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Obesity and colorectal cancer

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ABSTRACT

Excess body weight, as defined by the body mass index (BMI), has been associated with several diseases and includes subjects who are overweight (BMI≥25–29.9 kg/m^2) or obese (BMI≥30 kg/m^2). Overweight and obesity constitute the fifth leading risk for overall mortality, accounting for at least 2.8 million adult deaths each year. In addition around 11% of colorectal cancer (CRC) cases have been attributed to overweight and obesity in Europe. Epidemiological data suggest that obesity is associated with a 30–70% increased risk of colon cancer in men, whereas the association is less consistent in women. Similar trends exist for colorectal adenoma, although the risk appears lower. Visceral fat, or abdominal obesity, seems to be of greater concern than subcutaneous fat obesity, and any 1 kg/m^2 increase in BMI confers additional risk (HR 1.03). Obesity might be associated with worse cancer outcomes, such as recurrence of the primary cancer or mortality. Several factors, including reduced sensitivity to antiangiogenic-therapeutic regimens, might explain these differences. Except for wound infection, obesity has no significant impact on surgical procedures. The underlying mechanisms linking obesity to CRC are still a matter of debate, but metabolic syndrome, insulin resistance and modifications in levels of adipocytokines seem to be of great importance. Other biological factors such as the gut microbita or bile acids are emerging. Many questions still remain unanswered: should preventive strategies specifically target obese patients? Is the risk of cancer great enough to propose prophylactic bariatric surgery in certain patients with obesity?

INTRODUCTION

According to the WHO, overweight and obesity are defined as abnormal or excessive fat accumulation in adipose tissue that may impair health (http://www.who.int/mediacentre/factsheets/fs311/en/). The WHO definition for overweight is a body mass index (BMI, weight/(height in m)^2) ≥ 25 kg/m^2 and for obesity BMI≥30 kg/m^2. In 2008, 1.5 billion adults of 20 years and older were overweight. Of these, over 200 million men and nearly 300 million women were obese. The US 2009–2010 National Health and Nutrition Examination Survey showed an age-adjusted mean BMI of 28.7 (95% CI 28.3 to 29.1) for men and also 28.7 (95% CI 28.4 to 29.0) for women, and an adult obesity prevalence of 35.5% in men and 35.8% among women—unchanged from 2003–2008.[1] Obesity prevalence in US children and adolescents was 16.9%, unchanged from 2007–2008.[2] A study conducted in Australia, New Zealand and the UK in working nurses and midwives found that 62% were outside the healthy weight range.[3] In contrast, despite an increase over the past 30 years, obesity is half as common in France as in the USA or the UK (14.5% in 2009).[4] It is 10.1% among women and 11.4% among men in China.[5] As fat is principally deposited in two compartments, the subcutaneous and visceral compartments, it is interesting to note in this last study an associated increased prevalence of abdominal obesity (27.8% of men and 45.9% of women).[6] Only about two-thirds of patients with the metabolic syndrome (MS) are obese.[7 8] In contrast, some obese subjects are metabolically healthy.[9] MS is key linking obesity to most of its related complications such as diabetes, cardiovascular diseases or an increased risk of cancer in different sites, but may vary across different ethnic groups. The accumulation of ectopic fat, for example, in skeletal muscle and liver, might be strongly associated with MS,[9] whereas subcutaneous fat might be protective.[10] Recommendation to measure waist circumference and waist-to-height or waist-to-hip ratios rather than BMI recognises the important role played by abdominal obesity in MS, and the fact that BMI might overestimate obesity.[11] The publication of specific waist circumference cut-offs to define abdominal obesity is not supported by solid epidemiological and metabolic data[12 13]; furthermore ethnicity alters the relationship between visceral fat and MS.[14]

Colorectal cancer (CRC) remains the fourth most incident cancer in the USA with a cumulative lifetime risk of developing CRC of 5% in the general population[15]; it is the third leading cause of cancer-related deaths.[16] The relationship between body weight and different cancers is now well recognised.[17] For colon cancer, the relative risk attributable to obesity is 1.24 for men; it ranges between 1.04 and 1.13 depending on the country.[17] In 2006, there were 412 900 new cases of CRC diagnosed in 30 European countries, with an estimated personal attributable risk of 10.92% (95% CI 9.59% to 12.24%) in men and 2.57% (95% CI 0% to 5.51%) in women for colon cancer, and 5.05% (95% CI 3.45% to 6.67%) for rectal cancer in men, corresponding to 15.844 (95% CI 11.304 to 20.735) excess CRC cases.[18]

We review how obesity might promote CRC occurrence and its behaviour, and attempt to quantify the impact of both medical and surgical treatments while highlighting associated metabolic changes.

METHODS

Search strategy

We performed a systematic review searching EMBASE, MEDLINE, ISI Web of Knowledge and Pubmed using a highly sensitive search strategy to identify reports with a combination of controlled vocabulary and text words related to, first, colon or CRC (neoplasia, carcinoma, tumour, metastasis, malignancy), and second, obesity and overweight.

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Recursive searches and cross references were carried out using a 'similar articles' function and hand searches of articles identified. We included all adult human studies in French or English, published between September 1980 and May 2012.

Inclusion criteria

We identified all meta-analyses, other systematic reviews, case–control, cohort or observational studies that assessed colon, rectal or CRC prevalence in obese compared with non-obese subjects. The WHO BMI definition of obesity ≥30 kg/m^2 was adopted, but we also included studies in which BMI was defined as ≥25 kg/m^2 for Asian populations.[19]

Study selection

Data were extracted by two independent reviewers (MB and MM). When recent meta-analyses or systematic reviews were retrieved, the included studies were not reported individually. We also assessed epidemiological data that supported a relationship between obesity and CRC, such as associations with increased incidences of CRC, colorectal adenomas (CRAs), weight loss, outcomes, surgery and response to chemotherapy and/or targeted therapies.

Meta-analyses were prioritised, when available. To limit the number of references, when observational studies were too numerous to report individually, the most recent ones (past 5 years) were selected. Studies discussing pathophysiological mechanisms were assessed in a narrative way, aiming to balance the arguments for and against different biological hypotheses.

All articles addressing biological mechanisms were grouped into three subsections defined a priori: MS and visceral adipose tissue (VAT), adipocytokines, and insulin resistance and insulin-like growth factor 1 (IGF-1).

RESULTS

From 3732 initial citations, we included 20 meta-analyses, 5 reviews, 113 observational studies and 50 additional supporting articles (figure 1). In the text and tables, results are presented as RR, IRR, HR and OR with their 95% CIs and tables.

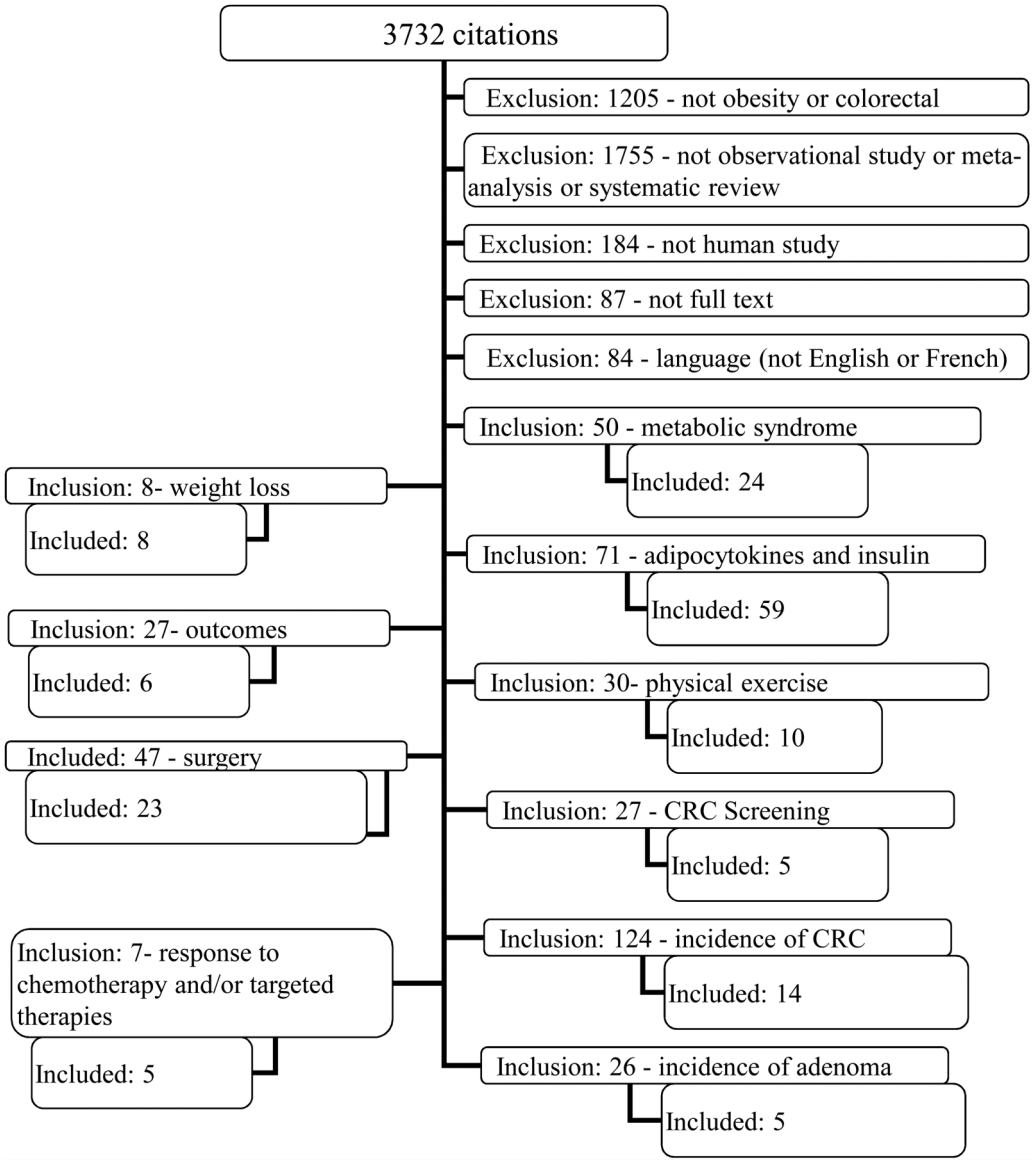

Figure 1 Quorum diagram.

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Obesity and CRC

Epidemiological data that support a relationship between obesity and CRC

Obesity is associated with an increased incidence of CRC

Interpretation of results is hampered by varying methodologies and definitions of obesity. We report all published meta-analyses on this subject, and summarised the most recent studies with the largest study populations (>10 000 patients), dichotomising results by gender.

Eight meta-analyses and systematic reviews were retrieved; three were not included: Bersgstrom *et al*[20] included only 19 studies from 1966 to 1997; Harriss *et al*[21] reported on the colorectal portion of the Renehan *et al*[17] study (the latter was thus excluded); Ning *et al*[22] reported different BMI categories, making comparisons difficult. The remaining five meta-analyses published between 2007 and 2009 are detailed in table 1.

Men: The incidence of colon cancer, rectal cancer and CRC was significantly greater in men with obesity in all studies, with RR varying from 1.24 (1.20 to 1.28)[21] to 1.71 (1.33 to 2.19)[23] for colon cancer, from 1.09 (1.06 to 1.12)[21] to 1.75 (1.17 to 2.62)[23] for rectal cancer, and from 1.37 (1.21 to 1.56)[23] to 1.95 (1.59 to 2.39)[24] for CRC. Significant associations were also found between the incidence of cancer and men with obesity in most of the subgroups analysed, such as colon subsites, BMI and country of origin, after adjusting for physical activity, smoking, alcohol consumption or family history. Waist circumference and increasing waist-to-hip ratios were also associated with significant increases in colon cancer and CRC. The RR was not significant for rectal cancer in one study.[23]

Women: The association between obesity and colon cancer, rectal cancer or CRCs was weaker among women. Indeed, the incidence of colon cancer was found to be significantly greater in women with obesity in only one of two studies,[23 25] RR=1.12 (1.07 to 1.18), and the incidence of CRC in two of the three studies[23 24 26] RR=1.15 (1.06 to 1.24). No significant association was reported in two studies assessing rectal cancer specifically.[23 25] Subgroup analysis results varied (table 1).

Among most recent articles, Matsuo *et al*[27] assessed 300 000 Japanese subjects, reporting a significant association between BMI and CRC (HR (per 1 kg/m^2 increase in BMI)=1.03 (1.02 to 1.04) and 1.02 (1.00 to 1.03) for men and women, respectively). Two studies showed a significant increase in colon cancer in men but not women (HR (per 5 kg/m^2 increase in BMI)=1.12 (1.04 to 1.21)[28] and 1.25 (1.08 to 1.45).[29] A Chinese study including only women found a significant, U-shaped, quadratic association between BMI and colon cancer risk, with an increased risk of CRC in underweight (BMI<18.5 kg/m^2) and obese subjects (p for trend=0.014), but not for rectal cancer.[30] Finally, in the last cohort study, a non-significant association was found between BMI and CRC (HR (per 1 kg/m^2 increase in BMI)=1.06 (0.98 to 1.15)).[31]

In summary, BMI appears to be consistently associated with an increased risk of CRC, colon or rectal cancer in men, but less so in women. This gender difference might be explained by sex differences in prevalence and age of onset of MS, or a protective effect of oestrogen attributable to induction of apoptosis and inhibition of cell proliferation.[32]

Obesity is associated with an increased incidence of CRA

Four meta-analyses assessed obesity and CRA (table 2).[33–36] Although the results were expressed differently (BMI per 5-unit increase,[33] BMI cut-off value[35 36] or 10 cm increase in waist circumference[34]), all showed a small but significant association, with similar trends across races, country of origin, measured or self-reported BMI, and site other than rectal adenoma. The significance of the association persisted after adjustment for physical activity, family history of CRC, energy or alcohol intake, smoking habits or non-steroidal anti-inflammatory drug use (table 2). In addition, the most recently published meta-analysis found a dose–response relationship (Ref=BMI<25; OR=1.21 and 1.32 for BMI=25–30 and BMI=30, respectively).[36]

In contrast to CRC, increased CRA risk is observed in women and men with obesity. A meta-analysis suggested a greater but non-significant increase in CRA risk among pre-menopausal versus post-menopausal women with obesity (OR=2.48, 0.56 to 11.05; and OR=1.06, 0.77 to 1.45, respectively).[36]

A more recent case–control study comparing 1771 patients with diagnosed adenomas and 4667 polyp-free controls confirmed that a greater waist circumference was significantly associated with increased CRA risk (OR=1.32, 1.17 to 1.49).[37] In addition, MS was significantly associated with finding adenomas (OR=1.44, 1.23 to 1.70), regardless of histological type, CRA number or location other than rectum.[37]

In summary, obesity based on BMI values is consistently associated with a significant increase in CRA risk in men and women.

Weight loss in patients with obesity and the risk of CRC

Few studies have assessed CRC incidence and mortality after bariatric surgery. Three studies reported on overall cancer mortality: The Swedish Obese Subjects randomised trial[38] compared 2010 patients with obesity (BMI≥34 kg/m^2 in men and ≥38 kg/m^2 in women) undergoing bariatric surgery with 2037 controls with obesity receiving conventional treatment,[38] while others were retrospective cohort studies.[39 40] All three studies showed that weight loss after bariatric surgery was associated with a 39–60%[38 39] risk reduction in cancer-related mortality. The numbers of deaths were too small for adequately powered site-specific analyses. Two of the studies suggested non-significant decreases in CRC incidence attributable to bariatric surgery (HR=0.52, 0.19 to 1.39 for women only;[41] and OR=0.70, 0.43 to 1.15 for men and women combined[40]).

A population-based Austrian cohort monitored changes in the weights of 28 711 men and 36 938 women for a period of 7 years, after which participants were followed for incident cancers over 8 years on average.[42] This study suggested that whereas weight change, loss or gain, had no effect on cancer incidence in all patients as a whole, weight loss (>0.10 kg/m^2/year) strongly reduced the risk of CRC in men (HR=0.50, 0.29 to 0.87).[42]

In summary, the limited available data suggest weight loss may be associated with decreased CRC incidence. Weight loss obtained through diet alone or with bariatric surgery interferes with gut microbial–host metabolic crosstalk[43] and is associated with a reduction in MS,[44] and in levels of vascular endothelial growth factor (VEGF), insulin and leptin,[45] thus providing a mechanistic rationale for these clinical observations.

Obesity and outcomes in patients with CRC

Studies assessing obesity and CRC outcomes have yielded discordant results. Meyerhardt and colleagues initially showed obesity was associated with a significant increase in overall mortality among women with stage II–III colon cancer,[46] but 5 years later in a separate study, published that BMI was not significantly associated with increased risks of colon cancer recurrence or death, although gender-specific results were not provided.[47] A cohort study of 4288 patients with Dukes B and C

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Table 1 Published meta-analyses on colorectal cancer incidence

Study Year Country	Number of studies Database and period searched Number of patients	Reported	Outcomes	RR (95% CI)
Guh *et al*[24] 2009 Canada	12 cohort studies Medline and EMBASE (until January 2007) ISI Web of Science, Google Scholar Not reported	Pooled IRRs were reported. Obesity is defined as BMI≥30	*Main outcome* Incidence obesity and *colorectal* cancer Men Women *Subgroup analysis* Country of origin: North America Men Women Country of origin: Europe Men Women Waist circumference Men Women	 **IRR 1.95 (1.59 to 2.39)** **IRR 1.66 (1.52 to 1.81)** **IRR 1.86 (1.40 to 2.46)** **IRR 1.47 (1.30 to 1.66)** **IRR 2.00 (1.40 to 2.87)** **IRR 1.74 (1.68 to 1.81)** **IRR 2.93 (2.31 to 3.73)** **IRR 1.55 (1.27 to 1.88)**
Harriss *et al*[21] 2009 USA	28 studies (25 cohort, 3 case control) MEDLINE (1966 to December 2007) and EMBASE (1974 to December 2007). 43415 incident colon cancers (men, 22440; women, 20975), and 23946 incident rectal cancers (men, 14894; women, 9052	Estimates of the risk ratio associated with every 5 kg/m^2 increase in BMI were reported	*Main outcome* Incidence obesity and colon cancer Men Women Incidence obesity and rectal cancer Men Women *Subgroup analysis* BMI self-reported (colon cancer) Men Women BMI self-reported (rectal cancer) Men Women BMI measured (colon cancer) Men Women BMI measured (rectal cancer) Men Women Country of origin: North America (colon cancer) Men Women Country of origin: North America (rectal cancer) Men Women Country of origin: European and Australia (colon cancer) Men Women Country of origin: European and Australia (rectal cancer) Men Women Country of origin: Asian-Pacific (colon cancer) Men Women Country of origin: Asian-Pacific (rectal cancer) Men Women Adjustment for physical activity (colon cancer) Men Woman Adjustment for physical activity (rectal cancer) Men Women Adjustment for smoking (colon cancer) Men Women Adjustment for smoking (rectal cancer) Men Women Adjustment for alcohol (colon cancer) Men Women Adjustment for alcohol (rectal cancer) Men	 **RR 1.24 (1.20 to 1.28)** **RR 1.09 (1.04 to 1.14)** **RR 1.09 (1.06 to 1.12)** RR 1.02 (0.99 to 1.04) **RR 1.32 (1.21 to 1.44)** **RR 1.10 (1.06 to 1.16)** **RR 1.08 (0.98 to 1.22)** **RR 1.12 (1.03 to 1.22)** **RR 1.22 (1.19 to 1.26)** **RR 1.08 (1.01 to 1.15)** **RR 1.09 (1.06 to 1.13)** RR 1.00 (0.98 to 1.03) **RR 1.35 (1.21 to 1.50)** **RR 1.13 (1.06 to 1.19)** RR 1.03 (0.94 to 1.13) **RR 1.12 (1.03 to 1.22)** **RR 1.21 (1.18 to 1.24)** **RR 1.04 (1.00 to 1.07)** **RR 1.09 (1.06 to 1.12)** RR 1.00 (0.98 to 1.03) **RR 1.32 (1.20 to 1.46)** RR 1.15 (0.95 to 1.39) RR 1.05 (0.90 to 1.23) RR 1.08 (0.82 to 1.43) **RR 1.32 (1.22 to 1.44)** **RR 1.10 (1.05 to 1.17)** **RR 1.12 (1.03 to 1.22)** **RR 1.11 (1.01 to 1.23)** **RR 1.26 (1.21 to 1.32)** **RR 1.11 (1.06 to 1.17)** **RR 1.11 (1.06 to 1.16)** **RR 1.08 (1.01 to 1.15)** **RR 1.32 (1.22 to 1.43)** **RR 1.10 (1.06 to 1.15)** **RR 1.08 (1.02 to 1.16)**

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Table 1 Continued

Study Year Country	Number of studies Database and period searched Number of patients	Reported	Outcomes	RR (95% CI)
			Women	**RR 1.10 (1.02 to 1.19)**
			Adjustment for family history (colon cancer)	
			Men	**RR 1.27 (1.18 to 1.37)**
			Women	**RR 1.12 (1.04 to 1.20)**
			Adjustment for family history (rectal cancer)	
			Men	**RR 1.15 (1.04 to 1.27)**
			Women	**RR 1.22 (1.04 to 1.42)**
Dai el al[23] 2007	15 cohort studies PubMed, EMBASE and the Cochrane Library up to January 2007 6458 incidences of colorectal cancer among 1058883 participants	Weighted pooled RRs were reported with obesity defined as BMI≥30	*Main outcome*	
			Incidence obesity and colon cancer	
			Men	**RR 1.71 (1.33 to 2.19)**
			Women	RR 1.10 (0.92 to 1.32)
			Incidence obesity and rectal cancer	
			Men	**RR 1.75 (1.17 to 2.62)**
			Women	RR 1.12 (0.84 to 1.49
			Incidence obesity and colorectal cancer	
			Men	**RR 1.37 (1.21 to 1.56)**
			Women	RR 1.07 (0.97 to 1.18)
			Subgroup analysis	
			Waist circumference (colon cancer)	
			Men	**RR 1.68 (1.36 to 2.08)**
			Women	**RR 1.48 (1.19 to 1.84)**
			Waist circumference (rectal cancer)	
			Men	**RR 1.26 (0.90 to 1.77)**
			Women	RR 1.23 (0.81 to 1.86)
			Increasing waist–hip ratio (colon cancer)*	
			Men	**RR 1.91 (1.46 to 2.49)**
			Women	**RR 1.49 (1.23 to 1.81)**
			Increasing waist–hip ratio (rectal cancer)*	
			Men	**RR 1.93 (1.19 to 3.13)**
			Women	RR 1.20 (0.81 to 1.78)
Moghaddam *et al*[26] 2007	31 studies (23 cohort and 8 case-control) EMBASE and MEDLINE to April 2007 69619 incidences of colorectal cancer	Pooled RRs for general obesity were estimated continuously (per 2-unit increment in BMI) and using a binary measurement (comparing individuals with obesity (BMI≥30 kg/m^2) with those in the reference range of BMI<25 kg/m^2	*Main outcome*	
			Incidence obesity and colorectal cancer	
			Men	**RR 1.46 (1.36 to 1.56)**
			Women	**RR 1.15 (1.06 to 1.24)**
Larsson *et al*[25] 2007	31 cohort studies MEDLINE from 1966 to April 2007 44777 incidences of colon or rectal cancer (3128274 men and 2419875 women)	RR per unit increase in the anthropometric measurements: a 5-unit increase for BMI, a 10 cm increase for waist circumference, and a 0.1-unit increase for waist–hip ratio	*Main outcome*	
			Incidence obesity and colon cancer	
			Men	**RR 1.30 (1.25 to 1.35)**
			Women	**RR 1.12 (1.07 to 1.18)**
			Incidence obesity and rectal cancer	
			Men	**RR 1.12 (1.09 to 1.16)**
			Women	**RR 1.03 (0.99 to 1.08)**
			Subgroup analysis	
			Waist circumference (colon cancer)	
			Men	**RR 1.33 (1.19 to 1.49)**
			Women	**RR 1.16 (1.09 to 1.23)**
			Waist circumference (rectal cancer)	
			Men	**RR 1.12 (1.03 to 1.22)**
			Women	RR 1.09 (0.99 to 1.20)
			Increasing waist–hip ratio (colon cancer)	
			Men	**RR 1.43 (1.19 to 1.71)**
			Women	**RR 1.20 (1.08 to 1.33)**
			Increasing waist–hip ratio (rectal cancer)	
			Men	**RR 1.22 (0.81 to 1.83)**
			Women	RR 1.15 (0.95 to 1.39)
			BMI self-reported (colon cancer)	
			Men	**RR 1.36 (1.27 to 1.46)**
			Women	**RR 1.17 (1.08 to 1.26)**
			BMI self-reported (rectal cancer)	
			Men	**RR 1.16 (1.01 to 1.34)**
			Women	**RR 1.16 (1.06 to 1.24)**
			BMI measured (colon cancer)	
			Men	**RR 1.27 (1.23 to 1.32)**
			Women	**RR 1.07 (1.01 to 1.15)**
			BMI measured (rectal cancer)	
			Men	**RR 1.12 (1.09 to 1.15)**

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Table 1 Continued

Study Year Country	Number of studies Database and period searched Number of patients	Reported	Outcomes	RR (95% CI)
			Women	RR 1.01 (0.98 to 1.03)
			Country of origin: North America (colon cancer)	
			Men	**RR 1.39 (1.31 to 1.48)**
			Women	**RR 1.17 (1.08 to 1.25)**
			Country of origin: North America (rectal cancer)	
			Men	RR (only 1 study)
			Women	**RR 1.17 (1.05 to 1.31)**
			Country of origin: European (colon cancer)	
			Men	**RR 1.27 (1.22 to 1.32)**
			Women	**RR 1.04 (1.02 to 1.07)**
			Country of origin: European (rectal cancer)	
			Men	**RR 1.12 (1.09 to 1.15)**
			Women	RR 1.01 (0.98 to 1.04)
			Country of origin: Asian (colon cancer)	
			Men	**RR 1.27 (1.08 to 1.49)**
			Women	RR 1.32 (0.96 to 1.83)
			Country of origin: Asian (rectal cancer)	
			Men	**RR 1.16 (1.05 to 1.28)**
			Women	RR 1.09 (0.85 to 1.40)
			Adjustment for physical activity (colon cancer)	
			Men	**RR 1.33 (1.24 to 1.43)**
			Women	**RR 1.16 (1.07 to 1.25)**

*Compared with those in the lowest quintile.
Bold text highlights statistically significant results.
BMI, body mass index; IRR, incidence rate ratio.

colon cancer showed increased recurrence or metachronous tumours (HR=1.38, 1.10 to 1.73), overall mortality (HR=1.28, 1.04 to 1.57) and colon cancer specific mortality (HR=1.36, 1.06 to 1.73) in very obese patients (BMI≥35 kg/m^2).[48] More recently, the Cancer Prevention Study II Nutrition Cohort suggested that pre diagnosis, but not post diagnosis, BMI was associated with an increased risk of overall mortality (RR=1.30), colon cancer specific mortality (RR=1.35, 1.01 to 1.80) and cardiovascular mortality (RR=1.68, 1.07 to 2.65).[49]

Additional independent risk factors that have been shown to affect mortality from CRC cancer include MS (RR=2.92, 1.88 to 4.52; and RR=2.02, 0.95 to 4.27 for patients with obesity without and with MS, respectively),[50] physical exercise (PE) (improved survival in 526 CRC cases with an adjusted HR=0.73, 0.54 to 1.00) and increase in body fat (disease-specific deaths, HR (per 10 kg body fat)=1.33, 1.04 to 1.71).[51]

Other factors explaining the increased risk of mortality probably include late diagnosis, aggressiveness of the cancer and diminished treatment response.

In summary, it is suggested, although inconsistently, that obesity might be associated with a decrease in overall survival in patients with CRC, independently of MS, with possible gender-specific differences.

Factors that confound the association between obesity and CRC

Physical exercise (PE)

Two recent meta-analyses, by the same authors, found that PE was associated with a significantly decreased risk of CRC (OR=0.76, 0.71 to 0.82)[52] and CRA (OR=0.84, 0.77 to 0.92).[53] It has been speculated that obesity may be associated with specific eating behaviours, such as high consumption of red or processed meat or low consumption of fibres or folate, favouring CRC occurrence. Several studies, however, have found that the protective effects of PE and the deleterious effects of obesity persisted after adjustment for these possible confounding factors.[54 55] A recent systematic review suggested PE was associated with a decrease in most of the factors discussed below, such as insulin, insulin resistance, IGF-1, IGF binding protein 3 (IGFBP-3) or leptin.[56] Physical activity can also decrease colon transit time, particularly in the recto-sigmoid region, and thus contact time of alimentary carcinogens with the colon mucosa.[57] However, previous reports have suggested physical activity does not necessarily improve gastrointestinal transit.[58]

Another link between obesity, PE and CRC might be related to low levels of vitamin D, which have been associated with an increase in CRC risk, irrespective of BMI.[59] Patients with obesity may exhibit low levels of vitamin D for at least two reasons: the sequestration of vitamin D in adipose tissue[60] and a decrease in production.

CRC screening

The increased prevalence of CRC in patients with obesity might be partly explained by reduced adherence to screening strategies. A study comparing screening of normal weight patients to that of the latter displayed a reduced rate of CRC screening, whether by opportunistic colonoscopy or faecal occult blood testing.[61] A recently published meta-analysis highlighted possible racial disparities, suggesting that BMI was not associated with CRC screening.[62] Nevertheless, white women and men with obesity had lower rates of CRC screening than their normal BMI counterparts. For women, the trend was significantly associated with obesity classes.[62] Additional findings were reported in a prospective study that assessed reporting of CRC screening and the probability of agreeing with statements denoting attitudes/perceptions about CRC and screening.[63] This study showed that overweight women and those with obesity were 40% less likely to undergo CRC screening compared with

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Table 2 Published meta-analyses on colorectal adenoma

Study Year Country	Number of studies Database and period searched Number of patients	Reported	Outcomes	Risk ratios (95% CI)
Okabayashi *et al*[36] 2012	23 articles (2 nested cohort from RCT, 19 prospective cohort, 4 retrospective studies) EMBASE (from 1980 to August 2011), MEDLINE (from 1950 to August 2011), and PsycINFO (from 1967 to August 2011)	ORs for BMI 25–30 and BMI≥30 compared with BMI<25	BMI risk of colorectal adenoma Study quality Higher study quality Lower study quality Ethnicity Western countries Asian countries Gender Men Women Degree of adenoma progression	**OR 1.24 (1.16 to 1.33)** **OR 1.23 (1.14 to 1.31)** **OR 1.20 (1.00 to 1.44)** **OR 1.18 (1.04 to 1.34)** **OR 1.35 (1.27 to 1.44)** OR 1.16 (0.94 to 1.45) OR 1.19 (1.01 to 1.33) OR 1.11 (0.90 to 1.36)
Ben *et al*[33] 2012	36 articles (16 case–control studies, 13 cross-sectional studies and 7 cohort or nested case–control studies) Medline, ISI Web of Science, and EMBASE until 31 July 2011 29860 cases of CRA	Dose–response meta-analysis of the relationship of a 5-unit increase in the BMI	BMI risk of colorectal adenoma Gender Men Women Race White East Asian Country of origin USA Europe Asia Height and weight ascertainment Self-reported Measured Site of adenoma Colon Rectum Size of adenoma, mm <10 ≥10 Type of adenoma Non-advanced Advanced (restricted definition) Advanced (broad definition) Adjustments Adjustments for physical activity Adjustments for smoking Adjustments for energy intake Adjustments for alcohol intake Adjustments for NSAID use	**RR 1.19 (1.13 to 1.26)** (BMI per 5-unit increase) **RR 1.43 (1.23 to 1.67)** (BMI cut-off) **RR 1.15 (1.05 to 1.26)** **RR 1.08 (1.02 to 1.14)** **RR 1.12 (1.04 to 1.21)** **RR 1.29 (1.11 to 1.51)** **RR 1.18 (1.09 to 1.26)** **RR 1.16 (1.06 to 1.27)** **RR 1.29 (1.11 to 1.51)** **RR 1.14 (1.07 to 1.21)** **RR 1.31 (1.16 to 1.49)** **RR 1.17 (1.06 to 1.28)** RR 0.85 (0.74 to 0.99) **RR 1.53 (1.18 to 1.98)** **RR 1.49 (1.16 to 1.91)** **RR 1.36 (1.17 to 1.58)** **RR 1.70 (1.12 to 2.58)** **RR 1.39 (1.14 to 1.68)** **RR 1.19 (1.16 to 1.28)** **RR 1.21 (1.11 to 1.33)** **RR 1.20 (1.01 to 1.42)** **RR 1.18 (1.10 to 1.26)** **RR 1.15 (1.07 to 1.24)**
Hong *et al*[34] 2012	21 articles (4 case–control studies, 12 cross-sectional studies, and 5 cohort studies) MEDLINE and EMBASE database up to October 2011 10242 cases of CRA	Dose–response meta-analysis of per 10 cm increase in WC and 0.1-unit increase in WHR	Waist circumference WHR Gender Men (WC) Men (WHR) Women (WC) Women (WHR) Race Asian (WC) Asian (WHR) Non-Asian (WC) Non-Asian (WHR) Adjustments Adjustments for physical activity (WC) Adjustments for physical activity (WHR) Adjustments for alcohol intake (WC) Adjustments for alcohol intake (WHR) Adjustments for NSAID use (WC) Adjustments for NSAID use (WHR) Adjustments for family history of CRC (WC) Adjustments for family history of CRC (WHR)	**RR 1.39 (1.24 to 1.56)** **RR 1.22 (1.10 to 1.36)** **RR 1.38 (1.11 to 1.70)** **RR 1.24 (1.00 to 1.56)** **RR 1.34 (1.14 to 1.58)** RR 1.21 (0.92 to 1.61) **RR 1.38 (1.17 to 1.56)** RR 1.15 (0.97 to 1.35) **RR 1.39 (1.20 to 1.61)** **RR 1.26 (1.11 to 1.43)** RR 1.16 (0.97 to 1.39) **RR 1.20 (1.05 to 1.38)** **RR 1.38 (1.15 to 1.65)** **RR 1.15 (1.02 to 1.30)** **RR 1.42 (1.24 to 1.62)** **RR 1.21 (1.07 to 1.35)** **RR 1.33 (1.13 to 1.55)** **RR 1.19 (1.06 to 1.32)**
Lee *et al*[184] 2011	25 studies (9 cross-sectional studies published, 11 case–control studies and 5 prospective	Weighted pooled RRs were reported with obesity defined as: moderate adiposity, BMI≥30 for	Waist circumference Gender Men	**RR 1.42 (1.30 to 1.56)** **RR 1.39 (1.10 to 1.76)**

Continued

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Table 2 Continued

Study Year Country	Number of studies Database and period searched Number of patients	Reported	Outcomes	Risk ratios (95% CI)
	cohort studies) PubMed (1964 to June 2010) and EMBASE (1975 to June 2010) 20903 cases of CRA in 300671 participants	European or American populations and BMI≥25 for Asian populations; lower adiposity, BMI≥25 for European or American populations and BMI≥23 for Asian populations	Women	**RR 1.37 (1.08 to 1.73)**
			Race	
			Asian	**RR 1.88 (1.30 to 2.71)**
			Western country	**RR 1.30 (1.11 to 1.52)**
			Height and weight ascertainment	
			Self-reported	**RR 1.29 (1.11 to 1.51)**
			Measured	**RR 1.84 (1.29 to 2.62)**
			Site of adenoma	
			Distal colorectum	**RR 1.46 (1.23 to 1.72)**
			Total colorectum	**RR 1.45 (1.17 to 1.78)**
			Size or histology of polyps	
			Large or advanced polyps	**RR 2.16 (1.49 to 3.14)**
			Small and non-advanced polyps	**RR 1.51 (1.15 to 1.99)**

BMI, body mass index; CRA, colorectal adenoma; CRC, colorectal cancer; NSAID, non-steroidal anti-inflammatory drug; RCT, randomised controlled trial; WC, waist circumference; WHR, waist to hip ratio.

normal-weight subjects. The reason for this lower adherence to screening policy in subjects with obesity has yet to be determined. Indeed, the study by Messina *et al*[63] suggested that although women with obesity were less aware than those with normal BMI that obesity increased the risk of CRC (OR=0.5, 0.3 to 0.9), and were less worried about CRC (OR=0.5, 0.3 to 0.8), these factors were unlikely to explain the observed differences in screening rates.

In summary, decreased adherence to CRC screening policies, more pronounced in women than men, does not explain the observed association between obesity and increased risks of CRC in men, or CRA in men and women. However, decreased screening adherence may be associated with the weaker association observed between obesity and CRC in women. There are several limitations in the data supporting the impact of decreased adherence to screening policies among subjects with obesity and the increased risk of CRC. First, the absolute difference is quite small, usually less than 10%;[61 63] second, the findings were mostly described for women with morbid obesity.[61–63] It therefore seems unlikely that reduced cancer screening in subjects with obesity would be sufficient to account for any significant differences.

Relationships between obesity, treatments and CRC outcomes

Obesity and surgery for CRC

Our systematic review did not identify any existing meta-analyses or systematic reviews that assessed short-term surgical outcomes for CRC in patients with obesity.

A meta-analysis of eight studies[64] and one narrative review that included 33 studies[65] reported on laparoscopic colorectal surgery among patients with obesity. Both reviews concluded obesity was associated with increased conversion rates, operating times and postoperative morbidity, whereas no significant impact of obesity was evidenced on other outcomes such as intraoperative blood loss, the number of dissected lymph nodes, perioperative mortality and reoperation rates.

Twenty fully published observational studies were retrieved during the literature search for CRC surgery in patients with obesity.[66–85] Of these, 12 included the use of laparoscopic operative techniques alone,[66 68 70 74–76 79 81–84 86] while 7 were Asian studies defining obesity as BMI≥25 kg/m^2 [66 74 75 79 84–86] or ≥28 kg/m^2.[82] Duration of hospital stay was the most commonly reported outcome, with only 3 of 16 studies reporting significantly longer stays for patients with obesity.[66 71 86]

Three of 16 studies reported significantly increased complication rates in patients with obesity,[66 78 83] whereas none reported increased mortality. All four studies reporting on intraoperative blood loss showed significantly greater values in patients with obesity.[66 67 81 86] Three of nine studies found significantly more wound infection in patients with obesity.[66 68 83] Sepsis was assessed in three studies, with no significant differences.[67 73 78]

A significantly greater number of nodes were removed in patients without obesity in 1 of 12 studies.[66] Park *et al*[86] reported a larger number of lymph nodes removed in patients without obesity than in patients with BMI=25.0–29.9 kg/m^2, but no differences compared with patients with higher BMI (>30.0 kg/m^2).

Overall, no clear relationship has been shown between obesity and operative and postoperative outcomes except for a modest but significant trend in overall complication rates. Meaningful contemporary summary data are needed.

Obesity and response to chemotherapy and/or targeted therapies

It has been suggested that obesity, particularly visceral obesity, and its related metabolic changes promote angiogenesis.[87] Thus it can be speculated that patients with obesity might exhibit an impaired response to chemotherapy, particularly protocols that include targeted therapies. In addition, in some patients with obesity, increased plasma levels of insulin may further decrease therapeutic effect.[88] A study of 120 patients with metastatic CRC receiving bevacizumab-based treatment (n=80) or chemotherapy alone (n=40)[89] found that high BMI, and visceral and subcutaneous fat areas were significantly associated with absence of response to the bevacizumab-based treatment but not the chemotherapy group.[89] Mean time to progression (TTP) was significantly shorter in patients with high BMI values (9 vs 12 months; p=0.01). In a multivariable analysis, high visceral fat area was independently associated with response, TTP and overall survival (HR=7.18, 1.69 to 30.6; HR=2.80, 1.35 to 5.79; and HR=2.88, 1.13 to 7.32, respectively).[89] These results were confirmed by others in a separate cohort of 49 consecutive patients (VFA significantly lower in respondents 111.9±12 cm^2 vs non-respondents 210.8±58 cm^2, p=0.03).[90] Indirect support for these findings was also provided by a recent analysis of two large phase III studies (the CAIRO and CAIRO2 studies)[91] in

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which a high BMI was associated with better median overall survival for patients receiving chemotherapy alone versus targeted therapy plus chemotherapy. The authors hypothesised a possible decreased efficacy of bevacizumab in patients with obesity.

The rationale for the reported relationships between obesity and CRC

A quick overview is presented in figure 2.

MS and visceral adipose tissue

The term MS describes a state of metabolic dysregulation characterised by insulin resistance with increased fasting glucose, hyperinsulinaemia, proinflammatory and procoagulant changes, and a predisposition to type 2 diabetes, dyslipidaemia (increased triglycerides and reduced high-density lipoprotein cholesterol), premature atherosclerosis and other disorders.[92]

The occurrence of MS is strongly affected by the presence of visceral obesity, or VAT, and is influenced by hormonal factors,[7 93] but obesity is a remarkably heterogeneous condition and not every patient with obesity is characterised by comorbidities and the presence of MS.[94] In this regard, body fat distribution, especially VAT accumulation, has been found to be a major correlate of the MS cluster.[7]

Metabolic syndrome

In the metabolic syndrome and cancer project (Me-Can), a prospective international population-based study of 580 000 people assessing MS and cancer risk, after 12 years of follow-up, 2834 men and 1861 women had been diagnosed with CRC (RR=1.25 for men, 1.18 to 1.32; and 1.14 for women, 1.02 to 1.18).[95] Two studies reported a risk increase for CRC (OR=1.09, 0.74 to 1.60; OR=2.40, 1.36 to 4.25; and OR=2.57, 1.20 to 5.52 for one, two and three components vs none, respectively)[96] and CRA (OR=1.14, 1.38, 1.61*, 2.57* and 3.23* for one, two, three, four and five components vs none, respectively, *p<0.05)[97] as the number of MS components rises. Some authors suggested that MS, and more specifically waist circumference, appears to be an independent risk

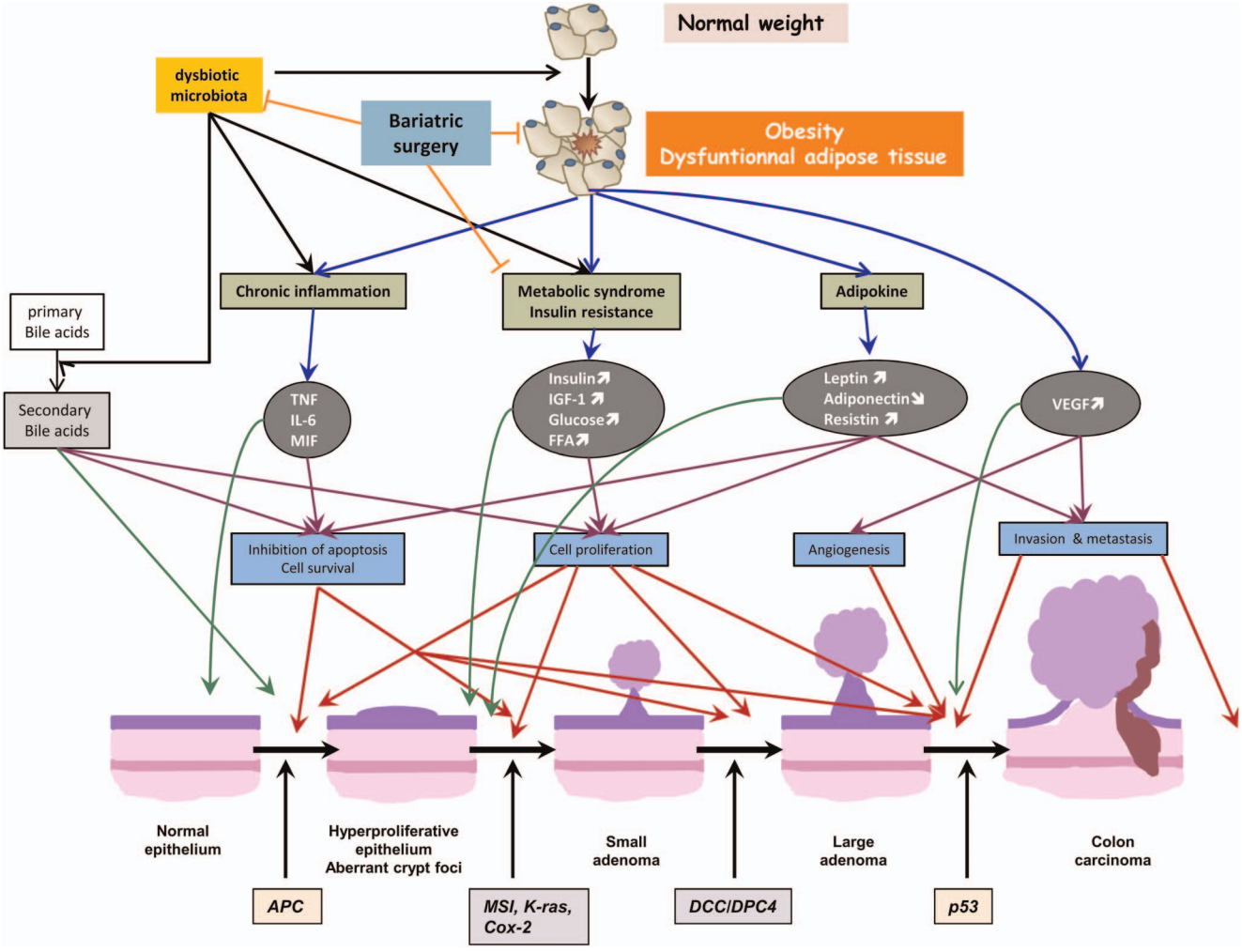

Figure 2 Summary of potential factors that are believed to relate obesity and colorectal cancer. Blue arrows indicate the metabolic consequences of obesity. Black arrows are for some of the suspected consequences of dysbiotic microbiota. Purple arrows are for the cellular events induced by obesity-related metabolic changes. Red arrows locate these cellular events in the carcinogenic process. Green arrows suggest the stage of the normal epithelium-to-carcinoma sequence when the different biological factors might start to act. And finally, orange lines suggest some of the potentially beneficial effects of bariatric surgery. FFA, free fatty acid; IGF-1, insulin-like growth factor 1; IL, interleukin; MIF, macrophage migration inhibitory factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor. APC, Adenomatous polyposis coli; MSI, microsatelite instability, K-ras, Kirsten-rat sarcoma, Cox-2, cyclooxygenase-2; DCC (deleted in colorectal carcinomas), DPC4 (deleted in pancreatic carcinomas, locus 4).

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factor for CRA,[97 98] whereas others have found no such relationship.[99]

It has been suggested that there is an interaction between hormonal factors and MS, as the risk of CRC with MS was either show to be observed only in men (OR=1.86, 1.21 to 2.86; OR=1.13, 0.66 to 1.93 for men and women, respectively)[100] or to be stronger in men (RR for CRC= 1.78 and 1.16 for men and women, respectively).[101] The same findings were reported for CRA (OR=1.44, 1.16 to 1.80; OR=1.04, 0.74 to 1.46 for men and women, respectively).[102]

However, the relationship with gender appears complex as MS is associated with an increased likelihood of metachronous neoplasia (mainly adenomas) among women (OR=1.37, 1.01 to 1.85) but not men (OR=0.99, 0.81 to 1.21).[103] However, when the analysis was restricted to advanced adenoma, waist circumference was associated with a significant risk in men (OR=1.41, 1.05 to 1.90) but not in women (OR=0.89, 0.55 to 1.42).[103] A small study suggested that worsened CRC outcomes in men with MS might be explained by a more aggressive phenotype.[104]

The other components of MS, that is, dyslipidaemia, hypertension and insulin resistance, also independently increase CRC[105] and CRA risks.[37]

A study that included 23 962 patients without MS and 9268 with MS (visceral obesity 7.2% and 55.9%, respectively) followed for 14.4 years found that MS was significant increased in those with CRC mortality (HR=2.15, 1.27 to 3.62).[50] Statistical significance was lost when analysis was restricted to colon cancer mortality (HR=1.72, 0.97 to 3.08).[50]

To summarise, there appears to be an association between MS and both CRA and CRC incidence and prognosis. These associations are stronger in men, yet their magnitude and the presence of possible confounding deserve further characterisation.

Several biological factors may explain the role of MS in the development and outcome of CRC: the most important is insulin resistance, while other factors include the associated increased production of insulin (IGF-1) and endothelial growth factors, and varying levels of several adipocytokines.[106]

Visceral adipose tissue

VAT has been identified as a risk factor for CRC (magnitude of risk ranging from RR=1.9, 1.1 to 3.3[107] to 4.01, 1.0 to 16.4[108]) and CRA (RR=1.58, 1.11 to 2.24),[109] either independently or in relation with other factors such as adiponectin (APN).[110] VAT volume is associated with CRA prevalence independently of BMI, with the strength of association varying across studies (example of ranges: from RR=1.6, 1.10 to 2.20,[109] to RR=5.92, 9% CI 1.22 to 28.65[111]). VAT may be a more accurate marker than waist circumference for increased CRC risk[112]; nevertheless the association between VAT and CRC has been questioned.[113]

Adipocytokines

Adipose tissue produces various growth factors, hormones and cytokines, known as adipocytokines. The adipocytokines include leptin, resistin, visfatin, Adiponectin (APN) and numerous cytokines including tumour necrosis factor α, interleukin (IL)-6, IL-8, IL-10 and IL-1 receptor agonist. Experimental and epidemiological data have shown that obesity leads to altered levels of several adipocytokines,[114] further contributing to an increased risk of CRC.

Adiponectin

APN is an adipocyte-derived insulin-sensitising hormone with circulating levels inversely proportional to obesity.[115] Following binding to two main receptors, AdipoR1 and AdipoR2, APN activates several intracellular signalling pathways (mainly adenosine monophosphate-activated protein kinase (AMPK) but also mammalian target of rapamycin (mTOR) and others), with resulting signal transduction and activator of transcription.[116]

A recent meta-analysis of 13 studies suggested that APN had a protective effect against CRC as, in men only, a 1 μg/ml increase in APN levels was associated with a 2% decrease in the risk of colorectal neoplasia.[117] This inverse association was confirmed by a second meta-analysis, which included 2632 cases of CRC or adenoma and 2753 healthy controls,[118] and a recent case–control study not included in the two meta-analyses.[119] It was suggested that low plasma levels of APN might be associated with CRC risk independently of other anthropometric measurements and other potential confounders, including family history, physical activity, current smoking and aspirin use.[120] Once again, the association between plasma levels of APN and the risk of CRC or CRA is controversial as some groups have disparate results.[121–123]

Plasma levels of APN and AdipoR1 and AdipoR2 expression in CRC tissue have been inversely associated with tumour differentiation.[124 125] In addition, low presurgical APN levels are found more frequently in patients with relapsing disease compared with non-relapsing disease (52% vs 26% respectively).[124] Treatment-induced variations in APN levels may also predict local recurrences and/or distant metastases in patients with rectal cancer treated with cetuximab.[126]

Several actions of APN could be involved in this protective effect against CRC. Though controversial,[127] APN has been described as exerting antiangiogenic properties leading to a significant inhibition of liver tumour growth and metastasis,[128] and CRC cell growth.[129] Other possible explanatory mechanisms for the anticancer role of APN include inhibition of cell proliferation,[130] and the induction of macrophage infiltration in tumours[131] and apoptosis.[130] APN may also suppress colon epithelial cell proliferation via inhibition of the mTOR pathway after a high-fat but not a standard diet.[132] Indeed, the number of chemically induced colon polyps was significantly greater in APN-deficient mice than in wild-type mice fed a high-fat diet (HFD), but not in APN-deficient mice fed a standard diet.[132] Finally, experimental studies have suggested that APN may play an important role in CRC prevention by modulating genes involved in chronic inflammation and tumourigenesis.[133]

To summarise, decreased levels of APN appear to be associated with an increased risk of CRC, although there are some discrepant studies. In addition, APN levels and AdipoR1 and AdipoR2 tumour expression might bear prognostic value.

Leptin

Unlike APN, leptin is mainly secreted by white adipose tissue, and circulating levels of leptin are higher in patients with obesity than in those without. The level of expression correlates with the severity of the obesity.[134 135] The binding of leptin to its receptors, ObRb, which are expressed in the colon epithelium, activates several signal transduction pathways, including Janus kinase signal transducer and activator of transcription 3, phosphatidylinositol 3 kinase (PI3K), and other pathways, such as the mitogen-activated protein kinase (MAPK), 5′AMPK, and the mTOR pathways, which have been implicated in CRC.[136 137]

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Although some studies reported normal serum leptin levels in patients with CRC,[138 139] a few case–control studies have shown an elevated risk of CRC associated with high serum leptin levels.[140–142] A case–control study nested within the Women's Health Initiative cohort of postmenopausal women, found that after adjustment for age, race, smoking, colonoscopy history, oestrogen level and insulin, only leptin remained significantly associated with CRC risk (HR comparing quartile four to one=1.84, 1.17 to 2.90).[143]

In addition to increasing CRC risk, plasma leptin and leptin receptor levels have been associated with more aggressive tumour phenotype.[104 144] An additional study of 108 Chinese patients with CRC reported a significant association between leptin/Ob-R expression and T and TNM staging, lymph node metastasis, distant metastasis, differentiation, and increased expression of phosphorylated PI3K, Akt and mTOR protein, suggesting that leptin may regulate the proliferation and apoptosis of CRC through the PI3K/Akt/mTOR signalling pathway.[145] However, a small study of 37 patients with CRA, 36 with CRC, and 25 controls found significantly lower plasma leptin levels in patients with CRC compared with those with CRA or controls.[146] Several factors might explain these discrepancies, including the realisation that leptin is not measured using a routine, standardised method, leading to large across-study differences.[104 143 144 146]

Studies assessing Ob-R tissue sample expression in CRC and normal adjacent mucosa found greater Ob-R expression in about 80% of CRC specimens; Ob-R expression also correlated with several clinicopathological parameters such as tumour differentiation and the presence of metastases.[135 147 148] Surprisingly both studies suggested that among patients with tumour, those with reduced Ob-R expression had worse outcomes than those with Ob-R overexpression, expressed either as progression free[135] or overall survival.[148] The study by Uddin *et al*[148] is limited by its retrospective design, a 16-year span during which CRC management evolved, and the subjective quantification of Ob-R expression.

Numerous studies have reported the carcinogenic effects of leptin, but overall, the role of leptin in CRC induction and growth remains unclear. Leptin inhibits apoptosis in human colon cancer cell lines and thus promotes proliferation of normal colonic epithelial and cancer cells.[148–150] A recent study suggested that leptin acts as a growth factor for CRC.[149] However, leptin has been shown by others to reduce the development of chemically induced precancerous colonic lesions—a finding that contradicts a possible role for leptin in fostering carcinogenesis.[151] These findings suggest that the relationship between obesity and CRC is multifactorial.[152] The discrepant observations may be explained by differing effects of leptin in in vitro and in vivo experiments and among different cell types; the genetic background may also be a factor, notably the *Apc* genotype, as detailed elsewhere.[153]

The role of leptin receptor (ObRb) polymorphism has also been investigated, but with no demonstrated association with CRA risk.[154]. However, this study confirmed an increase, 3.3 fold, in CRA for men exhibiting the highest leptin concentrations.

In summary, epidemiological studies support, although not unanimously, a relationship between high plasma levels of leptin and CRC risk. Experimental data suggest leptin may be involved in tumour growth rather than initiation.

Insulin resistance and IGF-1

Obesity is associated with an increase in insulin release and a decrease in insulin sensitivity, mediated by the decreased expression of insulin-receptor levels and reduced intracellular insulin signalling in response to insulin receptor binding.[155] This results in hyperinsulinaemia and insulin resistance,[156] with an associated increase in IGF levels. IGF-1 and IGF-2 are bound by six high-affinity binding proteins (IGFBP1–6) and other low-affinity binding proteins (IGFBP-related proteins); the higher the plasma levels of insulin, the greater the bioavailability of IGF through reduction of IGFBP1 and 2.[157] IGF is involved in the control of normal growth, maintenance of tissue homeostasis and a differentiated phenotype, alterations in the balance of proliferation and apoptosis, angiogenesis, cell adhesion, migration and wound healing.[158]

There is strong evidence from animal and human studies that cancer development is promoted by high concentrations of insulin and IGFs acting through the insulin/IGF axis. Stimulation of the IGF-1 receptor (IGF-1R), a tyrosine kinase, activates two main signalling pathways, PI3K-AKT and RAS-Raf-MAPK, which have multiple effects on gene regulation and protein expression, activation and translocation.[159 160] Another important pathway, the c-Jun N-terminal kinase (JNK) pathway, one of the subfamilies of MAPK, appears to play a crucial role in obesity and insulin resistance, and in colorectal carcinogenesis. Experimental data have shown that a HFD might increase insulin levels, inactivate AKT and increase JNK activity.[161] Interestingly, in this study, a HFD was associated with an increase in the number of aberrant crypt foci and the proliferation of colon epithelial cells. Both these effects were prevented by the use of a JNK inhibitor.[161] The IGF-1 receptor (IGF1-R) is expressed in normal non-transformed colon mucosa, and in human CRCs.[162] However, silencing or knocking out IGF-1R inhibits cell proliferation and enhances the sensitivity of human colon cancer cells to chemotherapy.[163] The deregulation of this pathway can thus give rise to malignancy.

Epidemiological studies and meta-analyses have assessed the relationship between IGF and CRC or CRA, but not specifically in patients with obesity. A recent 11-study meta-analysis, incorporating the most up-to-date information, reported a non-significant association between IGF-1 and CRC risk (RR=1.13, 0.97 to 1.32),[164] raising doubts about the findings of an older meta-analysis that had suggested a significant association between IGF-1 and increased CRC risk (OR=1.58, 1.11 to 2.27) based on fewer studies.[165]

As for a possible association between IGF and CRA, levels of IGF-I and insulin, and the IGF-I/IGFBP-3 ratio have been shown to be significantly greater in subjects with CRA compared with controls (OR 1.7, 1.0 to 2.9).[166] This finding was confirmed in a more recent study of 143 subjects, nested in a larger cohort study,[167] that showed subjects experiencing an increase of at least 50% in either IGF-1 or IGFBP3 exhibited a significantly greater CRA risk (OR for ever increase vs no increase=3.81, 1.30–10.8; and 2.83, 1.00–8.22 for IGF-1 and IGF-1/IGFBP3, respectively).[167]

In support of a gender difference in the relationship between obesity and CRC or CRA, a study conducted in healthy and lean subjects undergoing colonoscopy found a positive association between IGF-I and CRA (OR=1.63, 1.08 to 2.46), and an inverse correlation between IGFBP-1 and CRA (OR=0.49, 0.32 to 0.75) in men; no significant associations were found in women, suggesting insulin levels and the IGF axis act differently on colorectal carcinogenesis among men and women, at least at an early stage.[168]

A recently published case–control study that included African-American (231 cases and 306 controls) and white (297 cases, 530 controls) patients assessed the relationships between

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IGF-1 *(CA)$_{19}$*, IGF-2 *Apa1*, IGFBP-3, and APN gene polymorphism and CRC risk.[169] In white patients only, those homozygous for the IGF-1 *(CA)$_{19}$* repeat exhibited an increased CRC risk (OR=1.77, 1.15 to 2.73), while those carrying the IGF-2 *Apa1* A-variant exhibited a decreased CRC risk (OR=0.49, 0.28 to 0.88).[169] The investigators also suggested specific variants of IGF-2R might be associated with increased CRC risk (OR=2.2, 0.9 to 5.4), perhaps explained by modulating circulating levels of IGF-2.[170]

In keeping with clinical observations that suggest a more severe course of CRC in patients with obesity, it has also been suggested that IGF-I receptor might be implicated in the promotion of liver metastases.[171]

To summarise, insulin resistance and IGF-1 are associated with a slight increase in CRC and greater increase in CRA risks. As supportive data are few, even though there exists biological plausibility for a link between insulin resistance, IGF-1 and colorectal tumours, more epidemiological data are needed.

Other biological factors that may support a link between obesity and CRC: inflammation, bile acids and the microbiota

We have so far considered the putative explanatory roles of several biological entities, but numerous additional factors may be involved, such as inflammation, bile acids and the microbiota, that is, the human gut flora. Some of these, such as inflammation and bile acids, have been well studied, whereas the microbiota represents an emerging field of interest.[172] As most of these factors are inter related, any relationships with CRC are likely complex. Indeed, obesity and MS have long been recognised as chronic subclinical inflammatory conditions that may underlie increased CRC risk.[173] Several mechanisms can link inflammation to CRC, including oxidative stress, which in turn can affect the regulation of genes encoding for factors that play a role in colorectal carcinogenesis, such as p53, DNA mismatch repair proteins, and base-excision DNA-repair proteins, to name a few.[174] It has been suggested that microbiota is involved in the development of low-grade inflammation associated with obesity.[175] However, specific bacterial strains of the microbiota can exert anti-inflammatory properties.[176] In addition, the gut microbiota are well recognised as a predisposing factor for obesity, and are now considered one of the most important environmental factors with an impact on host physiology and metabolism.[177]

Bile acids are produced in the liver by the metabolism of cholesterol and are composed of cholic acid and chenodeoxycholic acid. These primary bile acids are converted to secondary bile acids, mainly deoxycholic acid and lithocholic acid, by the colonic microbiota. These secondary bile acids affect cancer development through tumour-promoting activities, and by inducing DNA damage and apoptosis.[178] It has also been suggested, in animal models, that bile acids can regulate the composition of the gut microbiota.[179] Although the microbiota is essential and beneficial to the host, various events, such as infection, diet, stress or inflammation, may impact microbial composition, leading to the formation of dysbiotic microbiota. It is now suggested that there is a direct relationship between the gut microbiota and the development of CRC.[180] To summarise, bile acids, inflammation and the gut microbiota have all been related to CRC; obesity and the microbiota can induce inflammation; obesity and a HFD can alter the microbiota and, conversely, the microbiota can promote obesity; and secondary bile acids are produced by the gut microbiota and can in turn alter microbiota composition and favour the development of tumours.

The involvement of bile acids in CRC might explain some of the aforementioned gender differences as hepatic bile acid synthesis is 15% lower in women taking oestrogen, thereby reducing this stimulus.[181 182]

Additional adipocytokines that may be of interest include resistin, a member of the newly discovered family of cysteine-rich proteins called 'resistin-like molecules'.[183]

CONCLUSIONS

This up-to-date review highlights some of the most important and recent findings characterising the relationship between obesity and CRC, while identifying possible underlying mechanisms, most of which remain controversial. Obesity increases the prevalence of CRC and influences outcomes, overall and in relation to specific CRC treatments, especially VEGF-targeting therapies. Weight loss, mostly after gastric bypass surgery, bears a significant impact on the course of CRC. A number of questions remain unanswered. How do we optimise the use of possible biological and clinical predictors such as leptin, APN, VAT area and the MS? How do we better assess CRC in patients with obesity, adapt CRC screening policies, and perhaps improve indications for gastric bypass surgery?

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