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# The Link between Obesity and Gastrointestinal Cancers: a Short Review

Fawzy AKAD[a], Veronica MOCANU[a, b], Bogdan FILIP[a, c], Manuela POROH[a], Teodor OBOROCEANU[a, b], Nada AKAD[a, d], Sorin Nicolae PEIU[a, e], Dragos SCRIPCARIU[a, c], Viorel SCRIPCARIU[a, c]

[a]"Grigore T. Popa" University of Medicine and Pharmacy Iasi, Romania

[b]Center for Obesity BioBehavioral Experimental Research, 16, Universitatii Street, 700115 Iasi, Romania

[c]Surgery Department, "Regional Institute of Oncology" Iasi, Romania

[d]Department of Endocrinology, "Saint Spiridon Emergency County Hospital" Iasi, Romania

[e]Department of Vascular Surgery, "Saint Spiridon Emergency County Hospital" Iasi, Romania

**ABSTRACT**

*Gastrointestinal cancer represents one of the most encountered oncologic pathologies and research studies are performed thoroughly in order to identify the exact causes and possible novel therapies. Obesity is a complex manifestation associated with numerous physiological and primarily molecular changes capable of tackling the behavior of tumoral cells and the nearby or faraway microenvironment. Adipose tissue has been once considered to have limited physiological roles, but in recent years it has been recognized as an active endocrine organ, secreting substances such as growth factors and adipokines. From an epidemiological perspective, obesity – particularly morbid obesity – is linked to an unfavorable progression of cancer. A key mechanism that may elucidate the association between obesity and cancer involves the insulin and insulin-like growth factor (IGF-1) pathway, sex hormones, and adipokines.*

**Keywords**: gastrointestinal cancer, obesity, growth factor, adipokines.

## INTRODUCTION

Gastrointestinal (GI) cancer accounts for one-third of all new cancer diagnoses and related deaths worldwide. Its incidence and mortality rates are increasing (1, 2). Several malignancies fall under the GI cancer umbrella, including esophageal cancer, colorectal cancer, hepatocellular carcinoma and pancreatic cancer (3, 4). Current research estimated that in 2018 there were 4 296 333 new GI cancer cases (excluding pancreatic cancer), accounting for 23.8% of all cases. The number of deaths was estimated at 2 953 693, representing 30.9% of cancer-related deaths. This makes GI cancer a

*Address for correspondence:*
*Akad Fawzy*
*Email: akad.fawzy@yahoo.com*

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major public health concern (1). The World Health Organization (WHO) predicts that globally, there will be a nearly 80% increase in the number of cancer deaths by 2030, with most of them occurring in low- and middle-income countries (5).

Epidemiological studies have demonstrated an association between the risk of cancer development and obesity. For GI cancer, the analysis identified a strong and potentially causal link between obesity and esophageal adenocarcinoma, colon cancer in men, biliary tract cancer, and pancreatic cancer. According to a 2016 report of the International Agency for Research on Cancer, individuals with a body mass index (BMI) of 40 kg/m$^2$ or higher have a relative risk of 1.5 to 1.8 compared to those with a normal BMI (18.0-24.9 kg/m$^2$) (6).

For decades, researchers have engaged in a longstanding debate regarding the adequacy of BMI as a diagnostic tool for obesity. Although nearly two centuries have passed since the inception of BMI, it remains the simplest, most cost-effective and easiest-to-calculate method for classifying individuals with obesity, based on their weight and height. The World Health Organization and other prominent international health organizations define overweight as a BMI of ≥25.0 kg/m$^2$ and obesity as a BMI of ≥30.0 kg/m$^2$, but BMI has several limitations. It fails to accurately reflect body adiposity due to variations in skeletal muscle and lean body mass (7).

Regarding the implication of BMI in cancer survival, a study involving 2 303 patients with non-metastatic colorectal cancer demonstrated that prediagnosis BMI, but not postdiagnosis BMI, was a significant predictor of survival among these patients (8).

Poorer prognosis and higher recurrence rates of cancer after radiotherapy or chemotherapy are more frequently observed in patients with obesity than lean ones. A large adjuvant chemoradiotherapy trial involving patients with stage II and stage III rectal cancer observed that a higher baseline BMI was linked to an increased rate of abdominoperineal resections, leading to a higher incidence of permanent colostomy. This inverse relationship between BMI and sphincter preservation was particularly evident among male patients. Additionally, obesity was a predictor of an increased risk of local recurrence in males, but not in females. Conversely, obesity did not affect overall mortality in either gender. Furthermore, increased adiposity was associated with reduced treatment-related toxicity during adjuvant therapy (9).

Bariatric surgery has been linked to a reduced risk of various obesity-related cancers. These include hepatocellular carcinoma, exocrine pancreatic cancer, gallbladder cancer, cholangiocarcinoma, colorectal cancer, renal cancer, esophageal adenocarcinoma, gastric cardia cancer, prostate cancer, postmenopausal breast cancer, endometrial cancer, ovarian cancer, thyroid cancer and multiple myeloma (10).

Obesity is defined by increased adipose mass arising from an energy imbalance. Adipose tissue is primarily made up of adipocytes but also contains pericytes, monocytes, macrophages, lymphocytes, fibroblasts, vascular endothelial cells and pluripotent stem cells. Previously, adipose tissue was thought to play limited physiological roles mainly as energy storage and protection from cold temperatures. Adipose tissue is acknowledged as an active endocrine organ that releases growth factors, chemokines and pro-inflammatory molecules referred to as 'adipokines'. These substances play a role in regulating metabolism and the immune system. Physiologically, adipokines regulate appetite, lipid metabolism, glucose homeostasis, insulin sensitivity and angiogenesis. They also play a role in controlling blood pressure and inflammatory processes (11).

In obesity, adipocyte hypertrophy leads to adipose dysfunction and inflammation by increasing the secretion of pro-inflammatory adipokines from adipocytes (12).

Alterations of adipocyte biology associated with adipocyte hypertrophy affect systemic organs. Epidemiologically, obesity is related to the risk of many types of cancers, including esophageal, gastrointestinal, colorectal, biliary, pancreatic, breast, endometrial, ovarian and kidney cancers (13-15). In this article, we review the contribution of adipose tissue to GI cancer development. ❑

## MATERIALS AND METHODS

This narrative review explores the multifaceted impact of obesity and GI cancer development. A literature search of the PubMed database was performed using the terms 'gastric cancer' and/or 'gastrointestinal cancer', 'obesity,

'adipokines', 'insulin-like growth factor', 'hyperinsulinemia', 'adipose tissue', 'leptin' from database inception to December 2023. A thorough assessment of key articles identified in the literature review was done. Through this method, our objective was to offer a nuanced comprehension of the current literature and its relevance to clinical practice.

## Obesity and cancer development: causal association

Obesity is an established risk factor for cancer development. We would like to highlight the potential to exploit this knowledge to uncover the mechanisms underlying the link between obesity and carcinogenesis. This approach could open new paths for cancer prevention and therapy.

### 1. Inflammation

As adipose tissue expands, it triggers an increase in proinflammatory adipokines, upsetting the balance between heightened inflammatory signals and reduced anti-inflammatory responses. This leads to chronic low-grade inflammation (16-18). Chronic adipose inflammation promotes cancer growth, stimulates angiogenesis and alters immune antitumor responses. Such a pro-inflammatory microenvironment in a tumor situs appears from inflammatory points named crown-like structures (CLS), a biomarker of inflammation (histology). These will induce synthesis of pro-inflammatory mediators and cytokines: cyclooxygenase-2 (COX-2), tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and interleukin adjacent to the tumor (IL-1β37). Inflammasome is another capital source of inflammation in adipose tissue in obese humans, it promotes the "maturation" of pro-inflammatory cytokines, between which IL-1β and IL-18. Adipocyte genomes express numerous inflammasome genes, including CASP1, NLRP3, PYCARD, IL-1β and TNFs, with approximately 40 of them being commonly encountered in obese people. In their activated form, inflammasomes induce an inflammatory microenvironment that fosters tumor growth and, ultimately, metastasis (19).

Some animal studies have shown that obese rats exhibit increased expression of inflammatory factors in their tumor cells, indicating that the tumor cells themselves are activated to produce inflammatory cytokines. The cells from the stroma of visceral adipose tissue and endothelial cells migrate to the site of the tumor (20).

Another factor we can include in understanding the connection between inflammation, obesity and carcinogenesis is the patient's diet. A dietary regime high in fat and refined sugar increases systemic inflammation (21). Consuming a diet abundant in vegetables, fruits, legumes and grains reduces inflammation in healthy adults (22).

### 2. Adipokine secretion

Adipokines are hormone-like polypeptides which are actively secreted by the white adipose tissue (WAT). Primarily produced by WAT, leptin is a polypeptide hormone that serves as a crucial regulator for appetite and energy homeostasis by interacting with specific receptors highly expressed in the hypothalamus. Leptin concentration in plasma is highly correlated with the percentage of body fat. This remark promotes the idea that the majority of obese persons are insensitive to endogenous leptin production (23). Some studies found that levels of serum leptin are tremendously lower in gastrointestinal cancer patients. As a plus, GI cancer patients have low insulin levels and present low insulin resistance and growth hormone levels. This study found a positive association between levels of serum leptin and insulin resistance. Moreover, there seems to be an inverse relationship between serum leptin levels and growth hormone levels. Consequently, reduced insulin and growth hormone levels may inhibit leptin secretion in patients with GI cancer (24). Another study described a polymorphism that may alter serum leptin levels, LEP G2548A. It has been linked to a modestly elevated overall cancer risk (odds ratio 1.27, 95% CI 1.05–1.54) (25).

Experimental GI cancer models showed an interaction between leptin and adiponectin. The latter downregulates leptin-induced proliferation in hepatocellular and esophageal carcinomas (26-27). Certain studies involving animal models found a correlation between reduced serum adiponectin levels and an elevated risk of developing hepatic and colorectal adenomas. Serum levels of adiponectin showed an inverse association with colorectal cancer risk in a meta-analysis (odds ratio 0.716, 95% CI 0.606–0.847), al-

though this association was not independent of BMI or waist circumference (28-30).

### 3. Hyperinsulinemia and the insulin-like growth factor axis

Circulating insulin concentration directly correlates with BMI increase, which explains why obese persons are insulin-resistant. The evidence transpiring from here is that insulin resistance becomes a risk factor for cancer development. It is proposed that hyperinsulinemia can contribute to cancer occurrence and progression *via* the growth effect promoted by elevated insulin levels.

Studies report that adipose stem cells (ASCs) play a huge role in tumor microenvironments and they are altered by obesity. According to many previous studies, in obesity-altered ASCs (obASCs) there are higher than normal levels of leptin. This finding was supported by demonstrating the metastasis-promoting effect of obASCs in estrogen receptor (ER) wild type and mutant xenografts, as well as in a mutant ER patient-derived xenograft model. Nevertheless, only in ER wild type xenografts obASCs promote tumor growth (31).

### 4. Peritumoral adipose tissue

Studies reveal that in obesity there are systemic alterations which affect tumor growth and metastasis. Additionally, there is communication between cancer cells and adipocytes surrounding the tumor. Tumor cells stimulate lipolysis in cancer-associated adipocytes, prompting them to differentiate into fibroblast-like cells. These cells produce proinflammatory cytokines, which in turn support tumor cell development (26). ❑

## DISCUSSION

Obesity is closely linked to dysfunctional metabolic pathways in adipocytes and adipose tissue overall, contributing to various chronic diseases. Elevated levels of free fatty acids (FFA), cholesterol, glycerol and triglycerides (TGL) in serum influence the initiation, progression and metastasis of tumors, particularly in breast cancer, as studied here. In vitro experiments have demonstrated that co-culturing mature adipocytes with breast cancer cells enhanced cancer cell proliferation, highlighting direct interactions between adipocytes and cancer cells through secreted compounds. Free fatty acids originate from daily dietary intake and accumulate as lipid vacuoles in the adipose tissue. The connection between total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and their impact on cancer growth remains unclear. Obesity triggers exosomes involved in modulating fatty acid oxidation and therefore contributes to tumor migration (32).

It is worth reviewing a specific study on colon cancer, as it provides mechanistic insights into the correlation between cancer and adipocytes. In this study, different colon cancer cell lines were cultured with adipose tissue, adipocytes or preadipocytes derived from leptin-deficient (ob/ob) or wild-type mice in a collagen-based three-dimensional culture system. All conditions facilitated the proliferation of colon cancer cells. Notably, the proliferative effect induced by adipocytes was dependent on leptin (33).

The reviewed studies indicate that metabolic changes in adipocytes in the tumor microenvironment support tumorigenesis. Additionally, Behan et al suggested that adipocytes might contribute to chemotherapy resistance, as they found that adipocytes reduced the effectiveness of vincristine, daunorubicin and dexamethasone against leukemia cells, promoting leukemia cell survival. The mechanisms identified by them included reduced apoptosis of leukemia cells in the presence of adipocytes and increased cell cycle activity in response to chemotherapy drugs (34). ❑

## CONCLUSION

Understanding mechanisms that promote cancer development in obese patients could pave the way for new anticancer strategies. Adipose tissue plays a crucial role in gastrointestinal cancer by influencing tumor growth, invasion and metastasis. Cancer cells can interact either directly or indirectly with adipocytes, and obesity may alter these interactions, thereby promoting tumor progression. ❑

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