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Body Mass Index and Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is one of the most common cancers in the world. Obesity is an established risk factor for colorectal carcinogenesis. Many epidemiological and experimental studies support this link and tumor-promoting effects of obesity. Body mass index (BMI) is a marker of general obesity. Obesity is also a global health problem and is defined by World Health Organization as $\text{BMI} > 30 \text{ kg/m}^2$. In this chapter, we give a general review about the mechanisms of obesity on colorectal carcinogenesis and the effects of obesity on clinical outcomes such as disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS), in adjuvant setting and metastatic disease, respectively.

Keywords: colorectal cancer, body mass index, obesity, carcinogenesis

1. Introduction

CRC is third most common cancer in men with age-standardized rate (ASR) 20.6 per 100,000 and second in women (ASR 14.3 per 100,000) in the world [1]. Approximately 1.4 million new cases and 693,900 deaths occurred in 2012. Wide geographical variation in its incidence is observed; the highest incidence is in Australia/New Zealand, the lowest is in Western Africa. Our country, Turkey takes place between them with ASR of 16.6 per 100,000 for both sexes. Environmental factors especially unhealthy lifestyle may increase the burden of CRC and important number of cases can be preventable by changing this lifestyle [2–5].

Obesity which is characterized by an excess of body fat is an established risk factor for colorectal carcinogenesis [6–12]. It is defined by World Health Organization (WHO) as $\text{BMI} > 30 \text{ kg/m}^2$ [13]. BMI is the most widely used metric of adiposity in adults and classified by WHO in 1995, 2000 and 2004 (**Table 1**). Obesity is a global health problem and its prevalence has increased worldwide in all age groups [14, 15]. Overweight individuals account for

Classification	BMI (kg/m ²)
Underweight	<18.50
Normal range	18.50–24.99
Overweight	≥25.00
Pre-obese	25.00–29.99
Obese	≥30.00
Obese Class I	30.00–34.99
Obese Class II	35.00–39.99
Obese Class III (severely obese)	≥40.00

Table 1. The international classification of BMI (Source: Modified from WHO and AICR).

approximately 30% of the global population (1.9 billion), and more than 650 million people are classified as obese in 2016 [13]. In a large prospective mortality cohort study in the United States, 20% of all cancer deaths in women and 14% in men could be attributed to obesity in 2003 [16]. World Cancer Research Fund (WCRF), American Institute for Cancer Research (AICR) and US National Cancer Institute (NCI) are classified CRC, cancers of kidney, esophagus (adenocarcinoma), gastric cardia, gallbladder, liver, pancreas, thyroid for both sexes and postmenopausal breast cancer, endometrial and ovarian cancers in women as obesity-related cancers [17, 18]. Cohort studies and meta-analyses strengthened the evidence and demonstrate that obesity increases the risk of colon cancer up to 33% as compared to the risk of anybody with a normal BMI [8, 9, 15, 19–21] (**Table 2**).

Cancer site	Bergström et al. [19]	Renehan et al. [21]				AICR 2014	
	RR	Relative risk (RR)				% link to excess body fat	
		Men	P value	Women	P value	Men	Women
Ovarian	NR	—	—	1.03	NS	—	5%
Breast (post-menopausal)	1.25	—	—	1.12	<0.0001	—	17%
Endometrium	2.52	—	—	1.59	<0.0001	—	50%
Kidney	1.84	1.24	<0.0001	1.34	<0.0001	20%	28%
Gallbladder	1.78	1.09	NS	1.59	0.04	11%	28%
Esophageal adenocarcinoma	NR	1.52	<0.0001	1.51	<0.0001	32%	38%
Pancreas	NR	1.07	NS	1.12	0.01	17%	20%
CRC	Colon: 1.33	Colon: 1.24 Rectum: 1.09	<0.0001 <0.0001	Colon: 1.09 Rectum: 1.02	<0.0001 NS	17%	15%
Thyroid	NR	1.33	0.02	1.14	0.001	NR	NR

NS: not significant, NR: not reported

Table 2. Obesity-related cancers [17, 19, 21].

A recent linear dose-response meta-analysis of four prospective studies showed that each 5 kg increase in adult weight gain was associated with an approximately 6% increased risk of colon cancer (RR = 1.06, 95% CI = 1.03–1.10) [8]. Similarly, another meta-analysis of 30 prospective studies reported an increased risk of colon cancer by each 5-unit increase of BMI in both men (RR = 1.30, 95% CI = 1.25–1.35) and women (RR = 1.12, 95% CI = 1.07–1.18), and this association was stronger in men ($p < 0.001$) [9]. BMI was positively associated with rectal cancer in men, but not in women. In this study, they showed also that increasing waist circumference (per 10 cm increase) and increasing waist-hip ratio (per 0.1 unit increase) were associated with colon cancer risk in both men and women. This study underlines that the variation of the association between obesity and colon and rectal cancer risk is depending on sex and cancer site.

In this chapter, we first overview about the role of obesity in colorectal carcinogenesis and the effect of obesity on clinical outcomes such as disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS), in adjuvant setting and metastatic disease, respectively.

2. The role of obesity in colorectal carcinogenesis

Obesity is a result of energy imbalance which is characterized by an overall rise in caloric intake and reduced physical activity caused by a sedentary lifestyle, besides genetic predisposition [22, 23]. Increased consumption of high carbohydrate food and beverages and dietary fat support total energy intake and priorities to reduce public obesity should focus on these environmental drivers. High BMI greater than 25 kg/m² reflects high body fatness [24]. The excess energy is stored as fat [23]. Obesity is associated with hyperplasia of the adipocytes which contain abnormally high free fatty acids (FFA) [25]. The exact pathophysiological mechanisms underlying the association between obesity and the risk of colorectal cancer are not fully understood but accumulated evidences coming from preclinical and clinical studies for the tumor-promoting effects of obesity has begun to illuminate many aspects of this connection [25].

2.1. Hyperinsulinemia and the insulin resistance

Adipose tissue excess or obesity, particularly abdominal obesity is linked to hyperinsulinemia, insulin resistance, hyperglycemia, and to the development of type 2 diabetes [9, 26]. High circulating insulin level is a well-established risk factor for cancer [27–29]. Epidemiological evidences indicate that high serum C-peptide which is a marker of pancreatic insulin secretion, and type 2 diabetes mellitus are associated with a greater risk of colorectal cancer [30–35].

Hyperinsulinemia is associated with elevated blood levels of free (unbound, bioavailable) insulin-like growth factor-1 (IGF-1) protein [36, 37]. Obesity-associated insulin resistance increases free IGF-1 levels in the postprandial state, unlike the reduction in insulin-sensitive lean people [38]. Inversely, IGF-binding protein-1 (IGFBP-1) concentrations decrease with increasing adiposity which may cause high concentrations of free IGF-1 [39, 40]. IGF-1 concentrations have been shown to be positively associated with colorectal cancer in prospective studies [30, 41–44].

Insulin is an anabolic hormone which coordinates glucose to either oxidation to provide energy or storage in the body after uptake in insulin-sensitive cells [45]. Insulin receptors (IRs) exist in IR-A, IR-B and IR-related receptor (IRR) isoforms and insulin has been shown also to have tumorigenic effects on preneoplastic cells which have insulin receptors [46, 47]. IRs and IGF receptors have an extracellular ligand-binding domain and an intracellular protein kinase domain. IGF-1 and insulin-like growth factor-2 (IGF-2) are mitogenic growth factors [46]. They have also metabolic functions. IGF receptors include IGF1R and IGF2R [48]. The binding of insulin and/or IGF ligands to cell surface receptors on cancer cells results in cell proliferation and survival [46, 49]. Upregulation of the IR and IGF1R has been demonstrated in human breast cancer and prostate cancer, respectively [50, 51]. IGF receptors are expressed physiologically in the mucosal and muscular layers of the colon and are overexpressed also in colon cancer cells [52, 53].

There are six high-affinity IGF-binding proteins (from IGFBP1 to IGFBP6); IGFBP1-IGFBP5 have higher affinities for IGF-1, whereas IGFBP6 has a higher affinity for IGF-2 [54]. IGFBPs affect the bioavailability of the IGFs in extracellular fluids [55]. IGFBP/IGF complexes first stabilize IGFs and protect them from degradation, and they inhibit the binding of IGFs to their receptors. Therefore, only released IGFs from IGFBPs by dissociation or protease-mediated cleavage can induce IGF signals [54, 56] (**Figure 1**).

The receptors (IRs, IGFs) bind the ligands (Insulin, IGF-1, IGF-2) with different affinities (**Table 3**) [48, 57–59]. IR-A has a higher IGF-2 affinity than IR-B [59]. IRR is an orphan receptor; its binding ligand is unknown and participates as a heterodimerization partner of the ligand binding family members [60].

Insulin/IGFs ligand binding to their receptors activate two major signaling pathways “the phosphatidylinositol 3'-kinase (PI3 kinase)-Akt” and “RAS-RAF-MAPK” [57]. These are classical insulin signaling pathways [61]. In the first pathway, IRs and IGFs interact with the intracellular insulin receptor substrate 1 (IRS1) after ligand binding and then promotes the PI3K/Akt cascade [62]. This pathway ultimately inhibits apoptosis [63, 64]. In the second pathway, another IRS protein Shc is phosphorylated by IR, and mediate signal transduction through the RAS-MAPK signaling pathway which plays a vital role in cell proliferation [65, 66]. There are several IRS proteins, including IRS1-6, Shc and Gab1 [61]. They are phosphorylated upon IR activation and the tyrosine-phosphorylated IRS sites function by docking with SH2 domain-containing proteins and mediate signal transduction to various downstream factors. **Figure 1** illustrates simplified signaling mechanisms of the “Insulin, IGFs/IR, IGFs” axis. Chronic hyperinsulinemia may reduce the hepatic production of IGFBP resulting in increased level of free IGFs [8, 37]. Finally, insulin and bioavailable IGFs promote carcinogenesis by inhibiting apoptosis and stimulating cell proliferation (mitogenesis) [62–64].

Activation of the PI3 kinase pathway was also associated pro-invasive phenotype [55]. The role of cell-matrix adhesion molecules (integrins) and cell-cell adhesion molecules (E-cadherin/catenins complex) was investigated in the IGF-1 induced migration. Disruption of the E-cadherin/catenin complex by the activation of IGF1R upon IGF-1 stimulation was shown in human colonic adenocarcinoma cell-line [67].

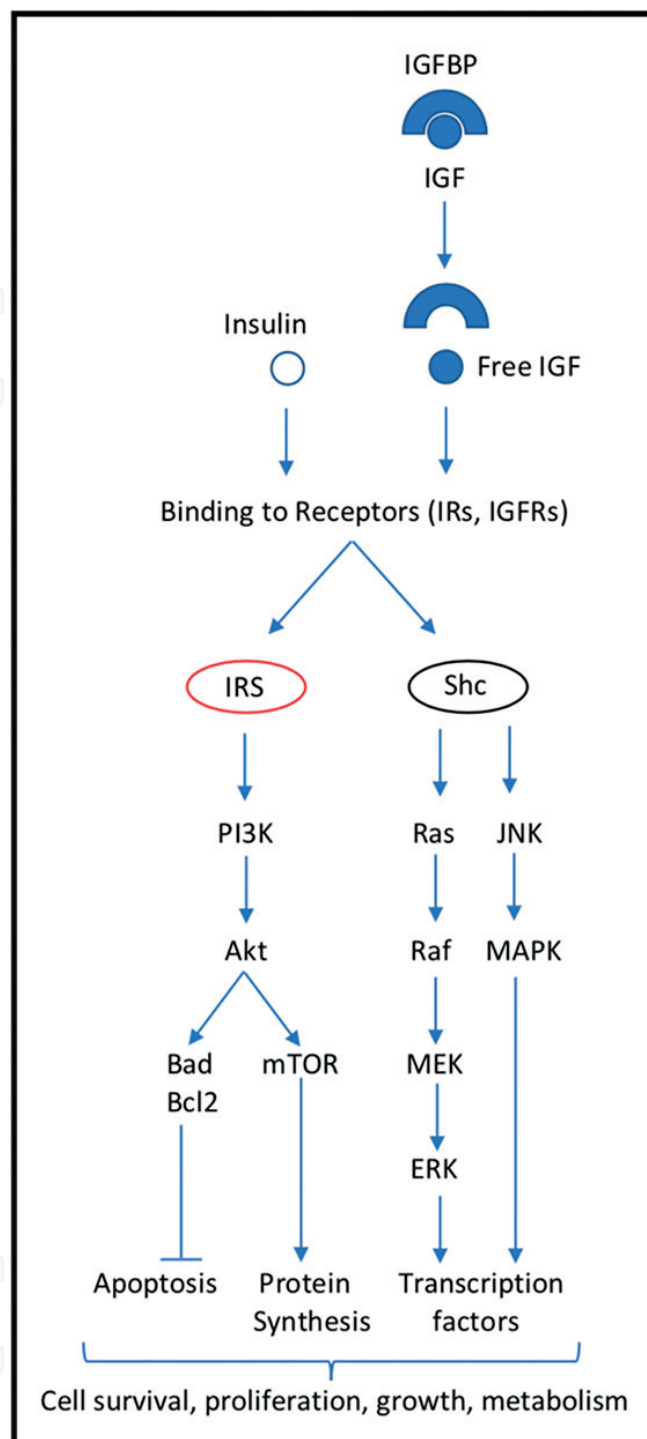


Figure 1. Schematic and simplified signaling mechanisms of the “Insulin, IGFs/IR, IGFRs” axis. Insulin and bioavailable IGFs promote carcinogenesis by inhibiting apoptosis and stimulating cell proliferation.

Cross talks of Insulin/IGF axis to other receptor tyrosine kinase pathways such as epidermal growth factor receptor (EGFR) pathway as well as IGF1R/EGFR heterodimers have also been demonstrated [55, 57]. These interactions may play a critical role in various cellular responses according to the growth factors, the ratio of the receptors and the microenvironment. Regarding mutations,

Receptors	Affinity		
	High	Low	Very low
IGF1R	IGF-1	IGF-2	Insulin
IGF2R	IGF-2 and other ligands*	IGF-1	Insulin
IR	Insulin	IGF-2	IGF-1

*Other ligands such as mannose-6-phosphate.

Table 3. Insulin, IGF ligands and their receptor affinities [48, 57–59].

when the mutation threshold in colon cancer was investigated, lower Kras mutations were detected in patients with high BMI [68]. But, in another study that evaluated associations of anthropometric factors with Kras and Braf mutation status in primary CRC, high BMI was found to be associated with the risk of Kras-mutated tumor in men, but not in women [69].

As a conclusion, obesity-related insulin/IGFs signaling pathways may result in evading apoptosis (or resisting cell death), sustaining proliferative signaling and activating invasion and metastasis, which are three of the ten hallmarks of cancer [70, 71].

2.2. Adipocyte-derived factors (leptin, adiponectin)

Adipose tissue is not inert storage depot for lipids, but it is an active endocrine organ [72]. It expresses and secretes a variety of bioactive peptides, known as adipokines. Besides adipocytes, adipose tissue contains connective tissue matrix, stromal and vascular cells, nerve tissue, and immune cells [73]. Adipocytes express and secrete specific endocrine hormones such as leptin and adiponectin; many other proteins are derived from the non-adipocyte fraction of adipose tissue [74].

Leptin is an adipocyte-specific hormone; it is a product of ob gene [75]. Leptin regulates food intake and body weight suppressing appetite and promoting metabolism. Obesity is associated with elevated serum levels of leptin and is often associated with leptin resistance [25]. Epidemiological studies show that high leptin levels are associated with an increased risk of colon cancer [76–78]. Leptin stimulates cell proliferation by probably MAPK phosphorylation and it is a promoter of cyclin D1 [25, 79, 80]. Leptin also promotes angiogenesis by the activation of PI3K and MAPK pathways [79]. Leptin receptors are expressed on normal epithelial and epithelial-derived tumor cells [81]. A study on obese mice that are genetically deficient in leptin receptors showed significant inhibition of colorectal tumor growth [82]. Leptin levels are correlated with high risk of tubular adenoma and the presence of 3 or more polyps [83, 84].

Other adipocyte-specific peptide hormone adiponectin is secreted mainly from visceral fat adipocytes and is inversely correlated with BMI [21]. It is most abundant adipokine and its circulating levels are higher in women than men. In contrast to leptin, adiponectin levels are significantly lower in obese individuals and a prospective study showed that low adiponectin concentrations was related to an increase in colorectal cancer risk [85, 86]. Physiologically, adiponectin enhances insulin sensitivity and glucose uptake [87]. Induction of insulin sensitivity reduces the circulating

levels of insulin and IGF-1. Besides this role in glucose metabolism, it stimulates also fatty acid oxidation [88]. Adiponectin has anti-angiogenic properties; it inhibits Vascular Endothelial Growth Factor-A (VEGF-A) [21, 25]. All of these observations support anti-cancer activity of adiponectin.

Adiponectin exerts its activity via two receptors: AdipoR1 and AdipoR2 [25]. Adiponectin inhibits colorectal cancer cell growth probably by downregulating mammalian target of rapamycin (mTOR) by adenosine monophosphate-activated protein kinase (AMPK) phosphorylation [89].

Inducing angiogenesis is another hallmark of cancer [70, 71].

2.3. Chronic inflammation

Chronic low-grade inflammation is a hallmark of obesity [90]. Increased production of lipids exacerbates inflammation. Increase in visceral adipose tissue (VAT) is accompanied by rising pro-inflammatory adipokines [tumor necrosis factor (TNF) alpha and interleukin (IL)-6 as well as leptin] [25, 81, 91, 92]. In contrary, as mentioned above, there is a decrease in the level of adiponectin which is an anti-inflammatory adipokine [91]. TNF-alpha expression is upregulated in parallel with the increase of BMI and this increase of expression of the TNF-alpha gene in white adipose tissue (WAT) establishes a link between inflammation, insulin resistance and hyperglycemia [93, 94]. Local and systemic chronic inflammation favors tumor initiation and progression [25]. One of the best examples of local chronic inflammatory conditions is inflammatory bowel disease which has an increased risk of colon cancer [95]. Free fatty acids (FFAs) coming from adipocytes are potent activators of macrophages that generate pro-inflammatory cytokines including IL-1beta, IL-6, TNF-alpha [96–98]. In this microenvironment of an obese host, the activation of nuclear factor (NF)-kappa B via Akt induces cell survival and promotes carcinogenesis [25, 55]. TNF-alpha may function in an autocrine and paracrine mode in the local adipose tissue, but a correlation was also shown between circulating TNF-alpha levels and colorectal adenomas [99, 100]. IL-6 stimulates PI3K/Akt pathway after binding IL-6 receptor (IL-6R), this leads to the expression of the cyclin D1 [101]. The action of IL-6 via JAK2/STAT3 signaling pathway may have a role in carcinogenesis by anti-apoptotic and proliferative mechanisms [102, 103]. Another inflammatory mediator is interferon gamma-inducible protein-10 (IP-10), also known as C-X-C motif chemokine-10 which is a chemo-attractant protein secreted by mature human adipocytes, and enhances local inflammation and tissue damage [104]. Like leptin, high levels of IP-10 are associated with the presence of polyps and tubular adenoma [83]. High serum concentrations of IP-10 are shown to be associated with poor prognosis in patients with CRC [105]. Inflammatory biomarker C Reactive Protein (CRP) and IL-6 were found to be correlated with the presence of CRC [106].

Adipose tissue contains high concentrations of CD4⁺ Th1, CD8⁺ lymphocytes with B cells and dendritic cells. In addition, high levels of anti-inflammatory Th2 and Treg cells exist [25]. In obese individuals, the net balance shifted to a pro-inflammatory state in tissue [107]. In this oncogenic micro-environment, the adipocytes can be seen to be surrounded by syncytium of phagocytic macrophages which is histopathologically described as crownlike structures (CLSs) [108, 109]. These adipocytes are undergoing necrosis, and subsequently, dead adipocytes are surrounded

by phagocytic adipose tissue macrophages (ATMs). Proinflammatory cytokine osteopontin (OPN) plays a role in the recruitment and accumulation of ATMs and the development of insulin resistance [110, 111]. Matrix metalloproteinase 9 (MMP9) is expressed and secreted into the circulation by ATMs, and it contributes to adipogenesis and angiogenesis [109]. Elevated leptin levels are also correlated with production of proangiogenic cytokines, such as VEGF, leading to angiogenesis [112, 113]. In fact, inflammation is a complex biological response to cellular stress [90]. Excess fuel or energy leads to cell stress at the level of organelles with increased reactive oxygen species (ROS) in the mitochondria due to FFA oxidation and the unfolded protein response in the endoplasmic reticulum caused by excess demands for protein synthesis for adipose tissue expansion [23, 114].

Glucose intake has also been shown to promote cancer growth via the inflammatory cascade, the 12-lipoxygenase pathway, in mice fed sucrose-enriched diet [115].

Chronic low-grade inflammation developing in adipose tissue during obesity can be transferred to other tissues such as liver, pancreas, skeletal muscle through the appearance of active inflammatory mediators in the bloodstream [116].

As a conclusion, tumor-promoting inflammation, which is one of the enabling characteristics, can contribute to multiple hallmarks of cancer including proliferative signaling, evading apoptosis, angiogenesis, invasion and metastasis [71]. It also supports mutations. This inflammatory biological state is thought to be associated with increased risk of obesity-related colon cancer [117].

2.4. Fat tissue and fatty acid metabolism

Adipose tissue depots are not metabolically equal [23]. In mammals, there are two kinds of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT) [116]. WAT has two compartments: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) [108, 118]. In adult humans, BAT volume is small, and its deposits are essentially cervical supra-clavicular, supra-adrenal and para-spinal regions [119, 120]. BAT promotes energy expenditure by triggering thermogenesis and suppressing diet-induced weight gain [116, 121]. Decreasing BAT activity in mice was shown to be stimulating hyperglycemia, rising plasma triglyceride levels and insulin resistance [122]. In humans also, BAT activity was found to be inversely related to BMI [123]. TNF- α has been shown to induce brown adipocyte apoptosis, and VAT inflammation may be linked to the lower BAT volume [124]. Visceral fat compared to subcutaneous fat is associated with higher insulin resistance [108, 118]. The maximum adipocyte size is lower than in visceral (omental) fat as compared with subcutaneous fat [125]. Therefore, visceral adipocytes are less able to reach greater sizes before death after simple rupture under the increased pressures of their intra-abdominal environment [109]. The rate of death of overproduced fat cells is not increased which is approximately 8–9% per year, in obese individuals [109]. These findings support increased CLSs and necrotic adipocyte death in obese people [109].

BMI is a marker of general obesity, and the markers of abdominal obesity are waist circumference and waist-to-hip ratio [108]. On the other hand, visceral fat area or volume reflects visceral obesity.

Experimental studies on mice suggest that excess fat intake by diet may increase both the number of mammalian intestinal stem cells (ISCs) which are the cell-of-origin for the development of cancer and the proliferation rate of ISCs [126–128]. Ex vivo treatment of intestinal organoid cultures with fatty acid constituents of the high fat diet may enhance the self-renewal potential of these organoid bodies [127]. High fat diet may also enhance the ability of more differentiated enterocytes (transit-amplifying cells) which are derived from ISCs [127]. These effects appear to be mediated by peroxisome proliferator-activated receptor delta (PPAR- δ) activation in colorectal epithelial cells [127, 128]. This activation may induce inflammation-associated colonic carcinogenesis [128].

A recent study suggested a link between obesity and sporadic microsatellite instability (MSI)-high CRC in women [129]. We know that fatty acid synthase (FASN) enzyme is involved in de novo lipogenesis catalyzing the reaction steps in the conversion of acetyl-CoA and malonyl-CoA to long-chain saturated fatty acids [130]. In one study using a large number of samples of CRC, FASN overexpression in CRC was found to be associated with MSI, independent of CpG island methylator phenotype (CIMP) [131]. FASN overexpression is commonly observed in human cancers, including CRC [132–134]. MSI-high CRC has a deficient mismatch repair system and has been associated with poorly differentiated and mucinous tumors [131, 134–136]. It is present approximately 15% of CRCs [131]. A possible association between obesity, FASN and MSI in CRC is very interesting. Another study showed that obesity and physical inactivity were associated with elevated risk of MSI-H colon cancer in men, but with non-MSI-H tumors in women [137]. An exact mechanism of these associations awaits further investigations.

Lipid metabolites function as cell signaling molecules directly related to the control of inflammation [90]. One example is sphingolipid metabolite sphingosine-1-phosphate (S1P) which is implicated in adenoma growth and is possibly involved in chronic inflammation and colon cancer via IL-6/STAT3/S1P-receptor 1 positive feedback link [138]. S1P/S1P kinase regulates cyclooxygenase-2 (COX-2), promoting arachidonate cascade which is implicated in colon carcinogenesis [139, 140]. Arachidonic acid (20:4 ω 6) is a precursor of prostaglandins (PGs) which are key mediators of inflammatory reactions [141]. High level of COX-2 expression is found in cancer cells. PGE2 is a major downstream effector of COX-2, and it inhibits apoptosis, favors invasion, motility and promotes angiogenesis. The efficacy of nonsteroidal anti-inflammatory drugs, especially selective COX-2 inhibitors, was shown in the reduction of colorectal polyps [142].

Feeding high-fat diet activates also the inflammasome and caspase-1 activation which controls adipocyte differentiation and insulin sensitivity [143].

Another new concept is the kynurenine pathway which is implicating in the metabolic syndrome [25]. Most foods contain amino acid tryptophan, and excessive food intake amplifies tryptophan catabolism. There is a clear correlation between plasma levels of tryptophan and its metabolites, leptin and BMI [144]. It seems that the increased tryptophan oxidation is an aspect of fat metabolism. Oxidative enzymes such as indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) catalyze tryptophan to kynurenine. IDO is activated by interferon- γ which is the response to immune system stimulation [145]. Kynurenine acts via the Aryl Hydrocarbon Receptor (AHR) to modulate transcription factors and microRNAs. The AHR is known to influence food intake to control body mass [25].

Growth factors	Pathways	Hallmarks of cancer
Insulin, IGFs	PI3K-Akt	Evading apoptosis (resisting cell death)
Insulin, IGFs	RAS-RAF-MAPK-Cyclin D1	Sustaining proliferative signaling
IGFs	Disruption of E-cadherin/catenin	Activating invasion and metastasis
Leptin	JAK2-STAT3-MAPK	Sustaining proliferative signaling
Leptin/VEGF	PI3K-MAPK	Inducing angiogenesis
Leptin, TNF-alpha, IL-6	Multiple pathways	Tumor promoting inflammation

Table 4. Obesity-related mechanisms of carcinogenesis.

Clustering of clinical findings made up of abdominal obesity (apple-shaped body), hyperglycemia with insulin resistance, dyslipidemia (high triglyceride, low high-density lipoprotein), and hypertension is accepted as metabolic syndrome [23]. It is clear that one of the consequences of metabolic syndrome is the increased risk of carcinogenesis.

Table 4 summarizes obesity-related mechanisms of carcinogenesis.

3. The effect of obesity on clinical outcomes

3.1. In the adjuvant setting

As we mentioned earlier, several studies have established a link between obesity and colon cancer risk, but there is little information about the effects of obesity on clinical outcomes after diagnosis and surgical treatment. In the first publication, Dignam et al. reported a significant increased risk for recurrence and death from colon cancer in very obese patients (BMI ≥ 35 kg/m²) who receive adjuvant chemotherapy [146]. They investigated the association of BMI with the outcomes of 4288 patients with Dukes B and C colon cancer. This study cohort was from cooperative group clinical trials. They observed 2074 events in this study population and hazard ratio (HR) for risk of recurrence was 1.38 (95% confidence interval [CI] = 1.10–1.73), and HR for risk of mortality was 1.28 (95% CI = 1.04–1.57) in very obese patients compared with normal weight patients.

The Adjuvant Colon Cancer Endpoints database also compared the outcomes in patients (N = 25,291) with stage II and stage III colon cancer receiving adjuvant chemotherapy, and they showed inferior outcomes both for obese as well as underweight patients [147]. Men with class 2 and 3 obesity (BMI ≥ 35.0 kg/m²) had a statistically significant reduction in DFS (HR: 1.16; 95% CI = 1.01–1.33; p = .0297) compared with normal-weight patients. These worse outcomes appeared to be cancer-related.

On the other hand, Cancer and Leukemia Group B (CALGB) 89803 trial investigators did not find any significant associations between an increased risk of recurrence and mortality and BMI in patients with stage III colon cancer [148]. In this study, they observed 369 events in 1053 patients. The difference between studies should be related to statistical power. Another

explanation is related to suboptimal adjuvant therapy (calculating dose according to a maximum body surface area of 2.0 m^2) in very obese patients in the study by Dignam et al.

3.2. In metastatic disease

In advanced colorectal cancer, there are more trials than in the adjuvant setting evaluating the role of obesity on clinical outcomes. In a pooled analysis from four large, prospective studies, among 6128 patients with metastatic CRC treated with first-line bevacizumab and chemotherapy, patients with the lowest BMI ($<25 \text{ kg/m}^2$) experienced the lowest median OS [149]. This study is presented at the World Congress on Gastrointestinal Cancer 2015. This observation concerning the relationship between worse outcome and the lowest BMI does not mean that obesity is an advantage in patients with mCRC [150]. Probably, in patients with mCRC with a lower BMI, the effects of cancer-related cachexia may be more deleterious. These patients may have less tolerance to the treatments. According to another explanation, obesity may promote angiogenesis and bevacizumab, which is an anti-VEGF monoclonal antibody and may have a vital role in obese patients.

There are also other trials with contradictory results [151–155]. In a trial investigating the influence of BMI on outcomes in advanced CRC patients receiving chemotherapy with or without targeted therapy, BMI was shown as an independent prognostic factor for survival in patients receiving chemotherapy (CT), but not in patients receiving CT plus targeted therapy [151]. In patients receiving only CT, median OS was 19.5 months for BMI category $>30 \text{ kg/m}^2$ versus 8 months for BMI category $<18.5 \text{ kg/m}^2$ ($p = 0.001$). In patients receiving CT plus targeted therapy, median OS was 21.4 months for BMI category $>30 \text{ kg/m}^2$ versus 16.6 months for BMI category $<18.5 \text{ kg/m}^2$ ($p = 0.8$). In another trial, the authors speculate that higher circulating levels of VEGF may confer resistance to bevacizumab [152]. In our retrospective trial, we found better time to progression (TTP) in patients who have BMI $< 25 \text{ kg/m}^2$ compared to patients who have BMI $> 25 \text{ kg/m}^2$; median TTP was 11.7 months versus 6 months, respectively ($p = 0.004$) [153]. All patients had been treated with fluoropyrimidine-based combination CT plus bevacizumab. We think that patients with high BMI may require higher dosages. In another similar trial, the investigators compared OS across the BMI groups for CRC, and they found that the OS was shorter for patients who were underweight and overweight compared to normal in the group of patients receiving CT + targeted therapy. There was no difference in OS for CT alone [154]. In a recent multicentric study, we demonstrated that obesity serves as a prognostic factor for mCRC patients who have been treated with bevacizumab-based regimens. In particular, among Kras wild-type left-sided tumor patients with bevacizumab-based regimens, the prognosis could be worse for obese patients than that for non-obese patients [155].

4. Conclusion

High BMI or obesity is an established risk factor in colorectal carcinogenesis. Adipose tissue excess, particularly abdominal obesity is linked to hyperinsulinemia, insulin resistance,

hyperglycemia, and to the development of type 2 diabetes which are the components of metabolic syndrome. Chronic low-grade inflammation is a hallmark of obesity, and obesity supports many hallmarks of carcinogenesis. It is clear that one of the consequences of metabolic syndrome is the increased risk of carcinogenesis. Targeting obesity and metabolic syndrome should be beneficial in the prevention and the treatment of colorectal cancer.

Conflict of interest

Authors declare no conflict of interest.

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