Al-Kindy College Medical Journal (KCMJ)

Review Article

Obesity-Induced Mechanisms in Colorectal Cancer Development: A Narrative Review

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Article history:
Received 18 February 2025
Accepted 29 March 2025
Available online 1 August 2025

https://doi.org/10.47723/t8v6bw38

Keywords: Colorectal cancer; Obesity, Pathophysiological relationship, Insulin, Interleukins, Gut's microbial ecology

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ABSTRACT

Obesity is a significant risk factor for colorectal cancer (CRC), influencing its development through multiple biological pathways. Elevated levels of insulin, insulin-like growth factor-1 (IGF-1), leptin, resistin, and inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) contribute to colonic cell proliferation and tumor formation. Additionally, obesity-induced hormonal imbalances, including decreased adiponectin and ghrelin, further increase CRC risk. Changes in gut microbiota due to obesity also play a role in carcinogenesis, highlighting the complex interplay between metabolic, inflammatory, and microbial factors. This review explores the pathophysiological mechanisms linking obesity to CRC, emphasizing its role as a modifiable risk factor. Insulin resistance, chronic inflammation, oxidative stress, and dysregulated adipokine secretion are key contributors to CRC progression in obese individuals. By analyzing molecular and epidemiological evidence, this review underscores the importance of early CRC screening for obese individuals, along with lifestyle modifications such as weight loss, dietary improvements, and increased physical activity. Furthermore, microbiome-targeted interventions, including probiotics and prebiotics, may help counteract obesity-driven dysbiosis and reduce CRC risk. Emerging biomarkers and therapeutic targets offer potential for developing obesity-specific CRC treatments. Given the rising global burden of CRC, integrating preventive healthcare strategies, public health initiatives, and clinical interventions is essential for reducing its incidence and improving patient outcomes. Addressing obesity through targeted preventive measures can significantly lower CRC-related morbidity and mortality, making it a crucial aspect of cancer prevention and management

Introduction

Colorectal cancer (CRC) provokes the scenario of serious global health concern in terms of cancer-related deaths worldwide. The fatality rates reported from CRC are surging, although there may be improvements in detection and treatment. It accounts for up to a percentage of 8–9% of all cancer-related death rates, making it accountable as the third most common yet unavoidable cause of cancer mortality [1]. In 2018, Around 4,880,000 new cancer diagnoses and 3,400,000 cancer-related fatalities were caused by gastrointestinal origin cancers (esophagus, stomach, colon-rectum, pancreas, liver), which accounted for around 26% of incidence and 34% of mortality. On the other hand, CRC accounted for about 1.8 million of the new cases. Most gastrointestinal malignancies are currently CRCs [2]. East Asia, South America, and Eastern Europe had a historically low rate

of incidence in cases of CRC, but between 1960 - 2018, that all changed due to dietary and lifestyle changes [2].

The rising incidence of CRC is strongly correlated with weight gain, which can be assessed by the comparative study of certain molecules released between lean and obese individuals as mentioned in Figure 1 below. Obesity affects the tumor microenvironment, according to recent epidemiological and molecular studies. Obesity factor is usually associated with a heightened risk of developing colorectal neoplasms, with research indicating a 26% and 47% greater risk for overweight and obese adults, respectively [3]. Intricate signaling cascades and deregulated cellular mechanisms under the influence of obesity factors assembled to generate cancer [4]. Obesity was described as a major factor responsible for a challenging metabolic disorder that affects cancer biology [5]. Chronic low-grade inflammation and obesity define it. Due to the complex interaction with adipose tissue, obesity promotes carcinogenesis by increasing adipokines, pro-inflammatory cytokines, and insulin resistance [6]. Patients with early-onset CRC demonstrate unique risk factors, wherein obesity plays a role in metabolic syndrome and intestinal inflammation, potentially expediting carcinogenesis. Chronic inflammation linked to obesity modifies macrophage metabolism, facilitating tumor growth [7].

There are certain biological interlinked mechanistic pathways which are induced due to obesity. Insulin resistance, hyperinsulinemia, and modified adipocytokine concentrations are the primary pathways connecting obesity to CRC [8]. The PI3K/AKT pathway, modulated by hormones regulated by obesity parameters, is integral to carcinogenesis [9]. Obesity, as a modifiable risk factor, interacts complexly with genetic predisposition and lifestyle factors, requiring a comprehensive approach to understanding the method needed for the prevention and thereby understanding the treatment modality required for patients with CRC.

A primary idea concerning the origin of this association suggests that being overweight causes a chronic sub-inflammatory state, which in turn causes macrophage polarization and a decrease in cells that inhibit the immune system, like T cells and natural killers [10].

The exact mechanisms driving this epidemiological shift are inadequately comprehended, necessitating an extensive inquiry into the elements influencing the onset and advancement of EOCRC. The linked concepts of obesity-based hormones like leptin and adiponectin, along with the macrophage-specific metabolite itaconate, which promotes cancer growth through many pathways involving changes in inflammatory gene expression, is one potential explanation [11].

Metabolic shifts induced by adipokines or cytokines related to obesity act as stressors, leading to tissue damage that might hasten the onset of neoplasia. Inflammation promotes cell proliferation, tumor development, growth, and metastasis after a genetic mutation activates an oncogene. CRC is a prominent neoplasm form profoundly associated with chronic inflammation. The epidemiological evidence linking obesity to CRC is reviewed in this comprehensive analysis. This review will specifically focus on recent studies, evaluate the molecular mechanism by which obesity may cause colorectal carcinogenesis, and discuss prevention and treatment.

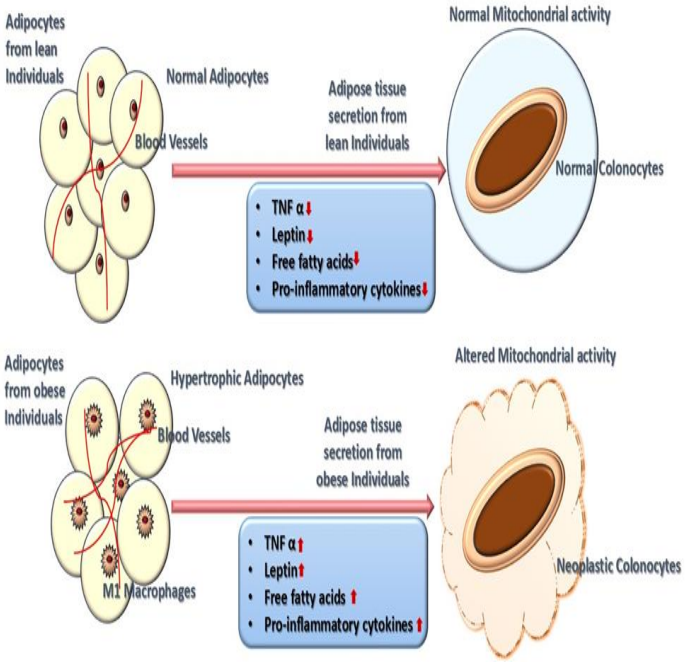

Figure 1: Essential molecular factors (TNF α, Leptin, Free fatty acids, Pro-inflammatory cytokines) released by adipose tissue and their comparative regulatory levels observed in lean and obese individuals

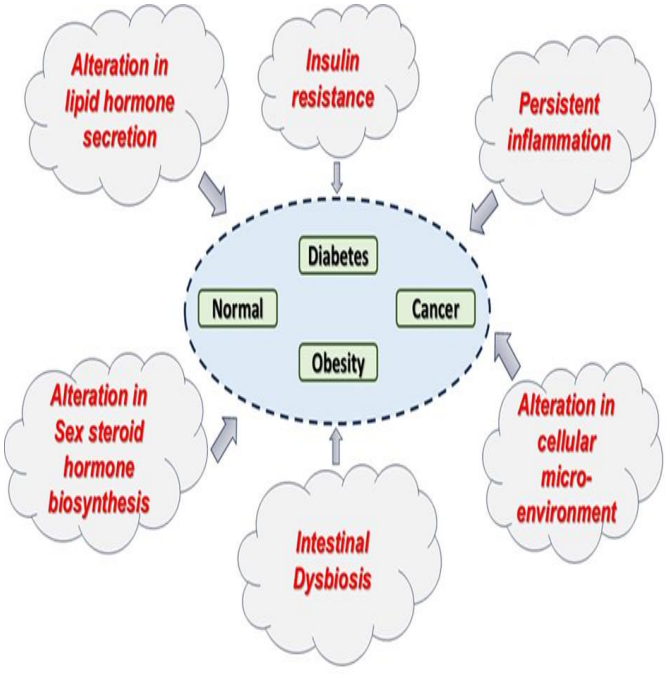

Figure 2: Evident obesity-based factors and their abnormal alteration accumulate so that normal cells are forced to transform into cancerous cells in CRC patients.

Table 1: Certain evidence from the literature review

PAPER- (Author & Year)	Objectives	Inference
Arnold et al., 2020 (2)	Global Burden of 5 Major Forms of Gastrointestinal Cancer	The global burden of gastrointestinal malignancies, particularly CRC, emphasizes the need for better preventive and early detection techniques.
Giovannucci E., 2022 (4)	Obesity and CRC: A Review of the Epidemiological Research and its Cancer Epidemiology Biomarkers & Prevention.	CRC is way more common in obese people and has worse results.
Iyengar et al., 2019 (12)	Association of the body fat index and its risk factor in the development of breast cancer in postmenopausal women with a normal body mass index: A proper secondary analysis of a randomized clinical trial is carried out, and an observational study is recorded.	Obesity-CRC is linked to chronic inflammation, adipokine signalling dysregulation, insulin resistance, gut microbiome changes, and metabolic dysregulation.
Jiang et al., 2022 (13)	Study of 1.	Obese people have higher pro-inflammatory adipokines and lower anti-inflammatory ones, which contribute to CRC development and progression.
Miranda et al., 2024 (14)	Obesity and CRC	Obesity-induced dysbiosis changes gut microbiota, causing intestinal inflammation and CRC-linked genotoxic chemicals.
Liu et al., 2019 (15)	Association of obesity as a base factor with risk of developing early-onset CRC (EOCRC) among women	Women with obesity are more likely to develop early-onset CRC, emphasizing the need to address obesity as a modifiable risk factor.
Singh et al., 2023 (1)	Harnessing the gut microbiome and CRC prevention: A review specifying current knowledge and future directions	Modulating gut microbiome diversity and function may reduce obesity-related CRC risk.
Colombo et al., 2022 (16)	Obesity-Associated Alterations in the gut microbiota composition and metabolite profile: Implications for CRC progression and therapeutic targeting.	Obesity-associated biomarkers predict CRC incidence, prognosis, and treatment response in longitudinal investigations, highlighting their therapeutic potential in personalized therapy.
Otani K et al., 2017 (17)	Adiponectin in gastrointestinal diseases.	Adiponectin, an anti-inflammatory adipokine, protects against gastrointestinal illnesses, suggesting it may treat obesity-associated CRC.
Xu, Yang et al., 2024 (18)	Role of tumor in obesity-associated CRC Progression and therapeutic resistance	A comprehensive investigation of obesity-associated biomarkers shows various molecular subtypes of CRC with varying therapy responses, emphasizing the necessity for obesity-specific treatment.
Jones, et al., 2024 (9)	Metabolic reprogramming in obesity-associated CRC: Therapeutic implications and future directions.	Adding obesity-associated biomarkers to CRC screening methods enhances early detection and risk stratification, especially in obese people.
Himbert et al., 2017 (19)	The Impact of Obesity on the Tumor Immune Microenvironment in CRC: Implications for Immunotherapy Response and Resistance	Integrating obesity-related biomarkers into standard clinical practice and population screening initiatives is feasible and economically viable, with the potential to reduce the burden of CRC occurrence in obese populations.

The role-play of such variable factors is involved in addressing the events of development into CRC. Obesity plays a pivotal role in being the actual baseline risk factor for the development of CRC, with several studies demonstrating its influence on both incidence and prognosis. The complexity involved in the association between the two factors that is obesity and CRC is quite a lot complex, so we can think of encompassing various epidemiological findings linked to interrelated molecular pathways. Obesity-related gut microbiota changes lead to the cause of CRC development risk, thereby highlighting the complex link between host metabolism and the intestinal microbiome in cancer etiology [20].

Pathophysiology factors induced by obesity for CRC development.

As genetic alterations accumulate, normal colonic epithelium becomes dysplastic. Numerous complicated pathophysiological parameters are indulged in mechanistic pathways which involve multiple variables in carrying forward the carcinogenic events from the normal epithelium of the colon and rectum. Connected processes include an increase in the concentration range and bioavailability of

insulin and insulin-like growth factor IGF-1; abnormal secretion of adipokines; chronic inflammation; elevated levels of locally produced sex steroids (such as estrogen); altered immune response; oxidative stress; and the composition of the colony of microflora in the intestines [21], all mentioned in Figure 2. Possible associations between obesity and metabolic dysfunctional syndrome categorization, insulin resistance mechanism with an altered form of lipid metabolic issues, endocrine abnormalities, and oxidative stress all together contribute towards the procedure leading to the actual development of CRC [22].

Obesity & the inflammatory molecules-derived pathways

The relationship between inflammation and CRC is well established, indicating that inflammatory mediators may significantly contribute to the onset of CRC at younger ages. Variants of CRC, including those arising from the sporadic microsatellite instability pathway and other epigenetic mutations, have been associated with inflammatory processes. These processes may occur before tumour development, result from tumours inducing an inflammatory response in the host, or arise from therapeutic interventions [23]. Chronic inflammatory processes, such as infections associated with irritable bowel diseases creating infectious conditions intertwined with several environmental factors like smoking and suboptimal dietary habits, have been an evident scenario to increase the observational developmental risk of CRC [23,24].

Inflammation that results in DNA damage occurs due to the imbalanced activation of cytokine receptor-mediated aspects of signaling pathways, which include the promotable chain auto-activation of major cellular components like nuclear factor kappa-light-chain-enhancer of activated B cells component (NF-kB), secondly that of tumor necrosis factor (TNF), and specific interleukin-1 (IL-1) [23,25]. Interleukin-1 (IL-1) functions as a major key factor in the activation of inflammatory mediators among the synthesized factors by stroma-based cells, monocytes, and mainly in the tumor epithelial cells, significantly contributing to the initiation and progression of cancer [25]. These processes are involved in the actual regulation of events which lead to tumor initiation and mode of progression. Interleukin-1 (IL-1) hereby also activates the STAT3 signaling pathway to get initiated. Inflammation is capable enough to lead direction towards the epigenetic modifications that can result in accordance deactivation of major prominent factors like tumor suppressor faction form of genes, such as IL-1β, IL-6, and TNF, which are involved in the regulation of major DNA methyltransferases within specific forms of the classical p53 and NOTCH pathways [23,26-27]. Inflammation undermines the integrity and hampers the intestinal barrier, exposing the actual intestinal stem cells to environmental pathogenic entities and increased interaction with gut microbiota, including bacteria that may facilitate tumorigenesis. It facilitates getting forward with events associated with tumor progression via the involvement of the hypoxia condition and thereby the recruitment of a certain group of myeloid plus lymphoid cells within the tumor microenvironment condition is certain. Hypoxia activates fibroblasts associated with cancer by enabling the synthesis of hypoxia-inducible factor 1-alpha (HIF1Σ). Because of this mechanism, chemokines like that of transforming growth factor-beta (TGFβ) are released into the tumor microenvironment (TME), which leads to a greater variety of cells inside it. Reducing the body's natural immune defence, increased adipose tissue causes hypoxia, which inhibits the creation and development of T cells [23,28]. CRC begins with inflammation and advances due to it. Inflammatory processes have long been linked to CRC onset; however, not all inflammatory processes have been linked to early-onset CRC development [29]. The association between the sporadic form of CRC formation and the rate of inflammation is a plausible hypothesis, yet these factors have been shown in Figure 3 below.

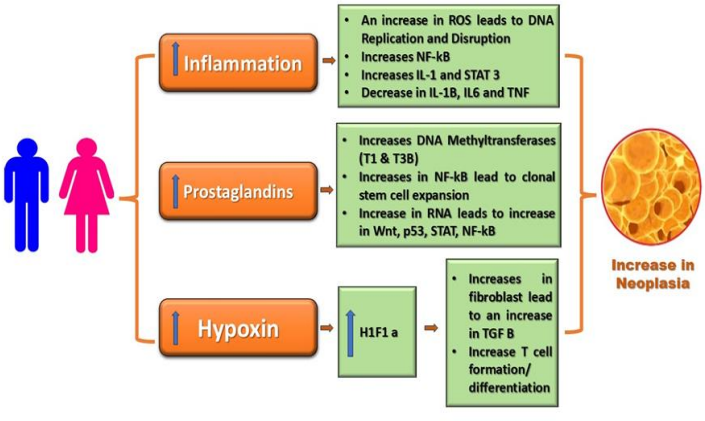

Figure 3: This diagram specifies the increased levels of three parallel factors involved, i.e., inflammation and prostaglandins, leading to an increase in Hypoxia condition in Obese subjects which leads to activation of a typical series of events and parameters in CRC neoplasia growth.

Obesity-Induced Components Involved in CRC Development

Type 2 diabetes mellitus & Insulin, insulin-like growth factors in CRC development

Obesity is associated with type 2 diabetes, which is further associated with CRC. Elevated insulin levels and insulin-like growth factor (IGF-1) correlate with enhanced proliferation of colon cells, leading to malignancy. The risk is significantly elevated in patients utilizing diabetic medications such as sulfonylureas and insulin [30]. Elevated glycated hemoglobin levels have been strongly associated with adverse clinical outcomes in CRC patients [31]. It also must be conducted and presented in a specific study with 976 individuals with a previous history of colonoscopies [32]. The findings demonstrated that individuals with DM had a greater prevalence of one or several colonic polyps and cancers than those without the condition [32]. Increased observation in insulin and glucose levels can develop the function to carry out the translocation and thereby induce the up regulatory factor of Rho-associated protein kinase 1 (ROCK-1)-tyrosine kinase-mediated pathway involvement, leading to the activation of proliferating cell nuclear antigen (PCNA) and subsequent centrosome mediated amplification, which is linked to an increased probability of carcinogenesis [33-34]. Insulin, insulin-like growth factor (IGF), insulin receptor (IR), signaling pathways, and IGF-binding protein contribute to cell-mediated proliferation and the inactivation of apoptosis, thus enabling carcinogenesis [35]. These

factors are mentioned and are affected by multiple factors, including diabetes mellitus, acromegaly, excess energy intake, hypertriglyceridemia, dietary patterns, and obesity [36]. Numerous pathways are implicated in the progression of CRC. In obese patients, there is an overexpression of insulin and IGF, which activates the mode of the PI3K/Akt signaling pathway. This activation contributes to enhanced cell survival and evident growth, thereby promoting the amplification of the carcinogenesis process. Src is an oncogenic protein, specifically a protein tyrosine kinase is activated, and that enhances cell growth, the proliferation of cells, its survival rate, and migration [36-37]. The protein possesses multiple domains like that of SH2, SH3, regulatory tails, etc, in its inactivated state within the normal cells. Upon activation, it typically induces phosphorylation and activates the PI3K/Akt pathway, thereby facilitating the progression of CRC (36-37). IGF-1 induces another cytoplasmic degradation method of P53, a tumor suppressor gene, resulting in unregulated cell proliferation effect and neoplasia [38] mentioned altogether in Figure 4.

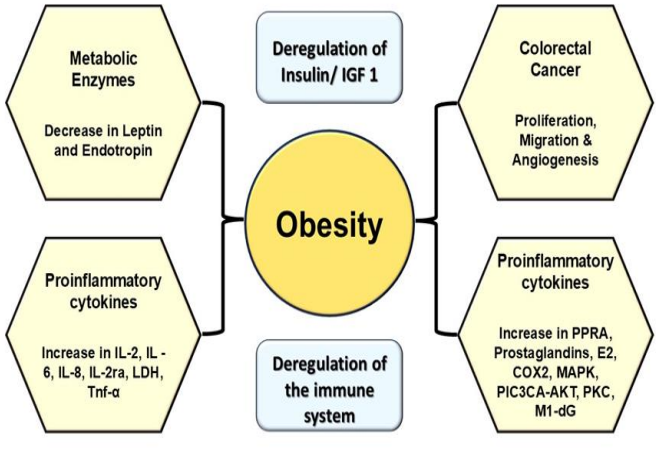

Figure 4: Deregulation in certain specific mechanisms: Insulin/IGF-1 factor and imbalances in the levels of immunological factors indulged in metabolic enzymes, Proinflammatory Cytokines which are majorly responsible in Proliferation, Migration and Angiogenesis phenomenon in CRC development.

Certain Obesity-Related Hormonal Factors in CRC

About Leptin in CRC Development

Due to its interference with signaling protein pathways along with that of the colon's adipokine receptor end, the leptin hormone contributes to the pathogenesis of CRC associated with obesity. Leptin is mostly produced by fat cells in the body and is one of many adipokines [39-40]. The signal-based protein, which acts as a transducer and source activator factor involving transcriptional, mitogen-activated protein kinase, and PI3K pathways, are among those it activates. Angiogenesis, cell proliferation/growth, and apoptosis are all aided by its activation, making it an essential player in CRC carcinogenesis. Scientific investigations have shown that different subgroups of CRC exhibit different levels of the leptin receptor, suggesting that leptin can trigger different tissue responses [41]. One potential function of the soluble leptin receptor (SOB-R) is to regulate leptin's functional properties. Interactions between SOB-R levels in the blood and the risk of colon cancer were found to be inverse in case-control research conducted by Aleksandrova et al., which included 1129 patients diagnosed with CRC and 1129 healthy controls [42]. Excessive levels of the leptin hormone, which is produced by fat cells, are commonly observed in obese people [43]. It starts a cascade of signaling pathways after regulating hunger via the Ob receptor. Resistance to the hormone leptin may develop in obese people whose blood leptin levels are already high. Activation of SOCS-3, a suppressor of cytokine signalling, decreases the actual sensitivity profile of the vagal nerve's projecting afferent dendritic branch and promotes carcinogenesis in obese individuals [43].

Adiponectin's role in tumour initiation and CRC development

Adiponectin is a major protein hormone secreted by adipocyte tissues, exhibiting an inverse relationship with adipocyte levels; consequently, its concentrations are reduced in individuals with obesity [44]. This promotes the AMPK pathway, which in turn curbs cell proliferation rate and retards the advancement of CRC [44]. The regulation of various cell growth homeostasis is primarily governed by the adiponectin hormone [17]. The risk of CRC is greatly exaggerated when the colonic epithelium is exposed to carcinogens and there is a drop in circulating adiponectin levels [17]. According to Yoneda et al. [45], the involvement of adiponectin receptors 1 and 2 in both normal colonic mucosa and CRC. Another study found that adiponectin has the efficiency to give protection against CRC and aids in glucose regulation by increasing insulin sensitivity, decreasing Bcl2, and starting the reactions directed towards the cell death mediated cascade through enhanced over-activation of P53 and Bax gene [46].

Itaconate evoking immune-based factor in CRC development

The macrophage metabolite itaconate is made up of the two main M1-like and M2-like types of macrophage structures. According to the consensus, M1-like macrophages make this chemical to control their inflammatory stress reactions [8]. Aconitate decarboxylase 1 (ACOD1) is a protein that is encoded by the gene IRG1, which is responsible for itaconate production. ACOD1 is an enzyme that converts cis-aconitate into the metabolite itaconate in the tricarboxylic acid (TCA) cycle [47]. By controlling glycolysis and inhibiting succinate dehydrogenase, it regulates cellular metabolism and causes succinate buildup. Through mediating oxidative stress reduction and promoting the components of anti-inflammatory associated transcription factors including nuclear factor erythroid-2 related factor 2 (NRF2), it a conate also serves to reduce inflammation. Several transcription factors are also affected by it, such as NF-kB, HIF1α, STAT3, and AP-1 [8,47.] Evidence suggests that peroxisome PPARγ is a need for IRG1 expression in macrophages. In peritoneal mouse macrophages, downregulation of PPARγ results in elevated IRG1 expression, indicating that PPARγ controls macrophage metabolism [8]. Furthermore, PPARγ is a very essential factor responsible for the differentiation of epithelial cells responsible for the differentiation of epithelial cells, and it has been shown that lower PPARγ expression in CRC (CRC) speeds up the pathology of CRC as mentioned in Figure 5 below.

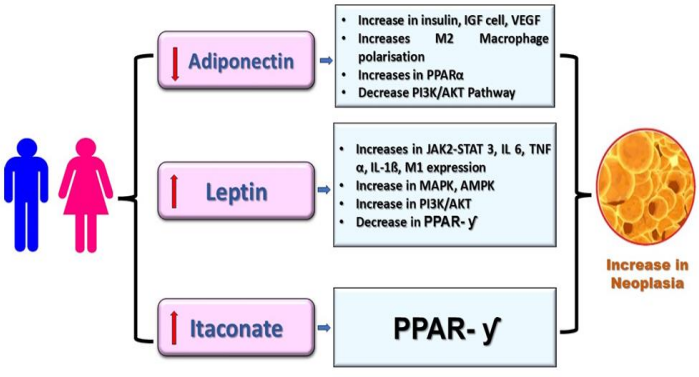

Figure 5: Diagram depicts the influence of hormonal components released by adipocytes showing decreased levels of Adiponectin inverse to increase in levels of Leptin and Itaconate, followed by activation of factors leading to CRC Neoplasia

Ghrelin's Role with Accordance to CRC Development

Ghrelin is mainly produced in the stomach, although the small intestine does release a tiny amount. Both normal and cancer cells have the potential to produce ghrelin. By binding to and activating the essential growth hormone secretagogue receptor (GHS-R), it increases the body's production of growth hormone. In the context of cancer and other critical illnesses, it helps with weight loss by maintaining energy balance. In addition, it triggers an array of signal transduction pathways (including RAS, PIK-3 form of kinases, Akt, and the mammalian target to that of rapamycin), which are essential in the development and progression of CRC [48-49].

Resistin in CRC development

CRC patients have levels of the adipocyte-secreted hormone resistin that are higher than normal [50]. According to Park et al. [51], the toll-like receptor-4 (TLR-4) is crucial because it can identify different parts of viruses and bacteria, trigger different immune responses, and help the host fight off illnesses caused by microbes by producing cytokines [52]. This is because resistin enhances the inflammatory response by competing with lipopolysaccharide molecules for the binding and activation of TLR-4 (53-54). Increased production of matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2), as well as vascular endothelial growth factor receptors (VEGFRs), is one mechanism by which resistin increases angiogenesis and endothelial cell proliferation. According to Mu H et al. [53], resistin plays a pivotal role in the manifestation of CRC by providently activating important inflammatory pathways and promoting the angiogenesis aspect.

Mode of estrogen-induced CRC

Due to the periphery, the overall conversion method involved in transforming androgens to estrogen within the adipocytes, obese individuals display increased estrogen levels. Two receptor activities are quite essential, namely estrogen receptor alpha (ER-alpha) and estrogen receptor beta (ER-beta), which support this process. In CRC cells, ER-beta causes them to die off, but ER-alpha encourages them to multiply quickly. The colon's principal receptor is ER-beta, and the increased estrogen levels linked to obesity help prevent CRC by acting on this receptor [54]. In addition to improving DNA repair mechanisms, activating ER-beta reduces levels of interleukin-6 (IL-6), which has anti-inflammatory benefits. CRC (CRC) patients, including those who are overweight, have a high prevalence of estrogen receptor alpha (ER-alpha), which may have a beneficial effect on CRC progression in later life stages. A lower incidence of CRC has been linked to postmenopausal hormone replacement treatment (HRT), demonstrating the preventive function of estrogen in CRC [54].

Role of Oxidative Stress Induced by Obesity in CRC

Human colorectal tumours, including adenomas and carcinomas, exhibit elevated levels of various oxidative stress markers. These include increased reactive oxygen species (ROS), as measured by chemiluminescence, nitric oxide (NO), 8-oxodG in DNA, lipid peroxides, glutathione peroxidase (GPx), and catalase (CAT), alongside decreased methylation of cytosine in DNA. In addition to lipid modifications, increased leukocyte activation was observed in carcinogenic tissue [55-56], suggesting a potential role of inflammatory cells in exacerbating oxidative stress [57] Genetic abnormalities were shown to occur less frequently in the colon tissues as opposed to the rectum tissues, according to study [58]. Increased oxidative stress associated with obesity can directly and indirectly impact DNA stability, thereby influencing tumorigenesis. Specifically, under conditions of oxidative stress, DNA nucleotides are subject to oxidation. The predominant oxidative modifications in the DNA content induced by certain reactive species include factors like 7, 8-dihydro-8-oxoadenine and 8-hydroxy-2′-deoxyguanosine (8-OHdG). Guanines are regarded as the most susceptible due to their comparatively low redox potential relative to other bases [59-60]. The oxidized form of guanine bases can act as sites for replication errors leading to substitutions. There is always a probability of up to 75% that DNA polymerase will incorporate adenine in place of cytosine opposite oxidized guanine [61]. Obesity facilitates the progression and several ways for the development of CRC and much by the generation of reactive oxygen species [62-63]. Reactive oxygen species (ROS) are crucial for optimal cellular function; however, excessive levels can have harmful consequences, particularly in promoting CRC. ROS can induce DNA breaks at critical sites, including tumour suppressor genes and oncogenes [64]. Thus, it degrades the proteins involved in the regulation of cell growth and proliferation, resulting in the progression of multiple cancer types [62-63]. Obesity can lead to chronic inflammation and elevate levels of leptin, protein kinase activation, polyol pathway activation, and additional mechanisms that may elevate levels and oxidative stress within cell [64].

Gut Microbial changes and induction mode of CRC

Diet has an eminent role in modulating intestinal microbiota. Obesity leads to dysfunction of gut microbiota, which is linked to early-onset CRC [65]. People who suffer from Crohn's disease or ulcerative colitis may be at a higher risk of developing CRC if they have intestinal dysbiosis [66]. There are certain groups of bacterial colonization in the gut depending upon which Patients with CRC exhibit an increase in Bacteroidetes and a decrease in Firmicutes, particularly within the Clostridia class, which are responsible for fermenting dietary fiber and other carbohydrates into butyrate, a

short-chain fatty acid that mitigates colonic inflammation and carcinogenesis. Intestinal dysplasia and stem cell mutations can be accelerated by microbial dysbiosis, which in turn can cause secretion involving several inflammatory mediators such as TNF-α, ILs, and IFNs [67]. Certain microorganisms can interact with tumors through oncometabolites, which in turn promote the development of cancer [68]. In CRC patients, there has been a noticeable shift in the fecal and mucosal microbiota when quantified is observed with less ecologically varied diversity. Eleven different types of microorganisms, or once-microbes, have been found to cause cancer in humans. Notably, certain specific strains of Escherichia coli produce the component colibactin, a potent DNA-related alkylator linked to CRC [69]. Elevated levels of these 3 common microbial entities Fusobacterium, Atopobium, and Porphyromonas genera are correlated with CRC [16,70-71]. The microbiome-based pathogenesis and the increased diversity along with differentiation in normal colon epithelium, point to a likely connection between lifestyle and environmental factors involved and the elevation of microbiota colony present in response to numerous inflammatory processes that try to maintain the integrity of the gut barrier. As a suggested study by Barot et al. [72], this dysbiosis could be an indication that the microbiome helps the tumor microenvironment avoid the host's defense responses.

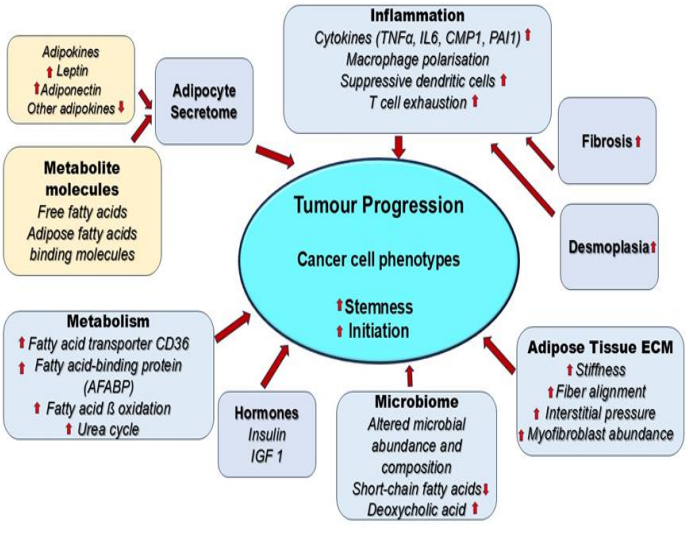

Figure 6: The diagram depicts the whole cumulative cross-talk networking between the metabolism of Adipocytic secretions influencing the other cell metabolic pathways and their role in tumor progression.

Conclusion

Expanding on the risk factors and prominent processes implicated in the etiology of CRC, this article explores the instinctive relationship between the correlation of obesity and CRC in a comprehensive review manner. Factors such as insulinemia caused by obesity, increased levels of leptin and resistin in the blood and several cytokines that change the composition of the gut microbiome and lead to oxidative stress are the main drivers of the pathophysiology. Obese people should undergo regular screenings by their doctors to detect any changes in the colonic mucosa that could lead to CRC. So, the study elucidates several mechanisms contributing to CRC in individuals with obesity, as observed in Figure 6 above, some of which necessitate additional research for validation. Modifications in diet and physical activity are crucial in the development of CRC and can serve as targets for treatment and prevention strategies. The study does not address any conceptualization of the aspect of medical management.

Recommendations

Regular screening for colorectal cancer (CRC) in obese individuals is essential, utilizing obesity-related biomarkers for better risk assessment. Lifestyle modifications, including weight loss through diet and exercise, along with a fiber-rich diet, can improve gut health and reduce inflammation. Therapeutic approaches such as adiponectin and ghrelin-based treatments, along with anti-inflammatory drugs, may help counteract obesity-driven CRC risks. Additionally, restoring gut microbial balance through probiotics and prebiotics can mitigate CRC-promoting dysbiosis. Public health initiatives should focus on raising awareness about the obesity-CRC link, implementing workplace wellness programs, and promoting obesity management to reduce CRC incidence.

Future research on obesity-associated colorectal cancer (CRC) should explore biomarkers for early detection, targeted therapies, gut microbiome interventions, and inflammation-related mechanisms. Studies on lifestyle modifications and public health strategies are essential for prevention. A multidisciplinary approach integrating molecular biology, nutrition, and clinical oncology can improve CRC management in obese individuals.

Acknowledgments

We are grateful to the Dean of IMS and SUM Hospital Bhubaneswar for the extended research facility at the Medical Research Laboratory. The authors also acknowledge Dr. Debasmita Dubey, MRL Lab, IMS and SUM Hospital Siksha 'O' Anusandhan University for providing necessary facilities and support.

Funding

This study received no external funding.

Conflict of Interest

The authors declare no competing interests.

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To cite this article: Sahu P, Dubey D, Panda SS, Tripathy SK. Obesity-Induced Mechanisms in Colorectal Cancer Development: A Narrative Review. Al-Kindy Col. Med. J. 2025;21(2):96-106. https://doi.org/10.47723/t8v6bw38