The association between obesity and gastrointestinal cancer

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Abstract: Obesity is now recognized as one of the foremost modifiable cancer risk factors. Numerous, large-scale epidemiological studies have demonstrated that there is a clear association between the risk of cancer development at a number of sites and raised body mass index. Despite an expanding body of epidemiological evidence in support of the link between obesity and cancer, the underlying molecular mechanisms responsible are poorly characterized. Adipocytes from obese subjects exhibit an altered endocrine function and secretory profile leading to an increased release of proinflammatory molecules, resulting in a chronic low-grade inflammatory state that has been linked to the development of cancer. The level of adipokine production from adipose tissue is strongly influenced by the immune cell populations present in adipose tissue. Studies of circulating adipokine measurement are prone to bias, and although animal models have indicated some areas of promise, evidence from human studies is lacking. Cross-talk between tumor cells and adjacent adipose tissue may be an important factor in the carcinogenic process.

Keywords: obesity, gastrointestinal cancer, adipokines, insulin resistance

Introduction: obesity and cancer epidemiology

Geographic and socioeconomic differences in cancer trends and incidences indicate that environmental factors affect the development of cancer. Changes in cancer epidemiology over the last number of decades cannot be accounted for solely by changing population demographics – including increased life expectancy, increased population numbers, or improved screening, detection, and treatment leading to increased numbers of people living with a cancer diagnosis. Since not enough time has elapsed in order for significant genetic changes to account for the increased cancer incidence, it is thought that it is attributable to environmental factors. There has been an evolution in society's structure from hunter–gatherer to peasant–farmer and increasingly urbanized to industrialized. Doubtless there have been a number of closely inter-related changes to body composition, physical activity, energy balance, and diet, and it is these environmental changes which are thought to be the cause of the alteration in cancer epidemiology.

The most compelling evidence for the association between environmental factors and cancer incidence comes from migrant studies. Migration of populations, from rural to urban environments and within and between countries has been used to show how migrant populations display changes in cancer incidence similar to their adopted country within one to two generations.¹ For example, a migrant Japanese population which moved to Hawaii developed a threefold increase in breast cancer incidence in the first generation of migrants and subsequently developed up to a fivefold increase

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in the second generation.² Similarly, the colorectal cancer incidence increased by fourfold in the first generation, but did not increase with subsequent generations, and the gastric cancer incidence, which is high in Japanese populations within Japan, decreased by almost 50% in the first generation and fell again in the second generation. Thus, these Japanese migrants developed cancer in the same pattern as their Caucasian Hawaiian neighbors than those of the same ethnicity in Japan. Similar changes among other migrant populations have been replicated in Australia,³ Canada,⁴ and the United States.⁵ Cancer incidence rates generally become similar to those of their adopted country in second generation immigrants – long before any new genetic differences could arise.

Interestingly, the increase in cancer due to environmental factors is similar in populations with clearly identifiable heritable risk factors for cancer development than those with sporadic cancers. For example, in an Icelandic population the risk of breast cancer by age 70 in BRCA-2 carriers increased from 18.6% in 1920 to 71.9% in 2002. This was matched by a parallel increase in the sporadic breast cancer rate, which rose from 1.8% to 7.5%.⁶

Excess nutrition and low physical activity can manifest itself as obesity. The prevalence of obesity has increased rapidly over the past 30 years.⁷ Being overweight or obese is the most prevalent body composition in some countries, for example, in the United States, where 72% of men and 67% of females are overweight or obese.⁸ Rates are increasing in a similar fashion in Western Europe, with 65% of men and 56% of women being overweight or obese in the United Kingdom.⁹ This trend shows no signs of abating as obesity rates are increasing among children,¹⁰ and overweight children tend to become overweight adults.¹¹

In countries where sedentary lifestyles and high-energy foods are abundant, it is easy to see how energy intake exceeds that expended. It has been estimated that ingestion of 5% more calories than expended may result in an accumulation of 5 kg of adipose tissue in a single year.¹² Humans are poorly able to distinguish foods with a high-energy content per mass, such as those high in fat and sugar, and this often leads to passive increases in calorie consumption, which is deposited as excess adipose tissue.¹³ In a recent analysis of the European Prospective Investigation into Cancer and Nutrition (EPIC) study, avoiding inactivity led to an equal reduction in all-cause mortality risk as did avoiding a high waist circumference, indicating that physical inactivity plays an independent role in mortality risk even in overweight patients.¹⁴

Morbidity and mortality, attributable to obesity, rise sharply with body mass index (BMI) $>30 \text{ kg/m}^2$,¹⁵ with the risk of premature death doubling as BMI exceeds 35 kg/m^2 .¹⁶ BMI alone is a poor measure of obesity as it may poorly reflect body composition, with raised BMIs found in patients with high muscle bulk.¹⁷ It also does not reflect differences in the site of fat distribution, and it is thought that visceral or central adiposity is more often associated with metabolic dysregulation in obesity.^{18,19} For a given BMI, men are at greater risk of mortality than women,²⁰ possibly relating to the increase in visceral adiposity in men versus women, which is not reflected by BMI. Conversely, energy restriction in laboratory animals has been shown to decrease spontaneous tumor occurrence in a meta-analysis.²¹ Mice genetically susceptible to the development of colon cancers have a reduced incidence of polyps when fed a calorie-restricted diet.²² Patients who had been hospitalized for anorexia nervosa prior to the age of 40 have been shown to have a 23%–76% decreased incidence of breast cancer (depending on parity).²³ Thus, the optimal dietary approach to cancer risk reduction is thought to be CRON – calorie restriction with optimal nutrition.²⁴

Epidemiological studies have provided convincing evidence for the association of obesity with cancer.^{25–27} The World Cancer Research Fund used a standardized approach in analyzing the evidence and concluded that there is convincing evidence of association between obesity and esophageal adenocarcinoma and pancreas, colorectum, breast (postmenopausal), endometrium, and kidney cancer.²⁸

The largest meta-analysis to date includes 282,000 patients from prospective observational studies with over 133 million person-years of follow-up.²⁹ This comprehensive analysis shows that high BMI is associated with an increased incidence of many types of cancer. The association is modest with risk estimates of 1.1–1.6 per 5 kg/m^2 incremental increase in BMI. This 5 kg/m^2 increase in BMI corresponds to a 15 kg weight gain in men and 13 kg in women, with an average BMI of 23 kg/m^2 .

Longitudinal epidemiological studies implicate obesity as a causal factor in the development of cancer. Further epidemiological evidence of causality comes from prospective studies of patients undergoing bariatric surgery with sustained long-term weight loss, such as those included in the Swedish Obese Subjects (SOS) study. At 10 years follow-up, the SOS study reports a reduced risk of developing cancer, which seems to be present in women alone (women: relative risk 0.58, 95% confidence interval [CI] 0.44–0.77 versus men: relative risk 0.97, 95% CI 0.62–1.52). Whether sex-specific

or due to insufficient length of follow-up and/or sample size, it remains an area for future study.³⁰

Obesity and cancer development: causal associations

Since obesity is now an established risk factor for cancer development, the next question is how this may be exploited in order to uncover mechanisms underpinning the link between obesity and carcinogenesis, thus opening future avenues for cancer prevention and therapy.

Inflammation

Excess adipose tissue results in elevated levels of proinflammatory adipokines, resulting in an imbalance between increased inflammatory stimuli and decreased anti-inflammatory mechanisms, leading to persistent low-grade inflammation.^{31–33} Adipose tissue, through the systemic alterations associated with obesity, may support the development of malignant potential in susceptible cells through supporting the other malignant processes within cancer cells, such as invasion and metastases, evasion of apoptosis, and promotion of angiogenesis and systemic inflammation. Inflammation provides the selective pressure that may drive the accumulation of mutations and results in poor immune surveillance of tumors once they develop.

Cytokines secreted by adipose tissue include the following inflammatory cytokines: TNF- α , IL-6, IL-8, IL-10, IL-1 receptor agonist (IL-1Ra), macrophage inflammatory protein 1 (MIP-1), and monocyte chemoattractant protein 1 (MCP-1). Some of these cytokines have an anti-inflammatory effect (IL-10 and IL-1Ra), but the majority are proinflammatory, and overall markers of systemic inflammation, such as C-reactive protein (CRP), are increased in the obese state.³⁴ The increased size and number of adipocytes in adipose tissue results in areas of hypoxia within the tissue. This hypoxia induces the secretion of inflammatory factors in order to promote angiogenesis.^{35–37} Inflammatory cytokines attract infiltrating immune cells, which in turn produce more inflammatory cytokines. In fact, the overall level of adipokine production from adipose tissue is strongly influenced by the degree of immune cell infiltration present in adipose tissue.^{38–41} Adipose tissue in obese people is infiltrated with macrophages, and the number of macrophages correlates with the degree of adiposity.⁴²

In obesity-associated systemic inflammation, there are increased circulating factors that activate the cells of the tumor microenvironment. The cells in the tumor microenvironment (including fibroblasts, neutrophils, T-cells,

macrophages, and mast cells) secrete factors which support proliferation and invasion of epithelium cells, which under normal circumstances would result in wound healing, but in the presence of mutated cancer cells, promotes their further proliferation and invasion.

Animal models provide some evidence supporting these mechanisms. Obese rat models have increased inflammatory transcription factor expression (TNF- α and NF κ B) in their tumor cells indicating activation of the tumor cells themselves to produce inflammatory cytokines which suppress the surrounding immune cells.⁴³ Furthermore, there is emerging evidence that adipose tissue stromal cells may be a source of stromal cells in tumor microenvironments.⁴⁴ Early adipocyte precursor stem cells can differentiate into stromal cells.⁴⁵ In animal models of obesity, adipose stromal cells and adipose endothelial cells from inflamed visceral adipose tissue migrate to tumor sites.⁴⁶ Stromal cells in the tumor microenvironment promote angiogenesis and support tumor progression.⁴⁷

Levels of inflammatory cytokines, such as IL-6 and TNF- α seem to be associated with more advanced tumors and hence poor prognosis,⁴⁸ perhaps reflecting the known association between cancer cachexia and increased inflammation.⁴⁹ However, there appears to be increased serum IL-6 in patients with a colorectal adenoma.^{50,51} Whether IL-6 is a biomarker of inflammation or plays a causal role in cancer development is an area for future study. Preclinical studies have shown promotion of progression of colon cancer cells by IL-6,^{52,53} and in animals of colon cancer, IL-6 seems to enhance colon tumor growth.⁵⁴

A potential confounding factor in the role of inflammation in obesity and carcinogenesis is the find that systemic inflammation is increased in patients with a diet high in fat and refined sugar.⁵⁵ Adherence to a Mediterranean diet (rich in vegetables, fruit, legumes, and grains) attenuates inflammation in healthy adults.⁵⁶ Studies in mice have indicated that this inflammation is mediated by changes in the gut microbiota,⁵⁷ and it may be that obesity is merely a marker of this metabolic dysregulation rather than a key driver in systemic inflammation. Diet-induced weight loss decreases systemic inflammation in a randomized controlled trial of obese patients, even if the amount of weight loss (on average 5.6%) was not enough to reverse the obese state.⁵⁸

Adipokine secretion

As an endocrine organ, adipose tissue produces an array of cytoactive compounds, including the aforementioned inflammatory cytokines, with biologic functions, which

influence metabolism. Obesity alters the amount of these proteins secreted and they may individually or collectively influence the development of cancer.

Leptin is primarily produced by white adipose tissue and acts to indicate satiety. In obesity, there is both increased production and relative resistance leading to further increases in production. It has proinflammatory and proliferative functions.⁵⁹ Serum leptin is increased in patients with obesity, but there is no clear association with circulating levels in patients and cancer risk.^{60,61} A polymorphism which may alter serum leptin levels, LEP G2548A, has been associated in a meta-analysis with a small increased overall cancer risk (odds ratio 1.27, 95% CI 1.05–1.54).⁶² There appears to be an interplay between leptin and adiponectin, at least in experimental models of gastrointestinal cancers with down-regulation of leptin-induced proliferation by adiponectin in both hepatocellular⁶³ and esophageal carcinomas.⁶⁴

Adiponectin is an abundant cytokine secreted by adipocytes in visceral fat depots, but levels are inversely associated with obesity.⁶⁵ Adiponectin has antiangiogenic and anti-inflammatory properties, and in animal models, it inhibits tumor growth.⁶⁶ Circulating levels are reduced in patients with postmenopausal breast cancer^{67–69} and appear to be correlated with survival outcomes.⁷⁰ Decreased expression of adiponectin is closely correlated with insulin resistance,^{71,72} and which mechanism is more closely correlated with carcinogenesis is unclear.

Adiponectin may also reduce expression of proinflammatory cytokines such as NF κ B by reducing the growth of macrophages⁷³ and other proteins via AMP kinase-induced downregulation of the proliferative mTOR pathway.^{74,75}

In animal models, low serum adiponectin levels are associated with increased development of hepatic⁷⁶ and colorectal adenomas.⁷⁷ Adiponectin serum levels are inversely associated with colorectal cancer risk as shown by a meta-analysis (odds ratio 0.716, 95% CI 0.606–0.847),⁷⁸ but this finding was not independent of either BMI or waist circumference.

Hyperinsulinemia and the insulin-like growth factor axis

One of the cardinal changes of the obese phenotype is hyperinsulinemia, and this has also been proposed as a procarcinogenic mechanism in patients with excess adipose tissue.

Insulin resistance is highly correlated with increased body weight and is reversed with weight loss.⁷⁹ The mechanisms by which obesity causes insulin resistance are not

fully elucidated, but it appears that inflammatory events are of central importance. Raised circulating free fatty acids, due to increased lipolysis in obese subjects, are a factor in the development of insulin resistance as they affect hepatic glucose production.⁸⁰ Insulin is a mitogen and is central to the maintenance of cells in the *in vitro* setting.⁸¹ Epidemiological studies report a consistent association between the presence of type 2 diabetes and cancers of the liver, pancreas, endometrium, breast, colorectal, bladder, non-Hodgkin's lymphoma, and kidney.⁸² Confounding factors such as obesity, diet, socioeconomic status, physical activity, and smoking make it difficult to unpick how insulin resistance translates into the upregulation of cancer cell growth.

Studies to clarify this have often used supraphysiological doses of insulin to promote tumorigenesis in animal studies,⁸³ but these doses are not clinically relevant in humans. So it is hypothesized that the coregulated and largely homologous insulin-like growth factor (IGF) system may mediate the cancer risk as activation of the IGF 1 receptor (IGF1R) leads to decreased apoptosis and increased invasiveness.^{84,85} Increased expression of IGF1R are reported in a number of cancer subtypes.^{86–88} Visceral obesity may influence the IGF1R expression in tumor tissue – in tumor samples from patients with esophageal adenocarcinoma, patients with abdominal obesity were more likely to have increased IGF1R mRNA expression and protein expression in their tumors.⁸⁸

Peritumoral adipose tissue

While there are a number of systemic alterations that occur within the obese state which may putatively impact tumor growth and metastasis, there is also cross-talk between cancer cells within a tumor and the peritumoral adipocytes. Tumor cells induced lipolysis in cancer-associated adipocytes, which induces them to undergo differentiation into fibroblast-like cells.⁶³ These cells produced proinflammatory cytokines, which in turn support tumor cells development.

Potential therapeutic avenues

Understanding mechanisms promoting cancer development in obese patients may lead to potential development of new anticancer targets. The role of bariatric surgery in delivering sustained large-volume weight loss is well established, with most procedures leading to excess weight loss of 60%–70% within 2 years of surgery.^{89,90} Whether this translates into a reduced cancer-related mortality is not clear. As previously mentioned, the largest single study of bariatric procedures

(the SOS study) has shown mixed results with respect to decreased cancer incidence.⁹¹ Reductions in IL-6, TNF- α , and CRP are reported following weight loss in cohort studies.⁹²

Disclosure

The authors report no conflicts of interest in this work.

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