Review Article

Crossroad between Obesity and Gastrointestinal Cancers: A Review of Molecular Mechanisms and Interventions

Abstract

The burden of gastrointestinal (GI) cancer is increasing worldwide, and in the past decade, cancer had entered the list of chronic debilitating diseases whose risk is substantially increased by hypernutrition. Obesity may increase the risk of cancer by the imbalance of various mechanisms including insulin and insulin-like growth factor1 (IGF-I) signaling, systemic inflammation, immune dysregulation, tumor angiogenesis, adipokines secretion, and intestinal microbiota that usually act interdependently. An increased understanding of the mechanisms underlying obesity-GI cancer link can provide multiple opportunities for cancer prevention. This review discusses various mechanisms involved molecular mechanisms linking obesity with GI cancers including esophagus, stomach, colorectal and hepatocellular. Furthermore, an optional intervention such as diet restriction and exercise is described, which may be preventive or therapeutic in GI cancer.

Keywords: *Gastrointestinal tract, molecular mechanisms, neoplasms, obesity*

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Introduction

Obesity, which is defined as regionally, globally or both excess and abnormal fat accumulation currently, is classified as one of the most important noncommunicable diseases. Obesity is a major risk factor for noncommunicable diseases including cancer, cardiovascular diseases, and diabetes mellitus and among which cancer is the leading cause of many disorders, death, and disabilities worldwide.[1]

According to world health organization (WHO) body mass index (BMI ≥25 Kg/m^2), more than 1.9 billion adults in 2016 are estimated to be overweight and 650 million people were obese based on BMI ≥30 Kg/m^2.[2]

World Cancer Research Fund (WCRF) has shown that currently seven cancers including esophageal adenocarcinoma, pancreas, colorectal, postmenopausal breast, endometrium, kidney, and liver have a causal relationship with obesity; therefore, there is strong evidence that obesity increases the risk of these cancers [Figure 1] illustrates obesity relationship with some types of cancer.[3]

In this regard, a recent case-control study by Tahergorabi *et al*. on 68 patients with gastrointestinal (GI) cancers and 100 control subjects without disease showed that the risk of GI cancer in people with high blood glucose was 3.35 times higher than that in those with normal blood glucose (OR 3.35, 95% CI, 1.41–7.94; P = 0.006), 2.37 times higher in subjects with lower HDL (OR 2.37, 95%CI, 1.18–4.78), and 10.4 times higher in overweight people (OR 10.4, 95% CI, 2.23–48.5), which are all considered as features of metabolic syndrome.[4]

Since GI system has many diverse types of epithelial cells and different tissues with various functions, it is reasonable that it can become dysregulated and prone to cancer development.[5]

A single mechanism is unlikely to contribute for all obesity-associated tumors, but interdependent mechanisms are likely to contribute for obesity-associated carcinogenesis including altered insulin and insulin-like growth factor 1 (IGF-I) signaling pathways, systemic inflammation and immune dysregulation, adipokines, and GI microbiota.[6]

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Molecular Mechanisms Linking Obesity and Gastrointestinal Cancers

Esophageal cancer

Esophageal cancer is the eighth most common cancer which shows a great geographic variation in incidence and mortality rates worldwide.[7] Adenocarcinoma is the most common histological type of esophageal cancer worldwide[8] and it is mostly limited to developed countries, but occurs in less developed regions with higher incidence like China, Iran, India, Japan, and the region around the Caspian Sea.[9] In many studies, obesity has been identified to be one of the risk factors for esophageal adenocarcinoma (EAC) in both men and women.[10]

Obesity, especially abdominal adiposity, is associated with a higher prevalence of gastroesophageal reflux disease (GERD) mechanically and systemically via metabolic/inflammatory pathways, which in turn leads to Barretts's esophagus (BE) and intestinal metaplasia and EAC.[11,12] BE is a premalignant disorder as a metaplastic columnar replacement of the normal stratified squamous epithelium of the distal esophagus in response to chronic acid exposure resulting from GERD.[13]

Mechanisms that mediate the association between obesity and esophageal cancer are explained as follows.

Insulin and IGF-I signaling

Obesity is strongly associated with a decrease in tissue response to insulin stimulation, hyperinsulinemia, and insulin resistance.[14] Several studies have demonstrated the role of insulin and IGF signaling in the development and progression of certain cancers and BE and EAC that are premalignant disorder.

Insulin is anabolic in tissues of insulin sensitive including muscle, adipose tissue, and liver as these tissues infrequently develop malignancies likely due to the protective effect of insulin regulation on metabolic processes.[6] Insulin with binding to its cognate receptors or IGF-I activates downstream cascades including phosphoinositide 3 kinase (PI3K)/mitogen activated protein kinase (MAPK) and mammalian target of rapamycin (mTOR) signaling pathways with its metabolic and cellular growth effects. These pathways trigger cascades for mitogenesis, antiapoptosis, angiogenesis, and tumor associated lymphangiogenesis and insulin hormone favors tumor development and metastasis.[15,16]

IGF-I is the most highly abundant isoform among multiple isoforms of IGF in circulation.[17] IGF-1 can contribute to cancer development and metastasis by stimulation of cell division and inhibition of apoptosis through the Ras-MAPK pathway in insulin-sensitive tissues than inducing FOXO1 transcriptional activity, which regulates metabolism.[18] In this context, viscerally obese subjects with EAC showed increased tumor expression of insulin-like growth factor 1 receptor (IGF1R) in gene expression analyses and patients whose tumors did not express IGF1R had longer survival than patients with IGF1R positive tumors.[19]

Adipokines and inflammatory factors

Abnormal circulating serum levels of adipokines, such as leptin and adiponectin released from visceral adipose tissue, and proinflammatory cytokines, such as TNF-α and IL-6 found in obesity and related disorders, have been associated with EAC but not esophageal squamous cell carcinoma (ESC) development and erosive esophagitis.[20]

Low serum levels of adiponectin have been demonstrated in EAC patients (but not ESC), which is in accordance with the findings of Duggan *et al*. that showed a nonlinear inversion association of adiponectin with the risk of developing EAC among patients with BE.[21,22] In this regard, HMW adiponectin has proinflammatory function and LMW isoform acts more antiinflammatory as high levels of LMW adiponectin are associated with decreased risk of BE, hence implying that some biological effects of adiponectin are isoform dependent.[23,24]

Leptin could have a role in BE and EAC development through stimulation of cell proliferation and apoptosis inhibition in EAC cell lines.[25,26] High leptin levels have been shown for progression to EAC in a cohort of patients with BE.[22]

Intestinal microbiota

Although esophagus is considered as a microbe-free site, by applying 16S rRNA sequencing technology, it was indicated that some specific microbes including Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria phyla were found in esophageal mucosa.[27] The most common phyla found in the samples of esophageal

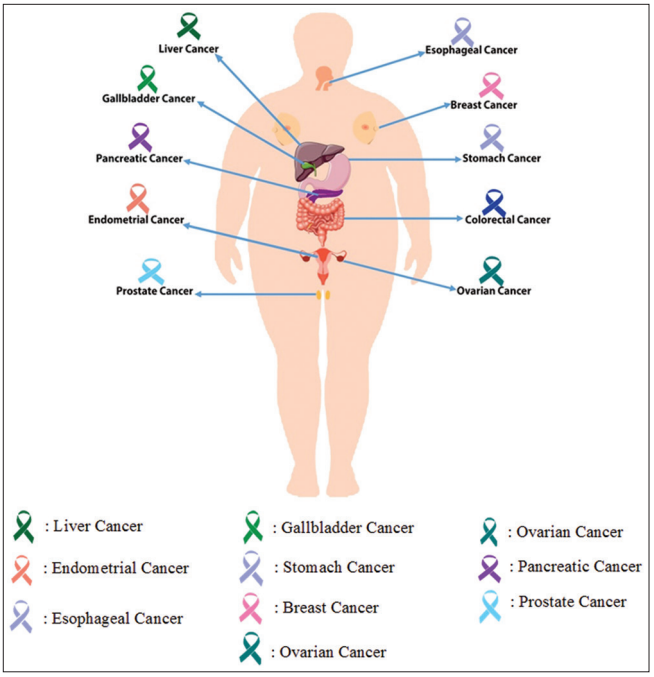

Figure 1: Obesity association with some types of cancer

squamous dysplasia (ESD) and esophageal squamous cell carcinoma (ESCC) stage I-II are gram-negative anaerobes/ microaerophiles such as Proteobacteria, Firmicutes, and Bacteroidetes compared to normal individuals and apparently microbial dysbiosis is associated with the tumorigenic process.[27,28] LPS derived from gram-negative bacterial cell wall participates through mechanisms such as promoting the release of inflammation-associate mediators including interleukins (IL-1b, IL-6, IL-8), and tumor necrosis factor-α (TNF-a)[29] and raising the levels of inducible nitric oxide synthase (iNOS) in the oncogenic process.[30]

Schematic representation mechanisms of obesity with esophageal cancer are shown in Figure 2.

Gastric cancer

Gastric cancer (GC) is ranked as the second cause of cancer-related death worldwide that manifest approximately 90% as gastric cancer adenocarcinoma (GCA). GCA are further categorized as distal or non-cardia-GCA_S and proximal or cardia-GCA_S.[6] The age-adjusted rates of GC are dramatically falling in all countries in the past 70 years but in Iran is considered as the most common cancer of death and its trend is increasing.[31] Gastric cancer is the first most common cancer in eastern Asia, but has low incidence rates in South Asia.[9]

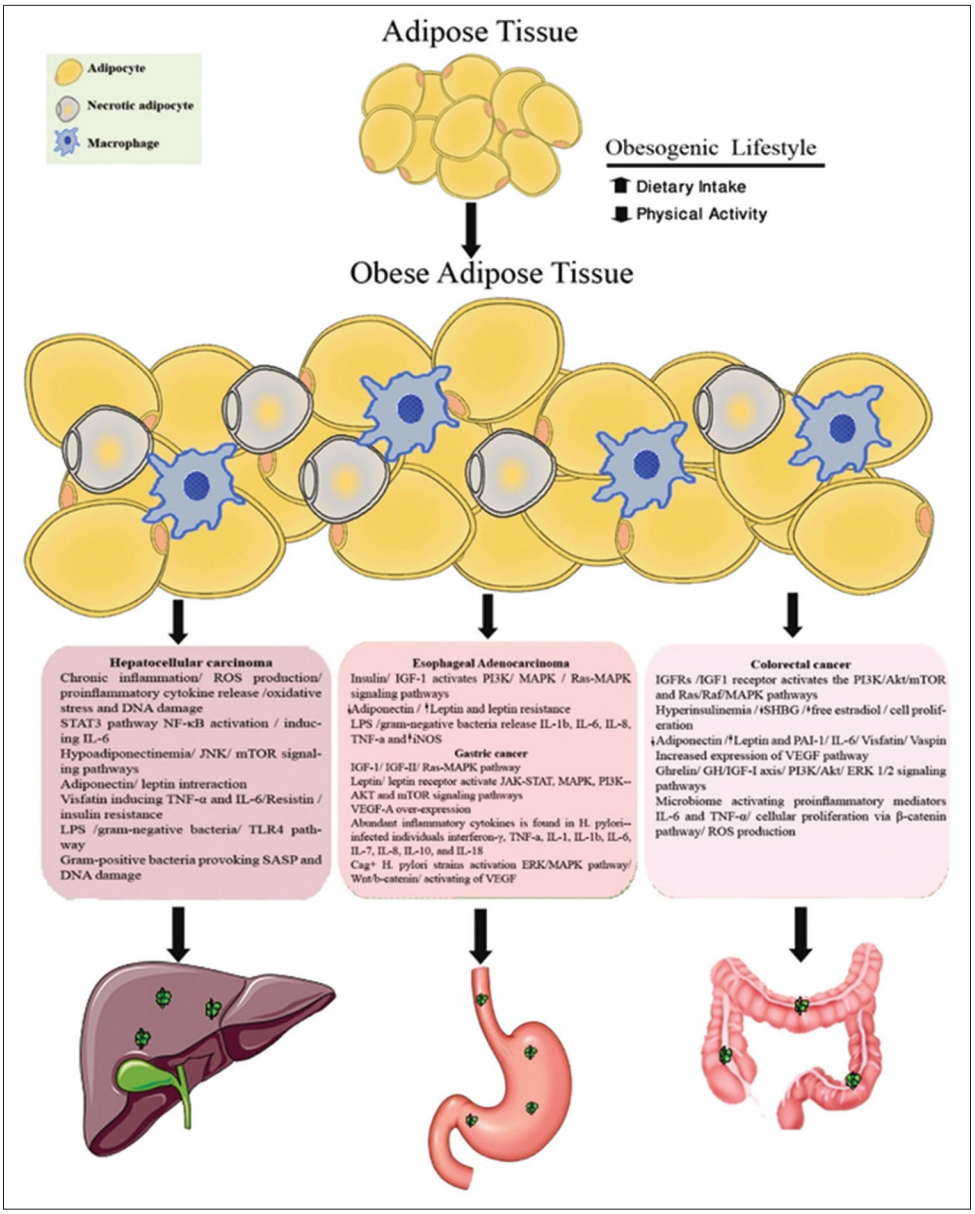

Figure 2: Mechanisms linking obesity to gastrointestinal cancers. Abbreviations: IGF-1, insulin growth factor-1; IL, interleukin; TNFα, tumor necrosis factor α, VEGF, vascular endothelial growth factor; LPS, lipopolysaccharide; TLR4, toll-like receptor 4; SHBG, sex hormone binding globulin; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription 3;PI3K/AKT/ERK1,2, phosphoinositide-3-kinase–protein kinase B/Akt/extracellular signal–regulated kinases; PAI-1, Plasminogen activator inhibitor-1;mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; SASP, senescence-associated secretary phenotype; NF-κB, nuclear factor-κappaB.

In the U.S cohort study on more than 1000 persons, the risk of gastric cardia adenocarcinoma increased twofold in associated with high BMI that emphasis on relationship between obesity with proximal GC.[32] Proximal GC is generally associated with GERD and obesity and tumors in the gastric cardia have a much poorer prognosis compared with the distal part of stomach.[13,33] In a Swedish study, population sample were divided into quartiles based on weight and it was shown that BMI ≥29 kg/m^2 or highest quartile had a 2.3-fold greater risk of proximal GC than those with BMI ≤23 kg/m^2 or lowest quartile.[34] Also, in a recent study in Iran, a significant relationship was found between being overweight and GC.[35]

Helicobacter pylorus is a major risk factor for distal GC; although there is no direct association between obesity and distal GC, indirectly obesity with facilitating cross-talk between inflamed gastric and adipose tissues as cytokine-mediated accelerates the development of *H. pylori*-associated GC.[13,36] Mechanisms that mediate the association between obesity and gastric cancer are explained as follows.

Insulin and IGF-1 signaling

IGF-I can contribute to cancer development and metastasis by stimulation of cell division and inhibition of apoptosis through the Ras-MAPK pathway. IGF-I acts not only as an endocrine hormone but also as a paracrine and autocrine hormone that interacts with the IGF-IR which is frequently overexpressed in tumors including osteosarcomas, gynecological, gastrointestinal, prostate, and lung cancers.[37,38] IGF-II similar to IGF-I is produced by the liver and acts both as endocrine and paracrine hormone which may be overexpressed in certain tumor cells including GI (increased IGF-II expression in gastric adenocarcinoma is associated with reduced survival) and gynecological tumors.[18,39]

IGF-I is expressed in healthy gastric mucosa, hyperplastic polyps, intraepithelial neoplasia, and adenocarcinomas and its levels increase progressively from benign lesions to cancer, thus indicating its pivotal role in tumor progression.[40] One study showed an increasing percentage of IGF1R positive cells in healthy stomach, hyperplastic tissue adjacent to carcinomas to cancer respectively also, increased rate of overall survival in GCA patients was associated with low levels of IGF1R mRNA.[41,42]

Adipokines and inflammatory factors

Leptin and its receptor are expressed in GCA and some studies showed higher concentrations of leptin in patients with intestinal metaplasia and even association of higher level of leptin with stage and histologic features of GCA.[43] Leptin by interacting with its transmembrane receptor activates signaling pathways that all favor cell growth, proliferation, glucose metabolism, and transformation including Janus kinase-signal transducer and activator of transcription (JAK-STAT, MAPK, PI3K-AKT), insulin receptor, and mechanistic target of rapamycin (mTOR).[44,45]

STAT3 is an intracellular signaling pathway responsible for carcinogenesis and metastasis through cellular processes like cell growth, proliferation, and glucose metabolism[46] and obesity by activating STAT3 pathway can accelerate gastric carcinogenesis in the presence of *Helicobacter pylori* infection.[47] Gastric STAT3 is activated in obesity by high leptin and IL-6.[46] Other proinflammatory cytokines responsible for proliferation of human GCA cells and inhibition of their apoptosis in obesity are TNF-α, Monocyte chemoattractant protein-1(MCP-1), and IL-17.[48,49]

Tumor angiogenesis

Previous studies, including a meta-analysis on survival data of 30 studies (n = 3999 patients), showed that vascular endothelial growth factor (VEGF-A) over-expression was linked to decreased overall survival and poor prognosis [HR = 1.49, 95% confidence interval (CI):1.22–1.77] in patients with gastric cancer.[50] Gastric cancer prognosis is related to the stage of cancer. Therefore, in recent years, there has been an increased interest for antitumor therapy with the involvement of antiangiogenic strategies in gastric cancer. Thus, novel drugs including bevacizumab, ramucirumab, and trastuzumab, and tyrosine kinase inhibitors such as sunitinib and sorafenib have been studied and used in gastric cancer.[51] Schematic representation mechanisms of obesity with gastric cancer are shown in Figure 2.

Colorectal cancer

Colorectal cancer (CRC) is one of the leading causes of mortality and morbidity in the world and it has the highest incidence and mortality among GI cancers. CRC is the third most common malignancy worldwide and also Asia.[52] Its incidence has been increasing in the last decade in Eastern Asia countries, such as China, Japan, South Korea, and Singapore.[9] Multiple factors, including BMI, correlate with increased cancer relative risk.

A meta-analysis showed that an increase of 5 kg/m^2 in BMI in men is correlated with relative risk (RR) of 1.24 for colon cancer, but in women, this relationship is complicated due to difference in fat distribution.[53] Mechanisms that mediate the association between obesity and colorectal cancer are explained as follows.

Insulin and IGF-I signaling

IGFRs are expressed in the mucosal and muscular layers of the normal colon and overexpressed in colon cancer cells.[53] Obesity and hyperinsulinemia increase expression of IGF-I and it shares extensive structural similarity with insulin. Therefore, binding IGFI to its receptor through the activation of the PI3K/Akt/mTOR and Ras/Raf/MAPK pathways can inhibit apoptosis, promote proliferation, and contribute to the development, progression, and metastatic potential of CRC.[55-57] A modest positive association was found between circulating IGF-I levels and CRC risk, based on a meta-analysis of ten prospective studies.[58]

Furthermore, insulin indirectly affects cancer development through modulation of other hormonal pathways. In hyperinsulinemia, free estradiol levels increase following significant reduction of sex hormone binding globulin (SHBG) levels, and estrogen through binding with cognate receptors (estrogen receptor: ER-α and ER-β) leads to cell proliferation, thus increasing the risk of CRC development.[59]

Adipokines and inflammatory factors

A growing number of evidence has shown an increased risk of colorectal adenoma and cancer in obese subjects and related disorders.[60] C-reactive protein (CRP) is a nonspecific marker of systemic inflammation that has been demonstrated in several retrospective case–control studies as at least 10-fold higher CRP concentrations in colorectal cancer patients compared with healthy controls.[61]

Visceral obesity is correlated with low serum levels of adiponectin and high concentrations of leptin, plasminogen activator inhibitor-1(PAI-1), and IL-6,[62] all of them being associated with an increased CRC risk.[63] Leptin has major importance for CRC in obesity which stimulates the proliferation, migration, and invasion of colon cancers in mice by the OB-R–(STAT3) pathway. Leptin increases proinflammatory cytokines production by colonocytes.[64-66]

Adiponectin by activation of AMPK and suppression of mTOR pathways inhibits cell growth in CRC, as demonstrated *in vitro* studies.[67,68] Also, anticarcinogenic effect of adiponectin may be related to its potent suppressive effects on proinflammatory cytokines.[69]

Tumor angiogenesis

Abnormal neo-angiogenesis is a feature of many tumor types including CRC.[70] VEGF pathway has increased expression in most human cancers and furthermore, the most important angiogenic growth factor in human CRC is VEGF.[71] VEGF increases the permeability of the post capillary venules, leading to leakage of the fibrinogen is conversion into fibrin, and stimulation of migration and proliferation of the endothelial cells. Therefore, it is rational for antiangiogenic therapy for CRC and like colorectal cancers.

Although cytotoxic chemotherapy is a standard treatment for CRC, antiangiogenic therapy has increased overall survival, particularly in metastatic settings. Bevacizumab, aflibercept, regorafenib, ramucirumab, and other novel drugs for CRC have been addressed.[72]

Intestinal hormones

Ghrelin is originally identified as an endogenous ligand of the growth hormone secretagogue receptor 1a (GHS-R1a) and as a potent regulator of the GH/IGF-I axis[73] whose dysregulation can positively involve in colon cancer carcinogenesis.[74] Several reports indicated that proliferative effect of ghrelin on human intestine cells and colon cancer is exerted via the PI3K/Akt and ERK 1/2 signaling pathways.[75,76] Schematic representation mechanisms of obesity with colorectal cancer have been shown in Figure 2.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the sixth most common cancer and ranks second in the world as a cause of cancer-related mortality.[77]

HCV and HBV infection together with burgeoning incidence of obesity, nonalcoholic fatty liver disease (NAFLD), and nonalcoholic steatohepatitis (NASH) and the other components of the metabolic syndrome are considered major HCC risk factors.[78] In Iran, the most common cause of HCC is HBV.[79] Geographical distribution of HCC is heterogeneous with high incidences seen in East and Southeast Asia, some of the Western Pacific islands and sub-Saharan Africa.[9]

Adipokines and inflammatory factors

Obesity is associated with nonalcoholic fatty liver disease (NAFLD), including simple steatosis, nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis that NASH in turn is risk factors for liver fibrosis and development of HCC.[80,81]

NAFLD and NASH are considered as risk factors for GI cancers, particularly colorectal adenomatous polyps and CRC. In this context, a study on 2917 participants checked up via colonoscopy, abdominal ultrasonography, and liver tests NAFLD was associated with increased risk of colorectal adenomatous polyps. Also, in a cross-sectional study by Wong *et al*., an association was shown between histological severity of NASH and higher risk of colorectal adenoma.[82,83]

In obesity is associated with chronic inflammation condition increases ROS (main source of free radicals are hepatocyte mitochondria, endotoxin-activated macrophages-Kupffer cells and neutrophils), which through direct interaction with DNA and damaging of specific genes related to cell growth and differentiation, play a pathogenic role in carcinogenesis.[84,85] Another mechanism for hepatocellular oxidative stress in NAFLD-NASH patients is oxidation of excess fatty acids induced oxidative stress, proinflammatory cytokine release, and oncogenic signaling changes.[86] Also, in obesity, there is insulin resistance and elevation of plasma concentration of insulin and IGF-1, which can increase reactive oxygen species (ROS) production.[85,87]

In addition, there are changes in adipokines level in obesity as leptin serum levels are usually increased. Hypoadiponectinemia found in obesity promotes liver tumor formation because adiponectin, through phosphorylation of c-Jun-N-terminal kinase (JNK) and JNK phosphorylation inhibition and mTOR phosphorylation inhibition, blocks liver tumorigenesis in nude mice.[88,89] Adiponectin

treatment suppresses leptin-induced cell proliferation of HCC cells by interfering with leptin. In both Cirrhotic and non-Cirrhotic HCC, increased serum levels of leptin and leptin expression correlation with cell proliferation on HCC cells happen.[90] Although levels of non-HMW adiponectin are considered as an attractive biomarker in predicting later development of HCC, results for serum leptin were negative.[91]

Another adipokine is pre-B cell colony enhancing factor (PBEF) (also called nicotinamide phosphoribosyltransferase, NAMPT or visfatin) mainly acts proinflammatory by inducing cytokines such TNF-α and IL-6 as in NAFLD patients are found increased serum concentration of NAMPT.[92,93]

Furthermore, resistin is an adipokine produced in adipose tissue, which is involved in insulin resistance. In the previous studies on biomarkers in histologically evaluated NAFLD patients, fibrosis was associated with increased serum levels of resistin and proinflammatory cytokines such as IL-8, MCP-1, and TNF-α; thus, resistin may be probably considered as a proinflammatory and profibrogenic adipokine in NAFLD.[94,95]

Chemerin another adipokine identified as the natural ligand of ChemR23 (chemerinR) is expressed in immature dendritic cells and macrophages; additionally, adipose tissue and liver have been recognized as source of this adipokine.[94] Several studies show that increased chemerin levels are correlated with NAFLD and its severity and features;[96] however, other studies fail to show such an association.[97,98]

Interventions Aimed at Obesity-Associated Gastrointestinal Cancer Prevention

Several strategies including lifestyle changes as caloric restriction and exercise have demonstrated benefits for prevention and therapy of obesity-mediated cancer promotion through three mechanisms including blocking synthesis and release of the signaling molecules including hormones, cytokines, and adipokines, disrupting inflammatory pathways at both the cellular and systemic levels, and blocking downstream intracellular pathways such as the P13K, Akt, mTOR pathway.[99]

Dietary and exercise interventions can decrease circulating levels of inflammatory biomarkers through reduction of insulin and IGF-I levels.[100,101] In Imayama *et al*. trial on 439 postmenopausal women who were overweight or obese and had enrolled in the Nutrition and Exercise for Women (NEW) trial, both exercise and/or a caloric restriction weight loss diet showed substantially decreased levels of CRP, serum amyloid-A (SAA) a protein, and IL-6 and a decreased neutrophil count relative to control subjects. Combined diet and exercise intervention showed a 41.7% reduction in CRP that was similar or even stronger than effects of antiinflammatory pharmacological therapy such as $NSAID_S$.[102,103]

The association between physical activity and colon cancer is yet unclear. Some studies including a recent case-control study on 136 CRC group and 154 control group in north of Vietnam showed that moderate physical activity was inversely associated with CRC risk and sedentary time was associated with an increased level of CRC risk by 57%. However, other studies have not demonstrated the benefit of physical activity in CRC; for example, in a recent meta-analysis, there was no significant decrease in risk of rectal cancer among physically active subjects (RR: 1.15, 95%CI: 0.83–1.64).[104-106] Thus, it seems that duration of physical activity and timing of carcinogenic exposure play an important role in the decrease of CRC risk as in a preclinical study, exercising during and before chemical exposure in a chemically induced intestinal tumor rat model caused a significant decrease in the number of tumors compared with exercise following chemical exposure, which had no effect.[107] Furthermore, concerning circulating levels of adipokines particularly leptin, several studies have demonstrated the benefit effects of dietary and exercise interventions.[108,109] In parallel, in the NEW trial, circulating levels of adiponectin increased by 9.5% in the diet group and 6.6.% in the combined diet and exercise group versus the control group and all intervention groups showed substantial decreases in circulating leptin level than the control group.[110]

Taken together, clinical and preclinical studies indicate that fundamental processes of cellular proliferation, death, and angiogenesis as key mediators of obesity-gastrointestinal carcinogenesis axis can be modulated via exercise and dietary weight-loss interventions.[111]

Conclusions

Obesity is a rapidly growing public health problem worldwide and it continues to grow at a pandemic rate. A growing body of evidence supports linking visceral obesity and cancer development at multiple sites in the GI tract including the esophagus, liver, colon, and gastric cardia. Herein, we have provided various mechanisms how obesity contributes to the pathogenesis and development of GI cancers that usually act interdependently. Also, optional interventions such as diet restriction and exercise which may be preventive or therapeutic were investigated. Therefore, it seems essential that health organizations and governments reduce the burden of obesity-associated GI cancers by adopting appropriate preventive policies for obesity.

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Conflicts of interest

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