REVIEWS

Excess body weight and obesity—the link with gastrointestinal and hepatobiliary cancer

Prashant Kant and Mark A. Hull

Abstract | Excess body weight (EBW) is an independent risk factor for many human malignancies, including cancers throughout the gastrointestinal and hepatobiliary tract from the esophagus to the colorectum. The relative risk of gastrointestinal cancer in obese individuals is approximately 1.5–2.0 times that for normal weight individuals, with organ-specific and gender-specific differences for specific cancers. The association between EBW and risk of premalignant stages of gastrointestinal carcinogenesis, such as colorectal adenoma and Barrett esophagus, is similar, implying a role for EBW during the early stages of carcinogenesis that could be relevant to preventative strategies. EBW also impacts negatively on gastrointestinal cancer outcomes. The mechanistic basis of the association between EBW and carcinogenesis remains incompletely understood. Postulated mechanisms include increased insulin and insulin-like growth factor signaling and chronic inflammation (both linked to the metabolic syndrome), as well as signaling via adipokines, such as leptin. The role of obesity-related changes in the intestinal microbiome in gastrointestinal carcinogenesis deserves further attention. Whether weight loss leads to reduced future gastrointestinal and liver cancer risk has yet to be fully explored. There is some support for the idea that weight loss negatively regulates colorectal carcinogenesis. In addition, data suggest a reduction in risk of several cancers in the first 10 years after bariatric surgery.

Introduction

A large body of epidemiological evidence links excess body weight (EBW) with an increased risk of many cancers, including those of the breast, endometrium, kidney and gastrointestinal tract.[1,2] Given the high prevalence of EBW and obesity (defined as a BMI $\geq 30 \, kg/m^2$) in most populations throughout the world, amounting to an estimated 1.6 billion adults globally,[3] EBW is now considered to be an important, potentially preventable cause of cancer.[4,5] It has been estimated that 3.2% of all incident cancers in men and 8.6% of all incident cancers in women in Europe are attributable to EBW.[6]

Several gastrointestinal and hepatobiliary cancers are represented in the list of recognized obesity-associated cancers, including colon, rectal, esophageal (adeno-carcinoma), gastric, gallbladder, liver (hepatocellular) and pancreatic cancer (Table 1). Other gastrointestinal cancers, including small intestinal cancer, may also have an association with EBW.[7] Importantly, some gastrointestinal cancers develop via a clinically recognized premalignant precursor phase, such as the colorectal adenoma (also known as a polyp) and Barrett esophagus. Evidence is now emerging that EBW is also associated with increased risk of these premalignant precursor stages (Table 1).[8–11] These findings provide an excellent stimulus to intervene with individual and population-level antiobesity measures prior to malignant change.

By contrast, current understanding of the effect that the reduction of EBW has on future gastrointestinal and hepatobiliary cancer risk is rudimentary despite the potential importance of this knowledge for cancer prevention in overweight individuals. Evidence also suggests that EBW can alter gastrointestinal cancer outcomes after diagnosis.

This Review discusses the association between EBW and cancer risk in the gastrointestinal and hepatobiliary tract, with particular emphasis on the premalignant phases of gastrointestinal and liver carcinogenesis that are most relevant to cancer prevention. Current understanding of the pathophysiological mechanisms linking EBW and carcinogenesis in the gastrointestinal and hepatobiliary tract is explored, and existing evidence that body weight reduction impacts on gastrointestinal carcinogenesis is summarized. Finally, the current literature describing the association between EBW and gastrointestinal cancer outcomes is discussed.

Carcinogenesis associated with EBW
Colorectal carcinogenesis
Colorectal cancer

Considerable observational evidence has established that EBW is an independent risk factor for colorectal cancer (CRC). In Europe, it is estimated that EBW accounts for 16% (12,700 incident cases) and 2.6% (3,200 incident cases) of CRC cases in men and women, respectively.[6] Similar estimates in the USA suggest that 14.2%

Leeds Institute of Molecular Medicine, University of Leeds, Wellcome Trust Brenner Building, St James's University Hospital, Beckett Street, Leeds LS9 7TF, UK (**P. Kant, M. A. Hull**).

Correspondence to:
M. A. Hull
m.a.hull@leeds.ac.uk

Competing interests
The authors declare no competing interests.

of all incident CRC cases are attributable to a BMI of over 25 kg/m^2.[12] A meta-analysis by Moghaddam *et al.*[1] reported an overall age-standardized relative risk (RR) of CRC of 1.4 (95% CI 1.2–1.5) for obese individuals versus individuals with normal BMI.[1] There are gender-specific and site-specific variations in CRC risk associated with EBW. A meta-analysis of 29 cohort studies reported that a step-wise increase in BMI of 5 kg/m^2 is associated with a RR of colon cancer of 1.2 (1.2–1.3) for men and 1.09 (1.04–1.14) for women.[2] The RR of rectal cancer was attenuated and was only increased significantly in obese men (RR 1.09 [1.06–1.12]), whilst no association between BMI and rectal cancer was shown in women.

Whereas BMI is a generalized measure of adiposity, other more specific anthropometric measures of body fat distribution have led to a more refined appreciation of the risk associated with CRC. There is a growing appreciation that the pathophysiological effects of visceral (or abdominal) adipose tissue (VAT) are more potent than those of subcutaneous adipose tissue (SAT) during gastrointestinal carcinogenesis (see Supplementary Box 1 online). The waist circumference or waist–hip ratio are generally accepted as simple measures of VAT. There are currently no globally accepted cut-off values for waist circumference or waist–hip ratio, although an NIH report concluded that men and women with a waist circumference of >102 cm and >88 cm, respectively, should be considered at 'high risk' of developing obesity-related disease.[13]

Meta-analyses have demonstrated an increased risk of CRC associated with increasing waist circumference and waist–hip ratio.[1,14,15] One pooled meta-analysis observed a RR of all CRC amongst men and women of 1.5 (1.4–1.7) for the highest versus the lowest categories of waist circumference.[1] When subdivided by gender and site, it is clear that this relationship is similar to that with BMI. Each 10 cm increase in waist circumference results in a 33% and 16% increased risk of colon cancer in males and females, respectively.[14] Corresponding estimates for

Key points

- Excess body weight (EBW) is a potentially preventable cause of several gastrointestinal and hepatobiliary malignancies, including colorectal, esophageal, liver and pancreatic cancer
- A positive association between EBW and premalignant conditions, such as colorectal adenoma and Barrett esophagus, implies that EBW promotes the early stages of carcinogenesis (which could be relevant for prevention)
- The mechanisms linking excess adiposity (particularly visceral or abdominal fat) and gastrointestinal carcinogenesis are unclear but may include insulin and insulin-like growth factor signaling, chronic inflammation, adipokine signaling and changes to the intestinal microbiome
- Whether weight loss reduces future gastrointestinal and liver cancer risk has not been addressed fully and requires further study
- EBW is also associated with worse outcomes from gastrointestinal cancer following diagnosis

each 0.1 unit increase in waist–hip ratio were 43% and 20%.[14] For rectal cancer, the association was only apparent in males (12% increased risk per 0.1 waist–hip ratio unit increase).[14] Evidence that VAT has an important pathophysiological role comes from a study in which a twofold increased risk of CRC in men and women with a waist circumference of >99.1 cm, compared with a waist circumference of <83.8 cm, persisted despite adjustment for BMI.[16]

Colorectal adenoma
The colorectal adenoma is the recognized premalignant precursor of the majority of CRCs. A positive association between EBW and risk of colorectal adenoma would imply that EBW can drive colorectal tumor initiation and colorectal adenoma promotion separate from malignant progression and CRC growth. Several studies have thus investigated the association between body weight and risk of colorectal adenoma (Table 2).[8,10,17–37] It is apparent that there is considerable heterogeneity in study design and analysis, which makes direct comparison of individual studies difficult. Unlike CRC, increased

Table 1 | Excess body weight and cancer of the gastrointestinal and hepatobiliary tract

Site	Cancer	Recognized premalignant condition	Increased risk associated with excess body weight?
Oral cavity/pharynx	Squamous cell carcinoma	Leukoplakia	No data
Esophagus	Adenocarcinoma	Barrett esophagus	Yes
	Squamous cell carcinoma	No	No
Stomach	Adenocarcinoma	Intestinal metaplasia and gastric atrophy	Yes
Biliary tree	Gallbladder adenocarcinoma	Adenoma; chronic cholecystitis	Yes
	Intrahepatic cholangiocarcinoma	No	Yes
Liver	Hepatocellular carcinoma	Nonalcoholic steatohepatitis (nonalcoholic fatty liver disease)	Yes
Pancreas	Adenocarcinoma	No	Yes
Small intestine	Adenocarcinoma	No	Yes
	Lymphoma	No	No data
Colon and rectum	Adenocarcinoma	Adenoma	Yes*
Anus	Squamous cell carcinoma	No	No data

*Gender-specific differences are apparent (risk greater for males than females).

Table 2 | Summary of studies investigating the risk of colorectal adenoma associated with EBW

Study	Country	Patient gender	Number of adenoma cases*	OR and HR[‡§]	Adjusted analysis
Neugut et al. (1991)[20]	USA	M + F	301 (133)	1.4 (0.8–2.5) M 2.1 (1.1–4.0) F[‖]	Age
Bayerdörffer et al. (1993)[37]	Germany	M + F	244 (78)	3.2 (1.2–9.0)[‖¶]	Age
Giovannucci et al. (1995)[22]	USA	M	328 (131)	1.5 (0.9–2.5)	Age, other[#]
Giovannucci et al. (1996)[23]	USA	F	303 (125)	1.5 (1.0–2.2)[‖]	Age, other[#]
Kono et al. (1996)[31]	Japan	M + F	201 (72)	1.1 (0.6–2.2)	Other[#]
Bird et al. (1998)[30]	USA	M + F	478 (139)	1.7 (1.0–2.8)[‖]	Age, gender, other[#]
Almendingen et al. (2001)[36]	Norway	M + F	28	0.6 (0.1–6.1)	Other[#]
Boutron-Renault et al. (2001)[32]	France	M + F	363 (208)	1.7 (1.0–3.1) small[‖] 2.1 (1.2–3.5) advanced[‖]	Age, gender, other[#]
Terry et al. (2002)[34]	USA	M + F	560 (119)	2.0 (1.4–2.9)[‖]	Age, gender, other[#]
Betes et al. (2003)[29]	Spain	M + F	259 (259)	2.1 (1.3–3.3)[‖]	Age, gender, other[#]
Lieberman et al. (2005)[25]	USA	M + F	329 (329)	1.1 (0.9–1.2)**	Age, other[#]
Wallace et al. (2005)[33]	USA	M + F	308 (69)	1.1 (0.8–1.4)	Age, gender, other[#]
Larsen et al. (2006)[19]	Norway	M + F	551 (108)	1.3 (1.0–1.8) small[‖] 1.6 (0.8–2.6) advanced[§§]	Age, gender, other[#]
Wolf et al. (2007)[35]	USA	F	187 (63)	0.8 (0.5–1.3)	Age, other[#]
Anderson et al. (2007)[26]	USA	M + F	2,439	2.4 (1.5–4.7) MF[‖] 1.3 (0.5–3.3) M 4.3 (2.0–9.1) F[‖]	Age, gender, other[#]
Sedjo et al. (2007)[18]	USA	M + F	136 (38)	1.3 (0.5–3.1) M 2.2 (1.1–4.1) F[‖]	Age, gender, other[#]
Yamaji et al. (2008)[24]	Japan	M + F	1,650 (502)	1.3 (1.1–1.6)[‖]	Age, gender
Wise et al. (2008)[17]	USA	F	1,189	1.4 (1.2–1.7)[‖]	Other[#]
Omata et al. (2009)[27]	Japan	M + F	194	1.3 (0.8–2.1)[‖‖‖]	No details
Sato et al. (2009)[10]	Japan	M + F	1,590	1.3 (1.2–1.5) M[‖] 1.1 (0.9–1.4) F	Age, gender
Kim & Lee (2009)[28]	South Korea	M + F	165	1.8 (1.0–3.1) M[‖] 1.4 (0.6–3.4) F	Age, other[#]
Siddiqui et al. (2009)[8]	USA	M + F	2,903 (2,903)	1.01 (1.0–1.02)[‖‡‡]	Age, other[#]
Morois et al. (2010)[21]	France	F	1,408 (599)	1.6 (1.2–2.0)[‖]	Other[#]

*The number of advanced colorectal adenoma cases (at least one of the following features: size ≥10 mm diameter, contains villous morphology, high-grade dysplasia or invasive cancer, multiple [≥3] colorectal adenomas) is given in brackets. ‡Unless indicated, the OR and/or HR is for the combined analysis of both males and females and for both small and advanced colorectal adenomas. §Unless indicated, the OR and/or HR is for the highest versus lowest BMI category. ‖Statistically significant. ¶OR for advanced colorectal adenomas only from a subgroup analysis (males in the 3rd and 4th quintile of age). No association observed for females, or small colorectal adenomas in either males or females. #Other adjustment includes at least one from the following: diet, exercise, smoking, alcohol, family history. **OR and/or HR per 5-unit increase in BMI over 30 kg/m². ‡‡OR and/or HR per 1-unit increase in BMI over 30 kg/m². §§Included eight cases of CRC in the advanced adenoma subgroup. ‖‖‖Included 19 cases of CRC. Abbreviations: CRC, colorectal cancer; EBW, excess body weight; F, female; HR, hazard ratio; M, male; OR, odds ratio.

EBW-associated risk in males is not apparent for colorectal adenoma. Neugut et al.[20] were the first to describe the increased prevalence of colorectal adenoma in obese females (odds ratio [OR] 2.1 [1.1–4.0] for the highest versus lowest quartile of BMI) but not males. Other cohort studies,[18,26] including the largest prospective study to date of 2,439 adenoma cases,[26] have also shown positive risk associations for females, but not for males. Morois and colleagues reported a linear association between colorectal adenoma risk and increasing BMI in a large-scale, prospective, cross-sectional European study of 17,391 women,[21] supporting the findings of previous studies.[17,23] The converse association has also been reported in a study in which obese males, but not obese females, had an increased risk of developing colorectal adenoma.[10,28] Reasons for the disparity in

gender association are not clear but may relate to heterogeneity of adjustments for other factors such as age and NSAID use.

Increasing evidence suggests that obesity may also increase colorectal adenoma growth. Screening studies have demonstrated that obese individuals have a higher risk estimate for 'advanced' (usually defined as size >1 cm in diameter and/or with villous architecture and/or high-grade dysplasia) compared with 'nonadvanced' colorectal adenomas (Table 2). Among 2,260 prospectively screened patients, Betes et al.[29] demonstrated that obese individuals have an OR of 2.1 (1.3–3.3) for advanced colorectal adenomas compared with individuals who have a normal BMI. Conversely, in a Norwegian study of 3,998 prospectively screened patients, the presence of small (<1 cm diameter), but not advanced, colorectal adenomas was

predicted by obesity.[19] There is also a linear relationship between EBW and advanced colorectal adenoma risk in one large retrospective study, in which over 2,900 US male veterans had a 1% increased risk of advanced colorectal adenoma for every 1-unit increase in BMI above 30 kg/m^2 after adjustment for age, NSAID usage and family history of CRC.[8]

The stronger relationship of VAT, as opposed to SAT, with CRC risk seems to be mirrored by the relationship between VAT and risk of colorectal adenoma. In a case–control study of 530 Koreans, increased waist circumference or waist–hip ratio was significantly associated with risk of colorectal adenoma independently of BMI.[28] Another larger Korean case–control study of 2,244 patients undergoing screening demonstrated a threefold (OR 3.1 [2.2–4.4]) increased risk of colorectal adenoma between the highest and lowest quintiles of VAT as measured by CT.[38]

The presence of the metabolic syndrome carries an RR of 1.5 [1.2–1.9] for the prevalence of all types of colorectal adenomas and a twofold higher risk of advanced colorectal adenomas.[39] The Korean studies have also reported that colorectal adenoma multiplicity, as well as individual colorectal adenoma risk, is significantly associated with abdominal obesity.[38,40]

Obesity may also increase adenoma recurrence. Data from a pooled analysis of seven studies demonstrated that BMI is associated with an increased risk of colorectal adenoma recurrence in men (but not women) who have a previous history of colorectal adenoma, which included both advanced and nonadvanced colorectal adenomas.[41]

There may also be a role for EBW at the earliest stages of colorectal carcinogenesis (prior to tumor initiation and colorectal adenoma growth) as emerging data suggest that putative mucosal biomarkers of future CRC risk, including increased epithelial cell mitosis frequency, are increased in obese and morbidly obese patients compared with normal-weight controls.[42]

Other factors contributing to increased risk of CRC

In addition to the probable direct effects of EBW on the biology of colorectal carcinogenesis, other factors may impact on increased CRC risk in obese patients. Two studies have reported that CRC screening uptake in both fecal occult blood and endoscopy programs, is lower in obese compared with normal weight individuals.[43,44] Moreover, increased BMI has been linked to reduced quality of bowel preparation, which could increase the miss-rate for colorectal neoplasia prior to presentation with CRC.[45]

Esophageal cancer and Barrett esophagus

Esophageal adenocarcinoma

Obesity is a risk factor for the development of esophageal adenocarcinoma but not squamous cell carcinoma. The incidence of esophageal adenocarcinoma in Western populations has risen more than fivefold in the past three decades[46] and GERD has been strongly implicated as a primary causative factor.[47] A concomitant increase in obesity prevalence over a similar period has prompted investigation of the link between EBW and esophageal adenocarcinoma in population-based case–control and cohort studies. In a meta-analysis of six studies, the pooled adjusted OR for esophageal adenocarcinoma for overweight individuals was 1.5 (1.2–2.0) and for obese individuals was 2.9 (1.9–4.2).[48] Unlike CRC, there does not seem to be any gender difference in the relationship between EBW and risk of esophageal adenocarcinoma.[2]

EBW is a known moderate risk factor (RR 1.5–2.0) for developing GERD symptoms,[49] and abdominal obesity (as measured by waist circumference) can predict GERD severity independently of BMI.[50] One hypothesis, therefore, is that EBW increases risk of esophageal adenocarcinoma solely via promotion of GERD. However, EBW may drive esophageal carcinogenesis independently of promotion of GERD. Whiteman *et al.* have demonstrated that in patients reporting at least one episode of symptomatic GERD per week, obese individuals had a considerably higher risk of esophageal adenocarcinoma (OR 16.5 [8.9–30.6]) than people without obesity (OR 5.6 [2.8–11.3]).[51]

Barrett esophagus

Barrett esophagus (or columnar-lined esophagus) occurs secondary to GERD and is considered to be the premalignant precursor to esophageal adenocarcinoma. Patients with Barrett esophagus have an individual lifetime risk of progression to esophageal adenocarcinoma of approximately 0.5–1.0% per year.[52]

Given the relationship between EBW, GERD and esophageal adenocarcinoma, one might expect a similar, consistent relationship between EBW, GERD and Barrett esophagus. However, the current literature on this topic are conflicting. One meta-analysis, with selection criteria based on endoscopic appearance, concluded that increased BMI was not associated with an increased risk of Barrett esophagus compared with controls matched for the degree of GERD. However, increased BMI was significantly associated with Barrett esophagus in comparison with population-based controls, which implies a link via indirect effects of GERD, rather than EBW itself.[11] A subsequent unadjusted meta-analysis of studies of histologically confirmed Barrett esophagus concluded that there was an OR of 1.5 (1.2–1.8) for Barrett esophagus among individuals with a BMI of >25 kg/m^2 compared with normal-weight controls.[53]

Another study attempted to investigate the effect of EBW on risk of Barrett esophagus in female nurses by adjusting for reflux symptoms and the use of antireflux medication.[9] In this study, obesity, but not overweight, was associated with Barrett esophagus, even after adjusting for GERD.

Consistent with the data on colorectal neoplasia, two case–control studies have demonstrated an increased risk of Barrett esophagus in individuals who have increased abdominal obesity, as measured by waist–hip ratio[54] or waist circumference,[55] independently of BMI. However, a separate study failed to detect an association between

Barrett esophagus and either waist–hip ratio or waist circumference in women.[9]

Only one observational study has investigated whether EBW influences malignant progression in Barrett esophagus; no association was observed between BMI and progression to low-grade dysplasia.[56]

Pancreatic cancer

Data from a large pooled analysis of 2,170 cases have demonstrated positive associations between several anthropometric measures and pancreatic cancer risk following adjustment for age, smoking and diabetes.[57] BMI was a significant risk predictor in females, with those with the highest quartile of BMI having an OR of 1.5 (1.1–2.1) compared with those in the lowest quartile. In the fully adjusted model, the association was not significant in men (1.3 [0.8–1.8]). Abdominal adiposity was also a strong predictor of pancreatic cancer risk in women only, with an adjusted OR of 1.9 (1.3–2.7) for the highest versus lowest quintile of waist–hip ratio.[57] Furthermore, a meta-analysis of prospective studies that included more than 8,000 cases of pancreatic cancer demonstrated a step-wise increase in pancreatic cancer risk of 1.2 (1.1–1.3) in men and 1.1 (1.0–1.2) in women with each 5kg/m^2 increase in BMI.[58] There is also evidence that onset of an overweight or obese state at a young age (20–49 years old) is associated with diagnosis of pancreatic cancer at an earlier age compared with normal-weight controls.[59] Type 2 diabetes mellitus (T2DM), which is often linked to obesity and the metabolic syndrome, is associated with an RR of 1.8 (1.7–2.0) for pancreatic cancer.[60] However, reverse causation bias is likely in this study as the risk was greater for those patients with a short history of diabetes (less than 5 years) compared with individuals who had a longer duration of diabetes,[60] particularly as insulin sensitivity and diabetic control improve following pancreatic resection.[61]

Unlike CRC and esophageal adenocarcinoma, no clinically relevant premalignant precursor lesion is recognized for pancreatic cancer. Chronic pancreatitis is associated with an increased risk of pancreatic cancer with a cumulative risk of 4.0% at 20 years.[62] However, there is currently no evidence linking EBW and chronic pancreatitis.

Gastric carcinogenesis
Stomach cancer

The link between EBW and the incidence of stomach cancer is unclear, with conflicting data from two independent meta-analyses. A meta-analysis of 10 cohort studies reported a summary hazard ratio (HR) of 1.2 (1.1–1.4) for overweight and obese individuals compared with those with a normal BMI.[63] This association held for males only, with significant associations only apparent for non-Asian populations. The null effect observed in Asian populations may partly be explained by more widespread surveillance and early detection of gastric neoplasia in these populations.[64] However, the summary HR estimate in this analysis was strongly driven by two studies with evidence of considerable heterogeneity

($I^2 = 81\%$).[63] One of these two studies was reported to have a risk estimate of 1.7, although the paper itself reported that no association was found (HR 1.1 [0.7–1.8]), and the other study included fatal gastric cancer cases only. By contrast, a meta-analysis of four cohort studies by Renehan et al.[2] did not find any association between increasing BMI and gastric cancer risk.

There are biological differences between cardia and noncardia stomach cancer, which may be reflected in the association with EBW.[65] Only cardia cancer risk seems to be increased in obese individuals.[63] Observational studies of gastric cancer risk are also probably hampered by confounding owing to the difficulty in determining the true nature of tumors at the gastro-esophageal junction as either esophageal or gastric in origin.

Chronic gastritis and intestinal metaplasia

Gastric carcinogenesis is a multistage process, which involves distinct histological stages from chronic gastritis through to gastric atrophy and intestinal metaplasia. Multiple risk factors for gastric carcinogenesis are recognized, including *Helicobacter pylori* infection, smoking, alcohol consumption and dietary factors.[66] However, the relationship between body size and premalignant stages of gastric carcinogenesis has yet to be explored.

Gallbladder carcinogenesis
Gallbladder cancer

Gallbladder cancer is rare in the Western world but is more common elsewhere, particularly in South American countries. It is known to arise on a background of gallstone disease or chronic cholecystitis,[67] and it has been estimated that up to 14% of incident cases of gallbladder cancer in Europe may be attributable to obesity.[6] In a large-scale, population-based study in Norway including 1,715 cases of gallbladder cancer, obesity was associated with an RR of gallbladder cancer of 1.4 (1.0–1.9) in men and 1.9 (1.6–2.2) in women compared with individuals with normal BMI.[68] A meta-analysis of four cross-sectional studies concluded that a moderate association between risk of gallbladder cancer and EBW existed in women only, with an HR of 1.6 (1.0–2.5), as opposed to men (1.1 [1.0–1.2]), for each 5kg/m^2 increase in BMI.[2] A subsequent large Chinese case–control study in a mixed-sex population has shown that increased waist–hip ratio was a strong predictor of risk of gallbladder cancer compared with cancer-free controls.[69]

EBW is a risk factor for gallstones, with an approximate sixfold to sevenfold increase in gallstone prevalence in obese individuals compared with individuals who have a normal BMI.[70] Gallstones are believed to be an age-independent risk factor for gallbladder cancer on the basis of a number of epidemiological studies concerning the presence,[71] size[72] and duration of stones.[73] However, the strength of any causal relationship remains controversial owing to the wide geographical variation in incidence of gallbladder cancer despite equivalent gallstone prevalence rates.[74] This discrepancy may be explained by variable rates of cholecystectomy in certain areas.[75] EBW might also increase the risk of gallbladder

cancer independently of the presence of gallstones. In the Chinese case–control study, the association between EBW and gallbladder cancer incidence was maintained even after adjustment for the presence of gallstones.[69]

Benign conditions linked to gallbladder cancer
The gallbladder adenoma (or polyp) is recognized to have malignant potential[76] and might be associated with EBW. In a large series of 264 gallbladder polyps, presence of the metabolic syndrome and increased waist circumference were independently associated with gallbladder polyp incidence.[77] Other studies have suggested that BMI might also be a risk factor for gallbladder polyposis, particularly in males.[78]

There is a paucity of data linking EBW with other likely histological precursors of gallbladder cancer, such as chronic cholecystitis and gastric metaplasia, although these entities are common in obese patients. In a study of 199 morbidly obese Taiwanese patients undergoing cholecystectomy at the same time as bariatric surgery, all had chronic inflammatory cell infiltration and 27% had gastric metaplasia, although only 10% had gallstones.[79]

Cholangiocarcinoma
EBW may also increase the risk of cholangiocarcinoma, which is a relatively rare cancer that has been increasing in incidence over recent decades.[80] One large UK-based case–control study of 372 cholangiocarcinoma cases estimated an OR of 1.5 (1.0–2.2) for obese patients versus those with a normal BMI.[81] Another retrospective case–control study of patients with cholangiocarcinoma identified from the Surveillance, Epidemiology and End Results (SEER) database in the USA, reported that obesity was a significant risk factor for intrahepatic, but not extrahepatic, cholangiocarcinoma.[82] However, there may be regional differences as a similar study in Denmark failed to show any significant increased risk of cholangiocarcinoma with increased BMI.[83]

Hepatic carcinogenesis
There is strong evidence that obesity is associated with an increased risk of hepatocellular cancer (HCC). Changes in HCC incidence and obesity prevalence have both followed a similar upward pattern, suggesting that obesity may account for a significant proportion of HCC cases over and above better recognized risk factors, such as viral hepatitis and alcohol.[84] Data from the UK Million Women Study showed that the risk of developing cirrhosis (a condition known to predispose to HCC) was linked to increasing BMI in a dose–response manner.[85]

Obesity is associated with nonalcoholic fatty liver disease (NAFLD), which is recognized as the hepatic manifestation of the metabolic syndrome. NAFLD encompasses a spectrum of histological states from isolated steatosis (fatty liver) and nonalcoholic steatohepatitis (NASH), through to fibrosis and cirrhosis. Population-based estimates for the prevalence of NAFLD range from 13% in nations where the prevalence of obesity is low, such as Japan,[86] to approximately 30% in the USA.[87] This figure rises to more than 90%

in patients who are morbidly obese.[88] The epidemiology of the link between EBW, NAFLD and HCC has been the subject of a recent systematic review and meta-analysis.[89,90] In addition, current understanding of the mechanistic link between obesity, NAFLD and hepatic carcinogenesis has been reviewed in detail elsewhere.[84] Therefore, only a brief summary of a large body of data is provided below.

Hepatocellular cancer
In a systematic review, seven out of 10 cohort studies reported significantly positive associations between BMI and HCC risk,[89] with the risk being greater for men than women. In a separate meta-analysis, which included eight of the above cohort studies, plus two other cohort studies, obesity was associated with an RR of HCC of 1.9 (1.5–2.4) compared with a normal BMI; a similar gender difference was apparent (male RR 2.4 [1.8–3.2]; female RR 1.7 [1.4–2.0]).[90] On the basis of prevalence data from the USA, it is estimated that 28% and 27% of cases of HCC in men and women, respectively, are attributable to EBW.[90]

EBW seems to be an independent risk factor for HCC separate from other causes of HCC. For example, in a study of 781,283 men from Korea, a region in which there is a high incidence of chronic HBV infection, obesity-associated HCC risk was maintained after controlling for HBV infection.[91] In a separate study of 19,271 patients with cirrhosis who were listed for liver transplantation, obesity was found to be an independent predictor of HCC in patients with alcohol-related cirrhosis (OR 3.2), but not in patients with cirrhosis resulting from viral or autoimmune hepatitis.[92] Another study of patients with HCV reported an HR of 1.9 (1.1–3.2) for overweight and 3.1 (1.4–6.8) for obese patients compared with their underweight counterparts.[93]

NASH
NASH is considered to be the predisposing state of NAFLD for hepatic carcinogenesis. This is consistent with the close link between carcinogenesis and local inflammation throughout the gastrointestinal tract. Mechanistically, genetic and diet-induced obesity has been demonstrated to drive HCC development via chronic inflammation in mice.[94]

However, the relative contribution of NASH, as opposed to protumorigenic mechanisms linked to cirrhosis, during hepatic carcinogenesis requires further investigation. There are case reports of HCC in patients with noncirrhotic NASH,[95,96] which implies that EBW can drive hepatic carcinogenesis via NASH independently of cirrhotic change. However, this may be a rare event as longitudinal studies have reported the incidence of HCC in patients with noncirrhotic NASH to be as low as 1–2%, whereas between 4–27% of cases of NASH transform to HCC following the development of cirrhosis.[84]

How does EBW drive carcinogenesis?
How EBW promotes carcinogenesis in different tissues, including several parts of the gastrointestinal
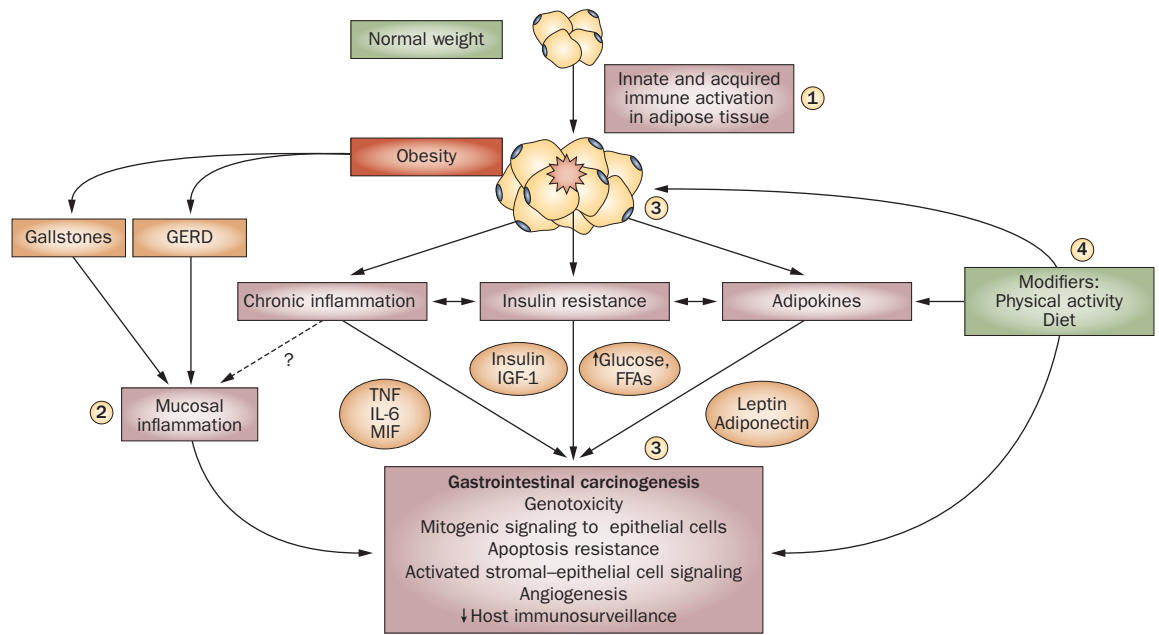
Figure 1 | Mechanisms linking excess adiposity in overweight and obese states with gastrointestinal and hepatobiliary carcinogenesis. This schematic outlines the putative mechanisms that link adipose tissue in excess body weight with the cellular and molecular mechanisms that are critical for carcinogenesis. (1) Excess adiposity is associated with innate and acquired immune activation. (2) Some gastrointestinal cancers are linked to local mucosal inflammation and/or irritation secondary to obesity-related pathologies, such as GERD or gallstones. (3) Alternatively, obesity may drive gastrointestinal carcinogenesis directly via several interlinked mechanisms leading to exposure to protumorigenic cytokines, growth factors and adipokines, as well as increased substrate availability to neoplastic cells. (4) Diet composition and physical activity are closely linked to excess body weight and may modify the effect of excess adiposity on carcinogenesis at several levels, including reduced adipose tissue mass, modulation of chronic inflammation separate from changes in adipose tissue mass, and other direct effects on target cells, particularly genotoxicity by dietary carcinogens. Abbreviations: FFA, free fatty acid; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; MIF, macrophage migration inhibitory factor; TNF, tumor necrosis factor.

and hepatobiliary tract, is still not understood but it is almost certainly a multifactorial process (Figure 1). A simple classification divides potential mechanisms into either indirect (for example EBW promotes GERD and gallstone formation, which then drive local inflammation-driven carcinogenesis), or direct, in which protumorigenic cell signaling occurs as a direct consequence of excess adiposity. Proposed direct mechanisms probably exhibit complex inter-relationships (Figure 1); for example, chronic inflammation and insulin resistance co-exist as part of the metabolic syndrome, with proinflammatory signaling causally related to target cell insulin resistance.[97]

Increased estradiol production is believed to contribute to the increased risk of postmenopausal breast cancer and endometrial cancer that is associated with EBW.[98] Moreover, therapeutic manipulation of sex hormone levels alters CRC risk in men and women.[99] However, whether differences in sex hormone metabolism between males and females contribute to gender-specific differences in gastrointestinal and liver cancer risk associated with EBW or whether gender differences are explained by differences in the distribution and biology of VAT and SAT between the sexes is not known. For the purpose of this Review, we consider sex hormones most likely to modify EBW-related gastrointestinal and liver cancer risk rather than representing a direct mechanistic link

between excess adiposity and carcinogenesis in the gastrointestinal tract.

Great interest has been shown in the role of the intestinal microbiome in control of body weight.[100] Therefore, the luminal microflora can be considered to be an etiological factor acting indirectly via modulation of body weight.[101] In addition, luminal microflora could have a direct protumorigenic role during colorectal carcinogenesis.

Putative molecular mechanisms linking obesity and carcinogenesis have previously been reviewed extensively.[98,102,103] Therefore, only recent data relevant to the gastrointestinal tract is reviewed in detail here.

Insulin and insulin-like growth factor signaling
A well-established hypothesis linking EBW and gastrointestinal carcinogenesis, particularly CRC and pancreatic cancer, is that insulin resistance leads to direct mitogenic and antiapoptotic signaling by insulin and the insulin-like growth factor (IGF) axis (Figure 1).[104] This hypothesis is supported by clinical observations, clinical biomarker data and mechanistic cell studies, but, as yet, few *in vivo* data have confirmed the relevance of protumorigenic insulin and IGF signaling in humans.

Increased CRC risk in patients with acromegaly, as well as increased CRC and pancreatic cancer risk

in patients with T2DM and the metabolic syndrome, suggests that insulin and IGF signaling contributes to EBW-related cancer risk.[60,105,106] Hyperinsulinemia in T2DM results in reduced hepatic synthesis of IGF binding protein (IGFBP) 1 and 2, which in turn leads to an increase in the circulating levels of bioactive, or 'free' IGF-1. Insulin, IGF-1 and IGF-2 activate the insulin, IGF-1 and IGF-2 receptors, triggering an intracellular cascade, which stimulates the proliferation of CRC cells[107] and promotion of tumor growth and metastasis.[106,108,109] Downstream targets of these receptors include extracellular-signal-regulated kinase (ERK) and phosphatidylinositol 3 kinase (PI3K) pathways that mediate mitogenic cell signals.[110] One critical downstream effector that has generated great interest is mammalian target of rapamycin (mTOR) and its downstream effector, S6 kinase 1, which both have a critical role in cellular nutrient sensing.[111] Metformin, which is widely used in the treatment of T2DM, has shown potential for CRC chemoprevention in mouse models of colorectal carcinogenesis[112,113] through a mechanism believed to include direct inhibition of mTOR by adenosine monophosphate kinase (AMPK).

The relationships between components of the insulin–IGF system and EBW are complex. In humans, although not all associations with BMI are linear, plasma levels of insulin and free IGF-1 are higher in obesity, whilst IGFBP-1 and IGFBP-2 levels are reduced.[104] Total IGF-1 levels peak at a BMI of approximately $28\,kg/m^2$ before reducing further in individuals with a BMI $>28\,kg/m^2$. A meta-analysis of five cohort studies revealed that the total IGF-1 level predicts the RR of CRC.[114] The association between colorectal adenoma risk and IGF biomarker levels is inconsistent. One study demonstrated a positive association between levels of serum insulin and the IGF-1:IGFBP-3 ratio and colorectal adenoma risk,[115] whilst another found a similar association only for 'high-risk' adenomas.[116] Another study failed to detect any association between risk of colorectal adenoma and IGF biomarker levels.[117]

In addition to colorectal neoplasia, decreased IGFBP-1 levels have been demonstrated to predict increased risk of pancreatic cancer.[118] IGF-1 is overexpressed in pancreatic cancer cells compared with normal pancreatic acini.[119]

Insulin and IGF signaling may also have a role in esophageal carcinogenesis. Genetic polymorphisms in the genes encoding the IGF-1 receptor[120] and IGF-2 receptor,[121] which are known to increase expression of these receptors in tumor tissue compared with matched normal epithelium, are associated with an increased risk of developing esophageal adenocarcinoma. Furthermore, IGF-1 gene polymorphisms have also been shown to be associated with risk of Barrett esophagus.[122]

Alternatively, it has been proposed that insulin resistance may lead to increased energy substrate (glucose, triglycerides and free fatty acids) availability to mucosal cells in the gastrointestinal tract, promoting tumor growth directly and/or increasing oxidative stress and DNA mutagenesis (Figure 1).

Chronic inflammation

EBW can be considered to be a state of chronic low-grade inflammation, as demonstrated by increased systemic levels of proinflammatory markers and cytokines, such as C-reactive protein (CRP) and interleukin (IL)-6.[123] Numerous proinflammatory cytokines, chemokines and other acute phase proteins, such as plasminogen activator inhibitor 1 and fibrinogen, are released from adipose tissue, which consists not only of adipocytes, but also immune cells, including macrophages (Figure 1).[124] In the lean state, adipose tissue contains CD4+ T lymphocytes with a T-helper-2 (T_H2) profile and a proportionately higher population of regulatory CD4+ T lymphocytes (T_{REG}) in relation to effector CD8+ T lymphocytes.[125] Obesity is associated with innate immune activation involving classic (M1) macrophage activation and a switch towards a T_H1 profile and dominant effector CD8+ T lymphocytes,[126] believed to be necessary for persistent adipose tissue inflammation.[125] The precise mechanism(s) underlying immune activation associated with excess adiposity are not understood although some evidence supports the idea that Toll-like receptor (TLR) activation by free fatty acids and/or lipopolysaccharide (LPS) drives immune activation in adipose tissue.[127]

Many of the 'classic' cytokines and growth factors that are synthesized and released by adipose tissue, such as IL-6, tumor necrosis factor (TNF) and macrophage migration inhibitory factor (MIF), are believed to have direct protumorigenic properties in the gastrointestinal and hepatobiliary tract (Figure 1).[128] However, it is not known whether increased systemic levels of protumorigenic factors act directly on gastrointestinal mucosal cells in an endocrine manner and/or whether a persistent systemic inflammatory state can drive induction of local tissue inflammation and subsequent production of the same factors, which then act in a paracrine manner. In an interesting study, Poullis et al.[129] demonstrated a positive relationship between levels of fecal calprotectin (a marker of local intestinal inflammation) and obesity in healthy volunteers, independent of the serum CRP level, which suggests that local intestinal inflammation may occur in individuals with EBW independently of overt gastrointestinal disease. NASH is the paradigm for the causal relationship between local tissue inflammation and carcinogenesis associated with EBW.[84] A study has demonstrated that 10% diet-induced weight loss is associated with a 25–50% reduction in proinflammatory gene expression (including TNF and IL-8) in human colorectal mucosa.[130] Further studies are required to confirm that weight loss reduces colorectal mucosal inflammation separate from the possible effects of increased physical exercise[131] and dietary change per se.

A close causal relationship is believed to exist between chronic inflammation and insulin resistance in the metabolic syndrome. One mechanism that has been proposed is nuclear factor κB (NFκB)-dependent inhibition of signaling downstream of the insulin receptor.[132]

There is some literature on the association between biomarkers of inflammation (particularly CRP) and

gastrointestinal cancer risk. In a meta-analysis of eight case–control studies, serum CRP level was demonstrated to be independently associated with an increased risk of CRC (RR 1.1 [1.0–1.3]). This relationship was only significant for men and for colon cancer, rather than for rectal cancer.[133] However, one case–control study[134] and another cross-sectional study[135] have demonstrated no relationship between CRP levels and risk of colorectal adenoma, although in the latter study a positive association with risk of colorectal adenoma was evident for serum IL-6 and TNF levels.[135] To date, no prospective study has investigated the association between increased levels of inflammatory biomarkers and future gastrointestinal and liver cancer risk.

Adipokines
Adipose tissue is an active endocrine organ that produces a range of hormones, collectively termed adipokines.[126] Leptin and adiponectin are the adipokines that have been studied in the greatest depth (Figure 1). Similar to the insulin–IGF signaling hypothesis, there are convincing clinical biomarker data linking adipokine levels with increased gastrointestinal and liver cancer risk, and there are some functional preclinical data from animal models (see below), but there is a paucity of evidence confirming the precise role that these proteins play at different stages of human gastrointestinal and hepatobiliary carcinogenesis.

Leptin
Serum leptin levels are increased in obesity.[136] The leptin receptor is overexpressed in CRC.[137] Leptin has mitogenic activity in intestinal epithelial cells,[138] reduces apoptosis in CRC cell lines[139] and has also been shown to promote growth of azoxymethane-induced colorectal tumors in mice.[140] Leptin is also implicated in esophageal carcinogenesis; mitogenic and antiapoptotic effects of leptin have been reported in esophageal adenocarcinoma cells *in vitro*.[141]

In a colonoscopy study in men, those with the highest tertile of circulating leptin levels had a BMI-adjusted 3.3-fold greater risk of colorectal adenoma than those with lowest tertile leptin levels.[142] The association between serum leptin levels and CRC is less clear although two prospective studies have shown positive associations with CRC in men.[143,144]

In a prospective study, there was a threefold increased risk of Barrett esophagus among men, but not women, in the highest quartile of serum leptin levels compared with the lowest, after adjustment for GERD symptoms.[145] Leptin also has mitogenic activity in HCC.[146]

Adiponectin
Adiponectin can be considered to be an insulin-sensitizing hormone, levels of which negatively correlate with BMI.[147] Adiponectin inhibits CRC cell growth, partly via modulation of AMPK activity and negative regulation of mTOR signaling.[148] Exogenous administration of adiponectin reduces growth of small intestinal polyps in the *Apc*[Min/+] mouse model

of intestinal tumorigenesis,[149] while an inverse association between rectal dyplastic aberrant crypt focus number in humans and plasma adiponectin has been reported.[150] A number of studies have reported plasma adiponectin levels to be inversely associated with the presence and multiplicity of colorectal adenomas[151–153] and early CRC (defined as stage pT1 or below), following adjustment for BMI.[154]

Two case–control studies have demonstrated a negative relationship of adiponectin and adiponectin receptors with gastric cancer, including noncardia gastric cancers.[155,156] Adiponectin may also have an inhibitory effect in esophageal carcinogenesis. In Barrett esophagus, expression of adiponectin receptors (Adipo-R1 and Adipo-R2) is downregulated. Adiponectin has been demonstrated to have antiproliferative properties in esophageal adenocarcinoma cell lines.[157] There is evidence that adiponectin antagonizes leptin activity during hepatic carcinogenesis.[158]

The intestinal microbiome
The intestinal microbiome in obese individuals is different from that in normal weight individuals, and there is growing appreciation of the role of gut ecology in the promotion of obesity.[100,159,160] A lesser relative abundance of *Bacteroides* species is found in obese versus lean individuals and the proportion of *Bacteroidetes* increases and *Firmicutes* decreases in association with diet-induced weight loss.[100] This alteration in gut ecology is also a consistent feature of weight reduction after bariatric surgery.[161] A case–control study determined that people with screening-detected colorectal adenoma had a significantly lower relative abundance of *Bacteroidetes* than controls, although mean body weight data from the two groups were not presented.[162]

Emerging data demonstrate that gut bacteria may be involved in colorectal carcinogenesis. In a rat model of azoxymethane-induced tumors, germ-free rats developed smaller and fewer tumors than conventionally colonized littermates.[163] There is also some evidence that levels of intramucosal and mucosal adherent bacteria are increased in patients with CRC.[164,165] It is possible, therefore, that the altered intestinal microbiome in individuals with EBW could drive carcinogenesis directly in the lower gastrointestinal tract.

One postulated mechanism linking the intestinal microbiome and EBW-driven chronic inflammation is systemic exposure to bacterial LPS secondary to changes in bacterial load and/or changes in gut permeability. In animal models, circulating LPS levels increase under high-fat-diet conditions and also cause metabolic perturbations resulting in insulin resistance.[166]

Does weight loss decrease future cancer risk?
A logical progression from the concept that EBW increases gastrointestinal and hepatobiliary cancer risk is that weight reduction should reduce subsequent cancer risk. Proof of the anticancer benefit of weight loss clearly has enormous public health consequences. However, to date, little evidence has accumulated to confirm or refute

the hypothesis that weight reduction negatively regulates gastrointestinal and hepatobiliary carcinogenesis.

The lack of data almost certainly reflects challenges in the design of observational studies in this field. Retrospective studies are subject to reverse causation bias, as weight reduction may be attributable to undiagnosed malignancy. Moreover, significant recall bias for self-reported weight is likely. Variation in individual weight over time is an important potential confounder in longitudinal cohort studies, with sustained weight loss rarely being achieved. The design of prospective studies of weight loss is also problematic. Investigation of CRC incidence requires long-term follow-up given the natural history of colorectal carcinogenesis over 10–15 years. Moreover, detection and removal of colorectal adenomas during follow-up is a significant confounder in longitudinal studies. The low incidence of esophageal adenocarcinoma progression in Barrett esophagus means that the size and duration of a study using esophageal adenocarcinoma as an end point would be unfeasibly large and lengthy. Similar methodological problems are likely to blight studies of patients with NAFLD, combined with the relative inaccessibility of the liver for tissue analysis.

Weight loss by behavioral changes

The Iowa Women's Health Study is the only major study that has prospectively investigated intentional dietary weight loss and CRC risk.[167] In this study of more than 20,000 healthy postmenopausal women, individuals who self-reported an intentional weight loss of at least 20 lb (approximately 9 kg) or more, at some point in their lives, had a nonsignificant 18% decrease in CRC incidence compared with weight-stable controls.[167] In a separate large cohort study of 65,000 Austrian adults with a mean follow-up of 8 years, neither weight loss nor weight gain was clearly associated with cancer incidence in the whole population, although a reduction in BMI of more than $0.1 \, kg/m^2$ per year was associated with a halving (HR 0.5 [0.3–0.9]) of the future risk of CRC in men when compared with men whose weight remained unchanged.[168]

Use of colorectal adenoma recurrence as a biomarker of CRC risk offers the opportunity to perform short-term studies. One Japanese study of screening colonoscopy demonstrated that individuals (who predominantly had normal BMI) who lost more than 5% of their initial body weight had lower rates of colorectal adenoma after 1 year compared with those whose weight was either unchanged or increased by 5%.[24]

There is evidence that behavioral change leading to weight loss reduces the severity of NASH.[169] We are not aware of any reported investigation of the consequences of intentional weight loss for future HCC risk.

Weight loss, physical activity and dietary change

It is self-evident that body weight, diet and physical activity are inter-related factors. A simple line of reasoning is that reduction in calorific intake and increased physical activity could reduce future cancer risk via a reduction in EBW. However, there is evidence that dietary composition and physical exercise can modulate chronic inflammation independently of changes in the mass of adipose tissue.[170,171] Moreover, calorie restriction has direct antineoplastic activity in preclinical models.[172] Increased physical activity, independent of change in body weight, has been shown to reduce biomarkers of NAFLD in short-term clinical studies.[173]

Further study of the inter-relationship between EBW, diet and level of physical activity is required in order to inform future health education programs. A large prospective cohort study from Denmark[174] demonstrated that compliance with 'healthy' lifestyle factors, including maintenance of a waist circumference of <88 cm in men, was associated with a significant reduction (RR 0.8 [0.7–1.0]) in colon cancer in men during follow-up of almost 10 years.

Weight loss following bariatric surgery

The consistent, significant degree of weight loss after bariatric surgery provides an excellent opportunity to determine whether weight loss alters future gastrointestinal cancer risk, with the obvious caveats that physiological changes following surgery may confound weight-loss-associated outcomes and that lengthy follow-up is still required. Three reports have described reduced cancer risks up to 10 years after bariatric surgery, with the largest risk reductions for hormone-responsive endometrial and postmenopausal breast cancer, but also evident for CRC.[175–177] By contrast, in a more-recent, population-based, case–control study of more than 13,000 patients undergoing bariatric surgery, there was no overall decrease in standardized incidence ratio for either breast or endometrial cancer, while the risk of CRC actually increased with time so that there was a twofold increase in risk after more than 10 years post-surgery.[178] Short-term reductions in cancer risk after bariatric surgery may be unexpected given the long natural history of gastrointestinal carcinogenesis, and could be explained by earlier diagnosis after bariatric surgery or a true biological effect of weight loss on existing tumor growth and/or progression. The possible increased risk of CRC beyond 10 years after surgery requires further investigation.

Does EBW alter cancer outcomes?

EBW also adversely affects short-term and long-term outcomes after diagnosis of gastrointestinal cancer. This is almost certainly multifactorial and is explained by effects of EBW on treatment efficacy and safety, as well as likely effects on disease progression, particularly metastatic potential.

Colorectal cancer

EBW adversely affects long-term survival following CRC diagnosis. The Iowa Women's Health Study investigated the prognostic influence of baseline anthropometric measures on CRC outcomes during a 20-year follow-up period.[179] After adjusting for age at diagnosis, smoking and stage of CRC at diagnosis, central adiposity, but not BMI, was a predictor of survival; women with the

highest tertile for waist–hip ratio had an HR of 1.37 (1.02–1.85) of CRC-related death compared with women with the lowest tertile waist–hip ratio.[179] In a prospective Australian cohort study of 528 incident CRC cases, each 10 cm increase in waist circumference was associated with a 20% (5–37%) reduction in CRC-specific survival.[180] Additionally, increasing body weight and a greater percentage of body fat, but not BMI, were significantly associated with increased CRC-related mortality during a median follow-up of 5.5 years after CRC diagnosis.[180] There is already preclinical evidence that obesity promotes liver tumor growth in mouse models of CRC liver metastasis.[181,182] However, we are unaware of any human observational study that has investigated the association between pre-morbid weight, post-diagnosis weight change and CRC recurrence.

In the short-term, a BMI >30 kg/m^2 and increased waist–hip ratio are associated with worse CRC resection outcomes.[179] Increased complication rates relate to rectal rather than colonic surgery and in men rather than women, and are explained by anastomotic leakage, increased blood transfusion requirements, longer surgery time and increased intra-abdominal collections in these patients.[183] Further studies have shown reduced sphincter-sparing outcomes, increased permanent colostomy rates following abdomino-perineal resection and a higher chance of local recurrence in men with obesity.[184] These data are likely to be also partly explained by the less challenging anatomy of the wider female pelvis, but also by the hindrance of increased abdominal adipose tissue in men.[185]

There is also increasing evidence that efficacy of chemotherapy is modulated by body size. Randomized controlled trials of adjuvant chemotherapy with 5-flurouracil-based regimens in patients with Dukes' B and C colon cancer have shown significantly worse overall survival and increased CRC recurrence rates in obese individuals compared with those who have a normal BMI.[186,187] Further evidence of chemoresistance in obesity was demonstrated in a study by Guiu and colleagues,[188] in which patients receiving treatment for metastatic CRC with bevacizumab who had increased VAT had reduced time to progression and overall survival, independent of BMI.

Esophageal cancer

The effect of obesity on esophageal adenocarcinoma outcomes has been harder to assess due to the negative energy balance and weight loss related to dysphagia prior to diagnosis. Consequently, the prevalence of obesity at diagnosis is lower than for CRC and there is a paucity of studies evaluating the impact of overweight and obesity on surgically-resectable esophageal adenocarcinoma. Data from a large cohort study show that obesity increases the rate of anastomotic leakage and increases blood transfusion requirements, but does not result in significant differences in overall morbidity, in-hospital mortality, or in overall and disease-free 5-year survival rates.[189] The occurrence of other intraoperative complications, such as recurrent laryngeal nerve paralysis and respiratory complications, is variable between studies and depends on whether the trans-hiatal or transthoracic approach is favored.[190,191] Other investigators have not shown any difference in the number of harvested lymph nodes or rates of negative resection margins in obese patients.[192]

Stomach cancer

No studies have specifically investigated outcomes from gastric cardia cancer. However, one study did examine 'proximal' gastric cancer surgical outcomes in a Korean population; the results demonstrated similar short-term complications, as well as similar recurrence and survival rates in obese versus normal weight patients.[193] In the largest study of its kind, including more than 7,900 Japanese patients with all forms of gastric cancer, overweight status was associated with an improved 5-year survival.[194] However, these data may not be generalizable to Western populations, in which obesity rates have been traditionally substantially higher than in Asia.

Pancreatic cancer

Evidence determining whether body size impacts on pancreatic cancer outcome is inconsistent. In one mouse model, obese mice that were injected with pancreatic cancer cells developed larger tumors, had more frequent metastasis and had decreased survival compared with lean mice.[195] In patients with pancreatic cancer, two studies have shown that increasing BMI is associated with increased pancreatic fistula formation and prolonged hospital stay,[196,197] although a similarly designed study previously showed no difference in fistula complications.[198] Increasing BMI also seems to increase the probability of lymph-node positivity from pancreatico-duodenal resections.[199] It has been suggested that BMI may be a poor discriminator of cancer outcome as one study showed that measures of VAT were superior in predicting higher wound and fistula complications. There are further inconsistencies in the effect of obesity on long-term survival from pancreatic cancer; studies have shown both improved[200] and worsened[59] 5-year survival following similar adjustments for disease stage.

Conclusion

EBW is a risk factor for multiple gastrointestinal and hepatobiliary cancers from the earliest, clinically apparent, premalignant phases of carcinogenesis and seems to also adversely affect cancer outcomes after diagnosis.

As obesity prevalence continues on an upward trajectory globally, the cancer burden related to EBW will rise. The epidemiological link between EBW and increased cancer risk is established but further work is required to strengthen the argument that EBW is a preventable and/or treatable factor for cancer prevention by weight loss. A recent model has highlighted the potential reduction in colon cancer incidence that is possible if ideal body weight is obtained at a population level.[201]

Further insights into the mechanistic basis of the link between EBW and carcinogenesis may lead to targeted chemoprevention strategies for obese individuals. In

particular, the role of the obesity-associated intestinal microbiome in driving the systemic chronic inflammatory response in obesity and in mucosal protumorigenic signaling deserves further attention.

Research into obesity-related adverse outcomes following gastrointestinal cancer diagnosis is in its infancy. In particular, an improved understanding of how EBW alters the biology and natural history of established cancer is required, alongside improved observational data on how EBW impacts on clinical care for patients with cancer.

Review criteria

The PubMed database was searched using the following terms: "obesity", "body weight", "gastrointestinal", "colorectum", "oesophagus", "gastric", "pancreas", "hepatocellular", "gallbladder", "cancer", "adenoma", "insulin", "inflammation" and "adipokine". Terms were searched alone and in combinations. Original articles, reviews, letters and editorials in the English language published between 1990 and January 2011 were considered. Reference lists were also hand searched to identify further relevant literature.

1. Moghaddam, A. A., Woodward, M. & Huxley, R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol. Biomarkers Prev.* **16**, 2533–2547 (2007).
2. Renehan, A. G., Tyson, M., Egger, M., Heller, R. F. & Zwahlen, M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371**, 569–578 (2008).
3. WHO. Obesity and overweight. Fact Sheet No 311. *World Health Organization* [online], http://www.who.int/mediacentre/factsheets/fs311/en/index.html (2006).
4. World Cancer Research Fund. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective* 2nd edn (American Institute for Cancer Research, Washington, 2007).
5. Vainoio, H. & Bianchinin, F. (Eds) International Agency for Research in Cancer. *Weight control and physical activity*. (IARC Press, Lyon, 2002).
6. Renehan, A. G. *et al.* Incident cancer burden attributable to excess body mass index in 30 European countries. *Int. J. Cancer* **126**, 692–702 (2010).
7. Wolk, A. *et al.* A prospective study of obesity and cancer risk (Sweden). *Cancer Causes Control* **12**, 13–21 (2001).
8. Siddiqui, A. *et al.* Obesity is associated with an increased prevalence of advanced adenomatous colon polyps in a male veteran population. *Dig. Dis. Sci.* **54**, 1560–1564 (2009).
9. Jacobson, B. C., Chan, A. T., Giovannucci, E. L. & Fuchs, C. S. Body mass index and Barrett's oesophagus in women. *Gut* **58**, 1460–1466 (2009).
10. Sato, Y., Nozaki, R., Yamada, K., Takano, M. & Haruma, K. Relation between obesity and adenomatous polyps of the large bowel. *Dig. Endosc.* **21**, 154–157 (2009).
11. Cook, M. B., Greenwood, D. C., Hardie, L. J., Wild, C. R. & Forman, D. A systematic review and meta-analysis of the risk of increasing adiposity on Barrett's esophagus. *Am. J. Gastroenterol.* **103**, 292–300 (2008).
12. Thygesen, L. C. *et al.* Prospective weight change and colon cancer risk in male US health professionals. *Int. J. Cancer* **123**, 1160–1165 (2008).
13. National Institutes for Health. *Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults. The evidence report.* (NHLBI, 1998).
14. Larsson, S. C. & Wolk, A. Obesity and colon and rectal cancer risk: a meta-analysis of prospective studies. *Am. J. Clin. Nutr.* **86**, 556–565 (2007).
15. Dai, Z., Xu, Y. C. & Niu, L. Obesity and colorectal cancer risk: a meta-analysis of cohort studies. *World J. Gastroenterol.* **13**, 4199–4206 (2007).
16. Moore, L. L. *et al.* BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. *Int. J. Obes.* **28**, 559–567 (2004).
17. Wise, L. A., Rosenberg, L., Palmer, J. R. & Adams-Campbell, L. L. Anthropometric risk factors for colorectal polyps in African-American women. *Obesity* **16**, 859–868 (2008).
18. Sedjo, R. L. *et al.* Change in body size and the risk of colorectal adenomas. *Cancer Epidemiol. Biomarkers Prev.* **16**, 526–531 (2007).
19. Larsen, I. K., Grotmol, T., Almendingen, K. & Hoff, G. Lifestyle as a predictor for colonic neoplasia in asymptomatic individuals. *BMC Gastroenterol.* **6**, 5 (2006).
20. Neugut, A. I. *et al.* Obesity and colorectal adenomatous polyps. *J. Natl Cancer Inst.* **83**, 359–361 (1991).
21. Morois, S., Mesrine, S., Josset, M., Clavel-Chapelon, F. & Boutron-Ruault, M.-C. Anthropometric factors in adulthood and risk of colorectal adenomas. *Am. J. Epidemiol.* **172**, 1166–1180 (2010).
22. Giovannucci, E. *et al.* Physical activity, obesity, and risk for colon cancer and adenoma in men. *Ann. Intern. Med.* **122**, 327–334 (1995).
23. Giovannucci, E., Colditz, G. A., Stampfer, M. J. & Willett, W. C. Physical activity obesity and risk of colorectal adenoma in women (United States). *Cancer Causes Control* **7**, 253–263 (1996).
24. Yamaji, Y. *et al.* The effect of body weight reduction on the incidence of colorectal adenoma. *Am. J. Gastroenterol.* **103**, 2061–2067 (2008).
25. Lieberman, D. A., Prindiville, S., Weiss, D. G. & Willett, W. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA* **290**, 2959–2967 (2003).
26. Anderson, J. C. *et al.* Body mass index: a marker for significant colorectal neoplasia in a screening population. *J. Clin. Gastroenterol.* **41**, 285–290 (2007).
27. Omata, F. *et al.* Modifiable risk factors for colorectal neoplasms and hyperplastic polyps. *Intern. Med.* **48**, 123–128 (2009).
28. Kim, Y. & Lee, S. An association between colonic adenoma and abdominal obesity: a cross-sectional study. *BMC Gastroenterol.* **9**, 4 (2009).
29. Betes, M. *et al.* Use of colonoscopy as a primary screening test for colorectal cancer in average risk people. *Am. J. Gastroenterol.* **98**, 2648–2654 (2003).
30. Bird, C. L., Frankl, H. D., Lee, E. R. & Haile, R. W. Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. *Am. J. Epidemiol.* **147**, 670–680 (1998).
31. Kono, S., Shinchi, K. & Imanishi, K. Body mass index and adenomas of the sigmoid colon in Japanese men. *Eur. J. Epidemiol.* **12**, 425–426 (1996).
32. Boutron-Ruault, M.-C., Senesse, P., Méance, S., Belghiti, C. & Faivre, J. Energy intake, body mass index, physical activity, and the colorectal adenoma-carcinoma sequence. *Nutr. Cancer* **39**, 50–57 (2001).
33. Wallace, K. *et al.* The association of physical activity and body mass index with the risk of large bowel polyps. *Cancer Epidemiol. Biomarkers Prev.* **14**, 2082–2086 (2005).
34. Terry, M. B. *et al.* Risk factors for advanced colorectal adenomas: a pooled analysis. *Cancer Epidemiol. Biomarkers Prev.* **11**, 622–629 (2002).
35. Wolf, L. A., Terry, P. D., Potter, J. D. & Bostick, R. M. Do factors related to endogenous and exogenous estrogens modify the relationship between obesity and risk of colorectal adenomas in women? *Cancer Epidemiol. Biomarkers Prev.* **16**, 676–683 (2007).
36. Almendingen, K., Hofstad, B. & Vatn, M. H. Does high body fatness increase the risk of presence and growth of colorectal adenomas followed up *in situ* for 3 years? *Am. J. Gastroenterol.* **96**, 2238–2246 (2001).
37. Bayerdörffer, E. *et al.* Increased risk of 'high-risk' colorectal adenomas in overweight men. *Gastroenterology* **104**, 137–144 (1993).
38. Kang, H. W. *et al.* Visceral obesity and insulin resistance as risk factors for colorectal adenoma: a cross-sectional, case-control study. *Am. J. Gastroenterol.* **105**, 178–187 (2010).
39. Kim, J. H. *et al.* Is metabolic syndrome a risk factor for colorectal adenoma? *Cancer Epidemiol. Biomarkers Prev.* **16**, 1543–1546 (2007).
40. Kim, K. S. *et al.* The frequency and risk factors of colorectal adenoma in health-check-up subjects in South Korea: relationship to abdominal obesity and age. *Gut Liver* **4**, 36–42 (2010).
41. Jacobs, E. T. *et al.* Association between body mass index and colorectal neoplasia at follow-up colonoscopy: a pooling study. *Am. J. Epidemiol.* **169**, 657–666 (2009).
42. Sainsbury, A. *et al.* Increased colorectal epithelial cell proliferation and crypt fission associated with obesity and roux-en-Y gastric bypass. *Cancer Epidemiol. Biomarkers Prev.* **17**, 1401–1410 (2008).
43. Ferrante, J. M. *et al.* Colorectal cancer screening among obese versus non-obese patients in primary care practices. *Cancer Detect. Prev.* **30**, 459–465 (2006).
44. Rosen, A. B. & Schneider, E. C. Colorectal cancer screening disparities related to obesity and gender. *J. Gen. Intern. Med.* **19**, 332–338 (2004).
45. Borg, B. B., Gupta, N. K., Zuckerman, G. R., Banerjee, B. & Gyawali, C. P. Impact of obesity on bowel preparation for colonoscopy. *Clin. Gastroenterol. Hepatol.* **7**, 670–675 (2009).
46. Pera, M., Manterola, C., Vidal, O. & Grande, L. Epidemiology of esophageal adenocarcinoma. *J. Surg. Onc.* **92**, 151–159 (2005).

47. Lagergren, J., Bergstrom, R., Lindgren, A. & Nyren, O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *N. Engl. J. Med.* **340**, 825–831 (1999).

48. Hampel, H., Abraham, N. S. & El-Serag, H. B. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. *Ann. Intern. Med.* **143**, 199–211 (2005).

49. Corley, D. A. & Kubo, A. Body mass index and gastroesophageal reflux disease: a systematic review and meta-analysis. *Am. J. Gastroenterol.* **101**, 2619–2628 (2006).

50. Corley, D. A., Kubo, A. & Zhao, W. Abdominal obesity, ethnicity and gastro-oesophageal reflux symptoms. *Gut* **56**, 756–762 (2007).

51. Whiteman, D. *et al.* The role of obesity, gastroesophageal reflux and smoking in adenocarcinomas of the esophagus and esophago-gastric junction [abstract]. *Gastroenterology* **132**, A418 (2007).

52. Yousef, F. *et al.* The incidence of esophageal cancer and high-grade dysplasia in Barrett's esophagus: a systematic review and meta-analysis. *Am. J. Epidemiol.* **168**, 237–249 (2008).

53. Kamat, P., Wen, S. J., Morris, J. & Anandasabapathy, S. Exploring the association between elevated body mass index and Barrett's esophagus: a systematic review and meta-analysis. *Ann. Thorac. Surg.* **87**, 655–662 (2009).

54. Edelstein, Z. R., Farrow, D. C., Bronner, M. P., Rosen, S. N. & Vaughan, T. L. Central adiposity and risk of Barrett's esophagus. *Gastroenterology* **133**, 403–411 (2007).

55. Corley, D. A. *et al.* Abdominal obesity and body mass index as risk factors for Barrett's esophagus. *Gastroenterology* **133**, 34–41 (2007).

56. Oberg, S., Wenner, J., Johansson, J., Walther, B. & Willen, R. Barrett esophagus: risk factors for progression to dysplasia and adenocarcinoma. *Ann. Surg.* **242**, 49–54 (2005).

57. Arslan, A. A. *et al.* Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). *Arch. Intern. Med.* **170**, 791–802 (2010).

58. Larsson, S. C., Orsini, N. & Wolk, A. Body mass index and pancreatic cancer risk: a meta-analysis of prospective studies. *Int. J. Cancer* **120**, 1993–1998 (2007).

59. Li, D. *et al.* Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA* **301**, 2553–2562 (2009).

60. Huxley, R., Ansary-Moghaddam, A., de Gonzalez, A. B., Barzi, F. & Woodward, M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br. J. Cancer* **92**, 2076–2083 (2005).

61. Permert, J. *et al.* Is profound peripheral insulin resistance in patients with pancreatic cancer caused by a tumor-associated factor? *Am. J. Surg.* **165**, 61–66 (1993).

62. Lowenfels, A. B. *et al.* Pancreatitis and the risk of pancreatic cancer. *N. Engl. J. Med.* **328**, 1433–1437 (1993).

63. Yang, P. *et al.* Overweight, obesity and gastric cancer risk: results from a meta-analysis of cohort studies. *Eur. J. Cancer* **45**, 2867–2873 (2009).

64. Leung, W. K. *et al.* Screening for gastric cancer in Asia: current evidence and practice. *Lancet Oncol.* **9**, 279–287 (2008).

65. Goldblum, J. R. *et al.* Helicobacter pylori infection, not gastroesophageal reflux, is the major cause of inflammation and intestinal metaplasia of gastric cardiac mucosa. *Am. J. Gastroenterol.* **97**, 302–311 (2002).

66. Kelley, J. R. & Duggan, J. M. Gastric cancer epidemiology and risk factors. *J. Clin. Epidemiol.* **56**, 1–9 (2003).

67. Wistuba, I. I. & Gazdar, A. F. Gallbladder cancer: Lessons from a rare tumour. *Nat. Rev. Cancer* **4**, 695–706 (2004).

68. Engeland, A., Tretli, S., Austad, G. & Bjorge, T. Height and body mass index in relation to colorectal and gallbladder cancer in two million Norwegian men and women. *Cancer Causes Control* **16**, 987–996 (2005).

69. Hsing, A. W. *et al.* Body size and the risk of biliary tract cancer: a population-based study in China. *Br. J. Cancer* **99**, 811–815 (2008).

70. Stampfer, M. J., Maclure, K. M., Colditz, G. A., Manson, J. E. & Willett, W. C. Risk of symptomatic gallstones in women with severe obesity. *Am. J. Clin. Nutr.* **55**, 652–658 (1992).

71. Lazcano-Ponce, E. C. *et al.* Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J.* **51**, 349–364 (2001).

72. Warren, B. L. & Marais, A. W. Carcinoma of the gallbladder: a possible regional predisposition in the western Cape and the northern Cape. *S. Afr. J. Surg.* **33**, 161–164 (1995).

73. Shrikhande, S. V., Barreto, S. G., Singh, S., Udwadia, T. E. & Agarwal, A. K. Cholelithiasis in gallbladder cancer: coincidence, cofactor, or cause! *Eur. J. Surg. Oncol.* **36**, 514–519 (2010).

74. Randi, G., Franceschi, S. & La Vecchia, C. Gallbladder cancer worldwide: geographical distribution and risk factors. *Int. J. Cancer* **118**, 1591–1602 (2006).

75. Mohandas, K. M. & Patil, P. S. Cholecystectomy for asymptomatic gallstones can reduce gall bladder cancer mortality in northern Indian women. *Ind. J. Gastroenterol.* **25**, 147–151 (2006).

76. Duarte, I., Llanos, O., Domke, H., Harz, C. & Valdivieso, V. Metaplasia and precursor lesions of gallbladder carcinoma. Frequency, distribution, and probability of detection in routine histologic samples. *Cancer* **72**, 1878–1884 (1993).

77. Lim, S. H. *et al.* Is metabolic syndrome one of the risk factors for gallbladder polyps Found by ultrasonography during health screening? *Gut Liver* **1**, 138–144 (2007).

78. Segawa, K. *et al.* Prevalence of gallbladder polyps among apparently healthy Japanese: ultrasonographic study. *Am. J. Gastroenterol.* **87**, 630–633 (1992).

79. Liew, P. L. *et al.* Gallbladder disease among obese patients in Taiwan. *Obes. Surg.* **17**, 383–390 (2007).

80. Patel, T. Worldwide trends in mortality from biliary tract malignancies. *BMC Cancer* **2**, 10 (2002).

81. Grainge, M. J., West, J., Solaymani-Dodaran, M., Aithal, G. P. & Card, T. R. The antecedents of biliary cancer: a primary care case-control study in the United Kingdom. *Br. J. Cancer* **100**, 178–180 (2008).

82. Welzel, T. M. *et al.* Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: a population-based case-control study. *Clin. Gastroenterol. Hepatol.* **5**, 1221–1228 (2007).

83. Welzel, T. M. *et al.* Risk factors for intrahepatic cholangiocarcinoma in a low-risk population: a nationwide case-control study. *Int. J. Cancer* **120**, 638–641 (2007).

84. Starley, B. Q., Calcagno, C. J. & Harrison, S. A. Nonalcoholic fatty liver disease and hepatocellular carcinoma: a weighty connection. *Hepatology* **51**, 1820–1832 (2010).

85. Liu, B., Balkwill, A., Reeves, G. & Beral, V. Body mass index and risk of liver cirrhosis in middle aged UK women: prospective study. *BMJ* **340**, c912 (2010).

86. Omagari, K. *et al.* Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. *J. Gastroenterol. Hepatol.* **17**, 1098–1105 (2002).

87. Browning, J. D. *et al.* Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* **40**, 1387–1395 (2004).

88. Machado, M., Marques-Vidal, P. & Cortez-Pinto, H. Hepatic histology in obese patients undergoing bariatric surgery. *J. Hepatol.* **45**, 600–606 (2006).

89. Saunders, D., Seidel, D., Allison, M. & Lyratzopoulos, G. Systematic review: the association between obesity and hepatocellular carcinoma—epidemiological evidence. *Aliment. Pharmacol. Ther.* **31**, 1051–1063 (2010).

90. Larsson, S. C. & Wolk, A. Overweight, obesity and risk of liver cancer: a meta-analysis of cohort studies. *Br. J. Cancer* **97**, 1005–1008 (2007).

91. Oh, S. W., Yoon, Y. S. & Shin, S. A. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J. Clin. Oncol.* **23**, 4742–4754 (2005).

92. Nair, S., Mason, A., Eason, J., Loss, G. & Perrillo, R. P. Is obesity an independent risk factor for hepatocellular carcinoma in cirrhosis? *Hepatology* **36**, 150–155 (2002).

93. Ohki, T. *et al.* Obesity is an independent risk factor for hepatocellular carcinoma development in chronic hepatitis C patients. *Clin. Gastroenterol. Hepatol.* **6**, 459–464 (2008).

94. Park, E. J. *et al.* Dietary and genetic obesity promote liver inflammation and tumorigenesis by enhancing IL-6 and TNF expression. *Cell* **140**, 197–208 (2010).

95. Ichikawa, T. *et al.* Two cases of non-alcoholic steatohepatitis with development of hepatocellular carcinoma without cirrhosis. *J. Gastroenterol. Hepatol.* **21**, 1865–1866 (2006).

96. Kawada, N. *et al.* Hepatocellular carcinoma arising from non-cirrhotic nonalcoholic steatohepatitis. *J. Gastroenterol.* **44**, 1190–1194 (2009).

97. Wellen, K. E. & Hotamisligil, G. S. Inflammation, stress, and diabetes. *J. Clin. Invest.* **115**, 1111–1119 (2005).

98. Roberts, D. L., Dive, C. & Renehan, A. G. Biological mechanisms linking obesity and cancer risk: new perspectives. *Ann. Rev. Med.* **61**, 301–316 (2010).

99. Lin, J. H. & Giovannucci, E. Sex hormones and colorectal cancer: what have we learned so far? *J. Natl Cancer Inst.* **102**, 1746–1747 (2010).

100. Ley, R. E., Turnbaugh, P. J., Klein, S. & Gordon, J. I. Microbial ecology: human gut microbes associated with obesity. *Nature* **444**, 1022–1023 (2006).

101. Caesar, R., Fåk, F. & Bäckhed, F. Effects of gut microbiota on obesity and atherosclerosis via modulation of inflammation and lipid metabolism. *J. Int. Med.* **268**, 320–328 (2010).

102. Cowey, S. & Hardy, R. W. The metabolic syndrome: a high-risk state for cancer? *Am. J. Pathol.* **169**, 1505–1522 (2006).

103. Donohoe, C. L., Pidgeon, G. P., Lysaght, J. & Reynolds, J. V. Obesity and gastrointestinal cancer. *Br. J. Surg.* **97**, 628–642 (2010).

104. Renehan, A. G., Frystyk, J. & Flyvbjerg, A. Obesity and cancer risk: the role of the insulin-IGF axis. *Trends Endocrinol. Metab.* **17**, 328–336 (2006).

105. Larsson, S. C., Giovannucci, E. & Wolk, A. Diabetes and colorectal cancer incidence in the cohort of Swedish men. *Diabetes Care* **28**, 1805–1807 (2005).

106. Clayton, P. E., Banerjee, I., Murray, P. G. & Renehan, A. G. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. *Nat. Rev. Endocrinol.* **7**, 11–24 (2011).

107. Giovannucci, E. Insulin, insulin-like growth factors and colon cancer: a review of the evidence. *J. Nutr.* **131**, 3109S–3120S (2001).

108. Corpet, D. E., Jacquinet, C., Peiffer, G. & Tache, S. Insulin injections promote the growth of aberrant crypt foci in the colon of rats. *Nutr. Cancer* **27**, 316–320 (1997).

109. Samani, A. A., Yakar, S., LeRoith, D. & Brodt, P. The role of the IGF system in cancer growth and metastasis: overview and recent insights. *Endocr. Rev.* **28**, 20–47 (2007).

110. Sears, R. *et al.* Multiple Ras-dependent phosphorylation pathways regulate Myc protein stability. *Genes Dev.* **14**, 2501–2514 (2000).

111. Hursting, S. D. *et al.* Reducing the weight of cancer: mechanistic targets for breaking the obesity-carcinogenesis link. *Best Pract. Res. Clin. Endocrinol. Metab.* **22**, 659–669 (2008).

112. Hosono, K. *et al.* Metformin suppresses colorectal aberrant crypt foci in a short-term clinical trial. *Cancer Prev. Res.* **3**, 1077–1083 (2010).

113. Tomimoto, A. *et al.* Metformin suppresses intestinal polyp growth in ApcMin/+ mice. *Cancer Sci.* **99**, 2136–2141 (2008).

114. Renehan, A. G. *et al.* Insulin-like growth factor (IGF)-I, IGF binding protein-3, and cancer risk: systematic review and meta-regression analysis. *Lancet* **363**, 1346–1353 (2004).

115. Schoen, R. E. *et al.* Insulin-like growth factor-I and insulin are associated with the presence and advancement of adenomatous polyps. *Gastroenterology* **129**, 464–475 (2005).

116. Renehan, A. G. *et al.* High-risk colorectal adenomas and serum insulin-like growth factors. *Br. J. Surg.* **88**, 107–113 (2001).

117. Flood, A. *et al.* Serum concentrations of insulin-like growth factor and insulin-like growth factor binding protein 3 and recurrent colorectal adenomas. *Cancer Epidemiol. Biomarkers Prev.* **17**, 1493–1498 (2008).

118. Wolpin, B. M. *et al.* Circulating insulin-like growth factor binding protein-1 and the risk of pancreatic cancer. *Cancer Res.* **67**, 7923–7928 (2007).

119. Bergmann, U., Funatomi, H., Yokoyama, M., Beger, H. G. & Korc, M. Insulin-like growth factor I overexpression in human pancreatic cancer: evidence for autocrine and paracrine roles. *Cancer Res.* **55**, 2007–2011 (1995).

120. Zhao, R., Macdonald, K. & Casson, A. G. Insulin-like growth factor type I receptor gene expression and obesity in esophageal adenocarcinoma. *Mol. Carcinog.* **48**, 982–988 (2009).

121. Hoyo, C. *et al.* IGF2R polymorphisms and risk of esophageal and gastric adenocarcinomas. *Int. J. Cancer* **125**, 2673–2678 (2009).

122. McElholm, A. R. *et al.* A population-based study of IGF axis polymorphisms and the esophageal inflammation, metaplasia, adenocarcinoma sequence. *Gastroenterology* **139**, 204–212.e3 (2010).

123. Park, H. S., Park, J. Y. & Yu, R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-[alpha] and IL-6. *Diab. Res. Clin. Pract.* **69**, 29–35 (2005).

124. Nishimura, S. *et al.* CD8+ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat. Med.* **15**, 914–920 (2009).

125. Feuerer, M. *et al.* Lean, but not obese, fat is enriched for a unique population of regulatory T cells that affect metabolic parameters. *Nat. Med.* **15**, 930–939 (2009).

126. Balistreri, C. R., Caruso, C. & Candore, G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm.* **2010**, 802078 (2010).

127. Song, M. J., Kim, K. H., Yoon, J. M. & Kim, J. B. Activation of Toll-like receptor 4 is associated with insulin resistance in adipocytes. *Biochem. Biophys. Res. Commun.* **346**, 739–745 (2006).

128. Balkwill, F., Charles, K. A. & Mantovani, A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell* **7**, 211–217 (2005).

129. Poullis, A. bowel inflammation as measured by faecal calprotectin: a link between lifestyle factors and colorectal cancer risk. *Cancer Epidemiol. Biomarkers Prev.* **13**, 279–284 (2004).

130. Pendyala, S., Neff, L. M., Suárez-Fariñas, M. & Holt, P. R. Diet-induced weight loss reduces colorectal inflammation: implications for colorectal carcinogenesis. *Am. J. Clin. Nutr.* **93**, 234–242 (2011).

131. Martínez, M. E. *et al.* Physical activity, body mass index, and prostaglandin E2 levels in rectal mucosa. *J. Natl Cancer Inst.* **91**, 950–953 (1999).

132. Hotamisligil, G. S. Inflammation and metabolic disorders. *Nature* **444**, 860–867 (2006).

133. Tsilidis, K. K. *et al.* C-reactive protein and colorectal cancer risk: a systematic review of prospective studies. *Int. J. Cancer* **123**, 1133–1140 (2008).

134. Tsilidis, K. K. *et al.* C-reactive protein and colorectal adenoma in the CLUE II cohort. *Cancer Causes Control* **19**, 559–567 (2008).

135. Kim, S. *et al.* Circulating levels of inflammatory cytokines and risk of colorectal adenomas. *Cancer Res.* **68**, 323–328 (2008).

136. Considine, R. V. *et al.* Serum immunoreactive leptin concentrations in normal-weight and obese humans. *N. Engl. J. Med.* **334**, 292–295 (1996).

137. Aloulou, N. *et al.* Involvement of the leptin receptor in the immune response in intestinal cancer. *Cancer Res.* **68**, 9413–9422 (2008).

138. Liu, Z. H., Uesaka, T., Watanabe, H. & Kato, N. High fat diet enhances colonic cell proliferation and carcinogenesis in rats by elevating serum leptin. *Int. J. Oncol.* **19**, 1009–1014 (2001).

139. Rouet-Benzineb, P. *et al.* Leptin counteracts sodium butyrate-induced apoptosis in human colon cancer HT-29 cells via NF-kappaB signaling. *J. Biol. Chem.* **279**, 16495–16502 (2004).

140. Hirose, Y. *et al.* Enhancement of development of azoxymethane-induced colonic premalignant lesions in C57BL/KsJ-db/db mice. *Carcinogenesis* **25**, 821–825 (2004).

141. Ogunwobi, O., Mutungi, G. & Beales, I. L. P. Leptin stimulates proliferation and inhibits apoptosis in Barrett's esophageal adenocarcinoma cells by cyclooxygenase-2-dependent, prostaglandin-E2-mediated transactivation of the epidermal growth factor receptor and c-Jun NH2-terminal kinase activation. *Endocrinology* **147**, 4505–4516 (2006).

142. Chia, V. M. *et al.* Leptin concentrations, leptin receptor polymorphisms, and colorectal adenoma risk. *Cancer Epidemiol. Biomarkers Prev.* **16**, 2697–2703 (2007).

143. Stattin, P. *et al.* Plasma leptin and colorectal cancer risk: a prospective study in Northern Sweden. *Oncol. Rep.* **10**, 2015–2021 (2003).

144. Stattin, P. *et al.* Obesity and colon cancer: does leptin provide a link? *Int. J. Cancer* **109**, 149–152 (2004).

145. Kendall, B. J. *et al.* Leptin and the risk of Barrett's oesophagus. *Gut* **57**, 448–454 (2008).

146. Wang, S. N., Lee, K. T. & Ker, C. G. Leptin in hepatocellular carcinoma. *World J. Gastroenterol.* **16**, 5801–5809 (2010).

147. Arita, Y. *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem. Biophys. Res. Commun.* **257**, 79–83 (1999).

148. Sugiyama, M. *et al.* Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. *Int. J. Oncol.* **34**, 339–344 (2009).

149. Otani, K. *et al.* Adiponectin suppresses tumorigenesis in Apc(Min/+) mice. *Cancer Lett.* **288**, 177–182 (2010).

150. Takahashi, H. *et al.* Association of visceral fat accumulation and plasma adiponectin with rectal dysplastic aberrant crypt foci in a clinical population. *Cancer Sci.* **100**, 29–32 (2009).

151. Wei, E. K., Giovannucci, E., Fuchs, C. S., Willett, W. C. & Mantzoros, C. S. Low plasma adiponectin levels and risk of colorectal cancer in men: A prospective study. *J. Natl Cancer Inst.* **97**, 1688–1694 (2005).

152. Nakajima, T. E. *et al.* Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. *Cancer Sci.* **101**, 1286–1291 (2010).

153. Yamaji, T., Iwasaki, M., Sasazuki, S. & Tsugane, S. Interaction between adiponectin and leptin Influences the risk of colorectal adenoma. *Cancer Res.* **70**, 5430–5437 (2010).

154. Otake, S. *et al.* Decreased levels of plasma adiponectin associated with increased risk of colorectal cancer. *World J. Gastroenterol.* **16**, 1252–1257 (2010).

155. Ishikawa, M. *et al.* Plasma adiponectin and gastric cancer. *Clin. Cancer Res.* **11**, 466–472 (2005).

156. Otani, K. *et al.* Adiponectin receptors are downregulated in human gastric cancer. *J. Gastroenterol.* **45**, 918–927 (2010).

157. Konturek, P. C., Burnat, G., Rau, T., Hahn, E. G. & Konturek, S. Effect of adiponectin and ghrelin on apoptosis of barrett adenocarcinoma cell line. *Dig. Dis. Sci.* **53**, 597–605 (2008).

157. Sharma, D. *et al.* Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. *Hepatology* **52**, 1713–1722 (2010).

159. Backhed, F. *et al.* The gut microbiota as an environmental factor that regulates fat storage. *Proc. Natl Acad. Sci. USA* **101**, 15718–15723 (2004).

160. Backhed, F., Manchester, J. K., Semenkovich, C. F. & Gordon, J. I. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc. Natl Acad. Sci. USA* **104**, 979–984 (2007).

161. Furet, J. P. *et al.* Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers. *Diabetes* **59**, 3049–3057 (2010).

162. Shen, X. J. *et al.* Molecular characterization of mucosal adherent bacteria and associations with colorectal adenomas. *Gut Microbes* **1**, 138–147 (2010).

163. Vannucci, L. *et al.* Colorectal carcinogenesis in germ-free and conventionally reared rats: different intestinal environments affect the systemic immunity. *Int. J. Oncol.* **32**, 609–617 (2008).

164. Martin, H. M. *et al.* Enhanced *Escherichia coli* adherence and invasion in Crohn's disease and colon cancer. *Gastroenterology* **127**, 80–93 (2004).

165. Swidsinski, A. *et al.* Association between intraepithelial *Escherichia coli* and colorectal cancer. *Gastroenterology* **115**, 281–286 (1998).

166. Cani, P. D. *et al.* Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes* **56**, 1761–1772 (2007).

167. Parker, E. D. & Folsom, A. R. Intentional weight loss and incidence of obesity-related cancers: the Iowa Women's Health Study. *Int. J. Obes. Relat. Metab. Disord.* **27**, 1447–1452 (2003).

168. Rapp, K. *et al.* Weight change and cancer risk in a cohort of more than 65 000 adults in Austria. *Ann. Oncol.* **19**, 641–648 (2008).

169. St. George, A. *et al.* Effect of a lifestyle intervention in patients with abnormal liver enzymes and metabolic risk factors. *J. Gastroenterol. Hepatol.* **24**, 399–407 (2009).

170. Stewart, L. K. *et al.* The influence of exercise training on inflammatory cytokines and C-reactive protein. *Med. Sci. Sports Exerc.* **39**, 1714–1719 (2007).

171. Rankin, J. W. & Turpyn, A. D. Low carbohydrate, high fat diet increases C-reactive protein during weight loss. *J. Am. Coll. Nutr.* **26**, 163–169 (2007).

172. Tammariello, A. E. & Milner, J. A. Mouse models for unraveling the importance of diet in colon cancer prevention. *J. Nutr. Biochem.* **21**, 77–88 (2010).

173. Johnson, N. A. *et al.* Aerobic exercise training reduces hepatic and visceral lipids in obese individuals without weight loss. *Hepatology* **50**, 1105–1112 (2009).

174. Kirkegaard, H. *et al.* Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. *BMJ* **341**, c5504 (2010).

175. Sjöström, L. *et al.* Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. *Lancet Oncol.* **10**, 653–662 (2009).

176. Adams, T. D. *et al.* Cancer incidence and mortality after gastric bypass surgery. *Obesity* **17**, 796–802 (2009).

177. Christou, N. V., Lieberman, M., Sampalis, F. & Sampalis, J. S. Bariatric surgery reduces cancer risk in morbidly obese patients. *Surg. Obes. Relat. Dis.* **4**, 691–695 (2008).

178. Plecka-Ostlund, M. Risk of obesity-related cancer after obesity surgery in a population-based cohort study. *Ann. Surg.* **252**, 972–976 (2010).

179. Prizment, A. E., Flood, A., Anderson, K. E. & Folsom, A. R. Survival of women with colon cancer in relation to precancer anthropometric characteristics: the Iowa Women's Health Study. *Cancer Epidemiol. Biomarkers Prev.* **19**, 2229–2237 (2010).

180. Haydon, A. M. M., MacInnis, R. J., English, D. R. & Giles, G. G. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. *Gut* **55**, 62–67 (2006).

181. Wu, Y. J. *et al.* Insulin-like growth factor-I regulates the liver microenvironment in obese mice and promotes liver metastasis. *Cancer Res.* **70**, 57–67 (2010).

182. Earl, T. M. *et al.* Silencing of TLR4 decreases liver tumor burden in a murine model of colorectal metastasis and hepatic steatosis. *Ann. Surg. Oncol.* **16**, 1043–1050 (2009).

183. Benoist, S., Panis, Y., Alves, A. & Valleur, P. Impact of obesity on surgical outcomes after colorectal resection. *Am. J. Surg.* **179**, 275–281 (2000).

184. Meyerhardt, J. A. *et al.* Impact of body mass index on outcomes and treatment-related toxicity in patients with stage II and III rectal cancer: findings from intergroup trial 0114. *J. Clin. Oncol.* **22**, 648–657 (2004).

185. Moon, H. G. *et al.* Visceral obesity may affect oncologic outcome in patients with colorectal cancer. *Ann. Surg. Oncol.* **15**, 1918–1922 (2008).

186. Meyerhardt, J. A. *et al.* Influence of body mass index on outcomes and treatment-related toxicity in patients with colon carcinoma. *Cancer* **98**, 484–495 (2003).

187. Dignam, J. J. *et al.* Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. *J. Natl Cancer Inst.* **98**, 1647–1654 (2006).

188. Guiu, B. *et al.* Visceral fat area is an independent predictive biomarker of outcome after first-line bevacizumab-based treatment in metastatic colorectal cancer. *Gut* **59**, 341–347 (2010).

189. Grotenhuis, B. A. *et al.* Prognostic value of body mass index on short-term and long-term outcome after resection of esophageal cancer. *World J. Surg.* **34**, 2621–2627 (2010).

190. Healy, L. A. *et al.* Impact of obesity on outcomes in the management of localized adenocarcinoma of the esophagus and esophagogastric junction. *J. Thorac. Cardiovasc. Surg.* **134**, 1284–1291 (2007).

191. Scipione, C. N., Chang, A. C., Pickens, A., Lau, C. L. & Orringer, M. B. Transhiatal esophagectomy in the profoundly obese: implications and experience. *Ann. Thorac. Surg.* **84**, 376–383 (2007).

192. Melis, M. *et al.* An elevated body mass index does not reduce survival after esophagectomy for cancer. *Ann. Surg. Oncol.* doi:10.1245/s10434-010-1336-1.

193. Oh, S. J. *et al.* Effect of being overweight on postoperative morbidity and long-term surgical outcomes in proximal gastric carcinoma. *J. Gastroenterol. Hepatol.* **24**, 475–479 (2009).

194. Tokunaga, M. *et al.* Better 5-year survival rate following curative gastrectomy in overweight patients. *Ann. Surg. Oncol.* **16**, 3245–3251 (2009).

195. Zyromski, N. J. *et al.* Obesity potentiates the growth and dissemination of pancreatic cancer. *Surgery* **146**, 258–263 (2009).

196. Noun, R. *et al.* The impact of obesity on surgical outcome after pancreaticoduodenectomy. *JOP* **9**, 468–476 (2008).

197. Rosso, E. *et al.* The role of "fatty pancreas" and of BMI in the occurrence of pancreatic fistula after pancreaticoduodenectomy. *J. Gastrointest. Surg.* **13**, 1845–1851 (2009).

198. Lermite, E. *et al.* Risk factors of pancreatic fistula and delayed gastric emptying after pancreaticoduodenectomy with pancreaticogastrostomy. *J. Am. Coll. Surg.* **204**, 588–596 (2007).

199. Fleming, J. B. *et al.* Influence of obesity on cancer-related outcomes after pancreatectomy to treat pancreatic adenocarcinoma. *Arch. Surg.* **144**, 216–221 (2009).

200. Tsai, S. *et al.* Impact of obesity on perioperative outcomes and survival following pancreaticoduodenectomy for pancreatic cancer: a large single-institution study. *J. Gastrointest. Surg.* **14**, 1143–1150 (2010).

201. de Vries, E. *et al.* Lifestyle changes and reduction of colon cancer incidence in Europe: a scenario study of physical activity promotion and weight reduction. *Eur. J. Cancer* **46**, 2605–2616 (2010).