Sleeve Gastrectomy and Cancer

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1 Obesity and Cancer

It is without question today that obesity is directly attributed to an increased risk of developing cancer. In the European Union alone, approximately 70,000 out of the 3.5 million (2.0%) new cases of cancer each year are linked to overweight or obesity, while in the United States, that number is around 85,000 out of 1.4 million (5.8%) [1, 2]. It was initially thought that obesity increased only hormone-dependent cancers, such as post-menopausal breast cancer, endometrial cancer, prostate and colon cancer, however evidence is proving day by day that the effect is much broader. As of the evidence available today, an elevated body mass index (BMI) has also been proven to be linked with pancreatic, gallbladder, esophageal, renal, and thyroid cancers, as well as leukemia and non-Hodgkin lymphoma [3–6]. Large population-based studies from Austria, Sweden and Denmark have proven this but showed variations in the effect's obesity had on individual cancer types in addition to differences in incidence across age groups and genders [3–5]. A meta-analysis by Renehen et al., which included 282,137 patients across four continents, showed that a 5 kg/m^2 increase in BMI was strongly associated with an increase in the incidence of the aforementioned cancers [6]. Obesity related cancer incidence was higher in men than in women for colon and rectal cancers ($p<0{\cdot}0001$ and $p=0{\cdot}003$ respectively), and were higher in women than in men for renal cancer ($p=0{\cdot}004$). Interestingly, the incidence of two cancer types (lung and

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esophageal squamous cell cancers) were found to be negatively associated with obesity.

Beyond the fact that obesity increases the incidence of certain cancers, it is also evident today that it is also linked to an increase in cancer mortality. In one of the largest studies of its kind, a collaborative analysis of 57 papers from Europe and North America of approximately 900,000 patients observed that for each 5 kg/m^2 increase in BMI, there was on average 10% increase in cancer mortality (HR 1.10 [1.06–1.15]) [7]. In addition, the authors found the BMI range 22.5–25 kg/m^2 to have the lowest all-cause mortality among both genders.

2 Pathogenesis of Cancer in the Obese

The underlying mechanism behind what predisposes obese patients to developing certain cancers remains a topic of much debate. Because of the wide range of cancer types and different physiology of each, it is difficult to group them together and draw conclusions of causality.

However, most studies on the subject have given rise to theories that mostly centered around diet, hormonal theories, and chronic inflammation.

The high-calorie "western diet" is infamous today for being a root cause behind many diseases. There are innumerable studies observing the detrimental health effects of such diet, with numerous meta-analyses proving a direct association with breast, colon and prostate cancer [8–10]. In addition, most of these studies also observed a reduction in cancer risk with a more prudent dietary pattern (i.e. high in fruits, vegetables, and low in fat, cholesterol and processed food).

The western diet is also related to an increase in insulin production, which is one of the culprits behind obesity and cancer in the hormonal theory [1]. Insulin and insulin-like growth factor 1 (IGF-1) both play a complex role in the initiation of cellular pathways that ultimately lead to promote cellular proliferation and possible tumor growth [11].

Sex hormones also play a role in linking obesity and cancer, with recent evidence showing that the excess estrogen produced from aromatization in the adipose tissue can lead to stimulation of cell division and subsequent carcinogenesis [1].

Finally, adipose tissue itself has been found to increase the overall state of chronic inflammation by the release of the so-called adipokine hormones, a group of pro-inflammatory cytokines. From the many adipokines identified to-date, leptin is one of the most widely studied in the literature, with research linking elevated levels to colon, breast, and even prostate cancer [12]. Although the underlying pathogenesis remains to be well-established, it is believed the long-standing overall state of inflammation in obese patients results in overwhelming oxidative stress and subsequent direct DNA damage.

3 Current Literature

Before the emergence of sleeve gastrectomy (SG) as one of the most common bariatric surgery procedures, the two most common procedures were Roux-en-Y gastric bypass (RYGB) and adjustable gastric banding (AGB). Despite the recent surge in SG popularity, it remains a relatively new standalone bariatric operation, and to this day RYGB remains the gold standard bariatric procedure. As a result, there is a lack of extensive data in the literature with appropriate sample size that specifically study SG and its association with cancer risk. Furthermore, many studies pool all bariatric procedures together in their analysis without differentiating patients who had SG from other procedures, or divide surgeries broadly into either restrictive or malabsorptive. Below, we provide a summary of the evidence regarding studies that specifically included patients undergoing SG in their cohort. Most of the available data observed the effects on colorectal cancer (CRC), and will therefore form the bulk of this section.

4 Bariatric Surgery and Cancer Risk

One of the more recent papers is by Schauer et al. who conducted a large retrospective study of 22,198 subjects undergoing bariatric surgery (61% RYGB, 27% SG, and 5.6% AGB) who were matched to 66,427 non-surgical obese subjects [13]. After a mean follow-up of 3.5 years, 2,543 cancer incidents were identified. They found patients who underwent bariatric surgery were 33% less likely to develop any cancer during follow-up (HR 0.67 [CI 0.60–0.74, $p<0.001$]) compared with matched patients with severe obesity who did not undergo bariatric surgery. These included postmenopausal breast cancer (HR 0.58 [CI 0.44–0.77, $p<0.001$]), colon cancer (HR 0.59 [CI 0.36–0.97, $p=0.04$]), endometrial cancer (HR 0.50 [CI 0.37–0.67, $p<0.001$]), and pancreatic cancer (HR 0.46 [CI 0.22–0.97, $p=0.04$]).

5 Colorectal Cancer (CRC)

CRC is one of the most common cancers all over the world and studying the relationship between SG and the risk of its development is of great importance. Interestingly, the data is at times controversial, especially with regard to RYGB versus SG as well as colon versus rectal cancer. A recently published systemic review and meta-analysis investigating the effect of bariatric surgery on the risk of developing CRC included seven large studies involving 1,213,727 individuals [14]. With a mean duration of follow-up of more than 7 years it was observed that patients who underwent bariatric surgery had a greater than 35% reduction in the risk of developing CRC compared with obese non-operated individuals (RR 0.64 [CI 0.42–0.98]).

Arvani et al. analyzed the data of over one million patients within the United Kingdom national health service (NHS), of whom 39,747 patients (3.9%) underwent bariatric surgery [15]. Overall, they reported almost half the surgeries were a purely restrictive procedures while the other half had a combined restrictive and malabsorptive procedure. Compared to the background general population, they found no significant increase in CRC in patients undergoing obesity surgery (SIR 1.26 [CI 0.92–1.71]), while obese patients who did not undergo bariatric surgery had a significant increase likelihood of developing CRC (SIR 1.12 [CI 1.08–1.16]). Breaking down the results according to type of surgery showed no significant difference between restrictive and combined restrictive and malabsorptive procedures and the risk of CRC.

6 CRC in RYGB Versus SG and AGB

Recent evidence has emerged regarding the increase in CRC risk among patients undergoing specific types of bariatric procedures. Mackenzie et al. performed a propensity match control study comparing 8,794 obese patients who had SG, RYGB, or AGB to obese patients who did not have obesity surgery [16]. Predominantly malabsorptive procedures (RYGB) but not predominantly restrictive procedures (SG and AGB) were associated with over two-fold increase in the risk of CRC (OR 2.63 [CI 1.17–5.95]). Their findings emulate the results reported by the two Swedish studies by Derogar et al. and Ostlund et al. who reported a two-fold increase in the risk of CRC after RYGB specifically [17, 18]. The reason RYGB, but not SG or AGB, was associated with increased risk of CRC was hypothesized to be related to significant changes in the gut microbiome and the increase in specific inflammatory markers promoting hyper-proliferation of bowel mucosa following RYGB. Kant et al. also observed that putative mucosal biomarkers of colorectal cancer risk and mucosal pro-inflammatory gene expression (pro-tumorigenic cytokine macrophage migratory inhibitory factor) were increased at least three years after RYGB compared with preoperative values [19]. These findings, contrary to previous assumptions, are likely secondary to malabsorptive effects of the procedure and appear to be increased more prominently in the rectal compared to colonic mucosa. This translates to potential higher risk of rectal cancer following the malabsorptive procedures such as RYGB but not necessary the predominantly restrictive procedures such as SG.

7 Breast and Endometrial Cancers

Studies looking at trends in reduction of breast and endometrial cancers after bariatric surgery seem to mimic those for CRC. In the United Kingdom NHS study, there was a reported lower risk of breast cancer in operated patients compared to non-operated ones across both restrictive and combined restrictive and malabsorptive procedures (SIR 0.76 [CI 0.62–0.92] and SIR 1.08 [CI 1.04–1.11]

respectively) [15]. In addition, the Mackenzie et al. propensity score study found patients who had bariatric surgery (56.6% RYGB, 33.6% AGB, and 9.8% SG) exhibited a decreased risk of hormone-related cancers (OR 0·23 [CI 0.18–0.30]). This decrease was consistent for breast cancer (OR 0.25 [CI 0.19–0.33]) and endometrium cancer (OR 0.21 [CI 0.13–0.35]) [15]. In a study that included patients who underwent RYGB, SG, and AGB, Linkov et al. collected blood samples of 107 obese female patients before and 6 months postoperatively [20]. They studied several biomarkers associated with endometrial cancer including insulin, C-peptide, Leptin, adiponectin, C-reactive protein, and tumor necrosis factor alpha. Interestingly, they reported normalization of the cancer markers in the majority of their patients postoperatively.

8 SG and Gastro-esophageal Cancer

It has long been thought that the anatomical changes occurring around anastomotic sites in bariatric surgery predispose to neoplasia. This evidence came mostly from studies looking at long-term effects of partial gastrectomies after peptic ulcer surgeries [21]. The notion of whether or not this translates into bariatric surgery is still a topic of much debate, with the main issue being lack of evidence due to the scarcity of such cases. Most of the evidence is based solely on case reports, with the focus being on malabsorptive surgeries mostly due to the bile reflux in the gastric pouch [22]. This trend however, is changing, and a few gastro-esophageal cancers have been reported now in post SG cases. In a review from 2019, a total of 37 papers were found from 1991 to 2018 reporting post-bariatric gastro-esophageal cancers [23]. Of those, 19 cases occurred after gastric bypass procedures, 7 after vertical banded gastroplasty, 7 after AGB, and 7 after SG. Interestingly, the cancer cases reported after SG ranged in location from the distal esophagus to the antrum of the stomach, which questions whether or not they occurred de nova or were related to the actual surgery.

A recent finding that is gaining a lot of attention, however, is Barrett's esophagus (BE) after SG. Thought to be secondary to the increased gastro-esophageal reflux post-SG, a recent paper involving routine endoscopy post-SG observed an 18.8% prevalence of BE at least five years after SG [24]. Further research into the subject is of vital importance to set future follow-up guidelines and insure optimal and safe practice.

9 Conclusion

It is beyond any doubt that there exists a strong relationship between obesity and the pathophysiology of cancer development. This relationship appears to translate to an observed association between excess weight reduction and subsequent reduction in the risk of cancer. Bariatric surgery is today the most effective method of achieving sustainable weight loss, but the heterogeneity in the mechanism this is

achieved across the different procedure types has yet to be explained in an optimal way. SG being one of the relatively novel procedures to be utilized in managing morbid obesity with increasing frequency, still lacks data differentiating it from other techniques with regard to its effect on cancer development in obese patients. More studies focusing on each surgical techniques' outcomes rather than the pooled analysis approach used by most studies is needed to explain the differences in results observed today.

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