

# 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

## 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.<sup>[1]</sup>

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

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.<sup>[3]</sup>

In this regard, a recent case-control study by Taherogorabi *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.<sup>[4]</sup>

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.<sup>[5]</sup>

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.<sup>[6]</sup>

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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.<sup>[7]</sup> Adenocarcinoma is the most common histological type of esophageal cancer worldwide<sup>[8]</sup> 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.<sup>[9]</sup> In many studies, obesity has been identified to be one of the risk factors for esophageal adenocarcinoma (EAC) in both men and women.<sup>[10]</sup>

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 Barrett's esophagus (BE) and intestinal metaplasia and EAC.<sup>[11,12]</sup> 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.<sup>[13]</sup>

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.<sup>[14]</sup> 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.<sup>[6]</sup> 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.<sup>[15,16]</sup>

IGF-I is the most highly abundant isoform among multiple isoforms of IGF in circulation.<sup>[17]</sup> 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.<sup>[18]</sup> 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.<sup>[19]</sup>

#### 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- $\alpha$  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.<sup>[20]</sup>

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.<sup>[21,22]</sup> 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.<sup>[23,24]</sup>

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

#### 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.<sup>[27]</sup> The most common phyla found in the samples of esophageal

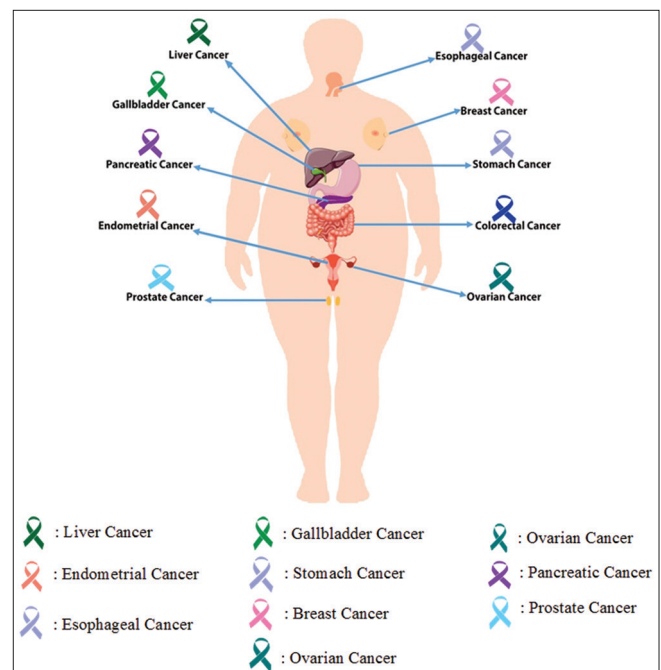


Figure 1: Obesity association with some types of cancer

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.<sup>[27,28]</sup> 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- $\alpha$  (TNF- $\alpha$ )<sup>[29]</sup> and raising the levels of inducible nitric oxide synthase (iNOS) in the oncogenic process.<sup>[30]</sup>

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<sub>s</sub> and proximal or cardia-GCA<sub>s</sub>.<sup>[6]</sup> 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.<sup>[31]</sup> Gastric cancer is the first most common cancer in eastern Asia, but has low incidence rates in South Asia.<sup>[9]</sup>

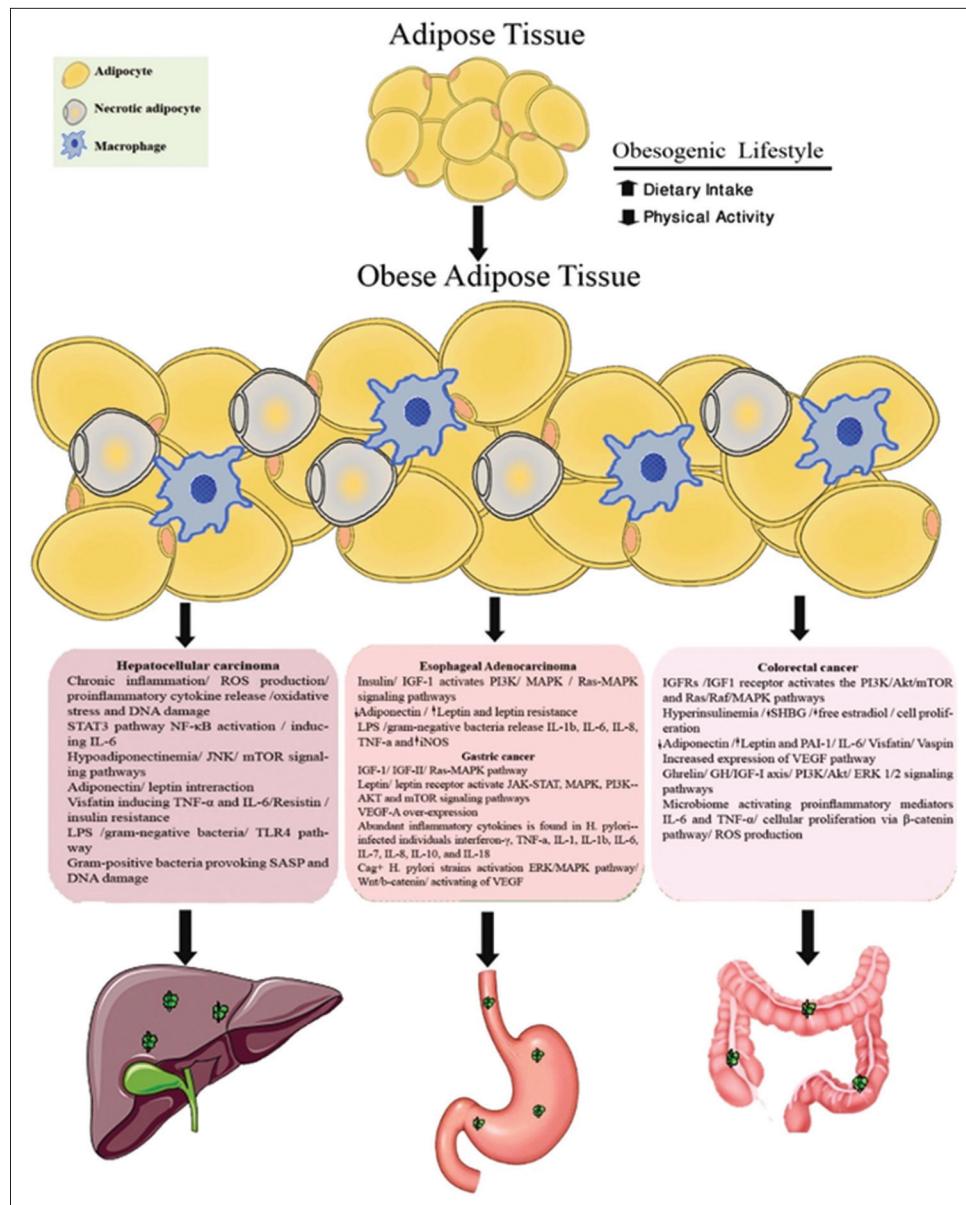


Figure 2: Mechanisms linking obesity to gastrointestinal cancers. Abbreviations: IGF-1, insulin growth factor-1; IL, interleukin; TNF $\alpha$ , tumor necrosis factor  $\alpha$ , VEGF, vascular endothelial growth factor; LPS, lipopolysaccharide; TLR4, toll-like receptor 4; SHBG, sex hormone binding globulin; 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 secretory phenotype; NF- $\kappa$ B, nuclear factor- $\kappa$ B.

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.<sup>[32]</sup> 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.<sup>[13,33]</sup> In a Swedish study, population sample were divided into quartiles based on weight and it was shown that BMI  $\geq 29$  kg/m<sup>2</sup> or highest quartile had a 2.3-fold greater risk of proximal GC than those with BMI  $\leq 23$  kg/m<sup>2</sup> or lowest quartile.<sup>[34]</sup> Also, in a recent study in Iran, a significant relationship was found between being overweight and GC.<sup>[35]</sup>

*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.<sup>[13,36]</sup> Mechanisms that mediate the association between obesity and gastric cancer are explained as follows.

#### *Insulin and IGF-I 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.<sup>[37,38]</sup> 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.<sup>[18,39]</sup>

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.<sup>[40]</sup> One study showed an increasing percentage of IGFIR 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 IGFIR mRNA.<sup>[41,42]</sup>

#### *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.<sup>[43]</sup> 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).<sup>[44,45]</sup>

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

#### *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.<sup>[50]</sup> 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.<sup>[51]</sup> 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.<sup>[52]</sup> Its incidence has been increasing in the last decade in Eastern Asia countries, such as China, Japan, South Korea, and Singapore.<sup>[9]</sup> Multiple factors, including BMI, correlate with increased cancer relative risk.

A meta-analysis showed that an increase of 5 kg/m<sup>2</sup> 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.<sup>[53]</sup> 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.<sup>[53]</sup> 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.<sup>[55-57]</sup> A modest positive association was found between circulating IGF-I levels and CRC risk, based on a meta-analysis of ten prospective studies.<sup>[58]</sup>

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- $\alpha$  and ER- $\beta$ ) leads to cell proliferation, thus increasing the risk of CRC development.<sup>[59]</sup>

#### *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.<sup>[60]</sup> 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.<sup>[61]</sup>

Visceral obesity is correlated with low serum levels of adiponectin and high concentrations of leptin, plasminogen activator inhibitor-1 (PAI-1), and IL-6,<sup>[62]</sup> all of them being associated with an increased CRC risk.<sup>[63]</sup> 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.<sup>[64-66]</sup>

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

#### *Tumor angiogenesis*

Abnormal neo-angiogenesis is a feature of many tumor types including CRC.<sup>[70]</sup> VEGF pathway has increased expression in most human cancers and furthermore, the most important angiogenic growth factor in human CRC is VEGF.<sup>[71]</sup> 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.<sup>[72]</sup>

#### *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<sup>[73]</sup> whose dysregulation can positively involve in colon cancer carcinogenesis.<sup>[74]</sup> 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.<sup>[75,76]</sup> 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.<sup>[77]</sup>

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.<sup>[78]</sup> In Iran, the most common cause of HCC is HBV.<sup>[79]</sup> 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.<sup>[9]</sup>

#### *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.<sup>[80,81]</sup>

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.<sup>[82,83]</sup>

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.<sup>[84,85]</sup> 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.<sup>[86]</sup> 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.<sup>[85,87]</sup>

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.<sup>[88,89]</sup> 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.<sup>[90]</sup> Although levels of non-HMW adiponectin are considered as an attractive biomarker in predicting later development of HCC, results for serum leptin were negative.<sup>[91]</sup>

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- $\alpha$  and IL-6 as in NAFLD patients are found increased serum concentration of NAMPT.<sup>[92,93]</sup>

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- $\alpha$ ; thus, resistin may be probably considered as a proinflammatory and profibrogenic adipokine in NAFLD.<sup>[94,95]</sup>

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.<sup>[94]</sup> Several studies show that increased chemerin levels are correlated with NAFLD and its severity and features;<sup>[96]</sup> however, other studies fail to show such an association.<sup>[97,98]</sup>

## 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.<sup>[99]</sup>

Dietary and exercise interventions can decrease circulating levels of inflammatory biomarkers through reduction of insulin and IGF-I levels.<sup>[100,101]</sup> 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<sub>s</sub>.<sup>[102,103]</sup>

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).<sup>[104-106]</sup> 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.<sup>[107]</sup> Furthermore, concerning circulating levels of adipokines particularly leptin, several studies have demonstrated the benefit effects of dietary and exercise interventions.<sup>[108,109]</sup> 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.<sup>[110]</sup>

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.<sup>[111]</sup>

## 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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## References

- Blüher M. Obesity: Global epidemiology and pathogenesis. *Nat Rev Endocrinol* 2019;15:288-98.
- Organization WH. Obesity and overweight World Health Organization Website. World Health Organization Website; 2018.
- Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer—Viewpoint of the IARC Working Group. *N Eng J Med* 2016;375:794-8.
- Tahergorabi Z, Moodi M, Zardast M, Ghayravani Z, Tavakoli T. Metabolic syndrome and the risk of gastrointestinal cancer: A case-control study. *Asian Pac J Cancer Prev* 2018;19:2205-10.
- Nock NL, Thompson CL, Tucker TC, Berger NA, Li L. Associations between obesity and changes in adult BMI over time and colon cancer risk. *Obesity* 2008;16:1099-104.
- Alemán JO, Eusebi LH, Ricciardiello L, Patidar K, Sanyal AJ, Holt PR. Mechanisms of obesity-induced gastrointestinal neoplasia. *Gastroenterology* 2014;146:357-73.
- sadat Yousefi M, Sharifi-Esfahani M, Pourgholam-Amiji N, Afshar M, Sadeghi-Gandomani H, Otroshi O, *et al.* Esophageal cancer in the world: Incidence, mortality and risk factors. *Biomed Res Ther* 2018;5:2504-17.
- Bird-Lieberman EL, Fitzgerald RC. Early diagnosis of esophageal cancer. *Br J Cancer* 2009;101:1-6.
- Pourhoseingholi MA, Vahedi M, Baghestani AR. Burden of gastrointestinal cancer in Asia; an overview. *Gastroenterol Hepatol Bed Bench* 2015;8:19-27.
- Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: A systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev* 2006;15:872-8.
- Solaymani-Dodaran M, Logan R, West J, Card T, Coupland C. Risk of oesophageal cancer in Barrett's oesophagus and gastro-oesophageal reflux. *Gut* 2004;53:1070-4.
- Chak A, Falk G, Grady WM, Kinnard M, Elston R, Mittal S, *et al.* Assessment of familiarity, obesity, and other risk factors for early age of cancer diagnosis in adenocarcinomas of the esophagus and gastroesophageal junction. *Am J Gastroenterol* 2009;104:1913-21.
- Zheng J, Zhao M, Li J, Lou G, Yuan Y, Bu S, *et al.* Obesity-associated digestive cancers: A review of mechanisms and interventions. *Tumor Biol* 2017;39:1010428317695020.
- Tahergorabi Z, Khazaei M. The relationship between inflammatory markers, angiogenesis, and obesity. *ARYA Atheroscler* 2013;9:247-53.
- Samani AA, Yakar S, LeRoith D, Brodt P. The role of the IGF system in cancer growth and metastasis: Overview and recent insights. *Endocr Rev* 2007;28:20-47.
- Belfiore A, Frasca F, Pandini G, Sciacca L, Vigneri R. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. *Endocr Rev* 2009;30:586-623.
- El Yafi F, Winkler R, Delvenne P, Boussif N, Belaiche J, Louis E. Altered expression of type I insulin-like growth factor receptor in Crohn's disease. *Clin Exp Immunol* 2005;139:526-33.
- Gallagher EJ, LeRoith D. Minireview: IGF, insulin, and cancer. *Endocrinology* 2011;152:2546-51.
- Doyle SL, Donohoe CL, Finn SP, Howard JM, Lithander FE, Reynolds JV, *et al.* IGF-1 and its receptor in esophageal cancer: Association with adenocarcinoma and visceral obesity. *Am J Gastroenterol* 2012;107:196-204.
- Francois F, Roper J, Goodman AJ, Pei Z, Ghumman M, Mourad M, *et al.* The association of gastric leptin with oesophageal inflammation and metaplasia. *Gut* 2008;57:16-24.
- Howard J, Beddy P, Ennis D, Keogan M, Pidgeon G, Reynolds J. Associations between leptin and adiponectin receptor upregulation, visceral obesity and tumour stage in oesophageal and junctional adenocarcinoma. *Br J Surg* 2010;97:1020-7.
- Duggan C, Onstad L, Hardikar S, Blount PL, Reid BJ, Vaughan TL. Association between markers of obesity and progression from Barrett's esophagus to esophageal adenocarcinoma. *Clin Gastroenterol Hepatol* 2013;11:934-43.
- Unger RH, Scherer PE. Gluttony, sloth and the metabolic syndrome: A roadmap to lipotoxicity. *Trends Endocrinol Metab* 2010;21:345-52.
- Rubenstein JH, Kao JY, Madanick RD, Zhang M, Wang M, Spacek MB, *et al.* Association of adiponectin multimers with Barrett's oesophagus. *Gut* 2009;58:1583-9.
- Ogunwobi O, Beales I. Leptin stimulates the proliferation of human oesophageal adenocarcinoma cells via HB-EGF and TGF $\alpha$  mediated transactivation of the epidermal growth factor receptor. *Br J Biomed Sci* 2008;65:121-7.
- Thompson OM, Beresford SA, Kirk EA, Bronner MP, Vaughan TL. Serum leptin and adiponectin levels and risk of Barrett's esophagus and intestinal metaplasia of the gastroesophageal junction. *Obesity (Silver Spring)* 2010;18:2204-11.
- Nasrollahzadeh D, Malekzadeh R, Ploner A, Shakeri R, Sotoudeh M, Fahimi S, *et al.* Variations of gastric corpus microbiota are associated with early esophageal squamous cell carcinoma and squamous dysplasia. *Sci Rep* 2015;5:8820.
- Patel T, Bhattacharya P, Das S. Gut microbiota: An indicator to gastrointestinal tract diseases. *J Gastrointest Cancer* 2016;47:232-8.
- Yang L, Francois F, Pei Z. Molecular pathways: Pathogenesis and clinical implications of microbiome alteration in esophagitis and Barrett esophagus. *Clin Cancer Res* 2012;18:2138-44.
- Lee S-J, Park H, Chang JH, Conklin JL. Generation of nitric oxide in the opossum lower esophageal sphincter during physiological experimentation. *Yonsei Med J* 2006;47:223-9.
- Farhood B, Geraily G, Alizadeh A. Incidence and mortality of various cancers in Iran and compare to other countries: A review article. *Iran J Public Health* 2018;47:309-16.
- Chow W-H, Blot WJ, Vaughan TL, Risch HA, Gammon MD, Stanford JL, *et al.* Body mass index and risk of adenocarcinomas of the esophagus and gastric cardia. *J Natl Cancer Inst* 1998;90:150-5.
- Crew KD, Neugut AI. Epidemiology of gastric cancer. *World J Gastroenterol* 2006;12:354-62.
- Lagergren J, Bergström R, Nyrén O. Association between body mass and adenocarcinoma of the esophagus and gastric cardia. *Ann Intern Med* 1999;130:883-90.
- Rastaghi S, Jafari-Koshki T, Mahaki B, Bashiri Y, Mehrabani K, Soleimani A. Trends and risk factors of gastric cancer in Iran (2005–2010). *Int J Prev Med* 2019;10:79.
- Helicobacter and Cancer Collaborative Group. Gastric cancer and Helicobacter pylori: A combined analysis of 12 case control

- studies nested within prospective cohorts. *Gut* 2001;49:347-53.
37. De Ostrovich KK, Lambertz I, Colby JK, Tian J, Rundhaug JE, Johnston D, *et al.* Paracrine overexpression of insulin-like growth factor-1 enhances mammary tumorigenesis in vivo. *Am J Pathol* 2008;173:824-34.
  38. Huang YF, Shen MR, Hsu KF, Cheng YM, Chou CY. Clinical implications of insulin-like growth factor I system in early-stage cervical cancer. *Br J Cancer* 2008;99:1096-102.
  39. Zhao R, DeCoteau JF, Geyer CR, Gao M, Cui H, Casson AG. Loss of imprinting of the insulin-like growth factor II (IGF2) gene in esophageal normal and adenocarcinoma tissues. *Carcinogenesis* 2009;30:2117-22.
  40. Wang HB, Zhou CJ, Song SZ, Chen P, Xu WH, Liu B, *et al.* Evaluation of Nr1f2 and IGF-1 expression in benign, premalignant and malignant gastric lesions. *Pathol Res Pract* 2011;207:169-73.
  41. Liu W, Yu R, Zhou G. Expression and significance of IGF-1R and VEGF in gastric carcinoma. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2009;25:529-30.
  42. Matsubara J, Yamada Y, Nakajima TE, Kato K, Hamaguchi T, Shirao K, *et al.* Clinical significance of insulin-like growth factor type I receptor and epidermal growth factor receptor in patients with advanced gastric cancer. *Oncology* 2008;74:76-83.
  43. Zhao X, Huang K, Zhu Z, Chen S, Hu R. Correlation between expression of leptin and clinicopathological features and prognosis in patients with gastric cancer. *J Gastroenterol Hepatol* 2007;22:1317-21.
  44. Garofalo C, Surmacz E. Leptin and cancer. *J Cell Physiol* 2006;207:12-22.
  45. Tahergorabi Z, Khazaei M. Leptin and its cardiovascular effects: Focus on angiogenesis. *Adv Biomed Res* 2015;4:79.
  46. Zhao L, Vogt PK. Class I PI3K in oncogenic cellular transformation. *Oncogene* 2008;27:5486-96.
  47. Ericksen RE, Rose S, Westphalen CB, Shibata W, Muthupalani S, Tailor Y, *et al.* Obesity accelerates Helicobacter felis-induced gastric carcinogenesis by enhancing immature myeloid cell trafficking and TH17 response. *Gut* 2014;63:385-94.
  48. Kai H, Kitadai Y, Kodama M, Cho S, Kuroda T, Ito M, *et al.* Involvement of proinflammatory cytokines IL-1 $\beta$  and IL-6 in progression of human gastric carcinoma. *Anticancer Res* 2005;25:709-13.
  49. Kuroda T, Kitadai Y, Tanaka S, Yang X, Mukaida N, Yoshihara M, *et al.* Monocyte chemoattractant protein-1 transfection induces angiogenesis and tumorigenesis of gastric carcinoma in nude mice via macrophage recruitment. *Clin Cancer Res* 2005;11:7629-36.
  50. Peng L, Zhan P, Zhou Y, Fang W, Zhao P, Zheng Y, *et al.* Prognostic significance of vascular endothelial growth factor immunohistochemical expression in gastric cancer: A meta-analysis. *Mol Biol Rep* 2012;39:9473-84.
  51. McCarthy T, O'Neil BH. Angiogenesis inhibitors in gastric cancer. *J Orphan Drugs: Res Rev.* 2014;4:55-61.
  52. Gandamani HS, Aghajani M, Mohammadian-Hafshejani A, Tarazoj AA, Pouyesh V, Salehiniya H. Colorectal cancer in the world: Incidence, mortality and risk factors. *Biomed Res Ther* 2017;4:1656-75.
  53. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: A systematic review and meta-analysis of prospective observational studies. *Lancet* 2008;371:569-78.
  54. Ouban A, Muraca P, Yeatman T, Coppola D. Expression and distribution of insulin-like growth factor-1 receptor in human carcinomas. *Hum Pathol* 2003;34:803-8.
  55. Valentinis B, Baserga R. IGF-I receptor signalling in transformation and differentiation. *Mol Pathol* 2001;54:133-7.
  56. Guo YS, Narayan S, Yallampalli C, Singh P. Characterization of insulinlike growth factor I receptors in human colon cancer. *Gastroenterology* 1992;102:1101-8.
  57. Singh P, Rubin N. Insulinlike growth factors and binding proteins in colon cancer. *Gastroenterology* 1993;105:1218-37.
  58. Rinaldi S, Cleveland R, Norat T, Biessy C, Rohrmann S, Linseisen J, *et al.* Serum levels of IGF-I, IGFBP-3 and colorectal cancer risk: Results from the EPIC cohort, plus a meta-analysis of prospective studies. *Int J Cancer* 2010;126:1702-15.
  59. Karczewski J, Begier-Krasińska B, Staszewski R, Popławska E, Gulczynska-Elhadi K, Dobrowolska A. Obesity and the risk of gastrointestinal cancers. *Dig Dis Sci* 2019;64:2740-9.
  60. Donohoe C, Pidgeon G, Lysaght J, Reynolds J. Obesity and gastrointestinal cancer. *Br J Surg* 2010;97:628-42.
  61. Tsilidis KK, Branchini C, Guallar E, Helzlsouer KJ, Erlinger TP, Platz EA. C-reactive protein and colorectal cancer risk: A systematic review of prospective studies. *Int J Cancer* 2008;123:1133-40.
  62. Tahergorabi Z, Khazaei M, Moodi M, Chamani E. From obesity to cancer: A review on proposed mechanisms. *Cell Biochem Funct* 2016;34:533-45.
  63. Ho GY, Wang T, Gunter MJ, Strickler HD, Cushman M, Kaplan RC, *et al.* Adipokines linking obesity with colorectal cancer risk in postmenopausal women. *Cancer Res* 2012;72:3029-37.
  64. Endo H, Hosono K, Uchiyama T, Sakai E, Sugiyama M, Takahashi H, *et al.* Leptin acts as a growth factor for colorectal tumours at stages subsequent to tumour initiation in murine colon carcinogenesis. *Gut* 2011;60:1363-71.
  65. Drew JE. Molecular mechanisms linking adipokines to obesity-related colon cancer: Focus on leptin. *Proc Nutr Soc* 2012;71:175-80.
  66. Padidar S, Farquharson AJ, Williams LM, Kelaiditi E, Hoggard N, Arthur JR, *et al.* Leptin up-regulates pro-inflammatory cytokines in discrete cells within mouse colon. *J Cell Physiol* 2011;226:2123-30.
  67. Sugiyama M, Takahashi H, Hosono K, Endo H, Kato S, Yoneda K, *et al.* Adiponectin inhibits colorectal cancer cell growth through the AMPK/mTOR pathway. *Int J Oncol* 2009;34:339-44.
  68. Kim AY, Lee YS, Kim KH, Lee JH, Lee HK, Jang S-H, *et al.* Adiponectin represses colon cancer cell proliferation via AdipoR1-and-R2-mediated AMPK activation. *Mol Endocrinol* 2010;24:1441-52.
  69. Saxena A, Baliga MS, Ponemone V, Kaur K, Larsen B, Fletcher E, *et al.* Mucus and adiponectin deficiency: Role in chronic inflammation-induced colon cancer. *Int J Colorectal Dis* 2013;28:1267-79.
  70. Konda B, Shum H, Rajdev L. Anti-angiogenic agents in metastatic colorectal cancer. *World J Gastrointest Oncol* 2015;7:71-86.
  71. Bendardaf R, El-Serafi A, Syrjänen K, Collan Y, Pyrhönen S. The effect of vascular endothelial growth factor-1 expression on survival of advanced colorectal cancer patients. *Libyan J Med* 2017;12:1290741.
  72. Nandikolla AG, Rajdev L. Targeting angiogenesis in gastrointestinal tumors: Current challenges. *Transl Gastroenterol Hepatol* 2016;1:67.
  73. Tahergorabi Z, Rashidi B, Khazaei M. Ghrelin does not modulate angiogenesis in matrigel plug in normal and diet-induced obese mice. *J Res Med Sci* 2013;18:939-42.



74. Strassburg S, Anker SD, Castaneda TR, Burget L, Perez-Tilve D, Pfluger PT, *et al.* Long-term effects of ghrelin and ghrelin receptor agonists on energy balance in rats. *Am J Physiol Endocrinol Metab* 2008;295:E78-84.
75. Waseem T, Duxbury M, Ashley SW, Robinson MK. Ghrelin promotes intestinal epithelial cell proliferation through PI3K/Akt pathway and EGFR trans-activation both converging to ERK 1/2 phosphorylation. *Peptides* 2014;52:113-21.
76. Yu H, Xu G, Fan X. The effect of ghrelin on cell proliferation in small intestinal IEC-6 cells. *Biomed Pharmacother* 2013;67:235-9.
77. Kew MC. Hepatocellular carcinoma: Epidemiology and risk factors. *J Hepatocell Carcinoma* 2014;1:115-25.
78. Mittal S, El-Serag HB. Epidemiology of HCC: Consider the population. *J Clin Gastroenterol* 2013;47(Suppl):S2-6.
79. Pourhoseingholi MA, Fazeli Z, Zali MR, Alavian SM. Burden of hepatocellular carcinoma in Iran; Bayesian projection and trend analysis. *Asian Pac J Cancer Prev* 2010;11:859-62.
80. Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: Biochemical, metabolic, and clinical implications. *Hepatology* 2010;51:679-89.
81. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: New mechanistic insights from epidemiology. *Nat Rev Cancer* 2015;15:484-98.
82. Wong VWS, Wong GLH, Tsang SWC, Fan T, Chu WCW, Woo J, *et al.* High prevalence of colorectal neoplasm in patients with non-alcoholic steatohepatitis. *Gut* 2011;60:829-36.
83. Hwang ST, Cho YK, Park JH, Kim HJ, Park DI, Sohn CI, *et al.* Relationship of non-alcoholic fatty liver disease to colorectal adenomatous polyps. *J Gastroenterol Hepatol* 2010;25:562-7.
84. Barash H, Gross ER, Edrei Y, Ella E, Israel A, Cohen I, *et al.* Accelerated carcinogenesis following liver regeneration is associated with chronic inflammation-induced double-strand DNA breaks. *Proc Natl Acad Sci* 2010;107:2207-12.
85. Muriel P. Role of free radicals in liver diseases. *Hepatology* 2009;3:526-36.
86. Baffy G, Brunt EM, Caldwell SH. Hepatocellular carcinoma in non-alcoholic fatty liver disease: An emerging menace. *J Hepatol* 2012;56:1384-91.
87. Calle EE, Kaaks R. Overweight, obesity and cancer: Epidemiological evidence and proposed mechanisms. *Nat Rev Cancer* 2004;4:579-91.
88. Kamada Y, Matsumoto H, Tamura S, Fukushima J, Kiso S, Fukui K, *et al.* Hypoadiponectinemia accelerates hepatic tumor formation in a nonalcoholic steatohepatitis mouse model. *J Hepatol* 2007;47:556-64.
89. Saxena NK, Fu PP, Nagalingam A, Wang J, Handy J, Cohen C, *et al.* Adiponectin modulates C-jun N-terminal kinase and mammalian target of rapamycin and inhibits hepatocellular carcinoma. *Gastroenterology*. 2010;139:1762-73, 1773.e1-5.
90. Sharma D, Wang J, Fu PP, Sharma S, Nagalingam A, Mells J, *et al.* Adiponectin antagonizes the oncogenic actions of leptin in hepatocellular carcinogenesis. *Hepatology* 2010;52:1713-22.
91. Aleksandrova K, Boeing H, Nöthlings U, Jenab M, Fedirko V, Kaaks R, *et al.* Inflammatory and metabolic biomarkers and risk of liver and biliary tract cancer. *Hepatology* 2014;60:858-71.
92. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, *et al.* Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *J Immunol* 2007;178:1748-58.
93. Moschen AR, Molnar C, Wolf AM, Weiss H, Graziadei I, Kaser S, *et al.* Effects of weight loss induced by bariatric surgery on hepatic adipocytokine expression. *J Hepatol* 2009;51:765-77.
94. Adolph T, Grander C, Grabherr F, Tilg H. Adipokines and non-alcoholic fatty liver disease: Multiple interactions. *Int J Mol Sci* 2017;18:1649.
95. Jamali R, Razavizade M, Arj A, Aarabi MH. Serum adipokines might predict liver histology findings in non-alcoholic fatty liver disease. *World J Gastroenterol* 2016;22:5096-103.
96. Yilmaz Y, Yonal O, Kurt R, Alahdab YO, Eren F, Ozdogan O, *et al.* Serum levels of omentin, chemerin and adiponin in patients with biopsy-proven nonalcoholic fatty liver disease. *Scand J Gastroenterol* 2011;46:91-7.
97. Pohl R, Haberi EM, Rein-Fischboeck L, Zimny S, Neumann M, Aslanidis C, *et al.* Hepatic chemerin mRNA expression is reduced in human nonalcoholic steatohepatitis. *Eur J Clin Invest* 2017;47:7-18.
98. Polyzos SA, Kountouras J, Anastasilakis AD, Geladari EV, Mantzoros CS. Irisin in patients with nonalcoholic fatty liver disease. *Metabolism* 2014;63:207-17.
99. Hursting SD, DiGiovanni J, Dannenberg AJ, Azrad M, LeRoith D, Demark-Wahnefried W, *et al.* Obesity, energy balance, and cancer: New opportunities for prevention. *Cancer Prev Res (Phila)* 2012;5:1260-72.
100. Lashinger LM, Ford NA, Hursting SD. Interacting inflammatory and growth factor signals underlie the obesity-cancer link. *J Nutr* 2013;144:109-13.
101. Zahedi H, Djalalinia S, Asayesh H, Mansourian M, Abdar ZE, Gorabi AM, *et al.* A higher dietary inflammatory index score is associated with a higher risk of incidence and mortality of cancer: A comprehensive systematic review and meta-analysis. *Int J Prev Med* 2020;11:15.
102. Imayama I, Ulrich CM, Alfano CM, Wang C, Xiao L, Wener MH, *et al.* Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: A randomized controlled trial. *Cancer Res* 2012;72:2314-26.
103. Foster-Schubert KE, Alfano CM, Duggan CR, Xiao L, Campbell KL, Kong A, *et al.* Effect of diet and exercise, alone or combined, on weight and body composition in overweight-to-obese postmenopausal women. *Obesity* 2012;20:1628-38.
104. Quang N, Hien NQ, Quang NT, Chung NT. Active Lifestyle Patterns Reduce the Risk of Colorectal Cancer in the North of Vietnam: A Hospital-Based Case-Control Study. *Cancer Control*. 2019 ;26:1073274819864666.
105. Oruç Z, Kaplan MA. Effect of exercise on colorectal cancer prevention and treatment. *World J Gastrointest Oncol* 2019;11:348-66.
106. Harriss D, Atkinson G, Batterham A, George K, Tim Cable N, Reilly T, *et al.* Lifestyle factors and colorectal cancer risk (2): A systematic review and meta-analysis of associations with leisure-time physical activity. *Colorectal Dis* 2009;11:689-701.
107. Kelly SA, Zhao L, Jung K-C, Hua K, Threadgill DW, Kim Y, *et al.* Prevention of tumorigenesis in mice by exercise is dependent on strain background and timing relative to carcinogen exposure. *Sci Rep* 2017;7:1-11. doi: 10.1038/srep43086.
108. Wang X, You T, Murphy K, Lyles MF, Nicklas BJ. Addition of exercise increases plasma adiponectin and release from adipose tissue. *Med Sci Sports Exerc* 2015;47:2450-5.
109. Kelly KR, Navaneethan SD, Solomon TP, Haus JM, Cook M, Barkoukis H, *et al.* Lifestyle-induced decrease in fat mass improves adiponectin secretion in obese adults. *Med Sci Sports Exerc* 2014;46:920-6.
110. Abbenhardt C, McTiernan A, Alfano CM, Wener MH,

Campbell KL, Duggan C, *et al.* Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. *J Intern Med* 2013;274:163-75.

111. Ulrich CM, Himmelfarb C, Holowatyj AN, Hursting SD. Energy balance and gastrointestinal cancer: Risk, interventions, outcomes and mechanisms. *Nat Rev Gastroenterol Hepatol* 2018;15:683-98.