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The role of adipose tissue in colorectal cancer

Ivanna Lazarchuk[1], Wojciech Plizga[1], Greta Stołecka[1], Mateusz Sydor[1], Shivika Parmar[1], Sławomir Woźniak[2]

Abstract

In this review we discuss the role of adipose tissue in colorectal cancer (CRC). CRC is one of the deadliest cancers worldwide and, in fact, the third most common. However, it can be mainly prevented by an adequate diet. We explored and studied articles in-depth in order to develop better understanding about CRC. We highlight, that markers such as TNF-α, IL-6 and IL-8/CXCL8 are the major players responsible for causing CRC. In addition, fat-induced insulin resistance also contributes to the risk of CRC. We emphasize that the best way to prevent colorectal cancer is to consume a fiber-rich diet and do physical activity on a regular basis. We aim to explore the importance of adipose tissue as an endocrine organ, how it relates to obesity as well as the crucial role adipose tissue play in progression of colon cancer.

Running title: Adipose tissue's role in colorectal cancer

Keywords: adiponectin, adipose tissue, cancer-associated adipocytes, colorectal cancer, obesity

[1]SKN (Students Scientific Society) Anatomia-Klinika-Nauka, Division of Anatomy, Department of Human Morphology and Embryology, Wroclaw Medical University, Wroclaw, Poland
[2]Division of Anatomy, Department of Human Morphology and Embryology, Wroclaw Medical University, Wroclaw, Poland
***Correspondence:** wojciech.lukasz.plizga@gmail.com
Full list of author information is available at the end of article

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Introduction

Colorectal cancer (CRC) is the third most common cause of cancer deaths in both sexes. Approximately 6% of the individuals will develop colorectal cancer within their lifetime, and about half of them will die from this disease [1]. Diet is the most important risk factor of CRC identified so far. According to the World Cancer Research Fund and the American Institute for Cancer Research CRC is mostly preventable by appropriate diet. It has been proven that red meat, processed meat, substantial consumption of alcoholic drinks, body and abdominal fat, and any other factors that lead to increased weight are causes of CRC. On the other hand, food containing dietary fiber as well as physical activity have been found to help prevent colon cancer [2]. While researchers faced difficulties in objectively measuring physical activity, studies have shown that the more physically active an individual is, the lower the risk of CRC [1]. Other, non-dietary factors of colon cancer include: tobacco smoking, chronic use of non-steroidal anti-inflammatory drugs and aspirin, inflammatory bowel disease (IBD), genetic predisposition and metabolic syndrome [2]. An inadequate diet affects the growth of adipose tissue (AT), the hormonal activity of which influences the progress of CRC [3]. Several studies indicate a correlation between obesity and a higher risk of CRC [4]. AT is the main energy store in the human body. It is mostly composed of adipocytes, cells that have the ability to store fat and nutrients in the subcutaneous tissue. These can be further divided into white adipose tissue (WAT) and brown adipose tissue (BAT). They differ in appearance, structure and function [5]. WAT is one of the largest tissues in the human body. In healthy, lean people, its mass ranges from 10% to 20% of body weight but its amount can increase up to 40% – 70%. WAT collects glucose and lipids circulating in the system, thus protecting against abnormal accumulation of triglycerides (TGs). However, both excess and deficiency of WAT lead to health problems such as fatty liver disease and insulin resistance. Moreover, AT is hormonally active, controlling many metabolic processes through the number of adipocytes. Changes in the number of adipocytes are correlated with many obesity-related metabolic problems, such as type 2 diabetes, metabolic syndrome and cardiovascular diseases [6]. BAT is responsible for thermogenesis. We distinguish two types of thermogenic adipocytes: the classical brown adipocytes found in the interscapular brown adipose organ and the so-called beige adipocytes primarily found in subcutaneous white adipose tissue (SAT) after adrenergic stimulation. Brown-like adipocytes occur within WAT depots in response to chronic cold exposure or administration of β3-adrenergic agonists or thiazolidinediones, a group of peroxisome proliferator activate receptors agonists. Both brown and beige adipose tissue share common similarities including multilocular lipid droplets, and a high mitochondrial content [7]. To sum up, we distinguish white and brown adipose tissue, which perform opposite functions. WAT provides energy in the form of TGs, while BAT releases it by thermogenesis [8]. AT has the ability to secrete proinflammatory cytokines, which as proven by many studies, are involved in the process of carcinogenesis. Additionally, inflammatory cells in obese AT produce reactive oxygen species (ROS), inducing mitogenic activity, and therefore being considered to be tumor-promoting signaling molecules. As obese people have excess AT that secretes proinflammatory factors and ROS, they have a higher risk of colorectal cancer [9].

Adipose tissue as an endocrine organ

AT is a complex endocrine organ that secretes adipokines, which are active biological substances that play a role in regulating various physiological processes through autocrine, paracrine and endocrine mechanisms. The list of hormones and cytokines that are collectively referred to as adipokines includes leptin, adiponectin, resistin, and numerous other cytokines that are associated with the immune system [10]. Recently published scientific studies demonstrate that these substances are also involved in the development and progression of cancer [11,12]. Leptin is a hormone secreted by adipose tissue that acts as a ligand to the receptor for leptin. Its primary function is to regulate appetite and energy expenditure. Nevertheless, leptin has also been demonstrated to exert an influence on the immune response, angiogenesis, reproduction and glucose and lipids metabolism. The level of this hormone is elevated in proportion to the mass of AT [13]. In malignant tissues of the breast, lung, colon, uterus, liver and ovaries, increased expression of leptin and its receptors has been observed [14]. Leptin has been demonstrated to play a role in the proliferation, migration, survival and invasiveness of tumor cells. Furthermore, evidence suggests that it also inhibits apoptosis in these cells [15,16]. A review article by Jiménez-Cortegana C et al., emphasizes that, in addition to its prooncogenic effects, leptin may also possess anticancer properties [17]. However, more research is needed to unravel the complexity of leptin's effects on cancer and to develop targeted therapies. Adiponectin is involved in several physiological processes, including lipid metabolism, energy regulation, immune response, inflammation and insulin sensitivity [18]. Plasma adiponectin levels are lower for obese than for lean individuals [19]. Moreover, the expression of the adiponectin receptors R1 and R2 is also observed to be decreased in those individuals with obesity [20]. This leads to a diminished capacity for the anti-inflammatory, pro-apoptotic and anti-proliferative effects of this adipokine [21]. It is also noteworthy

that adiponectin has the capacity to counteract the effects of leptin [22]. A reduction in circulating adiponectin and/or the ratio of adiponectin to leptin is linked to an elevated risk of developing breast, endometrial, prostate, liver and colorectal cancers [23]. The anti-tumor effects of adiponectin are achieved in two distinct ways. Primarily, adiponectin directly affects tumor cells, as demonstrated by the expression of adiponectin receptors in numerous tumor lines. Secondly, its capacity to enhance insulin sensitivity contributes to its anti-tumor properties [24]. Nevertheless, some scientific studies have indicated that adiponectin may, in certain instances, exert a pro-oncogenic influence [25–27]. Other adipokines, including visfatin, resistin, apelin and chemerin, have been the subject of studies that have demonstrated their potential to promote oncogenesis [28–31].

Excess adipose tissue is involved in the development of cancer because it participates in low-grade chronic inflammation by releasing hormones, and pro-inflammatory factors, including the previously mentioned leptin, but also interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), chemokine (C-C motif) ligand 2 (CCL2), plasminogen activator inhibitor-1 (PAI-1) and others [32,33]. The role of inflammation in the CRC tumor microenvironment (TME) is significant, with the ability to activate signaling pathways that regulate proliferation, migration and metastasis [34,35]. IL-6 represents one of the most extensively studied pro-oncogenic cytokines. It has been reported that it exerts an influence on several key oncogenic processes, including cell proliferation, survival, migration, invasion, metastasis, angiogenesis and inflammation [36]. An elevated concentration of IL-6 prompts the liver to synthesize and secrete C-reactive protein (CRP) [33]. A number of scientific studies have shown that pre-surgical elevated levels of IL-6 or CRP in patients with CRC are a reliable predictor of prognosis, with a higher risk of overall mortality [37–40]. IL-6 binds the IL-6-α receptor, which triggers Janus kinases activation, followed by recruitment and activation of cytosolic STAT-3 [41]. This pathway leads to tumor cell proliferation, survival, invasiveness and metastasis. At the same time, it strongly suppresses the anti-tumor immune response [42]. It should be noted that STAT3 is not solely activated by IL-6 but also by other cytokines, oncogenes and growth factors [43]. Another cytokine that is markedly produced in individuals with obesity is TNF-α [44]. TNF-α is secreted at elevated levels in IBD patients and has been implicated in the pathogenesis of IBD [45–47]. Moreover, elevated levels of TNF-α have been observed in the CRC microenvironment [48]. It has been established that the overexpression of TNF-α mRNA is linked to high-grade CRC, cancer progression and a reduced survival rate for patients [49]. TNF-α plays a role in the initial phase of the inflammatory response and stimulates the production of other cytokines. This process leads to activation of oncogenes and increased vascular permeability, angiogenesis, invasion and migration of tumor cells [50]. TNF-α has been demonstrated to stimulate nuclear factor-κB (NF-κB) activation, with the activation of the IκB kinase (IKK)/NF-κB pathway being indispensable for the development of colitis and colorectal carcinogenesis. NF-κB regulates the expression of genes associated with cancer proliferation, invasion, angiogenesis and metastasis. Key inflammatory factors such as TNFα, IL-6, IL-1 and IL-8 are further increased by constitutive activation of NF-κB. On the other hand, as mentioned earlier, inflammatory factors can activate NF-κB. This leads to a positive feedback loop that increases tumorigenesis [43]. Furthermore, certain cytokines that are induced in reaction to NF-κB in immune cells within the TME have been proven to result in STAT3 activation in not only malignant cells but also in immune cells [51].

Obesity and colon cancer risk

Obesity, characterized as an abnormal or excessive fat accumulation in adipose tissue is becoming a major global health problem [52]. The number of people living with obesity is growing at an alarming rate. The World Health Organization (WHO) estimated that in 2022, 43% of adults were overweight and from 1990 to 2022, the percentage of the world's adult population living with obesity has doubled, reaching 16% globally [53]. In addition to an increased risk of diseases such as diabetes, hypertension, stroke and cardiovascular disease [54,55], obesity also contributes to an elevated incidence and mortality associated with cancer [56–66]. The International Agency for Research on Cancer (IARC) Working Group concluded that there is strong evidence indicating a link between obesity and an increased incidence of 13 different cancers, including CRC [67]. Obesity is usually measured by body mass index (BMI) and defined as a BMI above 30. However, due to the inadequacies of this marker, the use of waist circumference (WC) is often preferred. A meta-analysis conducted by Ma Y et al., found that obese individuals carry a CRC risk of 1.33 times higher than those with a normal BMI. Interestingly, the relative risk of CRC was dependent on the sex of the subjects and for the male population it was 1.47 and for the female population it was 1.15. Moreover, the study showed that for the highest versus the lowest category of WC, the relative risk for CRC was up to 1.45 [62]. These results were consistent with the findings of the IARC working group, as they estimated that for obese individuals, the relative risk of CRC is 1.3 times greater than for non-obese individuals [68]. Furthermore, Kyrgiou M et al., in an umbrella review, examined the association of BMI with colon and rectal cancer, separate-

ly. They showed that per every 5 kg/m2 increase in BMI, the risk of colon cancer rises by 22% and rectal cancer by 7% with similar gender-dependent differences as in Ma Y et al. study [69]. On top of that, Gibson TM et al., showed that overweight or obese people with a history of CRC had a higher risk of developing a second obesity-related cancer compared to normal-weight people [70].

The mechanisms linking obesity to an increased risk of CRC development are both complex and not fully understood. One of these may be insulin resistance, which is associated with visceral adipose tissue (VAT). VAT, along with subcutaneous adipose tissue (SAT), is one of the main types of WAT and is located on the internal organs of the abdominal cavity. Most of the fat, in lean, healthy patients, is stored in subcutaneous adipose tissue (SAT). This tissue is considered more metabolically healthy and contains small, insulin-sensitive adipocytes that avidly absorb free fatty acids (FFAs) and TGs after a meal. In overweight and obese individuals, the storage capacity of the SAT is exceeded and there is a subsequent accumulation of fat in the VAT cells. As fat accumulates in visceral adipocytes, they expand and become dysfunctional and eventually develop inflammation [71]. The inflammatory process is triggered by the expression of c-Jun N-terminal kinase and IκB kinase in fat cells [72]. As adipocytes expand, they also increase the secretion of pro-inflammatory cytokines, such as TNF-α, which further enhance inflammation [71,73]. During this process, they also decrease the production of adiponectin, a protein hormone responsible for inhibiting VAT inflammation and maintaining insulin sensitivity [73,74]. In addition, Bensussen A et al., showed that under these conditions, the presence of insulin enhances the inflammatory process in adipocytes through its effect on the increase in the Th17 lymphocyte population [74]. The described mechanisms lead to the development of insulin resistance in visceral adipocytes, making them less sensitive to the anti-lipolytic properties of insulin [72]. In addition, VAT adipocytes show greater sensitivity to catecholamine-induced lipolysis [71]. Consequently, visceral adipocytes have enhanced lipolytic activity, leading to the breakdown of stored TGs and the subsequent release of FFAs into the bloodstream, which then travel to skeletal muscle and to the liver via the portal vein [75,76]. Despite being more metabolically active and releasing more FFAs, visceral adipocytes have lower rates of total tissue FFA uptake and poor ability to store FFAs for extended periods of time compared with subcutaneous adipocytes. An excess of FFAs in the bloodstream results in increased uptake by skeletal muscle and their accumulation in muscle fibers. This causes a lipotoxic effect, ultimately reducing the translocation of insulin-dependent GLUT4 receptors to the cell membrane surface, resulting in the development of insulin resistance in muscle cells. The release of FFAs into the portal circulation contributes to the development of hepatic insulin resistance as well. Firstly, similar mechanisms take place in the liver as in skeletal muscle. Secondly, in the liver, FFAs compete with glucose in oxidation pathways. As a result, glucose is not adequately utilized, and oxidation of FFAs further increases gluconeogenesis leading to hyperglycemia, creating a positive feedback loop for insulin resistance [76]. Furthermore, visceral adipocytes secrete adipokines that impair the function of receptors for insulin in cells [77]. In summary, the presence of VAT and its ability to release large amounts of FFA into plasma leads to the development of insulin resistance in various tissues, an increase in blood glycaemia and, consequently, hyperinsulinemia to compensate for the reduced ability to metabolize glucose.

The mechanism by which insulin promotes tumor initiation and progression in insulin-resistant patients is not fully understood. However, it was found that insulin can increase proliferation in both normal and malignant cells [78]. In addition, excess insulin affects the levels of insulin-like growth factors (IGFs), proteins responsible for cell proliferation, differentiation and apoptosis protection [79]. Hyperinsulinemia leads to reduced hepatic production of IGF-1-binding protein (IGFBP-1) and IGF-2-binding protein (IGFBP-2), consequently contributing to increased IGF bioavailability [80]. IGFs can bind to IGF receptors but also to insulin receptors [81]. Interestingly, all these receptors have been shown to be commonly expressed in malignant cells [79]. Moreover, elevated levels of circulating IGF-1 have been found to be involved in the development of certain tumors, such as breast, prostate and colorectal cancers [81–83]. Thus, insulin may not necessarily directly induce carcinogenesis, however, it may lead to it through its effect on IGF-axis.

The role of adipose tissue in colon cancer progression

TME of CRC is a heterogeneous collection of cells, comprising tumor cells and other cellular components such as stromal cells (cancer-associated fibroblasts (CAF), endothelial cells, adipocytes, tumor-associated macrophages T cells, natural killer cells and myeloid-derived suppressor cells), as well as its non-cellular components, including extracellular matrix (ECM) and soluble products such as chemokines, cytokines, growth factors and extracellular vesicles [84,85]. The TME also includes non-malignant cells, vessels, lymphoid organs or lymph nodes, nerves, intracellular components and metabolites, based in the center, periphery or vicinity of the tumor lesion [86]. The TME's cells cooperate both with each other and tumor cells, thus playing an important role in the development and progression of cancer, including CRC [87]. An inte-

gral part of the TME are adipocytes, which are progenitor cells that are located around the invasive tumor and can be transformed into cancer-associated adipocytes (CAAs). CAAs have a fibrotic phenotype and are localized within the invasive tumor area [88]. CAAs are important stromal elements in various TME, promoting cancer progression through direct or indirect effects on cell growth, neogenesis, migration, metastasis and drug resistance [89]. CAAs have been detected in a variety of cancer types, including colon, breast, ovarian, prostate and pancreatic cancers [90]. Based on the study by Dirat B. et al., it was proven that adipocytes surrounding the tumor are smaller in size with expanded interstitial space and a significant reduction in the number and size of lipids compared to mature adipocytes from VAT and SAT was observed [91,92]. The main function of the CAAs is to store lipids in the form of TGs which are broken down and released as FFAs when required [89]. Wen Y et al. by analyzing samples of patients with stage III and IV CRC, found that metastatic cancer cells interact with surrounding adipose tissue [93]. Appropriate staining showed the presence of invasive tumor cells in niches surrounded by rich adipose tissue and numerous infiltrating macrophages in close association with these cells and adipocytes. Moreover, the study showed that after co-culture of mature adipocytes with SW480 tumor cells, the accumulation of lipid droplets in cancer cells increases. In summary, the cancer cells are able to take up FFAs released from the adipocytes. Interestingly, the described study shows that colorectal cancer cells promote lipolysis in adipocytes [93]. CAA exhibit lipolytic properties by releasing FFAs. FFAs are then translocated and stored in tumor cells in lipid droplets. Subsequently, the released FFAs can be taken up by tumor cells for β-oxidation of fatty acids (FAO), serving to promote their growth [94]. Specialized transporters, such as CD36 or extrinsic vesicles (EVs) have been shown to be involved in the uptake of FFAs from the TME, the latter being a novel messenger between adipocytes and cancer cells. EVs translocate proteins and substrates, involved in FAO, into cancer cells and then increase FAO and energy delivery in cancer cells such as melanoma to enhance migration and invasion [89]. It is noteworthy that colon cancer cells also capture during nutrient deficiency [93]. This process is particularly intensified by obesity and contributes to cancer progression. Additionally, cancer cells show the ability to survive in nutrient-poor conditions through FFA uptake, which is important in fat-rich environments [87]. In addition to their lipolytic properties, CAA cells secrete higher amounts of chemokines such as CCL2, CCL5, IL-1β, IL-6, TNF-α, vascular endothelial growth factor (VEGF) and leptin [95]. These mediators activate different types of immune cells, stimulating their influx into the TME. Described mediators are responsible for the interaction of other cells in the TME such as CAAs and CRC susceptible cells, and also influence the activation of myofibroblasts. TNF-α, IL-6 and IL-8/CXCL8 have been identified as major inducers of CRC-associated cachexia involving CAAs [96]. CAAs increase catabolic metabolism, thereby releasing a variety of high-energy metabolites in the TME, especially lactate, FFA, glutamine, pyruvate and adenosine triphosphate [89]. In addition, another characteristic feature of CAA is the production of MMP-11, PAI-1, MMP1, fibroblast activating protein (FAP) and collagen VI, which are involved in ECM remodeling, being the next step in tumor progression [90]. As a result of the degradation of peri-cellular tissue and ECM, pro-angiogenic factors, namely VEGF and other cytokines, are released, leading to the formation of new blood and lymphatic vessels, thus providing an easy pathway for tumor cells to enter the bloodstream [84]. Commonly, cancer cells are embedded in a dense ECM comprising of collagen, proteoglycans, proteins and glycoproteins, the content of which in the matrix can significantly impede the effectiveness of both biologic and chemotherapeutic anti-cancer drugs [97]. Interestingly, a study by Wu X YA et al., found that type I collagen, being the major structural protein of ECM in TME, showed higher expression in tissues from metastatic colorectal cancer patients compared to samples from patients without metastases. The results of this study showed that treatment with type I collagen increases the number of CRC metastases to the lung [98]. CAAs are assumed to be one of the sources of cancer-associated fibroblasts (CAF), as they show increased fibroblastic macronuclei such as SMA and fibroblast-specific protein 1 [99]. CAF, compared to normal fibroblasts, proliferate more rapidly, thereby secreting more cytokines, matrix proteins and immune factors, making it possible for a given cell type to drive tumor progression, modulate ECM composition and interact with other cell types [97,100].

Treatment

Lifestyle modifications such as appropriate diet and physical activity, as well as drug treatment and bariatric surgery, have been shown to be effective in reducing the risk of colorectal cancer [101]. A meta-analysis by Lui L et al., showed that the WHO recommended physical activity (about 10 metabolic equivalent energy hours per week) reduces the risk of colorectal cancer and breast cancer by 7% [102]. This is because the catecholamines secreted during exercise have a regulatory effect on metabolic processes and the immune system. Regular exercise reduces the expression of pro-inflammatory genes, including TNF-α, MCP-1, IL-1β and F4/80, which affect carcinogenesis [99]. As has been proven in many studies, the biggest influence on the development of colorectal cancer is a poor diet that leads to excessive body fat [2]. A study by Song M et al., showed that high fiber intake, especially ce-

reals among patients with stage I-III colorectal cancer, low colorectal cancer-related mortality and all mortality [103]. Vitamin D is an equally important factor that plays a large role. McCullough ML et al., conducted a study involving 5706 colorectal cancer patients and 7107 control participants, which showed that higher levels of vitamin D led to a significant reduction in colorectal cancer risk both in men and women. The authors of this study suggest, that for a reduction in CRC risk, the optimal vitamin D concentration is 75-100 nmol/l, a concentration that is higher than currently recommended by the Institute of Medicine for bone health [104]. It is worth noting that alcohol consumption is linked to an increased risk of colorectal cancer. Alcohol has a carcinogenic effect, acting in a variety of ways, and a regular consumption, particularly excessive, is recognized as a significant contributor to the development of this cancer. A meta-analysis by Cai S et al., identified the presence of a modest positive association between heavy alcohol drinking (≥50 g / day) and CRC mortality [105]. Furthermore, Dashti SG et al., concluded that there is also a positive association with alcohol consumption (> 28 g / day or 2 drinks per day) and colorectal cancer [106]. After ingestion, ethyl alcohol (ethanol) is converted to acetaldehyde, exhibits carcinogenic effects by affecting intestinal cell DNA synthesis and interfering with cell repair and glutathione function, thereby increasing the risk of mutation and cancer development [101,107]. Pharmacological treatment of obesity can include mirabegron, which reduces body weight and decreases adipose tissue volume, and dapagliflozin, which inhibits lipogenesis and induces WAT browning [99]. However, it is worth remembering that it is not drugs but maintaining a healthy body weight, being physically active, consuming as much plant fiber as possible, avoiding red and processed meat and excess alcohol are the best methods of preventing colon cancer [108]. Another form of treatment for obesity is a bariatric surgery. Himbert C et al., found that obese people who did not undergo bariatric surgery had an increased risk of developing CRC [109]. In addition to weight loss, bariatric surgery is also associated with a reduction in the number of white blood cells responsible for inflammatory processes in the body [110]. Additionally, the surgery reduces oxidative stress and systemic inflammatory markers such as IL-6, CRP and PAI-1 [111]. To summarize, weight reduction may contribute to the efficacy of chemotherapy and radiotherapy, as well as reducing the risk of surgery.

Conclusions

While colorectal cancer only affects 6% of the population worldwide it is still something to be mindful of. Research has shown that there is a direct correlation between obesity and an increased risk of colorectal cancer. Adipose tissue, as an endocrine organ, secretes hormones such as adiponectin, leptin and resistin. As weight is gained, adiponectin levels fall and leptin rises. Studies have proven that changes in the adiponectin to leptin ratio are associated with an elevated risk of breast, endometrial, prostate, liver and colorectal cancer. In addition, excess adipose tissue has been found to be involved in the development of colorectal cancer due to its ability to oversecrete pro-inflammatory cytokines, in particular IL-6, TNF-α, CCL2 and PAI-1. The most studied cytokines, IL-6 and TNF-α have been observed to be elevated in patients with colorectal cancer. IL-6 stimulates the liver to synthesize and release C-reactive protein as well as triggers Janus kinases activation, leading to proliferation, survival, invasiveness and metastasis of cancer cells. TNF-α plays a role in an inflammation initiation and promotes the production of other cytokines contributing to oncogene activation and, consequently, to carcinogenesis. Adipose tissue also increases the amount of circulating free fatty acids, resulting in insulin resistance and hyperinsulinemia, which is associated with a higher risk of colorectal cancer. Furthermore, the tumor microenvironment comprises various types of cells, one of which are cancer-associated adipocytes. These cells have an impact on cancer progression by affecting cell growth, neogenesis, migration, metastasis and drug resistance. However, the evidence is clear that processed food products and alcohol consumption are the main causes of colorectal cancer. Thus, the best ways to reduce the risk of developing this cancer are physical activity on a daily basis, a proper, fiber-rich diet, vitamin D supplementation and limited alcohol intake. Moreover, bariatric surgery, a method used to reduce obesity, could potentially reduce the risk of colorectal cancer by limiting inflammation and oxidative stress. Future research should focus on prevention and treatment of colorectal cancer given that it is one of the deadliest cancers in the world.

Ethical approval

The study was a descriptive one. No humans or animals were a subject of examinations.

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Corresponding author

Wojciech Plizga, SKN (Students Scientific Society) Anatomia-Klinika-Nauka, Division of Anatomy, Department of Human Morphology and Embryology Wroclaw Medical University, 6a Chalubinskiego street, 50-367 Wroclaw, Poland; e-mail: wojciech.lukasz.plizga@gmail.com.

Conflict of interest statement

The authors declare no conflict of interest.

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