Effects of Bariatric Surgery on Incidence of Obesity-Related Cancers: A Meta-Analysis

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Background: The aim of this meta-analysis was to investigate possible relationships between bariatric surgery and incidence of obesity-related cancers. Obesity is an established risk factor for obesity-related cancers but the effects of bariatric surgery on incidence of obesity-related cancers are uncertain.

Material/Methods: We searched 4 electronic databases to identify eligible studies: PubMed, Embase, Web of Science, and Google Scholar. Five observational studies were eligible and included in this meta-analysis. Random-effects or fixed-effects odds ratio (OR) and its corresponding 95% confidence interval (CI) were pooled.

Results: Meta-analysis of these 5 observational studies revealed that bariatric surgery was associated with a significantly (p=0.0004) reduced incidence of obesity-related cancers (OR=0.43, 95%CI, 0.27–0.69) when compared with control individuals. Pooled estimated data showed that bariatric surgery is associated with a 24% lower colorectal cancer (CRC) risk. No publication bias was detected by Egger’s or Begg’s tests.

Conclusions: Although bariatric surgery may significantly reduce incidence of obesity-related cancers, considering the limitations of these included studies, these findings should be confirmed by further well-designed studies.

MeSH Keywords: Bariatric Surgery • Colorectal Neoplasms • Obesity

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Background

Colorectal cancer (CRC) is among the most common cancers in the world. Obesity is a well-established risk factor for obesity-related cancers, especially for CRC [1,2]. The prevalence of obesity has doubled worldwide since 1980 and at least 500 million people are classified as obese (body mass index [BMI] ≥30 kg/m²).

Lifestyle-behavioral and pharmacological interventions for weight loss remain the major approaches to obesity prevention and management [3–5], but with limited success. Surgical treatment for obesity (bariatric surgery) should be considered in patients with BMI >40 kg/m² or for those with other significant obesity-related comorbidities but BMI 35–40 kg/m². Bariatric surgery has been shown to be successful in achieving significant sustained weight loss with low operative mortality and proven safety in older (>55 years) obese patients [6–8]. Weight loss after bariatric surgery yields important health benefits, including resolution of type 2 diabetes in most treated patients and lower total mortality, attributed mainly to reduced incidence of major cardiovascular events and cancer overall [9,10]. A meta-analysis of 21 observational studies from Ma et al. [11] indicated that obesity is associated with increased thyroid cancer risk, except for medullary thyroid cancer.

Given the role of overweight and obesity in increasing obesity-related cancers risk, one might expect that weight loss achieved through bariatric surgery would result in reduced risk of obesity-related cancers. We performed a systematic review and meta-analysis aiming to summarize the relationship between bariatric surgery and incidence of obesity-related cancers.

Material and Methods

Our systematic review was conducted according to Cochrane and the Centre for Reviews and Dissemination guidelines and is reported according to PRISMA guidelines [12–14].

Search strategy and study selection

PubMed, Embase, Web of Science, and Google Scholar were independently searched by 2 investigators (Xiang-wu Yang and Shai-hong Zhu) to identify potential eligible studies. The original searches were performed in October 2014 and updated in January 2015. In addition, the reference lists of relevant reviews and studies retrieved were manually searched to identify additional eligible studies.

The above databases were searched using a combination of indexed terms and text word searches of title, abstract, and keywords. The following indexed words were used: “overweight or obese,” “behavioral or lifestyle-based or pharmacological or bariatric surgery or weight loss” and “obesity-related cancer or cancer.” This search strategy was adapted for use with other databases, and further details are available on request. The search was restricted to human studies with abstracts published in English. Databases were searched from inception and thus no date limits were applied.

Two reviewers (Peng-zhou Li and Li-yong Zhu) performed the initial screening of titles and abstracts against the inclusion and exclusion criteria to identify potentially relevant papers. Full-text versions of potentially relevant papers identified from the initial screening were retrieved. In cases of disagreement in the initial screening stage, full text of the articles involved was retrieved. Where multiple articles from the same study were found, only the report with the longest follow-up period was included.

Both reviewers screened all full-text articles to generate the final list of articles to be included in the systematic review and meta-analysis.

Data extraction and quality assessment

The following data were extracted using a standardized form: study design, country of origin, period of study, follow-up period, baseline characteristics of population, inclusion/exclusion criteria, description of the intervention, and any relevant outcome measures (as described above). Data extraction was performed by 1 reviewer and was verified by another reviewer. Disagreements were resolved by discussion.

Quality assessment of non-randomized studies was performed using the Newcastle-Ottawa scale (NOS) [15]. Study quality was not an exclusion criterion.

Statistical analysis

We combined studies reporting obesity-related cancers incidence using a random- or fixed-effects meta-analysis. Heterogeneity levels in these studies were quantified using the I² statistic, and the 95% confidence interval (CI) for I² was calculated using the Higgins et al. method [16,17]. Statistical analyses were performed using the Review Manager (RevMan) computer program, version 5.3. Copenhagen: the Nordic Cochrane Centre, the Cochrane Collaboration, 2014.

Results

The studies generated a total of 142 publications, of which titles and abstracts were screened. Five studies that met our inclusion criteria were included in the present review and...
No studies reporting on obesity-related cancers outcomes after bariatric surgery were excluded on the basis of study design or quality. A flow diagram of the article selection process is shown in Figure 1.

**Study characteristics**

The included studies were all registry-based, retrospective studies. They reported on obesity-related cancers incidence in a total study population of 26,331 individuals after bariatric surgery and 82,903 obese controls (Table 1). All studies had a predominance of female subjects (mean 79% and 66.8% in the bariatric surgery and control groups, respectively). McCawley et al. [21] included female subjects only.

Adams et al. [18] identified controls with a self-reported BMI ≥35 kg/m² on their driver’s license identification application. The other 4 included studies identified the control population using the diagnosis of morbid obesity as recorded on respective data registries [18–22]. The study by Adams et al. [18] was unique in reporting baseline BMI data and using BMI to match the bariatric surgery and control groups. This study and only 1 other used age- and sex-matched controls [18]. None of the studies specified the treatment (if any) given to the control groups. Gastric bypass was either the sole or the most commonly employed surgical procedure used in the included studies (Table 1).

Follow-up BMI data was reported in only 1 study and this was for the bariatric surgery group only (mean BMI reduction 31.9%; 95% CI, 31.1–32.2) [18]. The other 4 studies did not report on any weight loss measure outcomes. Christou et al. [19] reported a lower CRC risk in the bariatric surgery group compared with the non-surgically treated controls (unadjusted RR 0.32; 95% CI, 0.076–1.313, p=0.063). Adams et al. [18]...
also reported reduced CRC risk in the bariatric surgery group (HR 0.70; 95% CI, 0.43–1.15, p=0.15).

Table 2. Quality assessment of the studies using the NOS.

| Author       | Selection (max. 4) | Comparability (max. 2) | Exposure (max. 3) | Total (max. 3) |
|--------------|--------------------|------------------------|-------------------|---------------|
| Adams 2009   | 4                  | 2                      | 3                 | 9             |
| Christou 2008| 4                  | 1                      | 3                 | 8             |
| Derogar 2013 | 4                  | 0                      | 3                 | 7             |
| McCawley 2009| 3                  | 0                      | 1                 | 4             |
| Sjöström 2009| 4                  | 2                      | 3                 | 9             |

NOS – Newcastle-Ottawa criteria.

Study quality and publication bias

Quality assessment scores using the NOS tool are summarized in Table 2 [15]. Four of the studies had high scores (7–9, max score=9) using the NOS tool, whereas the other had a lower score (4). There were too few studies to perform a funnel plot analysis of potential publication bias.

Quantitative results (meta-analysis)

Data from the 5 bariatric surgery studies were included in a meta-analysis to estimate the overall effect of surgery on obesity-related cancers diagnosis using a random-effects model (Figure 2). Subgroup analysis was carried out to explore the

Figure 2. Forest plot of new obesity-related cancers diagnosis rates in the bariatric surgery and no surgery groups.
Figure 3. Forest plot of new diagnosis rates for different cancer types in the bariatric surgery and no surgery groups.
In the analysis of our data, we were unable to perform regression analysis to investigate the potential influence of different cancer types and found that the estimated data were significantly altered by colorectal cancer (p=0.57) (Figure 3). The meta-analysis revealed that weight loss after surgery was associated with significantly (p=0.0004) lower risk of subsequent obesity-related cancers diagnosis (OR 0.43; 95% CI, 0.27–0.69) (Figure 2). The meta-analysis also showed that weight loss after surgery was associated with significantly (p=0.02) lower risk of subsequent CRC diagnosis (OR 0.76; 95% CI, 0.61–0.95) (Figure 4).

**Discussion**

To the best of our knowledge, this is the most complete systematic assessment and meta-analysis of the effects of bariatric surgery on the subsequent risk of obesity-related cancers. Our meta-analysis of data from 5 observational studies involving 109 234 individuals followed for 5–12.3 years (where reported) revealed that bariatric surgery is associated with a 57% lower (p=0.0004) subsequent risk of obesity-related cancers diagnosis. This association was consistent across the 5 included studies. No studies reporting on obesity-related cancers outcomes after bariatric surgery were excluded on the basis of study design or quality; therefore, these results summarize the evidence currently available.

Our meta-analysis also revealed that bariatric surgery is associated with a 24% lower (p=0.02) subsequent risk of CRC diagnosis. This association was consistent across the 4 included studies. No studies reporting on CRC-related outcomes after bariatric surgery were excluded on the basis of study design or quality; therefore, these results summarize the evidence currently available.

Obesity is a complex multi-system health problem and it is acknowledged that a “one system fits all” mechanism is unlikely [23]. Given that bariatric surgery reduces inflammatory markers, reduces genomic damage, and/or enhances antineoplastic responses, one would expect a reduction in obesity-related cancers risk after bariatric surgery [24–26].

The major limitation of this review is the small number of studies that met our inclusion criteria. The studies reviewed here, all on bariatric surgery, were observational and results from meta-analyses of observational studies should be treated with caution [27]. There were no RCTs that addressed our proposed questions directly. Such RCTs would be difficult to conduct due to requiring many participants with lengthy follow-up to achieve sufficient power to detect any effect. The studies included in our meta-analysis had different lengths of follow-up. Because of insufficient data in the primary studies, we were unable to perform regression analysis to investigate...
the effect of length of follow-up. However, the consistency in outcomes across the 5 studies suggests that the heterogeneity in duration of follow-up is unlikely to have biased the outcome.

Overweight or obese patients undergoing bariatric surgery are more likely to be motivated to lead a healthier lifestyle than untreated obese controls. In addition, 4 of the 5 studies included in our meta-analysis identified controls using the diagnosis of morbid obesity, which is an approach that could have selected less healthy obese individuals as controls [19,20,28].

Many environmental and lifestyle factors influence the risk of obesity-related cancers; therefore, it is possible that factors other than weight loss following bariatric surgery are responsible for the apparently protective effect against obesity-related cancers observed in the present study [1]. Despite attempts to adjust for some confounders by design in some of the included studies (e.g., use of age- and sex-matched controls), potential confounding factors such as cigarette smoking and alcohol drinking were not adjusted for in any of the included studies. Despite the inability to adjust for smoking or alcohol use because of a lack of direct data, Derogar et al. attempted to examine possible effects by performing a sensitivity analysis in which those with smoking- and alcohol-related diagnoses were excluded from the analysis [20]. A lower proportion of individuals had such a diagnosis in the bariatric surgery than in the control group (9.7% vs. 15.0%, respectively), but this exclusion did not change their findings.

Conclusions

There is a lack of high-quality evidence about the effects of bariatric surgery on the subsequent risk of obesity-related cancers. To date, all relevant data are from non-randomized observational studies. Our meta-analysis of observational studies has shown that bariatric surgery (predominately using Roux-en-Y gastric bypass) was associated with 57% lower obesity-related cancers risk and 24% lower CRC risk. Well-designed prospective clinical studies of the long-term effects of weight loss interventions, including bariatric surgery, on obesity-related cancers risk are required.

Conflict of interest

All the authors declare that they have no conflicts of interest.

References:

1. Wiseman, M., The second World Cancer Research Fund/American Institute for Cancer Research expert report. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Proc Nutr Soc, 2008; 67(3): 253–56
2. Ning Y, Wang L, Giovannucci EL: A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. Obes Rev, 2010; 11(1): 19–30
3. Kramer FM, Jeffery RW, Forster JL, Snell MK: Long-term follow-up of behavior treatment for obesity: patterns of weight regain among men and women. Int J Obes, 1989; 13(2): 123–36
4. Curioni CC, Lourenco PW: Long-term weight loss after diet and exercise: a systematic review. Int J Obes (Lond), 2005; 29(10): 1168–74
5. Anderson IW, Konz EC, Frederich RC, Wood CL: Long-term weight-loss maintenance: a meta-analysis of US studies. Am J Clin Nutr, 2001; 74(5): 579–84
6. O’Brien PE, McPhail T, Chaston TB, Dixon JB: Systematic review of medium-term weight loss after bariatric operations. Obes Surg, 2006; 16(8): 1032–40
7. Buchwald H, Estok R, Fahrbach K et al: Trends in mortality in bariatric surgery: a systematic review and meta-analysis. Surgery, 2007; 142(4): 621–32; discussion 632–35
8. Lynch J, Belgaumkar A: Bariatric surgery is effective and safe in patients over 55: a systematic review and meta-analysis. Obes Surg, 2012; 22(9): 1507–16
9. Buchwald H, Estok R, Fahrbach K et al: Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med, 2009; 122(3): 248–56.e5
10. Sjöström L: Review of the key results from the Swedish Obese Subjects (SOS) trial – a prospective controlled intervention study of bariatric surgery. J Intern Med, 2013; 273(3): 219–34

A study by the same group has shown a hyperproliferative state in rectal mucosal biopsies 6 months after RYGB when compared to obese controls [29]. A similar increase in proliferation status was not seen after a sleeve gastrectomy [30]. The hypothesis states that the predominantly “malabsorptive” bariatric procedures, such as RYGB, may expose the colorectal mucosa to harmful luminal contents and, given the latency in CRC carcinogenesis, this effect becomes more apparent with time after surgery.

11. Ma J, Huang M, Wang L et al: Obesity and risk of thyroid cancer: evidence from a meta-analysis of 21 observational studies. Med Sci Monit, 2015; 21: 283–91
12. Liberati A, Altman DG, Tetzlaff J et al: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ, 2009; 339: b2700
13. Shuster JJ: Review: cochrane handbook for systematic reviews for interventions, Version 5.1. 0, published 3/2011. Julian PT Higgins and Sally Green, Editors, 2011, Wiley Online Library
14. Cochrane E: Systematic reviews: CRD’s guidance for undertaking reviews in health care. Lancet Infectious Diseases, 2010; 10(4): 226
15. Wells GA, Shea B, O’Connell D et al: The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000
16. Ioannidis JP, Patsopoulos NA, Evangelou E: Uncertainty in heterogeneity estimates in meta-analyses. BMJ, 2007; 335(7626): 914–16
17. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med, 2002; 21(11): 1539–58
18. Adams TD, Stroup AM, Gress RE et al: Cancer incidence and mortality after gastric bypass surgery. Obesity (Silver Spring), 2009; 17(4): 796–802
19. Christou NV, Lieberman M, Sampalis F, Sampalis JS: Bariatric surgery reduces cancer risk in morbidly obese patients. Surg Obes Relat Dis, 2008; 4(6): 691–95
20. Derogar M, Hull MA, Kant P et al: Increased risk of colorectal cancer after obesity surgery. Ann Surg, 2013; 258(6): 983–88
21. McCawley GM, Ferriss JS, Geffel D et al: Cancer in obese women: potential protective impact of bariatric surgery. J Am Coll Surg, 2009; 208(6): 1093–98
22. Sjöström L, Gummesson A, Sjöström CD et al: Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol, 2009; 10(7): 653–62

23. Roberts DL, Dive C, Renehan AG: Biological mechanisms linking obesity and cancer risk: new perspectives. Annu Rev Med, 2010; 61: 301–16

24. Rao SR: Inflammatory markers and bariatric surgery: a meta-analysis. Inflamm Res, 2012; 61(8): 789–807

25. Hofer T, Fontana L, Anton SD et al: Long-term effects of caloric restriction or exercise on DNA and RNA oxidation levels in white blood cells and urine in humans. Rejuvenation Res, 2008; 11(4): 793–99

26. O’Callaghan NI, Clifton PM, Noakes M, Fenech M: Weight loss in obese men is associated with increased telomere length and decreased abasic sites in rectal mucosa. Rejuvenation Res, 2009; 12(3): 169–76

27. Egger M, Schneider M, Davey SG: Spurious precision? Meta-analysis of observational studies. BMJ, 1998; 316(7125): 140–44

28. McCawley GM, Ferriss JS, Geffel D et al: Cancer in obese women: potential protective impact of bariatric surgery. J Am Coll Surg, 2009; 208(6): 1093–98

29. Sainsbury A, Goodlad RA, Perry SL et al: Increased colorectal epithelial cell proliferation and crypt fission associated with obesity and roux-en-Y gastric bypass. Cancer Epidemiol Biomarkers Prev, 2008; 17(6): 1401–10

30. Kant P, Dexter S, Hull MA: Rectal mucosal biomarkers of colorectal cancer risk are increased in morbidly obese patients but not significantly different six months after sleeve gastrectomy. Gut, 2011; 60(suppl.1): A114–A114