important association, more research is needed to address several important issues to help advance future work in the field. First, a key question is whether a definitive randomized clinical trial is needed and, if so, is it feasible to undertake. Such a study would require an extremely large budget, large numbers of patients at many sites who are followed up for more than 10 to 20 years because bariatric surgery candidates are young and cancer may not develop for many years. Therefore, it may be more practical to consider such randomized clinical trials among patients at high risk for specific types of cancer, such as women at risk for endometrial cancer or breast cancer. The persistent concern with drawing definitive conclusions from any of the current observational studies is the role of unmeasured confounding and potential selection bias. Despite adjustments in the statistical modeling and thorough sensitivity analyses, the concern is that people who choose to undergo bariatric surgery are drawn from a different population than those who do not choose to undergo surgery. In addition, extensive lifestyle changes and smoking cessation are required for bariatric surgery candidates. One option to minimize these factors would be to compare people who qualify for bariatric surgery but choose not to undergo surgery and remain in a lifestyle program vs those who undergo surgery.

The results from the studies that have assessed bariatric surgery and cancer risk are also not generalizable to men or people from all ethnic and racial backgrounds. With these considerations, a potential next step, short of a randomized clinical trial, could be a very large, more diverse, multicenter cohort study that does not rely on administrative data and could be linked to national tumor registries and death indexes, and has access to more detailed individual patient information.

Second, future studies should address differential cancer screening between groups. Most studies that have evaluated the association between bariatric surgery and cancer risk have little detail on cancer screening, early detection, and treatment in the study cohorts. The study by Aminian et al\(^4\) noted that patients in the bariatric surgery group were more likely to have screening tests for breast, colon, and prostate cancer compared with patients in the nonsurgical control group. In fact, best practices in bariatric surgery recommend completed preoperative cancer screening for all surgery candidates.\(^12\) It makes sense that patients who are candidates for bariatric surgery and patients who have undergone bariatric surgery may have more enhanced cancer screening compared with individuals who are not pursuing bariatric surgery. This screening could contribute to removing candidates with cancer from eligibility for bariatric surgery (lowering cancer rates), possibly increasing later cancer rates in patients who undergo bariatric surgery via increased surveillance, or both.

Third, more investigation should be directed at the potential factors that influence the association between bariatric surgery and cancer and how those factors could be studied more specifically so treatment can be individualized and then directed toward patients who will benefit the most. It is likely that cancer risk reduction after bariatric surgery varies by sex, age, race and ethnicity, type of bariatric surgery, alcohol and smoking status, cancer site, diabetes status, body mass index, and other factors. The threshold of weight loss necessary to observe a decrease in cancer risk should also be carefully assessed as a mediator of potential risk reduction.

In addition, there is a need to understand the specific biological mechanisms of effect responsible for the observed change in cancer risk because these mechanisms have not been clearly investigated and elucidated in humans.\(^13\) Some of these potential mechanisms include increased insulin sensitivity, decreased inflammation, altered gut microbiome, epigenetic changes, decreased conversion to estrogen, and lower cell proliferation. There is strong interest in conducting additional research, considering that the understanding of the mechanisms involved may help inform new targeted therapies to reduce the risk of obesity-associated cancer.\(^13\)

In summary, bariatric surgery appears to be associated with a decreased risk of incident cancer and cancer mortality. More work needs to be done through large, well-designed studies that would include data on cancer screening, data from tumor registries, more detailed individual patient data, and investigations of the basic mechanisms of effect. If this association is further validated, it would extend the benefits of bariatric surgery to another important area of long-term health and prevention. This additional information could then further guide for whom bariatric surgery is most beneficial.

**REFERENCES**


