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Review article

The impact of bariatric surgery on colorectal cancer risk

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Abstract Obesity is considered a risk factor for different types of cancer, including colorectal cancer (CRC). Bariatric surgery has been associated with improvements in obesity-related co-morbidities and reductions in overall cancer risk. However, given the contradictory outcomes of several cohort studies, the impact of bariatric surgery on CRC risk appears controversial. Furthermore, measurement of CRC biomarkers following Roux-en-Y gastric bypass (RYGB) has revealed hyperproliferation and increased pro-inflammatory gene expression in the rectal mucosa. The proposed mechanisms leading to increased CRC risk are alterations of the gut microbiota and exposure of the colorectum to high concentrations of bile acids, both of which are caused by RYGB-induced anatomical rearrangements. Studies in animals and humans have highlighted the similarities between RYGB-induced microbial profiles and the gut microbiota documented in CRC. Microbial alterations common to post-RYGB cases and CRC include the enrichment of pro-inflammatory microbes and reduction in butyrate-producing bacteria. Lower concentrations of butyrate following RYGB may also contribute to an increased risk of CRC, given the anti-inflammatory and anticarcinogenic properties of this molecule. Laparoscopic sleeve gastrectomy appears to have a more moderate impact than RYGB; however, relatively few animal and human studies have investigated its effects on CRC risk. Moreover, evidence regarding the impact of anastomosis gastric bypass on one is even more limited. Therefore, further studies are required to establish whether the potential increase in CRC risk is restricted to RYGB or may also be associated with other bariatric procedures. (Surg Obes Relat Dis 2022;■:1–14.)

Keywords: Bariatric surgery; Colorectal cancer risk; Microbiota; Bile acids; Short-chain fatty acids

Obesity (defined as body mass index [BMI] over 30 kg/m^2) is rising dramatically worldwide [1,2]. The prevalence of obesity doubled between 1980 and 2015 in more than 70 countries and increased in most other countries. In 2015, about 12% of the world's adult population was obese, and by 2030, the prevalence of obesity is expected to increase to 42% [2,3]. Obesity has become a severe public health issue due to its associated morbidity and mortality [4]. Excess body weight has been correlated with type II diabetes, cardiovascular diseases, nonalcoholic fatty liver disease, and several cancers [5–7].

Therapeutic options for obesity include medical treatment and bariatric surgery. Surgical treatment is a valid option for patients who have failed to lose weight or maintain long-term weight loss despite appropriate nonsurgical treatment. Bariatric surgery should be considered for patients

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with a BMI equal to or over 40 kg/m^2 or with a BMI between 35.0 and 39.9 kg/m^2 and associated co-morbidities that are expected to improve with weight loss [8,9]. In the last decades, the demand for bariatric surgery has increased significantly in many countries and is expected to increase further, given the increasing prevalence of obesity. According to global reports conducted by the International Federation for the Surgery of Obesity and Metabolic Disorders, the total number of bariatric surgery procedures performed worldwide increased from 146,301 in 2003 to 696,191 in 2018 [10,11]. Several studies have proven the superiority of bariatric surgery over nonsurgical treatment in promoting long-term weight loss, as well as resolving or improving type II diabetes, reducing the incidence of adverse cardiovascular events, and lowering the mortality rate [12–16].

Both weight loss–dependent and weight loss–independent mechanisms associated with bariatric procedures have been proposed to be involved in reduced cancer incidence and improved prognosis. These mechanisms include decreases in systemic inflammation and oxidative stress as well as changes in gastrointestinal hormones and alterations in the gut microbiota and metabolism of fat, glucose, and bile [17,18]. The protective effects of bariatric surgery in relation to cancer risk and development are most evident for obesity-associated malignancies such as hormone-related and gastrointestinal tumors [19–21]. In contrast, the effect of bariatric surgery on colorectal cancer (CRC) is uncertain and controversial, given that some studies report an increase in risk [22,23], while others document a reduction in risk for this cancer [24,25].

CRC is the third most commonly diagnosed cancer and the second leading cause of cancer deaths, with an estimated number of 1.9 million new cases and around 935,000 deaths worldwide in 2020 [26]. CRC is a multifactorial disease resulting from genetic, environmental, and lifestyle factors and is associated with several risk factors that cannot be modified. These include age, personal history of inflammatory bowel disease, and familial history of CRC. Additional risk factors are related to lifestyle, such as obesity, sedentary life, unhealthy nutritional habits, alcohol consumption, and smoking [27–31].

Since obesity is a risk factor for CRC, weight loss achieved with bariatric surgery is expected to reduce the risk of this cancer. However, several studies have yielded conflicting results, reflecting the complex and controversial nature of this association [22–25]. Therefore, in this review, we aimed to evaluate whether bariatric surgery leads to an increased risk of CRC and to investigate the mechanisms that may be involved.

Materials and methods

A literature search using PubMed was conducted to identify articles relevant to the review topic. Search terms used were "colorectal cancer," "bariatric surgery" or "Roux-en-Y gastric bypass" or "sleeve gastrectomy," "colorectal cancer risk," "biomarkers of colorectal cancer," "gut microbiota" or "microbiome," "bile acid metabolism," "short-chain fatty acids," "butyrate." Additional articles were identified from the references of the included studies.

Case reports, comments, and non-English publications were excluded from the review. In total, 95 papers (published between 1984 and 2021) were included in the review; of these, 66 were research articles, 27 were literature reviews, 1 was a systematic review, and 1 was a meta-analysis.

Bariatric procedures

Bariatric procedures are classified into 3 main groups according to their mechanism of action in promoting weight loss. Malabsorptive bariatric surgery limits the absorption of nutrients by bypassing part of the small intestine to some degree [9]. In restrictive procedures, the size of the stomach is considerably reduced in order to induce an early sense of satiety in patients during food intake [32,33]. A further major category of bariatric procedures combines malabsorptive and restrictive components; these techniques involve significant reduction of available gastric capacity in conjunction with the bypassing of a section of the proximal small intestine [34].

Laparoscopic sleeve gastrectomy (LSG), a restrictive procedure, is currently the most commonly performed bariatric technique worldwide [35]. LSG involves the transection and removal of the greater curvature portion of the stomach, leaving only a narrow tube along the lesser curvature. The popularity of this procedure is likely due to its promotion of significant weight loss and improvement in metabolic conditions, alongside a reduced risk of complications, compared with malabsorptive procedures [33].

Roux-en-Y gastric bypass (RYGB), currently the second most common bariatric technique, is a combined restrictive and malabsorptive procedure [35]. This involves the creation of a gastric pouch from the upper stomach that is then anastomosed to the jejunum, forming the Roux or alimentary limb through which ingested nutrients flow. Anastomosis of the biliopancreatic limb with the jejunum allows the interaction of bile acids (BAs) and pancreatic secretions with nutrients in the common limb [36]. One anastomosis gastric bypass (OAGB) is a variation of gastric bypass, consisting of a single anastomosis of the gastric pouch to a loop of jejunum 150–200 cm from the ligament of Treitz [37,38].

CRC risk after bariatric surgery

Although bariatric surgery has proven to reduce overall cancer incidence, cohort studies have reported conflicting results on the impact of bariatric surgery on CRC. For instance, in 2010, Ostlund et al. conducted a population-based cohort study of bariatric surgery patients to test whether the risk of obesity-related cancer decreased with

time after obesity surgery. The results of the study showed that CRC risk gradually and significantly increased with follow-up time after bariatric surgery. Patients followed up for more than 10 years showed a 2-fold increased risk. Such increases were not observed for the other main obesity-related malignancies, including breast, prostate, and endometrial cancer [39].

Another population-based study, conducted by Derogar et al., identified an increased risk of CRC in patients with obesity undergoing surgery. An overall standardized incidence ratio (SIR) of 1.60 for CRC was reported for the obese surgery cohort, increasing to 2.00 after 10 years. In contrast, the SIR in the obese no-surgery cohort was 1.26, remaining stable over time [25]. This increased risk of CRC more than 10 years after surgery is consistent with the long natural history of colorectal carcinogenesis, from normal mucosa to malignant lesions. In both studies, bariatric surgeries consisted of restrictive procedures such as vertical banded gastroplasty and adjustable gastric banding, as well as malabsorptive procedures such as gastric bypass [25,39].

In addition, a large cohort study performed by Mackenzie et al. revealed an association between higher CRC risk and RYGB, although this association was not reported for sleeve gastrectomy or gastric banding [24].

Likewise, a cohort study conducted across 5 Nordic countries demonstrated a higher risk of colon cancer in individuals who had undergone bariatric surgery, increasing further after $\geq$ 10 years. In contrast, the risk of rectal cancer was not significantly increased following bariatric surgery, although it appeared to increase with longer follow-up periods [40].

These findings are in parallel with the results of a retrospective study conducted by Hussan et al., who examined the risk of colorectal polyp formation following RYGB. To focus on the long-term impact of RYGB, the authors compared colonoscopies performed 5 years or more after surgery with presurgery colonoscopies. Results revealed a higher percentage of serrated polyps (precursors of CRC) 5 years or more after surgery, suggesting an increased risk of precancerous lesion formation following RYGB [41].

The impact of bariatric surgery is not limited to the incidence of CRC but also appears to affect prognosis. In 2016, a cohort study conducted by Tao et al. revealed that patients with CRC who had previously undergone bariatric surgery experienced higher mortality rates and a poorer prognosis than patients with CRC with obesity who had not undergone such surgery. When analyzed separately, the mortality rate was increased more than three-fold in patients with rectal cancer, while no statistically significant increase in mortality rate was found in patients with colon cancer [42].

The negative impact of bariatric surgery found in these studies conflicted with the results of a meta-analysis conducted by Afshar et al. This revealed bariatric surgery to be associated with a 27% lower risk of CRC, although few studies were included in this meta-analysis, and follow-up was limited. Thus, lower CRC risk may have been related to weight loss alone [22]. Similarly, an English retrospective observational study found that obesity surgery was not associated with a higher incidence of CRC. However, the limitations of this study included follow-up period (3 years) and a small obese surgery cohort, compared with the obese no-surgery population [43]. In addition, a nationwide survey of CRC incidence following LSG or RYGB (conducted in Italy by the Italian Society of Obesity Surgery) revealed a low incidence of CRC (0.10%) 10 years after surgery. While this suggested that bariatric surgery had little impact on CRC development, the absence of no-surgery patients with obesity control group and the small number of cases observed (22 CRC cases in 20,571 bariatric patients) meant that the evidence was relatively weak, especially in terms of comparison of LSG and RYGB [23].

The characteristics and findings of the investigations into CRC risk following bariatric surgery are summarized in Table 1. Their contradictory outcomes highlight the need to delve deeper into the mechanisms underlying this association.

Biomarkers of CRC

A number of studies have investigated changes in CRC biomarkers following bariatric surgery. A study carried out by Sainsbury et al. in 2008 investigated mucosal biomarkers—considered indicators of future CRC risk [44,45]—in normal-weight individuals (n = 21) and patients with obesity undergoing RYGB (n = 24) [46]. Mucosal biomarkers of proliferation such as rectal epithelial cell mitosis, crypt area, and crypt branching were quantified by carrying out whole crypt microdissection; apoptosis was also evaluated by immunohistochemical staining for neocytokeratin 18. Before surgery, patients with obesity exhibited higher levels of rectal epithelial cell proliferation than normal-weight individuals, consistent with the link between obesity and CRC risk. Six months after RYGB, analysis of the same patients revealed a two-fold increase in the number of mitoses per crypt, compared with presurgery values. This further increase in rectal epithelial cell mitosis post-RYGB was accompanied by a decrease in the number of apoptotic cells. Systemic and mucosal markers of inflammation were also analyzed, including serum levels of C-reactive protein (CRP), cytokines, and mucosal pro-inflammatory gene expression. As expected, serum levels of CRP, interleukin (IL) 6, tumor necrosis factor α (TNFα), and macrophage migration inhibitory factor (MIF) were higher in patients with obesity than in normal-weight controls. After surgery, the patients with obesity had lower levels of CRP and IL-6 but significantly increased levels of TNFα and MIF, both of which are implicated in colorectal mucosal inflammation and carcinogenesis [46–48]. Furthermore, the expression of pro-inflammatory genes cyclooxygenase-1 (COX-1) and COX-2 increased significantly following RYGB surgery [46]. COX-2, in particular,

Table 1
Studies on CRC risk following bariatric surgery included in the review

Author	Years	Participants	Type of bariatric surgery	Findings	Follow-up
Ostlund et al. [39]	1980–2006	• Obesity surgery cohort: 13,123	• Gastric banding • Vertical banding gastroplasty • Gastric bypass	• SIR: 1.52 (95% CI: 1.06−2.11) • SIR ≥10 yr: 2.14 (95% CI: 1.33–3.22)	• Mean follow-up: 9 yr
Derogar et al. [25]	1980–2009	• Obesity surgery cohort: 15,095 • Obesity no-surgery cohort: 62,016	• Vertical banded gastroplasty • Adjustable gastric banding • Roux-en-Y gastric bypass	• SIR obesity surgery cohort: 1.60 (95% CI: 1.25–2.02) • SIR obesity surgery cohort ≥10 yr: 2.00 (95% CI: 1.48–2.64). • SIR obesity no-surgery cohort: 1.26 (95% CI: 1.14–1.40) • SIR obese no-surgery cohort ≥10 yr: 1.27 (95% CI: 1.03–1.53)	• Median follow-up: 10 yr (range: 1–30 yr)
Mackenzie et al. [24]	1997–2012	• Obesity surgery cohort: 8794 • Obesity no-surgery cohort: 8794	• Gastric bypass (56.6%) • Gastric banding (33.6%) • Sleeve gastrectomy (9.8%)	• OR (bariatric surgery): 2.19 (95% CI: 1.21–3.96) • OR (gastric bypass): 2.63 (95% CI: 1.17–5.95)	• Median follow up: 55 mo
Tao W et al. [40]	1980–2015	• Obesity surgery cohort: 49,931 • Obesity no-surgery cohort: 492,427	• Gastric bypass (72.5%) • Restrictive surgery (9.6%) • Other (17.9%).	• Colon cancer: - SIR obesity surgery cohort: 1.56 (95% CI: 1.28–1.88) - SIR obesity surgery cohort >10–14 yr: 2.07 (95% CI: 1.36–3.01) • Rectal cancer: - SIR obesity surgery cohort: 1.14 (95% CI: 0.83–1.52) - SIR obesity surgery cohort ≥20 yr: 1.62 (95% CI: 0.78–2.98)	• N.A.
Hussan et al. [41]	1994–2018	• Presurgery cohort: 106 • Postsurgery cohort: 86	• Roux-en-Y gastric bypass	• Higher percentage of serrated polyps ≥5 yr post-RYGB compared with pre-RYGB (8.7% vs. 2.1%, $P = .04$; RR: 4.22 (95% CI: 0.97–18.4)	• Median follow-up: 9.4 yr
Tao W et al. [42]	1980–2012	• Obesity surgery cohort: 131 • Obesity no-surgery cohort: 1332	• Gastric bypass (26%) • Gastric banding (33%) • Vertical banded gastroplasty (36%) • Malabsorptive surgery (5%)	• Colorectal cancer mortality rate: disease-specific HR: 1.50 (95% CI: 1.00–2.19) • Colon cancer mortality rate: disease-specific HR: 1.10 (95% CI: 0.67–1.70) • Rectal cancer mortality rate: (disease-specific HR: 3.70 (95% CI: 2.00–6.90)	• Median follow-up for obesity surgery cohort: 3.7 yr • Median follow-up for obesity no-surgery cohort: 4.3 yr
Aravani et al. [43]	1997–2013	• Obesity surgery cohort: 39,747 • Obesity no-surgery cohort: 962,860	• Restrictive surgery (52%) • Restrictive and malabsorptive surgery (48%)	• SIR obesity surgery cohort: 1.26 (95% CI: 0.92–1.71) • SIR obesity no-surgery cohort: 1.12 (95% CI: 1.08–1.16)	• Median follow up for obesity surgery cohort: 3 yr • Median follow up for obesity no-surgery cohort: 2.5 yr
Ciccioriccio et al. [23]	2010–2015	• Bariatric surgery patients: 20,571	• Sleeve gastrectomy (70%) • Gastric bypass (30%)	• Sleeve gastrectomy: - SIR (male gender): 0.5 (CI: 0.2–0.72) - SIR (female gender): 0.6 (CI: 0.3–0.76) • Gastric bypass: - SIR (male gender): 1.07 (CI: 0.91–1.2) - SIR (female gender): 0.8 (CI: 0.32–0.94)	• Follow up: equally distributed between 5 and 10 yr

SIR: standardized incidence ratios; 95% CI, 95% confidence interval; OR: odds ratio; RR: relative risk; HR: hazard ratio; N.A.: not available.

is known to be overexpressed in CRC and appears to play a major role in its development and progression [49,50].

Interestingly, these mucosal biomarkers were quantified in the same group of patients (n = 19) 3 years after RYGB to determine their long-term persistence. Rectal epithelial cell mitosis and crypt size remained abnormally increased 3 years after RYGB, compared with preoperative values. COX-1 and COX-2 messenger RNA (mRNA) levels also remained elevated, similar to the values observed 6 months post-RYGB. A remarkable outcome of the study was the marked upregulation of MIF in the rectal mucosa 3 years after surgery. The authors observed a 40.5-fold increase in mucosal MIF mRNA levels compared with pre-RYGB values, as well as higher MIF protein levels in colorectal epithelial cells. However, serum MIF was reduced, compared with levels observed 6 months after surgery, indicating that MIF upregulation was a local pro-inflammatory phenomenon rather than a systemic response [51].

A similar study conducted by Afshar et al. investigated the impact of RYGB on biomarkers of CRC risk. This study included 22 post-RYGB patients and 20 normal-weight controls. Notably, in this case, the results revealed lower rectal crypt cell proliferation and reduced systemic and mucosal markers of inflammation 6 months after RYGB [52]. However, the contrasting outcomes of the 2 studies may have been due to the different characteristics of the populations and differences in the surgical procedures [46,52]. For example, the decreased levels of inflammatory markers identified by Afshar et al. may have been due to the lower mean BMI of patients in this study, compared with the patients studied by Sainsbury et al. Furthermore, a remarkable difference between the 2 investigations was the length of the bypassed tract: the biliopancreatic limb was 150 cm long in the study of Sainsbury et al., whereas it was 60–75 cm long in the study of Afshar et al. It has been suggested, therefore, that the length of the biliopancreatic limb may be a key factor in the hyperproliferation and inflammation of the rectal mucosa [46,52]. This is supported by the results of a study conducted by Appleton et al. on patients with obesity who had undergone jejunoileal bypass (JIB). In these patients, the bypassing of a long portion of the small intestine led to a marked and persistent increase in rectal crypt cell proliferation [53].

According to this hypothesis, these effects should not occur after restrictive bariatric procedures, where intestinal flow remains largely unaltered. Kant et al. tested this assumption by comparing mucosal biomarkers of CRC risk in patients undergoing LSG (n = 21) and normal-weight controls (n = 20). Unlike the results observed following RYGB, there was no significant change in rectal epithelial cell proliferation 6 months after LSG. Furthermore, mucosal MIF mRNA levels increased by 39% following LSG, but there were no changes in the expression of TNFα, IL-1, IL-6, COX-1, or COX-2 over the same period [54].

Levels of serum biomarkers and expression of pro-inflammatory genes prior to bariatric surgery, 6 months after RYGB, 3 years after RYGB, and 6 months after LSG (reported by different authors) are summarized in Table 2.

The mechanisms leading to hyperproliferation of the rectal mucosa following RYGB and malabsorptive procedures (but not LSG) are still unclear. Nonetheless, several possible pro-carcinogenic pathways have been proposed, as outlined below.

Alteration of gut microbiota

Alteration of the gut microbiota has been suggested to be one of the main potential mechanisms linking bariatric surgery to an increased risk of CRC. This hypothesis arises from the intriguing finding that some of the gut bacteria found to be increased after bariatric surgery have been associated with CRC due to their pro-carcinogenic properties.

Bariatric surgery (especially RYGB and malabsorptive procedures) induces major anatomical rearrangements in the gastrointestinal tract, altering nutrient transit and affecting gut physiology. Malabsorption, changes in the metabolism of BAs, alteration of pH, and modulation of enteric and adipose hormones all affect the composition of the gut microbiota [55–57]. Accordingly, changes in the gut microbiota following RYGB have been widely demonstrated. The most commonly reported alterations in post-RYGB patients are a marked increase in the phylum *Fusobacteria*, higher levels of the class *Gammaproteobacteria* and the genera *Bacteroides* and *Escherichia*, and a decrease in the abundance of the phylum *Firmicutes* [58–63].

The impact of LSG on gut microbiota composition has also been investigated. Three studies on human patients found that LSG led to changes in the fecal microbial community similar to those observed after RYGB; however, the alterations were more moderate than those seen following RYGB, demonstrating the lower impact of LSG [64–66]. These 2 bariatric procedures were further compared in terms of microbiota alteration by Shao et al. in a rat model. Analysis revealed a striking shift in the gut microbiota following RYGB. However, while RYGB was associated with a significantly higher proportion of *Proteobacteria*, the post-LSG microbiota was comparable to that of sham-operated rats [67].

Overall, these findings imply that bariatric surgery results in procedure-dependent alterations in gut microbiota. In comparison with LSG, RYGB results in greater modification of the gastrointestinal tract and intestinal environment, resulting in more severe and profound effects on microbiota composition [67,68]. This may be due to the effect of the shortened small intestine in RYGB, as increased oxygen concentration in the normally anaerobic distal lumen favors the presence of facultative anaerobes (such as *Gammaproteobacteria*) over obligate anaerobes (e.g., *Firmicutes*)

Table 2
Biomarkers of colorectal cancer

Biomarkers	Pre-surgery [46,51,52,54]	6 mo post-RYGB [46,52]	3 yr post-RYGB [51]	6 mo post-LSG [54]
Serum CRP	Higher levels in patients with obesity, compared with normal-weight controls [46,51,52,54]	• Significant reduction due to RYGB-induced weight loss [46] • 71% decrease following RYGB-induced weight loss [52]	Lower levels than at 6 mo postsurgery due to further weight loss [51]	Significant reduction due to LSG-induced weight loss [54]
Serum IL-6	Higher levels in patients with obesity, compared with normal-weight controls [46,51,54]	Significant reduction due to RYGB-induced weight loss [46]	Lower levels than at 6 mo postsurgery due to further weight loss [51]	No significant change, compared to presurgery values [54]
Serum TNFα	Higher levels in patients with obesity, compared with normal-weight controls [46,51,54]	Increased levels, compared with presurgery values [46]	Levels similar to presurgery values [51]	No significant change, compared to presurgery values [54]
Serum MIF	Higher levels in patients with obesity, compared with normal-weight controls [46,51]	Increased levels, compared with presurgery values [46]	Lower levels than presurgery and 6 mo post-RYGB values [51]	N.A.
Mucosal MIF mRNA levels	Similar levels in patients with obesity and normal-weight controls [52,54]	No significant change, compared to presurgery values [52]	Significantly increased levels, compared with presurgery values [51]	Significantly increased levels, compared with presurgery values [54]
COX-1 mRNA levels	Similar levels in patients with obesity and normal-weight controls [52,54]	• Significantly increased levels, compared with presurgery values [46] • Significantly decreased levels, compared with presurgery values [52]	Significantly increased levels, compared with presurgery values [51]	No significant change, compared to presurgery values [54]
COX-2 mRNA levels	Similar levels in patients with obesity and normal-weight controls [52,54]	• Significantly increased levels, compared with presurgery values [46] • No significant change, compared to presurgery values [52]	Significantly increased levels, compared with presurgery values [51]	No significant change, compared to presurgery values [54]
IL-6 mRNA levels	Similar levels in patients with obesity and normal-weight controls [52,54]	• Significantly increased levels, compared with presurgery values [46] • No significant change, compared to presurgery values [52]	Slightly elevated levels, compared with presurgery values (not significant) [51]	No significant change, compared to presurgery values [54]

Levels of serum biomarkers and pro-inflammatory gene expression prior to bariatric surgery, 6 months after RYGB, 3 years after RYGB, and 6 months after LSG.

RYGB: Roux-en-Y gastric bypass; LSG: laparoscopic sleeve gastrectomy; CRP: C-reactive protein; IL-6: interleukin-6; TNFα: tumor necrosis factor α; MIF: macrophage migration inhibitory factor; COX-1: cyclooxygenase-1; COX-2: cyclooxygenase-2; NA: Not available; mRNA, messenger RNA.

[56,61]. Furthermore, the bypassing of the upper small intestine in this procedure might result in the relocation of some of the typical small intestine microbiota, such as *Enterobacteriaceae*, to the large intestine [61].

Another important modification related to RYGB is the reduction in stomach size and subsequent alteration in pH. Indeed, reduced gastric volume is associated with significantly decreased acid secretion in the gastric pouch, leading to higher pH levels [69]. Evidence regarding the effect of LSG on gastric acid secretion is somewhat limited. However, it has been hypothesized that the anatomical rearrangements associated with this bariatric procedure could also contribute to reduced gastric acid secretion, albeit to a lesser extent than RYGB, as some acid-producing cells are still present [70]. Increasing the pH in the gastrointestinal tract induces major changes in gut bacterial populations since it produces a more favorable environment for *Bacteroides* and inhibits the growth of butyrate-producing bacteria [56,68]. This evidence is confirmed by the study of Walker et al. who tested, in vitro, the response of microbial communities to pH increase and found higher levels of the genus *Bacteroides* and a decrease of *Roseburia* spp. and *Faecalibacterium prausnitzii* abundance [71]. *Roseburia* spp. and *F. prausnitzii* are considered the main butyrate-producing bacteria in the human gut [72] and appear to have a protective role because of the beneficial and anti-inflammatory

effects of butyrate [73,74]. Decreased levels of both bacterial groups (belonging to the *Firmicutes* phylum) have been observed in postsurgery patients. [58,59,62,66].

An indirect effect of RYGB is altered microbial catabolism, which produces changes in metabolite levels. Gastric acid secretion, which normally ensures the activation of proteolytic enzymes and protein digestion, is reduced after RYGB [69]. As a consequence, more incompletely digested proteins reach the colon, leading to increased microbial protein catabolism. This, in turn, results in elevated production of toxic polyamines such as putrescine [58,75]. Fecal water from post-RYGB rats has been observed to be highly cytotoxic, likely correlating with a postoperative increase in the levels of fecal putrescine, given the deleterious effects of this polyamine on cell survival [58,76]. Importantly, it has been reported that the levels of putrescine and other polyamines are elevated in patients with cancer and are correlated with tumor stage and progression [77,78]. Relevant to this finding, putrescine appears capable of stimulating cell proliferation in a dose-dependent manner. Furthermore, the accumulation of putrescine has been associated with colon inflammation, high levels of pro-inflammatory cytokines, and increased gut permeability [79,80].

Various human studies have reported, in the gut, the increased presence of oral microbes including *Streptococcus* spp., *Veillonella* spp., and *Fusobacterium nucleatum* following RYGB [58,62,66]. Intestinal colonization by the oral microbiota could be related to increased pH and decreased acid secretion, which reduce the efficiency of the gastric barrier, facilitating the orofecal transit of bacteria [56,58].

Interestingly, there are several similarities between the fecal microbial profiles observed following bariatric surgery (particularly RYGB) and those of patients diagnosed with CRC. Indeed, several studies have analyzed and compared gut microbiota composition in patients with CRC and healthy individuals, revealing enrichment of the phylum *Fusobacteria* and the genera *Bacteroides* and *Escherichia* in the CRC group [81–86]. Furthermore, the results of these studies indicate significantly decreased abundance of the butyrate-producing genera *Faecalibacterium* and *Roseburia* in patients with cancer, compared with controls [82,83,86]. Zhu et al. found similar results using a murine model of CRC, observing increases in *Proteobacteria*, *Fusobacterium,* and *Bacteroides* populations and significant reductions in *Roseburia* and *Eubacterium* abundance [87]. Therefore, the microbial dysbiosis associated with CRC leads to both enrichment of pro-inflammatory microbes and depletion of butyrate-producing bacteria, resembling the effects of RYGB [88,89].

Alteration of microbiota composition is emerging as a major factor associated with inflammation and tumorigenesis that appears to modulate CRC risk and development [81]. Zackular et al. used a murine model of inflammation-associated CRC to determine the role of gut microbiota in the development of CRC. This study demonstrated that microbial alterations contribute to CRC through the initiation of inflammation and have a causal role in exacerbating tumor formation [88]. The authors hypothesized that enrichment of the genus *Bacteroides*, observed in the fecal samples of their murine model and in patients with CRC [81,82], may contribute to tumorigenesis [88]. In support of this hypothesis, Wu et al. found a positive correlation between *Bacteroides* abundance and tumor stage in patients with cancer [82]. Furthermore, according to a study conducted by Sobhani et al., *Bacteroides* populations were linked with high proportions of pro-inflammatory IL-17-producing cells in tumor samples and normal mucosa in patients with CRC [81]. *Escherichia coli*, a member of the *Gammaproteobacteria* class, is also enriched in post-RYGB patients [58–60] and has been found to be associated with colorectal carcinogenesis. Interestingly, the intestinal mucosa of patients with more advanced colorectal neoplasia is reportedly colonized by pathogenic and virulent *E. coli* strains with genotoxic properties [90,91].

Several studies have focused on the colorectal carcinogenic effects and tumor-promoting mechanisms of *F. nucleatum*, a pro-inflammatory bacterium. The increased presence of *F. nucleatum* in stool samples represents a further microbial alteration common to bariatric and CRC patients [58,82]. *F. nucleatum* has also been detected in premalignant colorectal lesions, suggesting its involvement in neoplastic initiation and the early stages of tumorigenesis [92,93]. Moreover, increased abundance of this species in patients with CRC has been associated with shorter survival time [94].

The similarity of the microbial changes observed in post-bariatric patients and patients with CRC (Table 3) is striking. Such changes highlight a potential mechanism by which the alteration of gut microbiota associated with bariatric surgery could lead to an increased risk of CRC.

BA exposure

BAs are metabolites of the gastrointestinal tract that facilitate the absorption of dietary lipids and fat-soluble molecules. They also play a role in the control of glucose homeostasis and regulation of energy metabolism [57,59,95]. Primary BAs are synthesized in the liver and stored in the gallbladder before secretion into the intestinal lumen; here, they are converted into secondary BAs by 7α-dehydroxylating bacteria [56]. The circulation of enterohepatic bile is affected by the altered gastrointestinal anatomy associated with RYGB and malabsorptive bariatric surgery [52,96]. In RYGB, bile secretion into the biliopancreatic limb and nutrient flow in the alimentary limb are uncoupled, coming together only in the distal gut. Consequently, the distal gut is exposed to high levels of nutrients and BAs [56,57]. Accordingly, several human studies have detected

Table 3
Microbial alterations following bariatric surgery and in colorectal cancer reported in studies conducted on murine models and human patients

Taxa	Alterations following bariatric surgery	Alterations in colorectal cancer
Bacteroidetes	↑ Damms-Machado et al., Tabasi et al. [64,65]	-
Bacteroides	↑ Furet et al., Shao et al., Kong et al. [60,63,67]	↑ Sobhani et al., Wu et al., Zhu et al., Zackular et al. [81,83,87,88]
Fusobacteria	↑ Palleja et al., Zhang et al., Graessler et al. [58,61,62]	↑ Wu et al., Kostic et al., He et al. [82,85,86]
Fusobacterium	-	↑ Wu et al., Wang et al., Zhu et al. [82,83,87]
Fusobacterium nucleatum	↑ Palleja et al. [58]	↑ Wu et al., Flanagan et al. [82,94]
Proteobacteria	↑ Palleja et al., Tremaroli et al., Zhang et al., Graessler et al., Shao et al., Li et al. [58,59,61,62,67,75]	↑ Wang et al., Zhu et al., He et al. [83,86,87]
Gammaproteobacteria	↑ Tremaroli et al., Zhang et al., Shao et al. [59,61,67]	↑ He et al. [86]
Escherichia	↑ Tremaroli et al., Kong et al. [59,63]	↑ Wu et al., Wang et al. [82,83]
Escherichia coli	↑ Palleja et al., Furet et al., Graessler et al. [58,60,62]	↑ Ma et al., He et al. [84,86]
Firmicutes	↓ Tremaroli et al., Zhang et al., Graessler et al., Damms-Machado et al., Tabasi et al., Li et al. [59,61,62,64,65,75]	↓ Kostic et al., He et al. [85,86]
Roseburia spp.	↓ Tremaroli et al. [59]	↓ Wu et al., Wang et al., Zhu et al. [82,83,87]
Faecalibacterium prausnitzii	↓ Palleja et al., Graessler et al. [58,62]	↓ Wu et al., He et al. [82,86]

a significant increase in serum primary and secondary BAs following RYGB and malabsorptive procedures [59,96–98].

Remarkably, high concentrations of BAs (especially deoxycholic acid) correlate significantly with hyperproliferation of the colonic mucosa, considered an early step in colorectal carcinogenesis [99]. It has been suggested that longer bypass limbs might be associated with higher levels of BAs in the gut lumen, inducing a hyperproliferative state in the colorectal mucosa [52,100]. Consistent with this hypothesis, marked increases in BA levels have been noted following JIB, which involves bypassing an extensive portion of the intestine [100]. Increased crypt cell proliferation rates and expansion of the proliferative zone in patients and murine models following JIB may therefore be due to chronic exposure of the colonic mucosa to high concentrations of BAs [53,100,101]. The correlation between elevated BA levels and increased colorectal proliferation applies to both RYGB and malabsorptive procedures as all of these techniques involve the bypassing of intestinal segments and subsequent alterations in BA flow.

Repeated and prolonged exposure of the intestinal tract to high concentrations of BAs appears to be an important etiologic factor in colorectal carcinogenesis and development [95,102]. Serum and fecal levels of secondary BAs are elevated in patients diagnosed with CRC and at-risk individuals, compared with healthy controls [103,104]. Furthermore, cholecystectomy has been associated with increased risk of colon cancer because of the resultant constant flow of bile and enhanced exposure of the colonic mucosa to BAs [105–107]. Collectively, these data highlight how altered BA concentrations can influence CRC risk.

BAs promote CRC initiation and progression by damaging the colonic epithelium, inducing oxidative stress and inflammation and activating specific signaling pathways [103,108]. Such pathways include nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling, which is involved in genome instability and mutation. In addition, activation of epidermal growth factor receptor is associated with cell proliferation, while the MAPK pathway enhances the invasiveness and angiogenic activity of cancer cells [108]. However, one of the most important cytotoxic effects of BAs is the increased production of reactive oxygen and nitrogen species, which can induce oxidative stress, DNA damage, and apoptosis [95,102,109]. In addition, long-term exposure

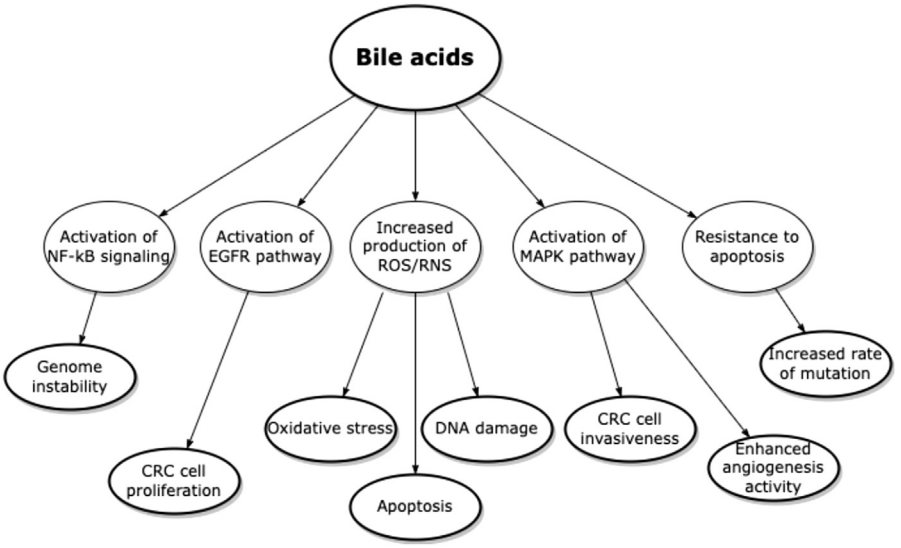

Fig. 1. Effects of bile acids (BAs) associated with colorectal carcinogenesis and development.

to high levels of BAs appears to select cells that are resistant to BA-induced apoptosis. Reduced apoptotic capability may lead to an increased rate of mutation and, thus, predispose to tumor development [102,109]. The multiple mechanisms through which BAs promote colorectal carcinogenesis and development are illustrated in Figure 1.

The influence of BAs on CRC risk is intimately linked with the gut microbiota since the latter allows the conversion of primary BAs to secondary BAs, known for their tumor-promoting properties. On the other hand, excess BAs induce these changes in the microbiota, favoring the enrichment of 7α-dehydroxylating bacteria [104].

Short-chain fatty acids

Short-chain fatty acids (SCFAs) derive from microbial fermentation of dietary fiber. These molecules provide energy sources for the intestinal epithelium and are involved in the regulation of gut physiology and immune homeostasis [71,74]. In particular, butyrate is known for its protective and beneficial effects, playing a major role in maintaining the health and integrity of the colonic mucosa [73,76]. Numerous studies have reported significantly reduced levels of SCFAs (acetate, propionate, and butyrate) following bariatric surgery [59,110–112], while butyrate concentrations have been demonstrated to be lower in the presence of a more alkaline pH in vitro [71]. Therefore, the observation of lower SCFA levels after bariatric surgery is consistent with decreased acid production in these patients [69]. Furthermore, the abundance of butyrate-producing bacteria *F. prausnitzii* and *Roseburia* spp. has been shown to decrease following bariatric procedures, profoundly affecting butyrate levels [58,59,62,66].

Dolara et al. demonstrated that higher concentrations of SCFAs are significantly associated with lower rates of colonic mucosal proliferation, highlighting their protective role against CRC [113]. This role was further confirmed by the finding of reduced concentrations of SCFAs in fecal water extracts from patients with CRC, compared with healthy controls [114]. Furthermore, there is increasing evidence for the anticarcinogenic properties and anti-inflammatory effects of butyrate on the colonic mucosa. Segain et al. showed that butyrate decreases TNF production and pro-inflammatory cytokine mRNA expression by inhibiting NF-kB activation, resulting in reduced inflammatory responses [115]. In addition, SCFAs upregulate the function of colonic regulatory T cells, which play a role in intestinal homeostasis and gut inflammation [116]. Notably, treatment of colonocytes with butyrate and antioxidants appears to reduce the genotoxicity and DNA damage induced by BAs [117].

The anticarcinogenic role of butyrate results from its ability to induce apoptosis and growth inhibition in CRC cells [118–120]. Induction of apoptosis by butyrate in CRC cell lines seems to occur through upregulation of the proapoptotic protein Bak and reduction of the levels of antiapoptotic Bcl-xL [118]. In addition, according to a study by Hague et al., apoptosis may result from the inhibition of histone deacetylase (HDAC) and subsequent changes in chromatin structure, leading to altered gene expression [119]. Inhibition of HDAC by butyrate was also observed by Donohoe et al., albeit in this case related to the inhibition of CRC cell proliferation. Interestingly, this SCFA exerted opposing effects on the colonic mucosa, stimulating the proliferation of normal colonocytes and inhibiting the growth of cancerous colonocytes [121]. This differential impact was suggested to be related to the Warburg effect, whereby cancer cells preferentially metabolize glucose anaerobically [122]. Thus, while normal colorectal cells use butyrate as an energy source for proliferation, cancerous cells instead rely

on glucose as their primary energy source, leading to the accumulation of butyrate. At high concentrations, unmetabolized butyrate enters cell nuclei and functions as an HDAC inhibitor, leading to the altered expression of genes relating to cellular proliferation, differentiation, and apoptosis [121]. In addition, Bordonaro et al. showed that butyrate downregulates the Wnt signaling pathway, commonly activated in CRC, unveiling another mechanism underlying the beneficial effects of this molecule [123].

Collectively, the evidence suggests that butyrate exerts protective, anticarcinogenic effects via multiple mechanisms (Fig. 2). Thus, the decreased levels of SCFAs reported following bariatric surgery [59,110–112] may contribute to an increased risk of CRC.

Strengths and limitations

The conflicting results produced by several cohort studies call into question the association between CRC risk and bariatric surgery. This review aimed to clarify the current understanding of the topic by summarizing the available data and proposing potential mechanisms.

However, this study presents some limitations, such as the lack of evidence regarding CRC risk following restrictive procedures. Indeed, most of the data included in the review focus on the impact of RYGB, while only a few studies have examined the effects of other bariatric procedures. Thus, no conclusions on the potential correlation between restrictive bariatric surgery and increased risk of CRC can be drawn.

Another limitation is the inclusion of studies conducted using murine models; their findings, although interesting and relevant to the topic, need to be validated by human studies.

Conclusions and future perspectives

Cohort studies have reported contradictory findings regarding the impact of bariatric surgery on CRC risk. However, analysis of CRC biomarkers in the rectal mucosa revealed hyperproliferation and inflammation following RYGB. Multiple mechanisms related to malabsorption and post-RYGB anatomical modifications could predispose to an increased risk of CRC. In particular, alterations in the gut microbiota may play a key role in CRC initiation and development. Significantly, similarities in the gut microbiota of post-RYGB and cancer patients have been described. Other mechanisms potentially contributing to CRC carcinogenesis include exposure of the colorectal mucosa to increased concentrations of BAs and reduced levels of SCFAs, both reported following RYGB. In conclusion, evidence from cohort and mechanistic studies suggests a potential association between RYGB and increased risk of CRC.

Future research is required to establish whether bariatric surgery induces a procedure-dependent increase in CRC risk. The necessity for further research is highlighted by the limited data currently available regarding the effects of other types of bariatric surgery on CRC. Furthermore, as LSG is currently the most commonly performed bariatric procedure [11], large cohort studies to evaluate the potential association of this technique with the long-term risk of CRC are essential. Long-term analysis of CRC biomarkers following LSG in larger cohorts of patients should also be carried out to determine the impact of this procedure on the colorectal mucosa. In addition, OAGB, the third most common bariatric procedure, is increasing in popularity worldwide, highlighting the need to investigate its effects [11].

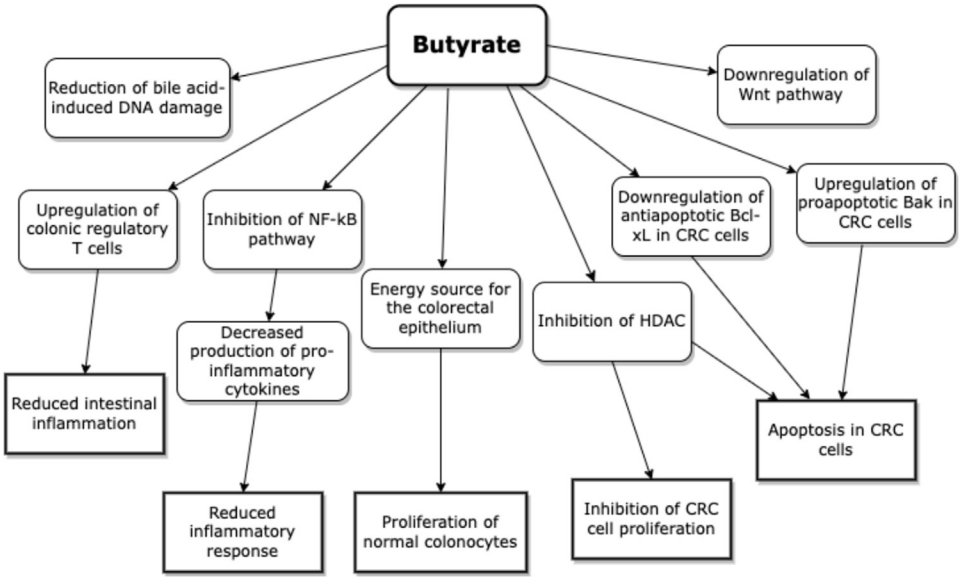

Fig. 2. Protective and beneficial effects of butyrate against colorectal cancer.

Alteration of microbial profiles in the gut has so far mainly been analyzed in the context of RYGB. However, the gut microbiota should also be characterized after other commonly performed bariatric procedures, given its potential role in colorectal carcinogenesis. Comparative analysis of microbial alterations in postbariatric and CRC patients could represent an important step toward determining the mechanisms involved in the association between bariatric surgery and CRC.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

References

[1] Finucane MM, Stevens GA, Cowan MJ, et al. Global burden of metabolic risk factors of chronic diseases collaborating group (body mass index). National, regional, and global trends in body-mass index since 1980: systematic analysis of health examination surveys and epidemiological studies with 960 country-years and 9·1 million participants. Lancet 2011;377(9765):557–67.

[2] GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 Years. N Engl J Med 2017; 377(1):13–27.

[3] Finkelstein EA, Khavjou OA, Thompson H, et al. Obesity and severe obesity forecasts through 2030. Am J Prev Med 2012;42(6):563–70.

[4] Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013;309(1):71–82.

[5] Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 2009;9:88.

[6] Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: from pathophysiology to therapeutics. Metabolism 2019;92:82–97.

[7] Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371(9612):569–78.

[8] Di Lorenzo N, Antoniou SA, Batterham RL, et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. Surg Endosc 2020;34(6):2332–58.

[9] Fried M, Yumuk V, Oppert JM, et al. International Federation for surgery of obesity and metabolic Disorders-European Chapter (IFSO-EC); European Association for the Study of Obesity (EASO); European Association for the Study of Obesity Obesity Management Task Force (EASO OMTF). Interdisciplinary European guidelines on metabolic and bariatric surgery. Obes Surg 2014;24(1):42–55.

[10] Buchwald H, Williams SE. Bariatric surgery worldwide 2003. Obes Surg 2004;14(9):1157–64.

[11] Angrisani L, Santonicola A, Iovino P, Ramos A, Shikora S, Kow L. Bariatric surgery survey 2018: similarities and disparities among the 5 IFSO chapters. Obes Surg 2021;31(5):1937–48.

[12] Sheng B, Truong K, Spitler H, Zhang L, Tong X, Chen L. The long-term effects of bariatric surgery on type 2 diabetes remission, microvascular and macrovascular complications, and mortality: a systematic review and meta-analysis. Obes Surg 2017;27(10):2724–32.

[13] Buchwald H, Avidor Y, Braunwald E, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004;292(14):1724–37.

[14] Gloy VL, Briel M, Bhatt DL, et al. Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials. BMJ 2013;347:f5934.

[15] 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):248–256.e5.

[16] Sutanto A, Wungu CDK, Susilo H, Sutanto H. Reduction of major adverse cardiovascular events (MACE) after bariatric surgery in patients with obesity and cardiovascular diseases: a systematic review and meta-analysis. Nutrients 2021;13(10):3568.

[17] Castagneto-Gissey L, Casella-Mariolo J, Casella G, Mingrone G. Obesity surgery and cancer: what are the Unanswered questions? Front Endocrinol (Lausanne) 2020;11:213.

[18] Ashrafian H, Ahmed K, Rowland SP, et al. Metabolic surgery and cancer: protective effects of bariatric procedures. Cancer 2011; 117(9):1788–99.

[19] Schauer DP, Feigelson HS, Koebnick C, et al. Bariatric surgery and the risk of cancer in a large multisite cohort. Ann Surg 2019;269(1):95–101.

[20] Tao W, Santoni G, von Euler-Chelpin M, et al. Cancer risk after bariatric surgery in a cohort study from the five Nordic countries. Obes Surg 2020;30(10):3761–7.

[21] Wiggins T, Antonowicz SS, Markar SR. Cancer risk following bariatric surgery-systematic review and meta-analysis of national population-based cohort studies. Obes Surg 2019;29(3):1031–9.

[22] Afshar S, Kelly SB, Seymour K, Lara J, Woodcock S, Mathers JC. The effects of bariatric surgery on colorectal cancer risk: systematic review and meta-analysis. Obes Surg 2014;24(10):1793–9.

[23] Ciccioriccio MC, Iossa A, Boru CE, et al. CRIC-ABS 2020 GROUP. Colorectal cancer after bariatric surgery (Cric-Abs 2020): Sicob (Italian society of obesity surgery) endorsed national survey. Int J Obes (Lond) 2021;45(12):2527–31.

[24] Mackenzie H, Markar SR, Askari A, et al. Obesity surgery and risk of cancer. Br J Surg 2018;105(12):1650–7.

[25] Derogar M, Hull MA, Kant P, Östlund M, Lu Y, Lagergren J. Increased risk of colorectal cancer after obesity surgery. Ann Surg 2013;258(6):983–8.

[26] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3): 209–49.

[27] Mármol I, Sánchez-de-Diego C, Pradilla Dieste A, Cerrada E, Rodriguez Yoldi MJ. Colorectal carcinoma: a general overview and future perspectives in colorectal cancer. Int J Mol Sci 2017;18(1):197.

[28] Dai Z, Xu YC, Niu L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. World J Gastroenterol 2007;13(31):4199–206.

[29] Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of colorectal cancer. Int J Cancer 2018;142(9):1748–58.

[30] McNabb S, Harrison TA, Albanes D, et al. Meta-analysis of 16 studies of the association of alcohol with colorectal cancer. Int J Cancer 2020;146(3):861–73.

[31] Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer 2009;124(10):2406–15.

[32] Wolfe BM, Kvach E, Eckel RH. Treatment of obesity: weight loss and bariatric surgery. Circ Res 2016;118(11):1844–55.

[33] Phillips BT, Shikora SA. The history of metabolic and bariatric surgery: development of standards for patient safety and efficacy. Metabolism 2018;79:97–107.

[34] Aarts EO, Mahawar K. From the knife to the endoscope-a history of bariatric surgery. Curr Obes Rep 2020;9(3):348–63.

[35] Welbourn R, Hollyman M, Kinsman R, et al. Bariatric surgery worldwide: baseline demographic description and one-year outcomes from the fourth IFSO global registry report 2018. Obes Surg 2019;29(3):782–95.

[36] Pucci A, Batterham RL. Mechanisms underlying the weight loss effects of RYGB and SG: similar, yet different. J Endocrinol Invest 2019;42(2):117–28.
[37] Wiggins T, Majid MS, Agrawal S. From the knife to the endoscope-a history of bariatric surgery. Curr Obes Rep 2020;9(3):315–25.
[38] Robert M, Espalieu P, Pelascini E, et al. Efficacy and safety of one anastomosis gastric bypass versus Roux-en-Y gastric bypass for obesity (YOMEGA): a multicentre, randomised, open-label, non-inferiority trial. Lancet 2019;393(10178):1299–309.
[39] Ostlund MP, Lu Y, Lagergren J. Risk of obesity-related cancer after obesity surgery in a population-based cohort study. Ann Surg 2010;252(6):972–6.
[40] Tao W, Artama M, von Euler-Chelpin M, et al. Colon and rectal cancer risk after bariatric surgery in a multicountry Nordic cohort study. Int J Cancer 2020;147(3):728–35.
[41] Hussan H, Drosdak A, Le Roux M, et al. The long-term impact of roux-en-Y gastric bypass on colorectal polyp formation and relation to weight loss outcomes. Obes Surg 2020;30(2):407–15.
[42] Tao W, Konings P, Hull MA, Adami HO, Mattsson F, Lagergren J. Colorectal cancer prognosis following obesity surgery in a population-based cohort study. Obes Surg 2017;27(5):1233–9.
[43] Aravani A, Downing A, Thomas JD, Lagergren J, Morris EJA, Hull MA. Obesity surgery and risk of colorectal and other obesity-related cancers: an english population-based cohort study. Cancer Epidemiol 2018;53:99–104.
[44] Lipkin M. Biomarkers of increased susceptibility to gastrointestinal cancer: new application to studies of cancer prevention in human subjects. Cancer Res 1988;48(2):235–45.
[45] Wong WM, Mandir N, Goodlad RA, et al. Histogenesis of human colorectal adenomas and hyperplastic polyps: the role of cell proliferation and crypt fission. Gut 2002;50(2):212–7.
[46] Sainsbury A, Goodlad RA, Perry SL, Pollard SG, Robins GG, Hull MA. 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.
[47] Gordon-Weeks AN, Lim SY, Yuzhalin AE, Jones K, Muschel R. Macrophage migration inhibitory factor: a key cytokine and therapeutic target in colon cancer. Cytokine Growth Factor Rev 2015;26(4):451–61.
[48] De Simone V, Franzè E, Ronchetti G, et al. Th17-type cytokines, IL-6 and TNF-α synergistically activate STAT3 and NF-kB to promote colorectal cancer cell growth. Oncogene 2015;34(27):3493–503.
[49] Negi RR, Rana SV, Gupta V, et al. Over-expression of cyclooxygenase-2 in colorectal cancer patients. Asian Pac J Cancer Prev 2019;20(6):1675–81.
[50] Liu Y, Sun H, Hu M, et al. The role of cyclooxygenase-2 in colorectal carcinogenesis. Clin Colorectal Cancer 2017;16(3):165–72.
[51] Kant P, Sainsbury A, Reed KR, et al. Rectal epithelial cell mitosis and expression of macrophage migration inhibitory factor are increased 3 years after Roux-en-Y gastric bypass (RYGB) for morbid obesity: implications for long-term neoplastic risk following RYGB. Gut 2011;60(7):893–901.
[52] Afshar S, Malcomson F, Kelly SB, Seymour K, Woodcock S, Mathers JC. Biomarkers of colorectal cancer risk decrease 6 months after roux-en-Y gastric bypass surgery. Obes Surg 2018;28(4):945–54.
[53] Appleton GV, Wheeler EE, Al-Mufti R, Challacombe DN, Williamson RC. Rectal hyperplasia after jejunoileal bypass for morbid obesity. Gut 1988;29(11):1544–8.
[54] Kant P, Perry SL, Dexter SP, Race AD, Loadman PM, Hull MA. Mucosal biomarkers of colorectal cancer risk do not increase at 6 months following sleeve gastrectomy, unlike gastric bypass. Obesity (Silver Spring) 2014;22(1):202–10.
[55] Aron-Wisnewsky J, Doré J, Clement K. The importance of the gut microbiota after bariatric surgery. Nat Rev Gastroenterol Hepatol 2012;9(10):590–8.
[56] Anhê FF, Varin TV, Schertzer JD, Marette A. The gut microbiota as a mediator of metabolic benefits after bariatric surgery. Can J Diabetes 2017;41(4):439–47.
[57] Ulker İ, Yildiran H. The effects of bariatric surgery on gut microbiota in patients with obesity: a review of the literature. Biosci Microbiota Food Health 2019;38(1):3–9.
[58] Palleja A, Kashani A, Allin KH, et al. Roux-en-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. Genome Med 2016;8(1):67.
[59] Tremaroli V, Karlsson F, Werling M, et al. Roux-en-Y gastric bypass and vertical banded gastroplasty induce long-term changes on the human gut microbiome contributing to fat mass regulation. Cell Metab 2015;22(2):228–38.
[60] Furet JP, Kong LC, Tap J, et al. Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. Diabetes 2010;59(12):3049–57.
[61] Zhang H, DiBaise JK, Zuccolo A, et al. Human gut microbiota in obesity and after gastric bypass. Proc Natl Acad Sci U S A 2009;106(7):2365–70.
[62] Graessler J, Qin Y, Zhong H, et al. Metagenomic sequencing of the human gut microbiome before and after bariatric surgery in obese patients with type 2 diabetes: correlation with inflammatory and metabolic parameters. Pharmacogenomics J 2013;13(6):514–22.
[63] Kong LC, Tap J, Aron-Wisnewsky J, et al. Gut microbiota after gastric bypass in human obesity: increased richness and associations of bacterial genera with adipose tissue genes. Am J Clin Nutr 2013;98(1):16–24.
[64] Damms-Machado A, Mitra S, Schollenberger AE, et al. Effects of surgical and dietary weight loss therapy for obesity on gut microbiota composition and nutrient absorption. Biomed Res Int 2015;2015:806248.
[65] Tabasi M, Eybpoosh S, Siadat SD, Elyasinia F, Soroush A, Bouzari S. Modulation of the gut microbiota and serum biomarkers after laparoscopic sleeve gastrectomy: a 1-Year follow-up study. Obes Surg 2021;31(5):1949–56.
[66] Farin W, Oñate FP, Plassais J, et al. Impact of laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy on gut microbiota: a metagenomic comparative analysis. Surg Obes Relat Dis 2020;16(7):852–62.
[67] Shao Y, Ding R, Xu B, et al. Alterations of gut microbiota after roux-en-Y gastric bypass and sleeve gastrectomy in Sprague-Dawley rats. Obes Surg 2017;27(2):295–302.
[68] Ciobârcă D, Cătoi AF, Copăescu C, Miere D, Crişan G. Bariatric surgery in obesity: effects on gut microbiota and micronutrient status. Nutrients 2020;12(1):235.
[69] Smith CD, Herkes SB, Behrns KE, Fairbanks VF, Kelly KA, Sarr MG. Gastric acid secretion and vitamin B12 absorption after vertical Roux-en-Y gastric bypass for morbid obesity. Ann Surg 1993;218(1):91–6.
[70] Steenackers N, Vanuytsel T, Augustijns P, et al. Adaptations in gastrointestinal physiology after sleeve gastrectomy and Roux-en-Y gastric bypass. Lancet Gastroenterol Hepatol 2021;6(3):225–37.
[71] Walker AW, Duncan SH, McWilliam Leitch EC, Child MW, Flint HJ. pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. Appl Environ Microbiol 2005;71(7):3692–700.
[72] Pryde SE, Duncan SH, Hold GL, Stewart CS, Flint HJ. The microbiology of butyrate formation in the human colon. FEMS Microbiol Lett 2002;217(2):133–9.
[73] Miquel S, Martín R, Rossi O, et al. Faecalibacterium prausnitzii and human intestinal health. Curr Opin Microbiol 2013;16(3):255–61.
[74] Tamanai-Shacoori Z, Smida I, Bousarghin L, et al. Roseburia spp.: a marker of health? Future Microbiol 2017;12:157–70.
[75] Li JV, Ashrafian H, Bueter M, et al. Metabolic surgery profoundly influences gut microbial-host metabolic cross-talk. Gut 2011;60(9):1214–23.

[76] Li JV, Reshat R, Wu Q, et al. Experimental bariatric surgery in rats generates a cytotoxic chemical environment in the gut contents. Front Microbiol 2011;2:183.

[77] Weiss TS, Bernhardt G, Buschauer A, et al. Polyamine levels of human colorectal adenocarcinomas are correlated with tumor stage and grade. Int J Colorectal Dis 2002;17(6):381–7.

[78] Novita Sari I, Setiawan T, Seock Kim K, Toni Wijaya Y, Won Cho K, Young Kwon H. Metabolism and function of polyamines in cancer progression. Cancer Lett 2021;519:91–104.

[79] Farriol M, Segovia-Silvestre T, Castellanos JM, Venereo Y, Orta X. Role of putrescine in cell proliferation in a colon carcinoma cell line. Nutrition 2001;17(11-12):934–8.

[80] Grosheva I, Zheng D, Levy M, et al. High-throughput Screen identifies host and microbiota Regulators of intestinal barrier function. Gastroenterology 2020;159(5):1807–23.

[81] Sobhani I, Tap J, Roudot-Thoraval F, et al. Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One 2011;6(1):e16393.

[82] Wu N, Yang X, Zhang R, et al. Dysbiosis signature of fecal microbiota in colorectal cancer patients. Microb Ecol 2013;66(2):462–70.

[83] Wang T, Cai G, Qiu Y, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. ISME J 2012;6(2):320–9.

[84] Ma Y, Zhang Y, Xiang J, et al. Metagenome analysis of intestinal bacteria in healthy people, patients with inflammatory bowel disease and colorectal cancer. Front Cell Infect Microbiol 2021;11:599734.

[85] Kostic AD, Gevers D, Pedamallu CS, et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 2012;22(2):292–8.

[86] He T, Cheng X, Xing C. The gut microbial diversity of colon cancer patients and the clinical significance. Bioengineered 2021; 12(1):7046–60.

[87] Zhu Q, Jin Z, Wu W, et al. Analysis of the intestinal lumen microbiota in an animal model of colorectal cancer. PLoS One 2014;9(6):e90849.

[88] Zackular JP, Baxter NT, Iverson KD, et al. The gut microbiome modulates colon tumorigenesis. mBio 2013;4(6):e00692-13.

[89] Saus E, Iraola-Guzmán S, Willis JR, Brunet-Vega A, Gabaldón T. Microbiome and colorectal cancer: roles in carcinogenesis and clinical potential. Mol Aspects Med 2019;69:93–106.

[90] Kohoutova D, Smajs D, Moravkova P, et al. Escherichia coli strains of phylogenetic group B2 and D and bacteriocin production are associated with advanced colorectal neoplasia. BMC Infect Dis 2014;14:733.

[91] Bonnet M, Buc E, Sauvanet P, et al. Colonization of the human gut by E. coli and colorectal cancer risk. Clin Cancer Res 2014;20(4):859–67.

[92] Kostic AD, Chun E, Robertson L, et al. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host Microbe 2013;14(2):207–15.

[93] Ito M, Kanno S, Nosho K, et al. Association of Fusobacterium nucleatum with clinical and molecular features in colorectal serrated pathway. Int J Cancer 2015;137(6):1258–68.

[94] Flanagan L, Schmid J, Ebert M, et al. Fusobacterium nucleatum associates with stages of colorectal neoplasia development, colorectal cancer and disease outcome. Eur J Clin Microbiol Infect Dis 2014;33(8):1381–90.

[95] Ajouz H, Mukherji D, Shamseddine A. Secondary bile acids: an underrecognized cause of colon cancer. World J Surg Oncol 2014;12:164.

[96] Patti ME, Houten SM, Bianco AC, et al. Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism. Obesity (Silver Spring) 2009;17(9):1671–7.

[97] Cole AJ, Teigen LM, Jahansouz C, Earthman CP, Sibley SD. The influence of bariatric surgery on serum bile acids in humans and potential metabolic and hormonal implications: a systematic review. Curr Obes Rep 2015;4(4):441–50.

[98] Nakatani H, Kasama K, Oshiro T, Watanabe M, Hirose H, Itoh H. Serum bile acid along with plasma incretins and serum high-molecular weight adiponectin levels are increased after bariatric surgery. Metabolism 2009;58(10):1400–7.

[99] Ochsenkühn T, Bayerdörffer E, Meining A, et al. Colonic mucosal proliferation is related to serum deoxycholic acid levels. Cancer 1999;85(8):1664–9.

[100] Steinbach G, Lupton J, Reddy BS, Kral JG, Holt PR. Effect of calcium supplementation on rectal epithelial hyperproliferation in intestinal bypass subjects. Gastroenterology 1994;106(5):1162–7.

[101] Bristol JB, Wells M, Williamson RC. Adaptation to jejunoileal bypass promotes experimental colorectal carcinogenesis. Br J Surg 1984;71(2):123–6.

[102] Bernstein H, Bernstein C, Payne CM, Dvorak K. Bile acids as endogenous etiologic agents in gastrointestinal cancer. World J Gastroenterol 2009;15(27):3329–40.

[103] Jia W, Xie G, Jia W. Bile acid-microbiota crosstalk in gastrointestinal inflammation and carcinogenesis. Nat Rev Gastroenterol Hepatol 2018;15(2):111–28.

[104] Ocvirk S, O'Keefe SJ. Influence of bile acids on colorectal cancer risk: potential mechanisms mediated by diet - gut microbiota interactions. Curr Nutr Rep 2017;6(4):315–22.

[105] Shao T, Yang YX. Cholecystectomy and the risk of colorectal cancer. Am J Gastroenterol 2005;100(8):1813–20.

[106] Lagergren J, Ye W, Ekbom A. Intestinal cancer after cholecystectomy: is bile involved in carcinogenesis? Gastroenterology 2001;121(3):542–7.

[107] Kim SB, Kim KO, Kim TN. Prevalence and risk factors of gastric and colorectal cancer after cholecystectomy. J Korean Med Sci 2020; 35(42):e354.

[108] Nguyen TT, Ung TT, Kim NH, Jung YD. Role of bile acids in colon carcinogenesis. World J Clin Cases 2018;6(13):577–88.

[109] Bernstein H, Bernstein C, Payne CM, Dvorakova K, Garewal H. Bile acids as carcinogens in human gastrointestinal cancers. Mutat Res 2005;589(1):47–65.

[110] Farup PG, Valeur J. Changes in faecal short-chain fatty acids after weight-loss interventions in subjects with morbid obesity. Nutrients 2020;12(3):802.

[111] Juárez-Fernández M, Román-Sagüillo S, Porras D, et al. Long-term effects of bariatric surgery on gut microbiota composition and faecal metabolome related to obesity remission. Nutrients 2021;13(8):2519.

[112] Yu D, Shu XO, Howard EF, Long J, English WJ, Flynn CR. Fecal metagenomics and metabolomics reveal gut microbial changes after bariatric surgery. Surg Obes Relat Dis 2020;16(11):1772–82.

[113] Dolara P, Caderni G, Salvadori M, et al. Fecal levels of short-chain fatty acids and bile acids as determinants of colonic mucosal cell proliferation in humans. Nutr Cancer 2002;42(2):186–90.

[114] Monleón D, Morales JM, Barrasa A, López JA, Vázquez C, Celda B. Metabolite profiling of fecal water extracts from human colorectal cancer. NMR Biomed 2009;22(3):342–8.

[115] Segain JP, Raingeard de la Blétière D, Bourreille A, et al. Butyrate inhibits inflammatory responses through NFkappaB inhibition: implications for Crohn's disease. Gut 2000;47(3):397–403.

[116] Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic treg cell homeostasis. Science 2013;341(6145):569–73.

[117] Rosignoli P, Fabiani R, De Bartolomeo A, Fuccelli R, Pelli MA, Morozzi G. Genotoxic effect of bile acids on human normal and tumour colon cells and protection by dietary antioxidants and butyrate. Eur J Nutr 2008;47(6):301–9.

[118] Ruemmele FM, Schwartz S, Seidman EG, Dionne S, Levy E, Lentze MJ. Butyrate induced Caco-2 cell apoptosis is mediated via the mitochondrial pathway. Gut 2003;52(1):94–100.

[119] Hague A, Elder DJ, Hicks DJ, Paraskeva C. Apoptosis in colorectal tumour cells: induction by the short chain fatty acids butyrate, propionate and acetate and by the bile salt deoxycholate. Int J Cancer 1995;60(3):400–6.

[120] Hague A, Manning AM, Hanlon KA, Huschtscha LI, Hart D, Paraskeva C. Sodium butyrate induces apoptosis in human colonic tumour cell lines in a p53-independent pathway: implications for the possible role of dietary fibre in the prevention of large-bowel cancer. Int J Cancer 1993;55(3):498–505.

[121] Donohoe DR, Collins LB, Wali A, Bigler R, Sun W, Bultman SJ. The warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. Mol Cell 2012; 48(4):612–26.

[122] Liberti MV, Locasale JW. The Warburg effect: how Does it Benefit cancer cells? Trends Biochem Sci 2016;41(3):211–8.

[123] Bordonaro M, Lazarova DL, Sartorelli AC. Butyrate and Wnt signaling: a possible solution to the puzzle of dietary fiber and colon cancer risk? Cell Cycle 2008;7(9):1178–83.