Mechanisms linking obesity and gastrointestinal cancers

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Abstract

Introduction and purpose: The worldwide prevalence of obesity increased threefold between 1975 and 2016. Obesity is a risk factor for gastrointestinal cancers, including the pancreas, liver, esophagus, colorectal, stomach cardia, and gallbladder. This work is an analysis of the available PubMed literature on relationship between obesity and gastrointestinal cancers and possible mechanisms linking them.
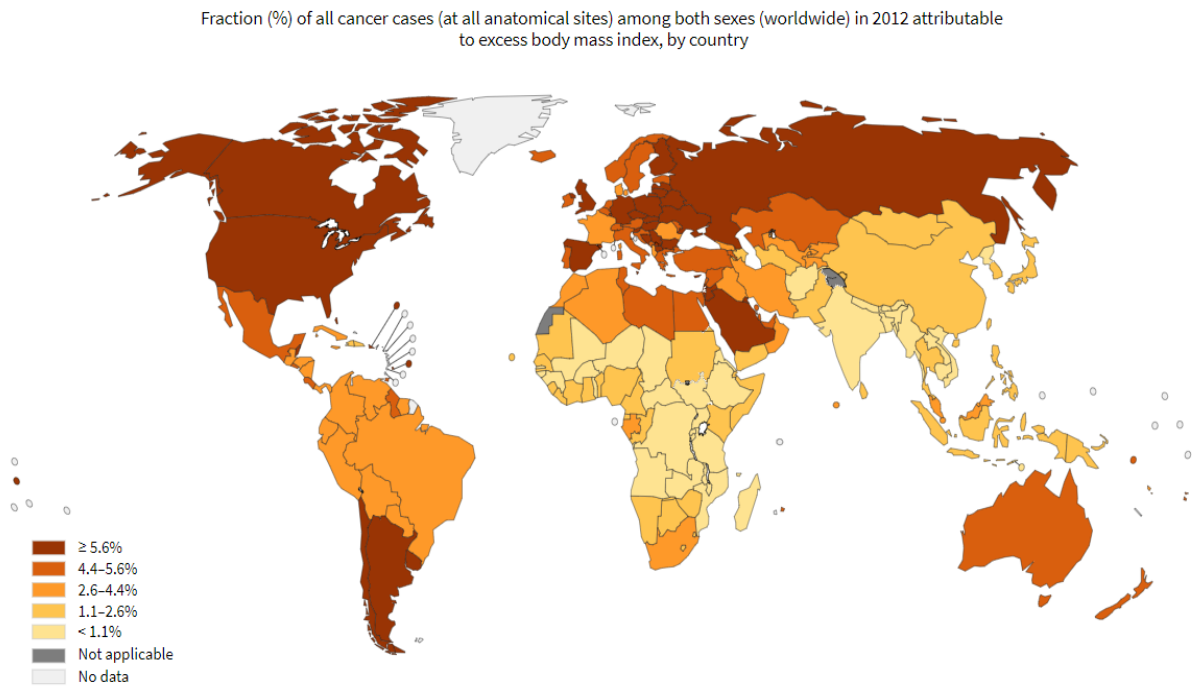
Brief description of the state of knowledge: There is a number of mechanisms responsible for obesity associated gastrointestinal cancers. Excess adiposity leads to: metabolic syndrome, chronic inflammation, altered production of steroid hormones and adipokines as well as changes in insulin and IGF1 signaling. This study examines the processes leading to obesity-associated colorectal, esophageal, gastric, and pancreatic cancers, which are known to be the most prevalent and lethal cancers worldwide. In this review, the mechanisms of gastrointestinal cancerogenesis such as changes in insulin and insulin-like growth factor signaling pathways, chronic inflammation associated to obesity, altered adipokine and inflammatory factors levels, are being discussed.

Conclusions: Thorough understanding of the biological processes connecting obesity, metabolic health and gastrointestinal cancers may help to discover new risk factors and biomarkers, improve preventive strategies and invent ground-breaking treatment.

Key words: obesity, gastrointestinal cancers, mechanisms of carcinogenesis.

1.   Introduction and purpose:

Obesity is a disproportion between body weight and height, typically it is a consequence of an excess adipose tissue. It is generally defined as an elevated body mass index (BMI) to at

Fraction (%) of all cancer cases (at all anatomical sites) among both sexes (worldwide) in 2012 attributable to excess body mass index, by country

Legend:
- ≥ 5.6%
- 4.4–5.6%
- 2.6–4.4%
- 1.1–2.6%
- < 1.1%
- Not applicable
- No data

least 30 kg/m2. The worldwide prevalence of obesity increased threefold between 1975 and 2016 [1]. Obesity leads to severe diseases such as hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke and many types of cancer [2] [3]. In 2016, the International Agency for Research on Cancer (IARC) reported that several types of cancer may be attributed to an excess BMI [4]. Overabundance of adipose tissue is a common cause of breast cancer and endometrial cancer. Obesity is also a risk factor for gastrointestinal cancers, including the pancreas, liver, esophagus, colorectum, stomach cardia and gallbladder [5] [6] [7] [8] [9] [10]. Cancers of the digestive tract account for ~25% of the global cancer burden and the incidence of these cancers has been increasing in recent years [11]. This work is an analysis of the available PubMed literature on the relationship between obesity and gastrointestinal cancers and possible mechanisms linking them.

Ryc.1. Fraction of all cancer cases (at all anatomical sites) among both sexes (worldwide) in 2012 attributable to excess body mass index, by country. https://gco.iarc.fr/causes/obesity/tools-map.

2.   State of knowledge:
2.1. MECHANISMS LINKING OBESITY AND GASTROINTESTINAL CANCERS.

There is a variety of mechanisms leading to obesity associated gastrointestinal cancers. Excess adiposity causes metabolic syndrome, chronic inflammation and altered production of steroid hormones. Adipokines, altered insulin and IGF1 signaling are also important factors in carcinogenesis.

Chronic Adipose Tissue Inflammation

Obesity is associated with chronic low-grade inflammation, which is more pronounced in the visceral than subcutaneous adipose tissue. There are multiple possible mechanisms responsible for initiation and development of inflammation of adipose tissue in obese patients, such as: lipopolysaccharide (LPS), dietary components and metabolites, death of adipocyte cells or hypoxia. Abnormal cytokine production, immune activation, and increased inflammatory signaling are also notable.

Adipose tissue is infiltrated by M1-macrophages, CD8+ T cells, natural killer (NK) cells, B cells. Macrophages secrete inflammatory factors such as IL 6 and TNFα, which have been associated with development of insulin resistance. What is more, elevated levels of anti-inflammatory mediators are observed - increased concentrations of IL10, IL4, and TGFβ are the most evident.

Treg cells are restricted in the adipose tissue of obese patients in comparison to patients with normal weight. Changes in an activity of Treg cells can increase inflammation in the adipose tissue and promote carcinogenesis [12]. Dysregulation of immune system is caused by decrease or loss of T helper 2 (Th2) cells in obese patients compared to patients with normal BMI. Tissues adjacent to lesions of the gastrointestinal tract are infiltrated by immune cells [13]. Inflammation can cause carcinogenesis in multiple different mechanisms, such as: productions of free radicals, suppression of immune system, hypoxia, upregulation of proliferative pathways, downregulation of apoptosis pathways and angiogenesis [14]. Visceral adipose tissue is a main source of obesity-derived inflammation [15].

Insulin and Insulin-Like Growth Factor 1 (IGF1) Signaling.

Insulin is an anabolic hormone that promotes glucose uptake, glycogenesis, lipogenesis, and protein synthesis of skeletal muscles and fat tissue.

Obesity is frequently associated with insulin resistance and hyperinsulinemia, probably out of necessity for regulating the increased levels of produced energy [16]. Hyperinsulinemia can induce the development of altered crypt foci, which are thought to be the first pathological lesions in carcinogenesis, as well as the rapid increase of cell divisions of colorectal epithelium in rodent models [17]. Moreover, insulin can affect cancer development by modulating other hormonal pathways (e.g. changes in sex hormones metabolism)

IGF1 is produced by the liver and it stimulates proliferation and inhibits apoptosis, hence it may contribute to cancer development and metastasis. Obese patients have been reported with higher level of IGF 1 than patients with normal weight [18]. IGF1 can bind to both Insulin-Like Growth Factor 1 Receptor (IGF1R) and Insulin Receptor.

IGF1R expression varies among neoplasm cells. IGF1 signals via its receptor to insulin receptor substrate 1, phosphatidylinositol 3-kinase (PI3K), AKT, and mammalian target of rapamycin (mTOR). IGF-1-AKT-TOR signal transduction pathways stimulate cell proliferation. Furthermore, excessive exposure of cells to IGF1 could promote carcinogenesis through the Ras–MAPK pathway [19].

Adipokines.

Adipokines are polypeptide growth factors and cytokines synthesized and secreted by adipose tissue. The levels of leptin and adiponectin have been found to differ in patients with gastrointestinal cancers. Leptin is secreted proportionally to the amount of white adipose tissue. Leptin expression in white adipose tissue is modified by insulin, estrogen, and inflammatory mediators like IL1B, IL6, and TNFα [20]. Free fatty acids, growth hormone, and peroxisome proliferator-activated receptor (PPAR) agonists reduce leptin secretion. Leptin binds to the receptors on stomach and colon cancer cells, resulting in the activation of the JAK–STAT, MAPK, PI3K–AKT, insulin receptor substrate, and mTOR signaling pathways [21]. Various cells and tissues, including cancer cell lines and immune cells, express a leptin receptor. Leptin stimulates cell division, invasion of tumor cells and inhibits apoptosis.

Adiponectin is secreted by mature adipocytes in an inverse correlation to total body fat mass [22]. Adiponectin has anti-proliferative and angiogenic effects.

Changes in sex hormones metabolism.

Adipose tissue is a main source of estrogen in men and postmenopausal women. In contrast to individuals with normal BMI, obese people tend to have higher levels of estradiol, which is produced in the aromatization process carried out by an aromatase enzyme. Obesity is also associated with hyperinsulinemia and reduced hepatic synthesis of sex hormone-binding globulin (SHBG). Therefore, the free sex hormones levels are elevated, which may increase the risk of cancer development by stimulating proliferation and angiogenesis and inhibiting apoptosis [23].

Intestinal Microbiota

Excess adiposity is associated with intestinal dysbiosis [24]. In obese, compared to individuals with normal weight, there is an altered ratio of the two major gut phyla: Bacteroidetes and Firmicutes (accordingly decreased and increased abundance of bacteroides species) [25]. Dysbiosis leads to a decrease in production of anti-inflammatory short-chain fatty acids, too.

2.2 GASTROINTESTINAL CANCERS AND OBESITY

This study investigates the mechanisms of obesity-associated colorectal, esophageal, gastric, and pancreatic cancers. These cancers are the most prevalent and lethal cancers worldwide. Expanding knowledge concerning their development may improve the treatment results.

Esophageal cancer

Gastroesophageal reflux disease (GERD), erosive esophagitis and esophageal cancer correlate with obesity [26]. GERD in obese patients is caused by a functional failure of gastroesophageal junction. Excess abdominal adipose tissue is responsible for increasing the intragastric pressure, while the tension of the lower esophageal sphincter (LES) is diminished. Additionally, hiatal hernia is more frequent in obese and leads to deterioration of GERD. Barrett's esophagus (BE) occurs due to the chronic inflammation, which is mainly caused by GERD.

BE is a metaplastic change in the mucosal cells and it is considered to be a precursor of esophageal carcinoma [27]. BE promotes cell divisions and stimulate anti-apoptotic pathways. As a result, the risk of genetic mutations is increased and it leads to the development of dysplasia and carcinogenesis. Finally, the altered serum levels of pro-inflammatory cytokines such as tumor necrosis factor-α (TNFα), interleukin-6 (IL-6) and adipokines (synthesized and secreted by an adipose tissue) promote the development of esophageal cancer.

Gastric cancer

While the incidence of non-cardia gastric cancer has lately decreased, the prevalence of cardia gastric cancer has increased. It is associated with increased BMI and obesity [28]. Chronic adipose tissue inflammation promotes development of gastric cancer, due to TNFα, IL6, and MCP1. Inflammatory factors stimulate cell divisions and inhibit pathways of apoptosis of human gastric cancer cell lines [29]. IGF1 levels increase progressively from benign lesions to cancer, which emphasize the role of IGF1 in development of gastric cancer (GC). Levels of leptin and leptin receptor are higher in patients with GC compared to the other individuals.

Pancreatic cancer

The most common histological type of pancreatic cancer (PC) is pancreatic adenocarcinoma (PAC). The results of meta-analysis showed that the relative risks (RRs) are 1.07 and 1.12 per 5 kg/m2 increase in BMI in men and women, respectively [30]. Increased levels of glucose, insulin, and C-peptide are associated with increased risk of PAC [31] [32]. Relationship between adipokine and leptin levels and development of PAC is unclear because patients usually lose weight before being diagnosed. Inflammation linked with obesity leads to dysregulation of immune system. Immune dysfunction is probably a result of hyperproduction of proinflammatory factors in macrophages and monocytes as well as generating free radicals and pathological changes in maturation of natural killer cells. Other mechanisms also play the crucial role in carcinogenesis: changes in sex hormones metabolism or neoangiogenesis induced by hypoxia and promoted by vascular endothelial growth factor.

Colorectal cancer

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide. In obese patients the risk of development CRC is 7%–60% higher compared to individuals with normal BMI [33]. Chronic inflammation of adipose tissue is associated with the secretion of hormones, growth factors and production of pro-inflammatory cytokines by adipocytes and it constitutes a risk factor for CRC. Hyperinsulinemia and IGF concentration are also connected to carcinogenesis. Hyperinsulinemia increases the level of bioactive IGF-1 because of decreased amount of the IGF-binding proteins [34]. Activation of IGF-1 receptors leads to an inhibition of apoptosis pathways and boosts proliferation [35]. Dysregulation of insulin and IGF-1 metabolism can induce the development of CRC. Adiponectin, leptin, resistin, and ghrelin also influence the carcinogenesis by stimulating the tumor growth, cell migration and progression from precancerous lesions to malignant tumors.

Oxidative stress and production of free radicals in obese patients are also involved in initiation, promotion and progression of CRC carcinogenesis [36]. Changes in the microbiota can also lead to the decrease of anti-inflammatory mediator levels and development of chronic inflammation.

3.   Conclusions:

Reduction of body weight should result in decreased number of diagnosed digestive system cancers - observational studies provide significant intermediary evidence that weight loss in obese patients can reduce cancer risk [37]. In order to thoroughly explain the role of excessive adipose tissue in carcinogenesis more studies concerning the relationship between the gastrointestinal cancers and obesity have to be conducted. A deeper understanding of the biological mechanisms connecting obesity, metabolic health and gastrointestinal cancers may allow to establish reliable biomarkers and risk factors as well as invent new preventive strategies and more effective treatment.

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