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Review article: obesity and colorectal cancer

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Summary

Background: Obesity is a growing global public health problem. More than half the European and North American population is overweight or obese. Colon and rectum cancers are still the second leading cause of cancer death worldwide, and epidemiological data support an association between obesity and colorectal cancers (CRCs).

Aim: To review the literature on CRC epidemiology in obese subjects, assessing the effects of obesity, including childhood or maternal obesity, on CRC, diagnosis, management, and prognosis, and discussing targeted prophylactic measures.

Method: We searched PubMed for obesity/overweight/metabolic syndrome and CRC. Other key words included 'staging', 'screening', 'treatment', 'weight loss', 'bariatric surgery' and 'chemotherapy'.

Results: In Europe, about 11% of CRCs are attributed to overweight and obesity. Epidemiological data suggest that obesity is associated with a 30%–70% increased risk of colon cancer in men, the association being less consistent in women. Visceral fat or abdominal obesity seems to be of greater concern than subcutaneous fat obesity, and any 1 kg/m^2 increase in body mass index confers more risk (hazard ratio 1.03). Obesity might increase the likelihood of recurrence or mortality of the primary cancer and may affect initial management, including accurate staging. The risk maybe confounded by different factors, including lower adherence to organised CRC screening programmes. It is unclear whether bariatric surgery helps reduce rectal cancer risk.

Conclusions: Despite a growing body of evidence linking obesity to CRC, many questions remain unanswered, including whether we should screen patients with obesity earlier or propose prophylactic bariatric surgery for certain patients with obesity.

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1 | INTRODUCTION

The World Health Organization (WHO) defines being overweight and obese as abnormal or excessive fat accumulation in adipose tissue that may impair a person's health (http://www.who.int/mediacentre/factsheets/fs311/en/). Persons who are overweight have a body mass index (BMI, weight/[height in m]^2) greater than or equal to 25 (BMI ≥25 kg/m^2), and persons with obesity have a BMI greater than or equal to 30 (BMI ≥30 kg/m^2).

Worldwide, obesity prevalence quadrupled for men and doubled for women between 1975 and 2016.[1] Between 1975 and 2016, the absolute number of obese adults increased almost sevenfold, 100–671 million.[1] In the United States, overall age-adjusted prevalence of obesity in 2014 was 37.7% (35.0% in men; 40.4% in women), trending towards a linear increase in women, but not in men over the previous decade.[2] Obesity prevalence varies widely by region, occupation and socio-economic level. Obesity is three times as common in the United States (37.7%) as it is in Europe (12.8%).[3] Recent data from China showed that from 1991 to 2015, prevalence of overweight increased from 4.6% to 21.1%, and obesity prevalence increased from 1.4% to 10.1%. Severe obesity increased from 0.2% to 4.0% (a relative increase of 1900.0%), as did overweight (relative increase of 358.7%) and obesity (relative increase of 621.4%).[4] In US children and adolescents, obesity prevalence is 17.0% and has mainly stabilised since 2005,[5] but epidemiological studies show an increase in other countries.[6]

Although BMI correlates strongly with absolute adiposity, there is a distinction between accumulation of two types of fat (subcutaneous and visceral) that play different roles in metabolic syndrome and colorectal cancer (CRC).[7]

Not all people with obesity are unhealthy,[8] and only about two-thirds of patients with metabolic syndrome are obese.[9,10] Recommendations to measure waist circumference and waist-to-height or waist-to-hip ratios instead of BMI acknowledge that abdominal obesity plays a central role in metabolic syndrome, and that BMI might overestimate obesity.[7] But no solid epidemiological or metabolic data support recommendations for specific waist circumference cut-offs to define abdominal obesity,[11,12] and the relationship between visceral fat and metabolic syndrome varies across ethnic groups.[13]

CRC, the third most incident cancer worldwide, makes up 10.0% of total cases and is the second most common cause of cancer-related death (9.4% of all cancer deaths).[14] In the United States, cumulative lifetime risk of developing a CRC is 5% in the general population.[15] Obesity has been associated with 13 cancers, including CRC and liver cancer,[16] with three cancers sites (endometrium, post-menopausal breast cancer and CRC) accounting for two-thirds of cancers attributable to excess BMI attributable cancers.[17] About 3.6% of cancers (481,000 new cases a year) are attributable to excess BMI, his association being higher in countries with very high and high human development index (5.3% and 4.8%, respectively) than in low human development index countries (1.6%).[17] Relative risk of colon cancer attributable to obesity is 1.24 for men overall, ranging between 1.04 and 1.13 across countries.[18] Of the 1,347,000 new CRC cases diagnosed worldwide in 2012, in men 42,300/736,000 (5,8%) and in women 42,300/60,700 (7.0%) were attributable to high BMI.[19] Similar estimates were reported for 384,402 incident cancers in France in 2015; of these 3380/43,000 incident CRC were attributed to obesity.[20]

In this article, we analyse epidemiological data on CRC in obese subjects, discuss the effects of obesity on CRC management and prognosis and consider measures designed to reduce CRC risk in this population.

2 | METHODS

2.1 | Search strategy

We performed our review by searching EMBASE, MEDLINE, ISI Web of Knowledge and PubMed. We employed a sensitive search strategy to identify reports by combining controlled vocabulary and free text terms related to (1) colon cancer or CRC (neoplasia, carcinoma, tumour, metastasis, malignancy) and (2) obesity and overweight. We conducted recursive searches and used the "similar articles" function to identify and cross-reference articles. We also hand searched for articles in the references of articles we identified. We performed a review of the literature including adult human studies in French or English, published between June 2012 and January 2022. In this review we have chosen not to detail the pathophysiological mechanisms involved in the increased risk of CRC in obese patients. However, Figure 1, adapted from a previous publication,[21] summarises the main mechanisms involved in altering the risk of CRC in obese people and more pathophysiological insight can be found in other publications on this topic.[21–24]

2.2 | Inclusion criteria

We identified meta-analyses, other systematic reviews, case–control, cohort and observational studies that assessed colon, rectal or CRC prevalence in obese persons and compared them to prevalence in non-obese subjects. We adopted the WHO BMI definition of obesity ≥30 kg/m^2 and also included studies in which BMI was defined as ≥25 kg/m^2 for Asian populations.[25]

3 | OBESITY AND COLORECTAL CANCER

3.1 | Epidemiological data that support a relationship between obesity and colorectal cancer

3.1.1 | Obesity is associated with increased incidence of colorectal cancer

Many studies and meta-analyses support an increased incidence of CRC in patients with obesity. Parameters to define obesity vary,

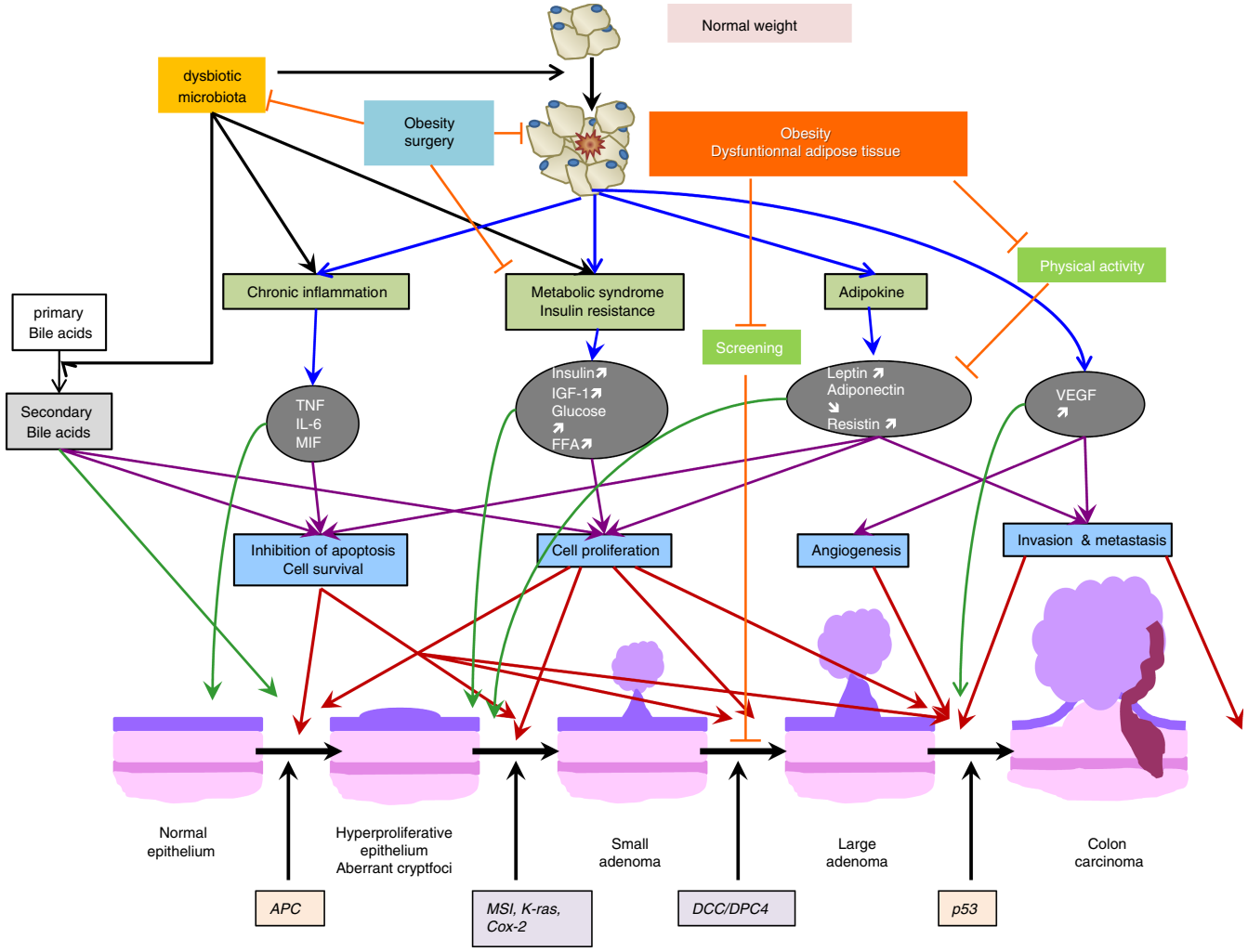

FIGURE 1 Summary of potential factors that are believed to relate obesity and colorectal cancer. Blue arrows indicate the metabolic consequences of obesity. Black arrows are for some of the suspected consequences of dysbiotic microbiota. Purple arrows are for the cellular events induced by obesity-related metabolic changes. Red arrows locate these cellular events in the carcinogenic process. Green arrows suggest the stage of the normal epithelium-to-carcinoma sequence where the different biological factors might start to act. And finally, orange lines are for suggested inhibitory effect which may be beneficial, as for positive effects of bariatric surgery, or detrimental for some confounding factors such as reduced adherence to screening or physical activity. Apc, adenomatous polyposis coli; Cox-2, cyclooxygenase-2; DCC, deleted in colorectal carcinoma; DPC4, deleted in pancreatic carcinoma; FFAs, free fatty acids; IGF-1, insulin-like growth factor-1; IL-6, interleukin; KRA, Kirsten rat sarcoma; MIF, macrophage migration inhibitory factor; MSI, microsatellite instability; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

but a recent study found waist circumference a better predictor of advanced colorectal neoplasia than BMI because it more accurately reflected visceral obesity, which is the most pro-carcinogenic.[26]

Kyrgiou et al.[27] conducted an umbrella meta-analysis to summarise evidence of links between obesity and 36 cancers. The link between CRC and obesity was graded "strong" (among several statistic criteria, the association of: p-value in random effects meta-analysis $<10^{-6}$, more than 1000 included in the meta-analysis, I^2 heterogeneity <50%, 95% CI excluding the null value) in 12 meta-analyses that considered BMI, colon and rectal cancer, in men. The link was "highly suggestive" (*p*-value in random effects meta-analysis $<10^{-6}$, more than 1000 included in the meta-analysis, the largest study in the meta-analysis nominally significant) in 17 other meta-analyses that considered BMI and waist circumference for colon cancer in men and women, and "suggestive" (*p*-value in random effects meta-analysis $<10^{-3}$, more than 1000 included in the meta-analysis) in 23 others that considered BMI for colon cancer in women, weight gain in CRC, waist circumference and waist-to-hip ratio in colon cancer.[27] Another recent meta-analysis of 47 prospective studies summarising the dose–response association between excess body weight measured with several parameters (RR 1.02, 1.01–1.02, per 5 kg increase in weight, RR 1.06, 1.04–1.07 per 5 kg/m^2 increase in BMI, RR 1.02, 1.02–1.03 per 10 cm increase in waist circumference, RR 1.03, 1.01–1.05 per 0.1 unit increase in waist-to-hip ratio) showed a significant increased CRC risk.[28] A working group of the International Agency for Research on Cancer reviewed more than 1000 epidemiological studies and reported CRC risk increased by 1.2–1.5 among patients with BMI

over 25 kg/m^2, and by 1.5–1.8 in people with BMI ≥30 kg/m^2.[16] The same association between waist circumference (highest versus low category of waist circumference) and CRC risk was reported in both genders analysed together, (RR 1.455, 1.327–1.596), or in men (RR 1.477, 1.300–1.677) and women analysed separately (RR 1.442, 1.296–1.604).[16,29]

In another meta-analysis of 56 studies, Ning et al.,[30] showed a dose–response between five BMI intervals (<23.0, 23.0–24.9, 25.0–27.4, 27.5–29.9 and >30.0 kg/m^2) and increased CRC risk: being 1.0 (reference), 1.14 (1.06–1.23), 1.19 (1.13–1.25), 1.24 (1.15–1.35) and 1.41 (1.30–1.53). In these studies, CRC risk increase seemed to be greater in men than in women. These data suggest CRC risk increases with being overweight or obese, regardless of the parameter measured (BMI, waist circumference, weight gain, or others).

There is a growing body of evidence to suggest that being obese, together with smoking,[31] is linked to early onset CRC, at least partly because of the metabolic syndrome.[32] Several recent systematic review,[33] and meta-analyses,[34] summarised the evidence and showed that in most large epidemiological studies or meta-analyses, being obese was associated with early onset CRC, with an estimated RR 1.54 (1.01–2.35).[34] Some studies reported inconclusive or opposite results,[35,36] and authors suggested that this finding could be explained by the pre-diagnosis loss of weight in patient with CRC,[116] and the negativity of other studies maybe due to the small sample size.[117] A meta-analysis of studies investigating adult and early-life CRC risk found that CRC risk was greater in men (RR 1.39, 95%CI, 1.20–1.62) than women.[37]

In addition to factors like lifestyle, microbiota, alcohol and meat consumption, excess weight in childhood or young adulthood may also contribute to the rising incidence of early-onset CRC in Western countries.[27,38,39] A prospective cohort of more than 85,000 women found increased early-onset CRC risk, with a multivariable RR 1.93 (1.15–3.25), in women with obesity; BMI > 23 at age 18 independently increased early-onset CRC risk (mRR: 1.63; 1.01–2.61).[40] More recently, a prospective cohort of women who received prenatal care between 1959 and 1966 in Oakland, California (N = 18,751 live births among 14,507 mothers) suggested that maternal obesity (≥30 kg/m^2) increased CRC risk in offspring 2.51-fold and birth weight over 4000 g increased CRC risk by 1.95-fold.[41]

In summary, epidemiological studies strongly suggest a positive association between obesity in adult and childhood and risk of overall and early-onset CRC. The association is greater in men than in women; and the association with maternal obesity must be confirmed.

3.1.2 | Obesity is associated with an increased incidence of colorectal adenoma

CRC usually develops through the well described adenoma-carcinoma sequence. Colorectal adenoma (CRA) are divided in two distinct subgroups: conventional adenoma and sessile serrated adenoma/polyps (SSA/P). Both are CRC precursors[42] but share distinct molecular pathway and risk factors. Although conventional adenomas were the most widely studied, it is now recognised that SSA/P are also CRC precursors, and may account for a non-negligible proportion of CRC, and a greater proportion of interval CRC than conventional adenoma. Some studies showed that excess BMI is an independent risk factor for both conventional and serrated adenoma/polyps subtype.[43,44] The most recent published meta-analysis (17 studies, 168,201 patients) using patients with BMI < 25 kg/m^2 serving as a reference, reported a constant 42%–44% increase of CRA risk in overweight (25–30 kg/m^2 summary odds ratio, SOR: 1.42; 1.24–1.63) and obesity groups (≥30 kg/m^2, 1.44; 1.30–1.61).[45] Subgroup analyses showed significantly higher risk in women (43%) than in men (7%), and in whites (72%) or Asians (44%) than in Africans (−12%).[45] When focusing on advanced CRA (defined as size >10 mm and/or villous component and/or high-grade dysplasia), the risk was also significantly higher in patients with BMI >25 kg/m^2, (summary OR: 1.52; 1.32–1.73).[45] This risk appeared to be greater in the highest BMI categories (OR:3.01, $p < 0.001$).[46] Since several studies suggest that risk of CRA (and advanced CRA) recurrence increases along with baseline BMI,[47,48] some authors suggest using BMI to stratify risk of CRA recurrence and reduce the surveillance colonoscopy interval for those with higher BMI.[49]

A recent study highlighted the differences between fat compartments, and reported a significant association with CRA for visceral adipose tissue and visceral-to-total fat ratio, but not with subcutaneous adipose tissue area.[46] Several other studies showed that besides BMI, significant increases of CRA were reported in patients with highest amount of visceral adipose tissue (HR and OR ranging from: 2.16; 1.26–3.71,[50] to 3.90; 2.11–7.20,[46] $p < 0.001$ when comparing lowest and highest quintile); or those with highest visceral-to-total fat ratio (OR: 2.51; 1.37–4.60, $p = 0.003$).[46] A meta-analysis of 12 studies confirmed that visceral-to-total fat ratio, measured by CT, correlate significantly with CRA and advanced CRA.[51] The dose response meta-analysis showed that the summary OR for each 25 cm^2 increase in visceral adipose tissue area was 1.13 (1.05–1.21).[51] The results remained significant even after adjusting for weight, BMI, waist circumference and subcutaneous adipose tissue, demonstrating the predominant role of visceral adipose tissue in this process.[51]

To sum up, higher BMI seems to correlate with incidence and the recurrence of CRAs, including advanced conventional CRA or SSA/P. The amount of visceral adipose tissue and visceral-to-total fat ratio seem to be major risk factors for developing CRAs.

3.2 | Factors that confound the association between obesity and colorectal cancer

3.2.1 | Physical activity

Physical activity appears to significantly lower colon cancer risk, through multiple pathways, including the reduction of metabolic syndrome, of chronic low-grade inflammation, or the promotion of protective microbiota.[52] Several studies report a reduction of CRC

incidence from 15% to 24%.[53,54] An umbrella review that included 19 reviews, 26 meta-analyses and 541 original articles reported "strong" evidence of the positive effect of recreative physical activity on colon cancer.[55] Two meta-analyses, one of which included 1.44 million adults[56] and the other 755,459 adults,[57] found that leisure time activity was associated with a significant (8%–14%) decrease in colon cancer. The more recent study, however, found this association only in men.[57]

The protective role of physical activity appeared to be dose-dependent. Patients who exercised more than an hour per week had a lower risk of colon cancer than those who exercised less than an hour per week.[58] Risk continued to decrease with the number of hours of physical exercise; the decrease was 40% in patients exercising more than 7 h per week.[57,59,60]

The protective effect of physical activity seems well-documented in men, but the relationship is not so clear in women,[57,61] except for post-menopausal women not on hormone replacement therapy.[62] It may be because baseline risk of CRC is much lower in women than men, that the protective effect of physical activity is more difficult to prove.

In conclusion, physical activity appears protective against colon cancer, risk decreasing proportionately with the number of hours spent training. Physical activity seems to play a role more for men than women. Increased risk of CRC associated with obesity may thus be confounded by the lower rate of leisure activity in obese subjects.[63,64]

3.2.2 | Colorectal cancer screening

There are two main questions to address: (1) Is being obese negatively associated with CRC screening adherence? and (2) Is the increased risk for CRC in individuals with obesity high enough to warrant screening them at a younger age?

It is possible that patients with obesity are less likely to adhere to screening recommendations, which may increase CRC prevalence in this group. A meta-analysis published almost a decade ago suggested BMI was not associated with CRC screening compliance overall, but certain categories of patients (white obese women) had significant lower colon cancer screening rates than white normal-weighted women (0.87, 0.82–0.93; 0.80, 0.65–0.99; and 0.73, 0.58–0.94, for class I obesity, 30–34.9 kg/m^2; class II obesity, 35–39.9 kg/m^2; and class III obesity, ≥40 kg/m^2, respectively).[65] Only one study (that found overweight and obesity in >70% of the population) reported that being obese was not a significant risk factor in missing a CRC screening test.[66] The rest of the literature confirmed that patients with obesity were less likely than those of normal weight to adhere to CRC screening recommendations.[67–69] A recent systematic review of the literature recapitulates the studies investigating the association between obesity and CRC-screening recommendations adhesion.[70] In this review, Siebert et al.[71] showed that men with Class III obesity (BMI ≥40) were significantly less likely to adhere to screening guidelines (38.7% vs 55.8%, adjusted OR: 0.35, 0.17, 0.75) than men of normal weight, but this was not true for obese women. Similarly, Anderson et al.,[67] reported that compared with normal-weighted counterparts, patients with obesity were less likely to undergo colonoscopy as CRC screening test (non-compliance RR 2.16, 1.20–3.89). Another study showed that obesity was a risk factor for CRC screening program discontinuation.[69] More recently, in the Netherlands, where screening uptake is over 80%, a survey found that being obese was associated with a significant decrease in CRC screening (OR: 0.8; 0.66–0.97).[70,72] It is still unclear why adherence to CRC screening recommendations is lower in obese subjects. Messina et al.[73] suggested that although obese women were less aware than normal-BMI women that obesity increased their CRC risk (OR: 0.5; 0.3–0.9) and were less worried about CRC (OR: 0.5; 0.3–0.8), these factors were not sufficient explanations for the differences between screening rates.

In summary, although data supporting the impact of decreased adherence to screening policies among obese subjects is limited (as is data on their increased CRC risk), decreased adherence to CRC screening policies may be more pronounced in patients with obesity compared with the normal-weighted target population. The absolute difference is quite small, usually under than 10%,[68,73] and most findings described morbidly obese subjects.[65,68,73] It is unlikely that attending fewer cancer screenings accounts for significant differences in cancer outcomes between individuals classed as being overweight and obese and those classed as normal weight, but lower screening adherence may explain a part of the incidence differences observed.

3.3 | Relationships between obesity, treatments, and colorectal cancer outcomes

Optimal management of patients with obesity with CRC may be hampered or altered in a number of ways, including physician choice of treatment, dose modifications, inaccurate disease staging and pharmacokinetic and/or pharmacodynamic changes due to obesity itself.[74]

3.4 | Obesity and radiological staging of colorectal cancer

Over the past few years, CRC treatment strategy has advanced. For example, neoadjuvant chemotherapy can have a beneficial effect on outcomes in patients with locally advanced CRC particularly to facilitate surgical monobloc resection. Accurate staging is essential to individually select and manage therapies. Today, contrast-enhanced computed tomography is the pivotal method for initial workup and staging of colon cancer (as well as MRI in rectal cancer local staging). However, the accuracy of clinical T-staging may vary greatly across patients, even in the same cancer center.[75] The amount of visceral adipose tissue may reduce the accuracy of CRC staging. A study of 216 patients with CRC found that 39% of patients were mis-staged by computed tomography.[76]

Lower visceral adipose tissue (<122 cm^2, $p < 0.001$) and proximal location of tumour ($p = 0.004$) were independent factors associated with higher probability of misstaging.[76] We could not find other studies evaluating the impact of visceral adipose tissue accumulation on the radiological staging of CRCs. This is a topic that deserves further investigations.

3.5 | Obesity and surgery for colorectal cancer

Overall, data on colorectal surgery in patients with obesity support a higher rate of post-operative complication, such as increased conversion rates after initial laparoscopy, longer operating times, and postoperative morbidity, but no effect on other outcomes such as intraoperative blood loss, perioperative mortality, and reoperation rates.[77,78] Independently from the surgical technique employed, patients with obesity are more prone to developing certain complications (such as surgical site infection).[77,79,80] A recent meta-analysis of 16 studies (pooling 9535 patients) estimated that the risk of surgical site infection for patients with BMI ≥30 was more than double that of patients with BMI < 30 kg/m^2 (OR: 2.13; 1.66–2.72, $p < 0.001$).[81] In Asian patients, those with BMI ≥25 kg/m^2 had a 63% higher risk of surgical site infection than those with BMI <25 (OR: 1.63; 1.29–2.06, $p < 0.001$).[81]

Focusing on oncologic colorectal surgery, a more recent meta-analysis of 13 observational studies (4550 patients) reported significant increased conversion rate (OR: 2.11; 1.58–2.81), postoperative morbidity (OR: 1.54; 1.21–1.97), wound infection (OR: 2.43; 1.46–4.03), and anastomotic leak (OR: 1.65; 1.01–2.71) in the obese group.[82] On the contrary to what has been described for other cancers,[82–84] the rate of positive margin (distal and circumferential), 5-year disease-free and overall survival,[82] do not convincingly differ between normal-weight and patients with obesity after laparoscopic,[82] or robotic,[84] surgery.

Another recent meta-analysis, including 29 studies totalling 56,293 patients, found an obesity rate of 19.3% among patients with cancer.[83] These patients with obesity were significantly more likely to have lymph node metastases (OR: 1.2; 1.1–1.2, $p < 0.001$), longer surgeries, more blood loss and conversions to open surgery (OR: 2.6; 1.6–4.0, $p < 0.001$), but there was no difference in length of stay or postoperative mortality.[83]

In all,[77,78,82,85,86] but one,[83] study, the number of lymph node retrieval was not statistically lower in the obese group. In the only study,[83] in which a significant lower number of lymph node retrieval was suggested, the small difference reported (−0.9, 95% CI −1.7 to −0.1, $p = 0.03$) is probably of marginal clinical impact.

3.6 | Obesity and response to chemotherapy and/or targeted therapies

Some suggest that obesity, particularly visceral obesity, and its related metabolic changes promote angiogenesis.[87] In particular, the ratio of visceral fat area/subcutaneous fat area may correlate with the level of circulating proangiogenic biomarker VEGF-A.[88] Patients with obesity may be less responsive to chemotherapy, especially protocols that include targeted therapies like anti-VEGF (bevacizumab).

A study of 120 patients with metastatic CRC who received bevacizumab-based treatment ($n = 80$) or chemotherapy alone ($n = 40$),[89] determined that high BMI, visceral fat area, and subcutaneous fat area were significantly associated with lack of response to bevacizumab-based therapy but not chemotherapy.[89] After anti-VEGF therapy initiation, patients with high BMI had a significantly shorter mean time to progression, compared with patients with normal BMI (9 vs 12 months, respectively, $p = 0.01$).[89] In multivariable analysis, high visceral fat area was independently associated with response (HR 7.18; 1.69–30.6), time to progression (HR 2.80; 1.35–5.79), and overall survival (HR 2.88, 1.13–7.32).[89] A separate cohort study of 49 consecutive patients confirmed this finding as visceral fat area was significantly lower in respondents (111.9 ± 12 cm^2 than in non-respondents (210.8 ± 58 cm^2, $p = 0.03$).[90] A recent analysis of two large phase III studies (CAIRO and CAIRO2) also provided indirect support for these conclusions. The paradoxical benefit conferred by a higher BMI in patients treated with chemotherapy alone disappeared in a similar cohort of patients treated with chemotherapy + targeted therapy.[91] The authors hypothesized that the efficacy of bevacizumab decreased in patients with obesity.

A more recent report on 563 patients with metastatic CRC who received first-line chemotherapy and bevacizumab suggested that patients had longer progression-free survival ($p = 0.030$) and 2-year survival rate ($p = 0.036$) than patients with obesity.[92] Controversial results are however reported by Miyamoto and colleagues[93] from a retrospective analysis of 5 phase-II studies comprising 157 patients.[93] Patients in the low visceral fat area group had significantly shorter median overall survival than those in the high visceral fat area group (21.1 vs 38.9 months; HR: 1.70; 1.06–2.70, $p = 0.03$). Low visceral fat area was identified as an independent predictive factor for improved overall survival (HR: 1.86; 1.15–3.00, $p = 0.01$).[93]

Similarly, a retrospective study of data from 237 patients with metastatic CRC treated with chemotherapy plus bevacizumab in second line from January 2014 to August 2018 in four reference oncological centres in Poland also suggested high BMI was independently associated with improvement in both progression-free survival (HR: 1.79; 1.13–2.84, $p = 0.015$) and overall survival (HR: 1.83; 1.12–2.99, $p = 0.047$).[94]

The risk of unreported bias in the published study,[94] e.g., over-selection of included patients, may explain these inconsistent results. This association should be tested before adapting treatment guidelines for chemotherapies and targeted therapies based on a patient's BMI or visceral fat area.

3.7 | Obesity and outcomes in patients with colorectal cancer

Several meta-analyses investigated the effect of being overweight and obese on CRC outcomes.

In the first meta-analysis of 16 prospective studies (58,917 patients with a median follow-up of 9.9 years),[95] both overall mortality and disease specific mortality were significantly increased in patients with obesity at diagnosis (RR: 1.25; 1.14–1.36, and RR: 1.22; 1.003–1.35, respectively). Being overweighted was not associated with either of these parameters. On the other hand, post diagnosis obesity was associated with significant overall (RR: 1.08; 1.03–1.13) but not specific disease mortality (RR: 0.95, 95% CI: 0.80–1.30). In another meta-analysis of 25 first-line metastatic CRC trials (21,149 patients) mostly focused on underweight patients,[96] the authors reported an L-shaped pattern for both overall and progression free survival, with better outcome for patients from 28 kg/m^2, and risk for overall and progression-free survival risks were similar in patients with higher BMI. Finally, the most recent and largest meta-analysis (45 studies, 607,266 patients from stage I to IV) reported a significant increase in CRC (OR:1.27; 1.11–1.45) and overall (OR 1.20; 1.06–1.36) mortality in patients with obesity compared with normal-weight.[97] Similar trends for CRC mortality were found when considering high versus normal waist circumference (OR:1.23; 1.01–1.50). This suggests a specific role of obesity in prognosis. Being overweight (but not obese) increase significantly CRC recurrence in the pooled analysis of eight studies (OR: 1.33;1.12–1.57).

Overall, obesity is linked to CRC mortality. However, this association may (partially) be explained by the effect of obesity on physicians' management.

Usually, chemotherapy dosage is calculated based on body weight or body surface area. In this setting, dose reduction or dose capping (at body surface area of 2 m^2) is common practice because physicians fear toxicity which may result from high doses.[98] However,[99] the recently updated guidelines of the American Society of Clinical Oncology continue to recommend full dosage chemotherapy for patients with obesity,[100] and a meta-analysis demonstrated no significant difference in full-dose chemotherapy-related toxic effect on patients with obesity.[101] These patients with metastatic CRC do not experience more toxicity or more frequent dose reduction because of toxicity. However, is has been suggested that progression-free survival (hazard ratio, HR: 1.21; 1.06–1.39, $p = 0.006$), was significantly impaired in patients with obesity treated with reduced doses.[102] Results for overall survival were not significant (HR: 1.12; 0.96–1.30, $p = 0.152$).[102]In adjuvant stage III CRC, a significant improved relapse-free survival was described (HR: 0.48; 0.27–0.85; $p = 0.01$), whereas overall survival just failed to reach statistical significance (HR: 0.53; 0.28–1.01; $p = 0.052$) in patients with BMI ≥30 kg/m^2 and body surface area ≥2 m^2 treated with full dose compared with those treated with reduced dose.[103] The effect of obesity on immunotherapy efficiency is unclear, but there is no indication that patients with high BMI have worse outcomes, although there is some evidence that immunotherapy is more effective in patients with high BMI.[104]

Thus, data suggesting that pre-diagnostic BMI correlates with mortality from CRC in an adverse dose–response relationship (in men but not in women)[105] and is associated with an increased recurrence-risk[95,106,107] should be taken with caution because confounding factors coming from the management and not the pathophysiology may occurs. It is harder to interpret the effects of post-diagnosis BMI on mortality and recurrence, but the largest meta-analysis reported that post-diagnosis large weight-gain (>10%) is associated with increased CRC mortality compared with stable weight (OR: 1.32; 1.02–1.72). Cancer treatments can change BMI, causing severe weight loss over a brief time period. In turn, this may increase sarcopenia, which is associated with post-treatment complications of CRCs.[108]

3.8 | Measures to mitigate the risk of colorectal cancer in obese subjects

3.8.1 | Weight loss in patients with obesity and the risk of colorectal cancer

Epidemiological evidence supports the association between obesity and CRC, it is unclear whether weight loss can reduce this risk.

A well-established, prospective, multicentre cohort study to explore the association between nutrition and lifestyle with cancer and other chronic diseases (based on EPIC, the European Prospective Investigation into Cancer and Nutrition) recently suggested that losing weight to reach a lower BMI category was inversely associated with CRC (HR: 0.69; 0.52–0.92) risk.[109] Findings were similar for post-menopausal women where intentional weight loss was associated with significant decrease in CRC risk (HR: 0.79; 0.63–0.99).[110]

Although bariatric surgery (BS) for weight loss is generally assumed to reduce cancer risk in patients with obesity, its effect on CRC is controversial. Two recent studies have examined CRC incidence and mortality after BS. These two meta-analyses (the largest seven studies together included 1.2 million patients with obesity) reported a significant (27%–34%) reduction in CRC risk in patients who had BS (RR: 0.73; 0.58–0.90 and 0.64; 0.42–0.98).[111,112] More recently a matched cohort study was published suggesting that Roux-en-Y gastric bypass reduces by 53% the risk of CRC in patients with morbid obesity (OR 0.47; 0.30–0.75).[113] In contrast, long-term follow-up in a prospective randomised clinical trial, the Swedish Obese Subjects study, found no significant CRC risk reduction for BS (adjusted HR = 0.89; 0.62–1.29).[114] But in the Schauer et al study, BS was associated with a significant 31%–35% reduction in CRC risk (HR: 0.59; 0.36–0.97, $p = 0.04$).[115] Risk reduction was marginal in the Rustgi et al. study,[116] (aHR: 0.66; 0.42–1.00), which was restricted to patients with non-alcoholic fatty liver disease.

A retrospective population-based study conducted on French electronic health data, comprising 74,131 patients who had had several types of BS and 971,217 control patients who had had no BS reported a significant CRC risk increase in subjects with obesity who did not have BS (standardised incidence ratio, sIR: 1.34; 1.32–1.36).[117] In BS patients, the sIR was 1.0 (0.90–1.09) and there was no difference between observed and expected CRC incidence in the general population.[117] This suggests that BS brings CRC risk to the level of the general population.[117] Similarly, an English population-based study of patients with obesity who had BS found standard

incidence ratio (sIR: 1.26; 0.92–1.71) did not increase (compared with the general English population), but sIR did increase in patients who had no BS (sIR: 1.12; 1.08–1.16).[118]

These discrepancies might be explained by study design of the randomised clinical trial,[114] or observational studies,[116,117] or by the type of surgery performed. For example, Mackenzie et al.[119] found that gastric bypass, but not sleeve gastrectomy, increased colon cancer risk, suggesting that the type of bariatric procedure may affect cancer development. The rational being that weight loss varies according to the type of procedure and that the type of procedure may have an impact on changes in gut microbiota or hormone levels.[119,120] CRA significantly decreased in patients with obesity who had BS (OR 0.56; 0.53–0.59). The effect was significantly higher after gastric bypass or sleeve gastrectomy than for adjustable gastric banding.[117]

In summary, available data suggest an association between weight loss and decreased CRC incidence. Weight loss from diet alone or from BS interferes with gut microbial-host metabolic cross-talk,[121,122] and is associated with reduced metabolic syndrome[123] and lower levels of VEGF, insulin and leptin,[124] which may explain the mechanism behind these clinical observations. However, the data associating BS with CRC risk is not strong enough to support a formal indication for BS to reduce this risk. Further epidemiological and pathophysiological studies are warranted to confirm, and quantify the amount of protective effects, as well as the underlaying mechanisms.

3.8.2 | Colorectal cancer screening starting earlier

Because incidence of early-onset CRC is increasing,[39] and because a microsimulation model suggested cost-effectiveness,[125] the 2018 American Cancer Society guidelines recommend CRC screening begin at age 45 instead 50.[126] The wisdom of this recommendation for the general population is under debate because the large relative increase in CRC incidence translates to a much smaller absolute increase. Moving the start to 45 poses the risk of exceeding endoscopic capacity. It will also be costly and may divert resources from older adults more likely to benefit from screening. Another argument against starting CRC screening earlier was that age was the sole predictor used in the different microsimulation models,[125] regardless other factors such as obesity, tobacco smoking or other lifestyle parameters, known or suggested to be responsible for this rising incidence in the youngest categories of age.[127]

Starting CTC earlier in patients with obesity may not be sufficient to counteract negative influence of obesity on CRC risk as apart from obesity at CRC diagnosis, obesity during childhood or young adulthood contributes to this increased risk.[40] A recent study investigating BMI at age 20 years, 30 years and about 10 years before diagnosis, showed constant increase in all these analyses, with relative risks of 2.56 (1.20, 5.44), 2.06 (1.25–3.40) and 1.88 (1.30–2.73) respectively.[128]

Similarly, authors described a dose–response increase (RR per 5 kg/m^2 increase from 1.36 1.15–1.61, 1.36 (1.18–1.58) to 1.44 (1.18–1.75) at age 30, 10 years before diagnosis and age 20, respectively.[128] Whether childhood obesity increased more specifically rectum,[128] or colon,[129] cancer remain to be determined.

For persons with obesity, it is worth considering early CRC screening, but the best starting age is not yet clear. Sung et al.[130] suggest that the increase in CRC incidence in persons with obesity over the last 20 years was greatest in subjects between 25–29 years old.[130]

Based on the results of a study conducted in Turkey, the authors strongly suggested routine CRC screening for those 40-49-year-old who were morbidly obese or who belonged to the average risk metabolic syndrome patient population, since the colorectal neoplasia rate was 35.6% in ≥50 years old and 22.1% in those 40–49 ($p = 0.053$); advanced colorectal neoplasia rates were similar in these age groups (8.4% in 40–49; 9.6% in 50–65; $p = 0.792$).[131] Some authors proposed a risk scoring model based on obesity to optimise patient surveillance by adjusting the interval of follow-up endoscopies.[49]

4 | CONCLUSIONS

This highlights significant recent findings about the relationship between obesity and CRC. Obesity in adult or childhood increase further CRC risk, and influences outcomes, overall and for specific CRC treatments, especially VEGF-targeting therapies. Weight loss, mostly after gastric bypass surgery, significantly affects the course of CRC. Several questions are still unanswered: How do we best explore and use possible biological and clinical predictors like leptin, adiponectin, the visceral adipose tissue area, and the metabolic syndrome? How can we improve assessment of CRC in patients and adapt CRC screening policies? And can we better determine indications for gastric bypass surgery?

AUTHOR CONTRIBUTIONS

Marc Bardou: Conceptualization (lead); data curation (lead); validation (lead); writing – original draft (lead); writing – review and editing (equal). **Alexia Rouland:** Formal analysis (supporting); methodology (equal); validation (equal); writing – original draft (equal); writing – review and editing (supporting). **Alan N Barkun:** Data curation (supporting); methodology (supporting); resources (equal); writing – original draft (supporting); writing – review and editing (equal). **Myriam Martel:** Conceptualization (lead); data curation (supporting); formal analysis (supporting); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Romaric Loffroy:** Conceptualization (supporting); validation (supporting); writing – original draft (equal); writing – review and editing (supporting). **Nicolas Chapelle:** Conceptualization (equal); data curation (equal); formal analysis (lead); methodology (lead); validation (lead); writing – original draft (lead); writing – review and editing (lead).

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