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META-ANALYSIS

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

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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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 world-wide 1980 and at least 500 million people are classified as obese (body mass index [BMI] ≥30 kg/m^2).

Lifestyle-based 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/m^2 or for those have other significant obesity-related comorbidities but BMI 35–40 kg/m^2. 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 index 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 I^2 statistic, and the 95% confidence interval (CI) for I^2 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 searches 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

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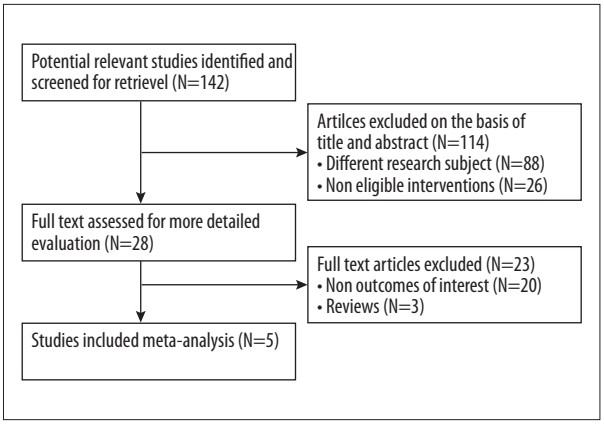

Figure 1. Flow diagram of study identification.

meta-analysis [18–22]. 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) [18–22].

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/m^2 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]

Table 1. Study characteristics.

Author	Year	Country	Type of study	Participants (n)	Females (%)	Age	Baseline BMI[a]	Type of bariatric surgery	Follow-up (years)
Adams et al.	2009	USA	Retrospective	S: 6,709	S: 86%	S: 38.9 (10.3)	S: 44.9 (7.6)	All RYGB	S: 12.3 (5.7)[c]
			Two cohort study	C: 9,609	C: 86%	C: 39.1 (10.7)	C: 47.4 (6.5)	–	C: 11.8 (5.6)[c]
Christou et al.	2008	Canada	Retrospective	S: 1,035	S: 66%	S: 45.1 (11.6)	S: 50.0 (8.2)	81.3% RYGB;	S: 5c
			Two cohort study	C: 5,746	C: 64%	C: 46.7 (13.1)	C: no data	18.7% VBG	C: 5c
Derogar et al.	2013	Sweden	Retrospective	S: 15,095	S: 77%	S: 39.0	S: no data	51% RYGB; 25% VBG;	S: 10 (1–30)[b]
			Two cohort study	C: 62,016	C: 63%	C: 49.0	C: no data	24% GB; 12% >1 procedure	C: 7 (1–30)[b]
McCawley et al.	2009	USA	Retrospective	S: 1,482	S: 100%	S: 41.7	S: 51.6	93.5% gastric bypass;	No data
			Two cohort study	C: 3,495	C: 100%	C: 46.9	C: no data	3.8% GB; 1.8% VBG	No data
Sjöström et al.	2009	Sweden	Retrospective	S: 2,010	S: 70.6%	S: 47.2(5.9)	S: 41.7	68.1% VBG;18.7% GB;	S: 10.8c
			Two cohort study	C: 2,037	C: 71%	C: 48.7(6.3)	C: 40.9	13.2% gastric bypass	C: 10.9c

S – surgery group; C – control group; RCT – randomised control trial; RYGB – Roux-en-Y gastric bypass; VBG – vertical banded gastroplasty; GB – gastric band; [a] mean (±standard deviation) (kg/m^2, where reported); [b] median (range); [c] mean (±standard deviation) (where reported).

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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.

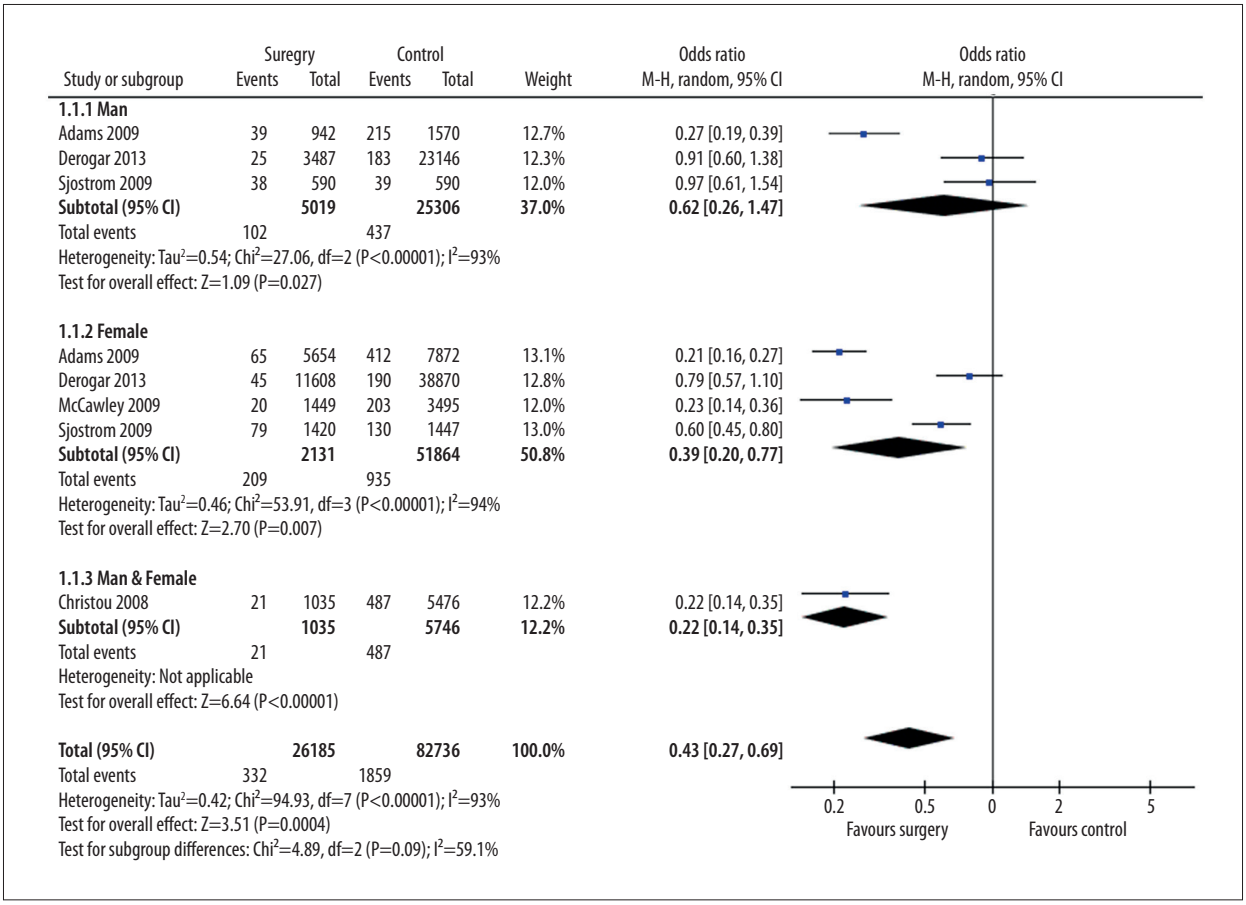

Figure 2. Forest plot of new obesity-related cancers diagnosis rates in the bariatric surgery and no surgery groups.

also reported reduced CRC risk in the bariatric surgery group (HR 0.70; 95% CI, 0.43–1.15, p=0.15).

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

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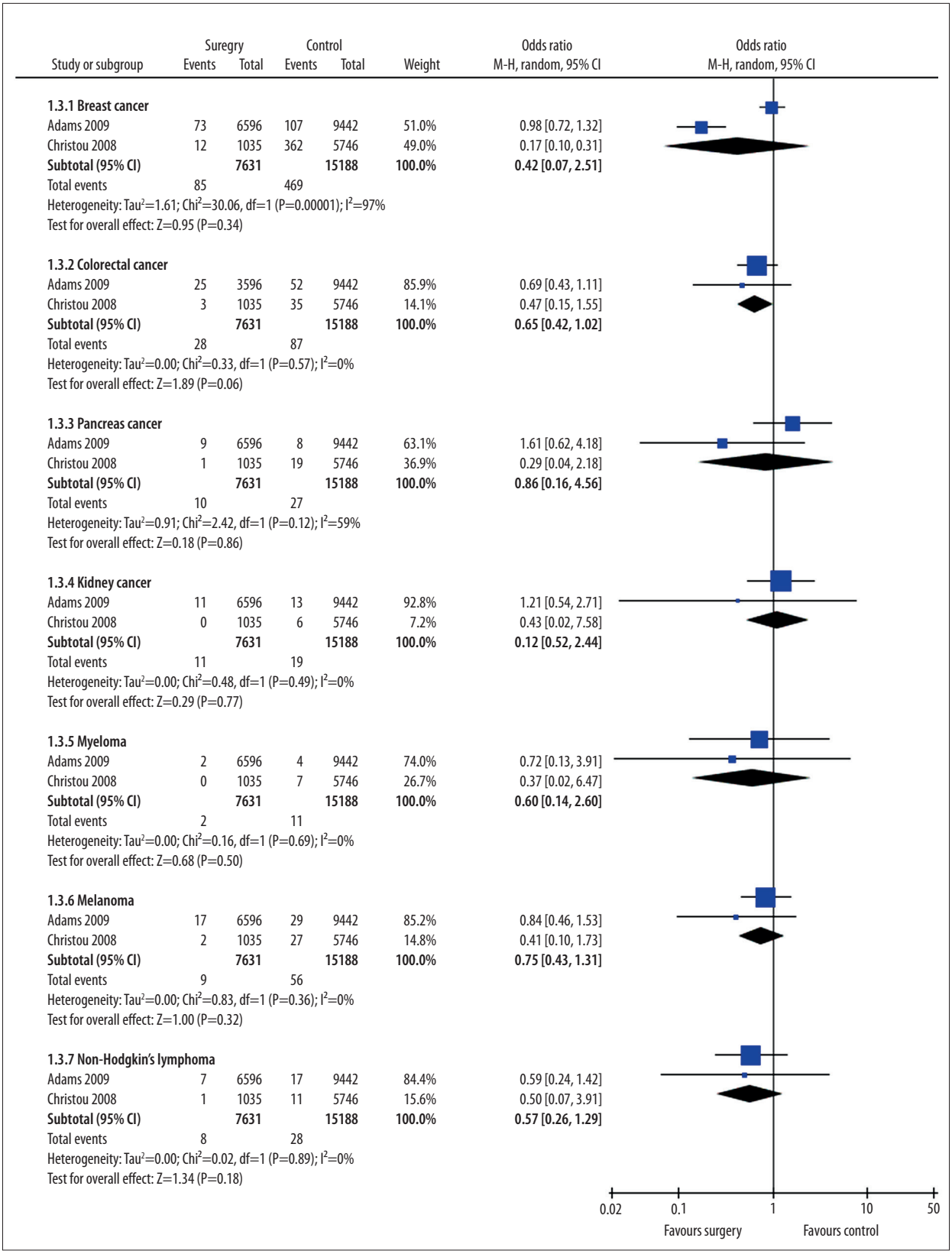

Figure 3. Forest plot of new diagnosis rates for different cancer types in the bariatric surgery and no surgery groups.

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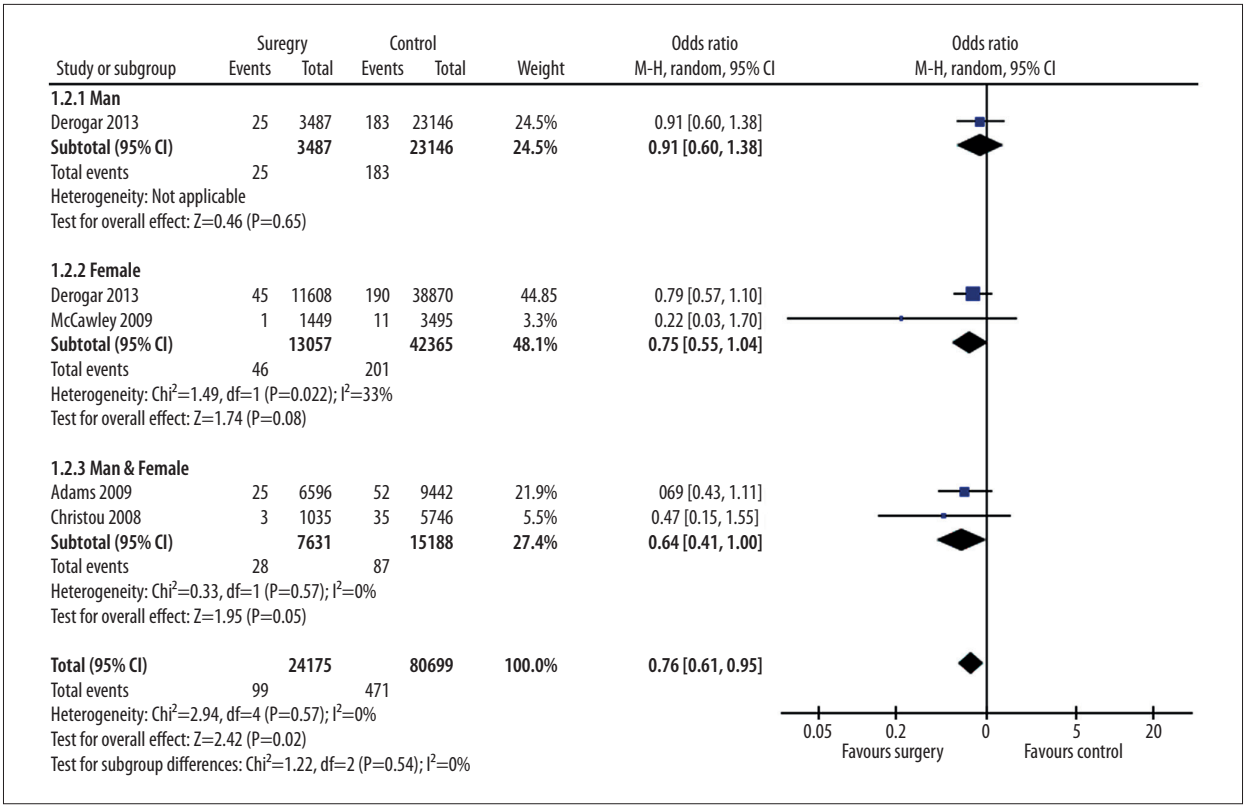

Figure 4. Forest plot of new CRC diagnosis rates in the bariatric surgery and no surgery groups.

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

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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.

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.

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.

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