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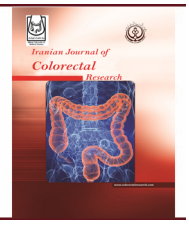

Time Will Tell – the Short Term Gain and Long Term Loss: Bariatric Surgery and Colorectal Cancer

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Abstract

Obesity is a growing worldwide epidemic, and its prevalence is continuously rising. Bariatric and metabolic surgery is the most effective treatment modality for long-term weight loss and resolution of associated comorbidities. It is well known that obesity increases overall mortality, and the link between obesity and increased cancer risk (mainly hormone-related cancers such as breast cancer and endometrial cancer) is firmly established. On the other hand, the association between intentional weight reduction through bariatric or metabolic surgery and reduced cancer risk, mainly none hormone-mediated cancers, remains poorly understood, with limited knowledge and conflicting data in the medical literature. Furthermore, the published outcomes regarding the effect of bariatric and metabolic surgery on the risk of colorectal cancer suggest a complex and poorly understood association. We herein review the literature regarding such an association and provide a plausible mechanism behind the increased risk of colorectal cancer after bariatric and metabolic surgery.

Keywords: Colorectal cancer, Obesity, Bariatric surgery

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Introduction

The link between obesity and increased risk of cancer is well established for multiple anatomical sites, mainly hormone-related cancers, particularly breast, prostate, and endometrial cancer. Bariatric and metabolic surgery is the most effective treatment modality for long-term weight loss and resolution of associated comorbidities. However, the association between surgical weight reduction through bariatric or metabolic surgery and the reduced cancer risk, mainly none hormone-mediated cancers, remains poorly understood with limited knowledge and conflicting data in the medical literature.

To date, published data regarding cancer risk after bariatric and metabolic surgery reveals a complex

picture with contradicting results. Early prospective cohort studies concluded a substantial decrease in cancer risk after weight reduction. Still, these studies lacked the ability to study and differentiate between different types of cancer. Furthermore, the effect of bariatric and metabolic surgery on the risk of colorectal cancer seems to be complex and poorly understood.

What Does the Literature Say?

Large population-based Nordic and UK studies identified a twofold increase in CRC incidence 5–10 years after bariatric surgery, while the incidence of other obesity-related cancers decreased (1, 2). In alignment, patients had a higher prevalence of serrated precancerous polyps five years after Roux-En-Y gastric bypass (RYGB) compared with pre-surgery in a single-center study (3). In 2013, Derogar et al. (1) studied 15,095 patients undergoing bariatric surgery and were the first to interpret site-specific cancer incidence post-bariatric surgery compared with obese patients who did not undergo bariatric surgery. They found a time-dependent increase in colorectal cancer risk ten years or more after bariatric surgery. On the contrary, in 2014, the systematic review and meta-analysis of Afshar et al. (4) concluded a reduced risk of colorectal cancer in obese patients who underwent bariatric surgery. To add further to the already present debate and conflicting data, a study in 2018 by Aravani et al. (5) using a UK based population failed to identify a change in colorectal cancer risk in patients who underwent bariatric surgery, but the drawback of this study was the fairly short follow up (median of 3 years). This was followed by a case-control study by Mackenzie et al. (6), which reported that the risk of colorectal cancer is higher in obese individuals who underwent obesity surgery when compared to those who did not. Add to this the article published by Tao et al. in 2020, suggesting that bariatric surgery is associated with an increased risk of colon cancer, while the support for an increased risk of rectal cancer was weaker.

In view of the above conflicting data and the growing debate regarding the risk of colorectal cancer and bariatric surgery, the challenge will be the ability to correlate the risk of colorectal cancer to the type of bariatric surgery, namely a malabsorptive procedure or a restrictive procedure. This opens the door to a new debate. Having said this, Derogar et al. (1) did not find any difference in the risk of colorectal cancer between RYGB and other surgical procedures. On the contrary, Mackenzie et al. (6) highlighted that the type of bariatric surgery played an important role in the future risk of colorectal cancer, reporting that an increased risk of colorectal cancer was observed in patients who underwent RYGB rather than restrictive procedures (gastric banding and sleeve gastrectomy).

Discussion

The RYGB procedure achieves its physiological benefits through bile flow alteration, reduction of gastric size, anatomical gut rearrangement and altered flow of nutrients, and vagal manipulation with subsequent enteric gut hormone modulation. On the other hand, restrictive procedures facilitate weight loss by reducing gastric size and modulating hormones.

Major alterations in the anatomy and physiology of the gastrointestinal tract post-RYGB lead to inflammation and changes in the gut microbiome. Malabsorption and surgical alterations post-RYGB may increase colorectal cancer risk by altering the microbiome. This alteration, in turn, is believed to predispose to increased risk of colorectal cancer post-bariatric surgery. In fact, data has shown that RYGB patients have significantly elevated levels of pro-inflammatory gene transcripts and rectal cell hyper-proliferation in their colonic mucosa even years after surgery (7, 8). From here, and given the possible association with colorectal cancer, patients undergoing bariatric and metabolic surgery should be closely monitored and must adhere to certain surveillance programs.

On the other hand, the matter mentioned above directly affects microbial composition. Specifically, studies show that colonic concentrations of *Escherichia coli* and Fusobacteria are increased post-RYGB (9, 10). Interestingly, Fusobacteria species have been linked to colorectal cancer (11). Furthermore, data from post-RYGB rat models demonstrate changes in the microbiome leading to increased fecal cytotoxicity (12), a measure associated with elevated colonic cancer risk (13). Add to this the increase of γ-proteobacteria and a decrease of Firmicutes. The shift toward more γ-proteobacteria as a major component of the microbiota and the elevation in p-cresol derivatives and another uremic toxin, indoxyl sulfate, could have long-term impacts on host health, possibly elevating the incidence of colorectal cancer. Additionally, studies have shown that short-chain fatty acids are decreased after RYGB, which may also increase colorectal cancer risk (14, 15).

Furthermore, the reduction of gastric size in sleeve gastrectomy and in RYGB and the bypassed segment of small bowel in RYGB result in ingested nutrients being exposed for a shorter period to digestive secretions and enzymes and hence, entering the small intestine earlier than the normal gastrointestinal configuration, and consequently reaching the colon earlier. Accordingly, the distal small intestine and the colon receive a higher load of nutrients that have not been exposed to the standard normal volume of digestive enzymes and secretions. This will result in increased protein putrefaction and fiber fermentation, leading to changes in the microbiome and thereby explaining the increased risk of colorectal cancer

seen in recent studies.

Hussan et al., in their work published in 2019, concluded that RYGB is associated with an increased risk of serrated polyps five years after surgery (3). Having said this, this possible increase in colorectal cancer risk after bariatric and metabolic surgery is multifactorial. We believe that this increased risk has two branches. The first is related to the patients' habits prior to bariatric surgery, and the second is directly related to lifestyle (unhealthy diet or poor exercise) after bariatric and metabolic surgery. On the other hand, malabsorption and microbiome changes due to RYGB may also play a role in creating a carcinogenic environment.

Cancer outcomes after bariatric surgery reveal a complex picture, with variable effects on future cancer risk depending mainly on the anatomic site and hormone dependence of the malignancy. However, according to current data, the risk of colorectal cancer might increase after bariatric surgery, especially when combined with plausible mechanisms like weight regain, colonic inflammation, and microbiome alterations, backboned with certain biomarkers. Every single factor mentioned likely contributes by a small fraction to the underlying mechanism of colorectal cancer development in patients with a history of bariatric surgery.

Current evidence remains insufficient to support any change in our clinical practice regarding the indications of bariatric surgery. However, this possible increased risk of colorectal cancer following bariatric and metabolic surgery mandates surgeons and physicians to at least adhere more to surveillance of patients undergoing bariatric surgery through regular colonoscopies, fecal occult blood testing, or stool DNA tests. This possible association highlights the importance of patient selection for bariatric surgery and follow-up, with special consideration of patients with risk factors for colorectal cancer. Further studies with more patients and longer follow-ups are recommended to prove this correlation. Meanwhile, strict adherence to surveillance programs for colorectal cancer is recommended, and educating our patients about this possible association is a must.

Conclusion

The use of bariatric and metabolic surgery in the treatment of obesity and obesity-related diseases has risen in the past two decades, and its metabolic benefits are evident. Data regarding colorectal cancer post-bariatric and metabolic surgery are conflicting, and colorectal cancer might be a unique problem in this population. A positive association of bariatric and metabolic surgery with colorectal cancer will lead clinicians to implicate special considerations for patients with other risk factors for colorectal cancer.

We believe that cohort studies with a follow-up of at least ten years after bariatric and metabolic surgery are required to properly document de novo colorectal cancers. Furthermore, better coding systems clearly defining restrictive and malabsorptive procedures are necessary for identifying procedure-specific associated colorectal cancer risk. Moreover, we suggest that the endoscopists clearly label colorectal cancer post-bariatric surgery as a specific entity to facilitate further studies. In fact, we recommend all colorectal cancers developing after bariatric and metabolic surgery be labeled as 'Post Bariatric Surgery ColoRectal Cancer' (PBSCRC).

Statement of Ethics

This research complied with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Ethical approval was not required.

Author Contributions

All authors contributed equally to the writing and preparation of the article.

Data Availability: All data are available upon request.

Conflicts of interest: None declared.

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