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Effect of bariatric surgery on oncologic outcomes: a systematic review and meta-analysis

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Abstract

Background Obesity is a major public health issue and is associated with increased risk of several cancers, currently a leading cause of mortality. Obese patients undergoing bariatric surgery may allow for evaluation of the effect of intentional excess weight loss on subsequent risk of cancer. We aimed to evaluate cancer risk, incidence, and mortality after bariatric surgery.

Methods A comprehensive literature search was conducted using PubMed/MEDLINE and Embase with literature published from the inception of both databases to January 2012. Inclusion criteria incorporated all human studies examining oncologic outcomes after bariatric surgery. Two authors independently reviewed selected studies and relevant articles from their bibliographies for data extraction, quality appraisal, and meta-analysis.

Results Six observational studies ($n = 51{,}740$) comparing relative risk (RR) of cancer in obese patients undergoing bariatric surgery versus obese control subjects were analyzed. Overall, the RR of cancer in obese patients after undergoing bariatric surgery was 0.55 [95 % confidence interval (CI) 0.41–0.73, $p < 0.0001$, $I^2 = 83$ %]. The effect of bariatric surgery on cancer risk was modified by gender ($p = 0.021$). The pooled RR in women was 0.68 (95 % CI 0.60–0.77, $p < 0.0001$, $I^2 < 0.1$ %) and in men was 0.99 (95 % CI 0.74–1.32, $p = 0.937$, $I^2 < 0.1$ %).

Conclusions Bariatric surgery reduces cancer risk and mortality in formerly obese patients. When stratifying the meta-analysis by gender, the effect of bariatric surgery on oncologic outcomes is protective in women but not in men.

Keywords Bariatric surgery · Cancer · Oncology · Meta-analysis

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Obesity is a major public health concern associated with several comorbid conditions, early mortality, and significant health care costs [1–3]. Overweight (body mass index greater than 25 kg/m^2) and obesity (body mass index greater than 30 kg/m^2) are important risk factors in the development of certain cancers, a leading cause of death in North America [1, 4–6]. Specifically, obesity is associated with increased risk and/or mortality from cancers of the gastrointestinal tract (esophagus, stomach, colon and rectum, liver, gallbladder, pancreas), genitourinary system (kidney), male reproductive system (prostate), female reproductive system (breast, ovary, uterus, cervix), and hematopoietic system (lymphoma) [1, 4–7].

Bariatric surgery is a safe procedure that results in sustained excess weight loss and reversal of obesity-related comorbidities and mortality [8–13]. Given the association between obesity and cancer risk, as well as the excess weight loss induced by bariatric surgery, interest has developed in examining the relationship between bariatric surgery and oncologic outcomes [12, 14–18]. The goal of this systematic review and meta-analysis was to examine the relationship between bariatric surgery and oncologic outcomes in adult patients.

Methods

Literature search

This systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [19]. PubMed/Medline and Embase were systematically searched with the assistance of a reference librarian from the inception of all databases to January 2012 (Fig. 1). Notable articles were probed for MeSH terms to encompass key phrases that would capture publications related to the overall concepts of "bariatric surgery," "obesity," and "neoplasms/cancer." Evaluation of the references of the most relevant articles retrieved supplemented the overall collection of research articles. Two authors (MCT and YC) independently evaluated all retrieved articles using prespecified eligibility criteria detailed below. All reasons for exclusion were documented and are detailed in Fig. 1.

Study selection

All studies based on human data relevant to the primary research question were included in this review. The exposure of interest, bariatric surgery, included restrictive and malabsorptive procedures. Outcomes were defined as cancer incidence, risk, or cancer-related mortality. Only studies with an appropriate control and intervention group in the form of a clinical trial, observational cohort, or case control study were analyzed.

We excluded studies with any of the following: nonhuman subjects, studies that did not include an appropriate control group, outcome that did not evaluate cancer risk, incidence, or mortality, or interventions other bariatric surgery for obese patients (e.g., medical management of obesity). Studies from which raw data were not extractable were also excluded.

Data extraction and analysis

Two authors (MCT and YC) independently extracted data from each study. Statistical analyses were conducted with available statistical expertise by Stata version 11.2 (StataCorp, College Station, TX). Relative risks (RRs) extracted from raw data were pooled to compare overall cancer risk in obese patients undergoing bariatric surgery versus obese control subjects using the DerSimonian–Laird random-effects meta-analysis [20]. Forest plots were generated to demonstrate the individual and pooled effect estimates and confidence intervals, and to allow visual inspection for study heterogeneity. The χ^2 test of homogeneity (Cochran Q statistic) and I^2 statistic were utilized to quantify heterogeneity. Meta regression and Galbraith plots were used to explore potential sources of between-study heterogeneity.

Influence analysis for studies that contributed to heterogeneity of pooled metaestimates was conducted [21]. Sensitivity analysis was conducted for studies that reported cancer mortality rather than incidence rate or risk [12, 22]. Additional sensitivity analyses were conducted for one study that evaluated only female bariatric surgery patients [18]. Cumulative analysis was also conducted to demonstrate effect of publication year on the evolution of the pooled estimate.

Subgroup analyses were performed for cancer type and gender. Meta-analysis by cancer type was conducted to evaluate the effect of bariatric surgery on site-specific cancers. Only studies for which raw data could be extracted by cancer type were included in this subgroup analysis [14, 16]. Meta-analysis by gender was also conducted on the basis of results of the systematic review, consistently showing differential effects between men and women of bariatric surgery on oncologic outcomes. Only studies for which raw data could be extracted by gender were included in this stratified analysis [15, 18, 23]. A test for homogeneity between the two gender subgroups was performed to evaluate the presence of effect modification [21].

Quality assessment of studies

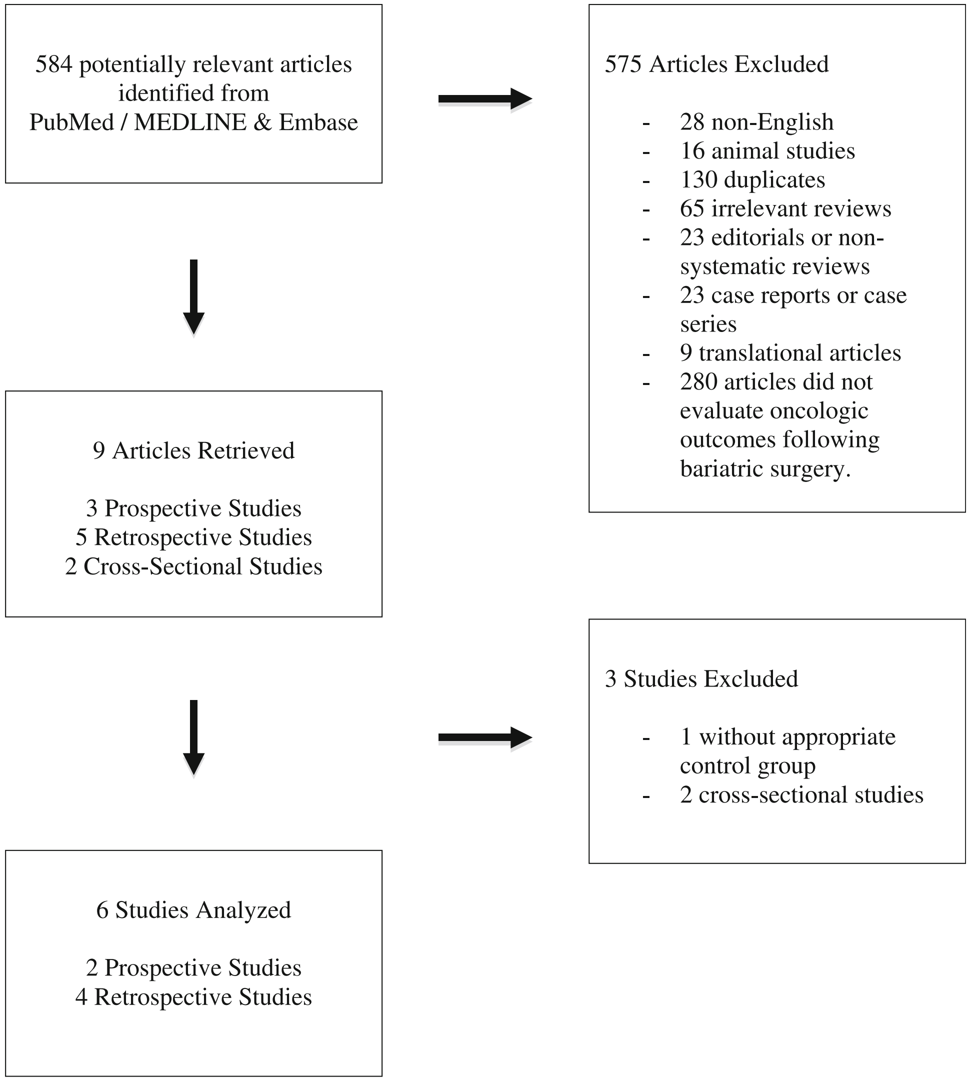
A uniform data collection form for both data extractors was developed to summarize studies reviewed. Any study that potentially met inclusion criteria on the basis of title and abstract were obtained in full and critically reviewed on the basis of quality assessment criteria developed by the Enhancing the Quality and Transparency of Health Research Network [24]. Publication bias was evaluated by constructing a funnel plot with visual assessment of asymmetry. The results of the funnel plot were corroborated using Begg's adjusted rank correlation and Egger's linear regression methods for statistical evaluation of potential publication bias [25, 26].

Results

Overall meta-analysis

Ten articles were selected for full-text evaluation and data extraction on the basis of review of title and abstract

Fig. 1 Study selection



(Fig. 1). There were no randomized clinical trials. Of the 9 observational studies considered for meta-analysis, 3 were prospective cohorts, 4 were retrospective cohorts, and the remaining 2 were cross-sectional studies. The two cross-sectional studies were excluded because they examined cancer prevalence in bariatric surgery patients without an appropriate control group [27, 28]. Another study was excluded because it compared the incidence rate of obesity-related cancers after bariatric surgery to the general population rather than to obese control subjects [29].

The characteristics of the six studies analyzed are summarized in Table 1. These studies ($n = 51{,}740$) provided data on cancer incidence or mortality among obese adult patients after bariatric surgery against obese control subjects who did not undergo surgical treatment for obesity [12, 15, 16, 18, 22, 23]. The overall effect of bariatric surgery on the RR of cancer is presented in Fig. 2. The metaestimate for overall RR of any cancer after bariatric surgery is 0.55 [95 % confidence interval (CI) 0.41–0.73, $p < 0.0001$]. A L'Abbé plot of the included studies for meta-analysis confirmed that the effect measure of RR was appropriate for these studies. A test for between-study heterogeneity revealed an $I^2 = 83$ % (95 % CI 64–92, $p < 0.0001$). Given this degree of between-study heterogeneity, we identified sources of heterogeneity using meta regression, Galbraith plots, and stratified (subgroup) analysis.

Meta regression by publication year ($p = 0.373$), study size ($p = 0.971$), and prospective study design ($p = 0.451$) demonstrated that these factors were not significant sources of heterogeneity. A Galbraith plot showed one study to be a particular outlier to the overall effect estimate [16]. We conducted influence analysis by systematically removing each included study to determine whether the metaestimate would significantly change qualitatively and quantitatively. With this outlier study removed, the metaestimate of RR was 0.72 (95 % CI 0.64–0.80, $p < 0.0001$) [16]. The

Table 1 Meta-analysis study characteristics

Study	Design	Population	Intervention	Control	Outcome
Adams et al. [22]	Retrospective Mean follow-up 7.1 years	$n = 15850$ USA (Utah)	$n = 7925$ Obese patients undergoing Roux-en-Y gastric bypass	$n = 7925$ Obese control subjects obtained from state registry individually matched for age, sex, BMI	Cancer mortality HR 0.40 (95 % CI 0.25–0.65) Cox models adjusted for matching factors of age, sex, and BMI
Sjöström et al. [12]	Prospective Mean follow-up 10.9 years	$n = 4047$ Sweden (SOS cohort)	$n = 2010$ Obese patients undergoing gastric band, vertical banded gastroplasty, or gastric bypass	$n = 2037$ Obese control subjects obtained from the general population, risk-set matched on multiple (18) variables	Cancer mortality HR 0.71 (all) (95 % CI 0.54–0.92) univariate analyses for cancer-related mortality
Christou et al. [16]	Retrospective Follow-up of 5 years	$n = 6781$ Canada (Montreal)	$n = 1035$ Obese patients undergoing vertical banded gastroplasty or Roux-en-Y gastric bypass	$n = 5746$ Obese control subjects obtained from provincial health insurance data matched for age, gender, and diagnosis of obesity	RR of all cancer diagnoses RR 0.22 (95 % CI 0.14–0.35) univariate analyses for RR of cancer over 5 years
McCawley et al. [18]	Retrospective Follow-up time up to 16 years	$n = 4977$ USA (Virginia)	$n = 1482$ Obese female patients undergoing gastric band, vertical banded gastroplasty or Roux-en-Y gastric bypass	$n = 3495$ Obese female control subjects obtained from university database with diagnosis of morbid obesity, not matched to intervention group	Change in prevalence of any cancer diagnosis in women only 3.6 % in surgical group vs. 5.8 % ($p = 0.002$) in control subjects over a 16-year period. Univariate analyses without any matching.
Adams et al. [15]	Retrospective Mean follow-up of 12.5 years	$n = 16038$ USA (Utah)	$n = 6596$ Obese patients undergoing Roux-en-Y gastric bypass	$n = 9442$ Obese control subjects obtained from state registry individually matched for age, sex, BMI	Incidence of all cancer diagnoses HR 0.76 (all) (95 % CI 0.65–0.89) HR 0.73 (F) (95 % CI 0.62–0.87) HR 1.02 (M) (95 % CI 0.69–1.52) Cox models adjusted for matching factors of age, sex, and BMI
Sjöström et al. [23]	Prospective Mean follow-up 10.9 years	$n = 4047$ Sweden (SOS cohort)	$n = 2010$ Obese patients undergoing gastric band, vertical banded gastroplasty, or gastric bypass	$n = 2037$ Obese control subjects obtained from the general population, risk-set matched on multiple (18) variables	Incidence of all first-time cancers HR 0.67 (all) (95 % CI 0.53–0.85) HR 0.58 (F) (95 % CI 0.44–0.77) HR 0.97 (M) (95 % CI 0.62–1.52) Cox model adjusted for statistically significant confounders by forward stepwise selection

BMI body mass index, *HR* hazard ratio, *CI* confidence interval, *RR* relative risk, *SOS* Swedish Obese Subjects cohort

systematic exclusion of any one study did not significantly alter the overall metaestimate: the effect estimate remained protective and excluded the null value of RR in all influence analyses.

We extended our sensitivity analyses to exclude studies that examined cancer mortality rather than risk or incidence [12, 22]. With these studies removed, the metaestimate of RR was 0.56 (95 % CI 0.39–0.80, $p = 0.002$) [12, 22]. One study that evaluated only women was also removed in addition to the previous studies, which gave a metaestimate of RR of 0.53 (95 % CI 0.32–0.87, $p = 0.012$) [18].

Meta-analysis stratified by gender

Stratification by gender was pursued to evaluate gender as a source of heterogeneity and to explore possible effect modification (Fig. 3). Random-effects meta-analysis stratified by gender demonstrates a protective effect of bariatric surgery on cancer risk for women, with a RR of 0.68 (95 % CI 0.60–0.77, $p < 0.0001$) and $I^2 < 0.1$ % for heterogeneity ($p = 0.463$ for between-study heterogeneity). There does not appear to be a protective effect for men in the stratified analysis, with a RR of 0.99 (95 % CI 0.74–1.32, $p = 0.937$) and $I^2 < 0.1$ % ($p = 0.930$ for between-study

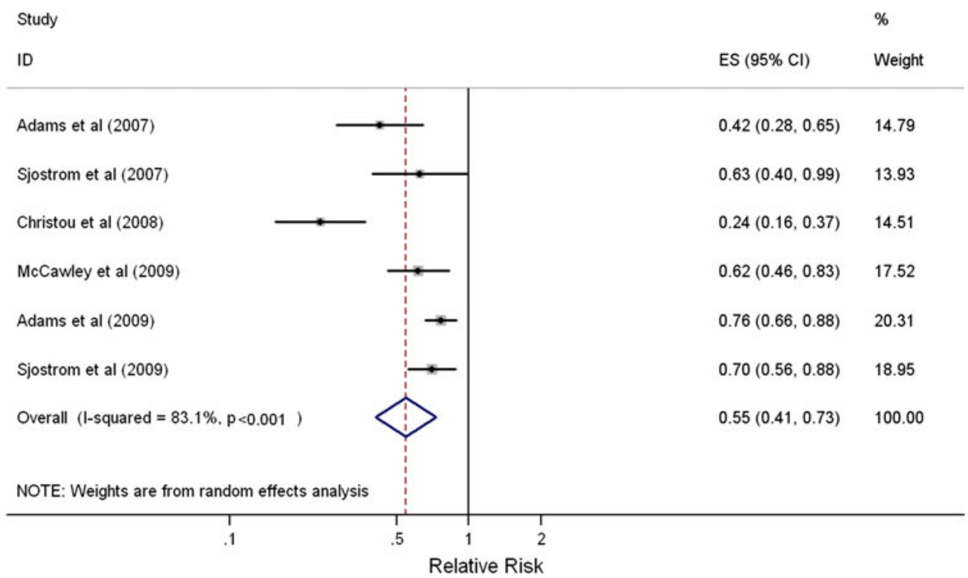


Fig. 2 Effect of bariatric surgery on cancer incidence and mortality

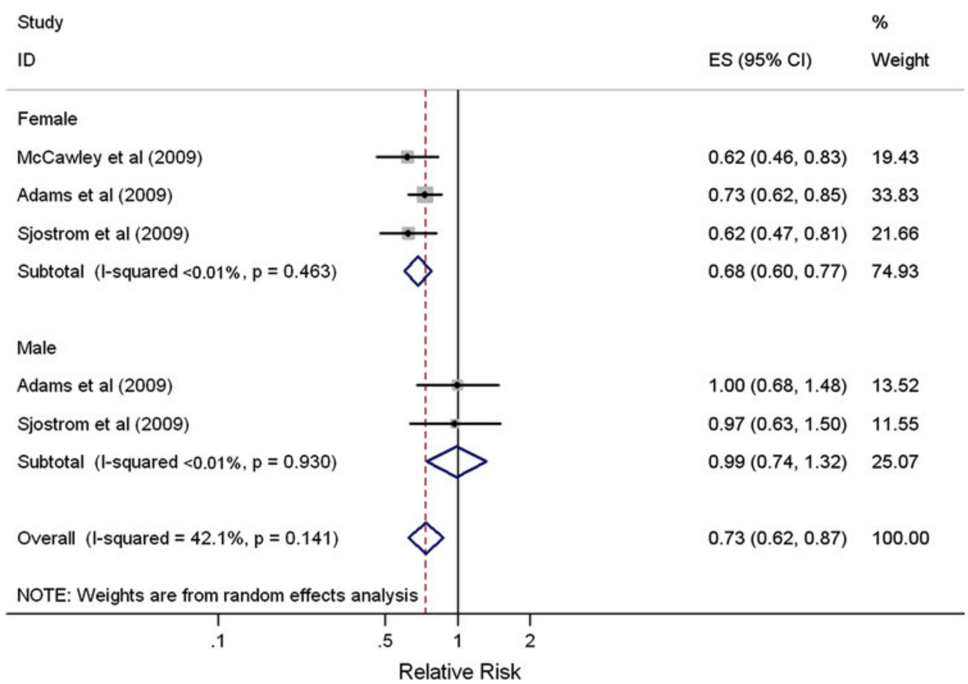


Fig. 3 Gender-specific effect of bariatric surgery on cancer incidence

heterogeneity). A test of homogeneity of the RR of cancer after bariatric surgery of men versus women was conducted, which confirmed effect modification by gender ($p = 0.021$).

Subgroup analysis by cancer type

We attempted to evaluate the effect of bariatric surgery on cancer risk and mortality by performing cancer type subgroup analysis. Of the cancer types that were presented, we were able to perform subgroup analyses on breast, colorectal, melanoma, non-Hodgkin lymphoma, and pancreatic cancer [16, 22]. The subgroup analyses did not reveal any statistically significant effect of bariatric surgery on any of these cancer types on oncologic outcomes (data not shown).

Evaluation of bias and quality components of studies

Publication bias was evaluated visually and quantitatively. A funnel plot constructed of the included studies demonstrated relative symmetry. Statistical confirmation of the lack of publication bias was carried out with Begg's adjusted rank correlation ($p = 0.221$) and Egger's regression ($p = 0.144$), both of which were not significant for the presence of publication bias.

The six observational studies that met our specified criteria to be entered into meta-analysis all evaluated various bariatric surgeries (gastric band, vertical banded gastroplasty, or gastric bypass) and oncologic outcomes (cancer risk, incidence, or mortality) against an appropriate control group, which was either a university hospital database, a state/provincial registry, or an obese control group selected from the general population [12, 15, 16, 18, 22, 23].

The two prospective studies represent the Swedish Obese Subjects cohort, which contemporaneously matched intervention subjects to control subjects on multiple factors [12, 23, 30]. Although the initial purpose of this database was to measure mortality outcomes with a secondary interest in cardiovascular and metabolic disease profile after bariatric surgery, this clinically rich database nevertheless allowed for rigorous statistical analysis [12, 23, 30].

The four retrospective studies may have been prone to biases such as lack of blinding and inability to measure and/or adjust for potential confounders. One study, which evaluated female bariatric surgery patients compared to obese female control subjects from a university hospital database, did not use matching or other methods of risk adjustment [18]. The other retrospective studies were able to appropriately match intervention subjects to control subjects on factors such as age, gender, and body mass index [15, 16, 22]. Only two of the four retrospective studies were able to conduct multivariate Cox proportional hazard models to control for several other confounders [15, 22].

Discussion

Main findings of meta-analysis and systematic review

Our meta-analysis suggests an overall reduced risk of cancer in obese patients after bariatric surgery relative to obese individuals who do not undergo surgery [RR 0.55 (95 % CI 0.41–0.73), $p < 0.0001$, $I^2 = 83$ %]. The protective effect of bariatric surgery on oncologic outcomes seems more pronounced for women [RR 0.68 (95 % CI 0.60–0.77), $p < 0.0001$, $I^2 < 0.1$ %] than men [RR 0.99, (95 % CI 0.74–1.32), $p = 0.930$, $I^2 < 0.1$ %]. A formal test of homogeneity confirms that the effect of bariatric surgery on oncologic outcomes is modified by gender ($p = 0.021$). Individual studies also observed effect modification by gender, with a protective effect of bariatric surgery seen in women but not men [15, 23]. In a stratified analysis, the hazard ratio for cancer incidence after bariatric surgery was 0.58 (95 % CI 0.44–0.77) in women compared to a hazard ratio of 0.97 (95 % 0.62–1.52) in men [23]. Another study suggests the hazard ratio for cancer incidence after bariatric surgery is 0.73 (95 % CI 0.62–0.87) in women and 1.02 (95 % CI 0.69–1.57) in men [15].

Implications for surgical practice

Obesity is associated with increased mortality and several comorbid conditions such as hypertension, dyslipidemia, diabetes, coronary artery disease, obstructive sleep apnea, and certain cancers [4, 10–12]. Bariatric surgery has been shown to provide sustained excess weight loss in obese individuals, reduce mortality, and improve or resolve obesity-related comorbidities [10, 12, 30]. Compared to medical therapy alone, bariatric surgery consistently results in greater long-term weight reduction in obese individuals [12, 17, 31]. Weight loss itself (without surgical intervention) has been shown to reduce risk of cancer [32]. Thus, bariatric surgery may protect against cancer risk and mortality by facilitating the process of achieving healthy body weight.

The mechanisms by which bariatric surgery induces sustained excess weight loss and the probable interplay with reducing cancer risk and mortality is an evolving field of research. Gastric bypass of a hormonally active foregut has implicated ghrelin and leptin as important physiological factors for appetite control and reduced caloric intake [33–35]. This is in addition to the mechanical restriction and/or malabsorption produced by bariatric surgery [36, 37].

Adipose tissue is also a hormonally active organ involved in the regulation of immune function, inflammation, insulin metabolism, peripheral aromatization of circulating androgens to estrogens, and cellular growth [6, 32, 38, 39]. The association between bariatric surgery and cancer risk may also be the consequence of metabolic derangements associated with obesity that are restored by either sustained excess weight loss, surgically induced caloric restriction, and/or bypass of a hormonally active foregut.

One excluded study from our meta-analysis compared cancer incidence of obese patients who had undergone bariatric surgery with that of the general population [29]. This study found that for obesity-related cancers (breast, prostate, colorectum, endometrium, kidney, pancreas, gallbladder, and esophagus), the overall incidence rate ratio was 1.04 (95 % CI 0.93–1.17) for all subjects who underwent bariatric surgery compared to the general population [29]. These findings suggest that bariatric surgery may decrease the risk of cancer in formerly obese subjects to a risk comparable to that of the general population. Thus, in addition to clinical effectiveness in weight reduction, resolution of comorbid conditions, bariatric surgery may provide additional benefit to obese patients by bringing their elevated risk of cancer back down to a baseline population risk.

Study limitations

The rigor of this systematic review and meta-analysis is limited by the available studies in the literature and the presence of any uncontrolled confounding or unmeasured biases in these studies. There was significant between-study heterogeneity in the overall meta-analysis and pooling differing measures of oncologic outcome (cancer mortality, risk, and incidence) further introduced heterogeneity. We explored sources of heterogeneity graphically with forest and Galbraith plots in addition to meta regression, sensitivity analyses, and stratified meta-analysis. Our stratified meta-analysis by gender demonstrates a far more acceptable degree of between-study heterogeneity than our overall meta-analysis.

There are some additional limitations. First, the effect of surgery itself versus induced intentional and excess weight loss on oncologic outcomes cannot be dissociated. Second, whether the effect of bariatric surgery on oncologic outcomes is the result of interfering with the initiation of carcinogenesis or halting further growth of subclinical neoplasia via surgically induced caloric restriction and/or malabsorption leading to excess weight loss cannot be determined in a meta-analysis. Both scenarios would lead to a reduced cancer incidence and mortality, and it would not be possible to determine which particular effect is a greater contributor to the intervention–outcome association.

Finally, potential bias may result from higher cancer screening implicit in the perioperative assessment and long-term follow-up after surgical management of obesity. Although increased preoperative cancer screening would decrease the apparent frequency of cancer in this group, increased surveillance after bariatric surgery would result in greater detection of malignancies that would not have been detected otherwise. This effect should actually bias our results toward the null and may even underestimate the true effect of bariatric surgery on oncologic outcomes.

Study strengths

A major strength of the meta-analysis is the independent review of retrieved articles and data extraction by two authors from the largest databases of biomedical journals (PubMed/Medline and Embase). This has minimized bias and error with respect to inclusion of articles for analysis, interpretation of results, appraisal of quality of evidence, and meta-analysis.

Conclusion

Bariatric surgery appears to decrease the risk of cancer relative to obese individuals who do not undergo surgery. This association is more marked among women than men. As bariatric surgery is a relatively new procedure, research exploring the association between surgically induced intentional weight loss in obese patients and oncologic outcomes remains an evolving field of study. Because randomized trials evaluating the role of bariatric surgery on cancer risk may not be ethically feasible, additional high-quality observational studies are necessary to further examine whether bariatric surgery can indeed reduce cancer burden and whether its effects are limited to women, as suggested in the current analysis.

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