DOI: http://dx.doi.org/10.12996/gmj.2025.4478

Leptin as a Biomarker of Cancer Prognosis: A Friend of Colorectal Cancer

Kanser Prognozunun Biyobelirteci Olarak Leptin: Kolorektal Kanserin Bir Dostu

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ABSTRACT

This review aims to evaluate the role of the peptide hormone leptin in the initiation and progression of cancer, with a particular focus on colorectal cancer (CRC). A comprehensive literature search was conducted in Google Scholar and PubMed databases to identify relevant studies published from 2020 and 2025. Articles investigating the influence of leptin and its receptors on cancer development and progression, particularly in CRC, were included without language restrictions. This review highlights that leptin promotes cancer progression by abrogating the efficacy of chemotherapeutic agents. Additionally, across the reviewed articles, some studies reported no causal relationship no statistically significant association between leptin and CRC. Although some articles report that leptin and its receptor have no association with the development and progression of cancer, the majority of articles implicate leptin in the development and progression of cancer, mainly in CRC. Due to these discrepancies, there is an urgent need for additional studies employing meticulously designed, standardized methodologies and rigorous control measures to annihilate potential confounding factors. These conflicting findings may be explained by differences in study designs and confounding factors, such as obesity. Obesity is a major risk factor for various forms of cancer and can trigger CRC by causing cellular changes such as mitochondrial dysfunction. In such cases, increased leptin levels may not directly mean that leptin causes CRC. Although evidence suggests a potential role for leptin in the development and progression of CRC, inconsistencies in the literature underscore the need for further research. Future studies should employ standardized methodologies and rigorous control for confounders to clarify leptin's mechanistic and clinical relevance in colorectal carcinogenesis.

Keywords: Leptin, leptin and colorectal cancer, leptin and cancer, leptin and anticancer agents, colorectal cancer

ÖZ

Bu derleme, peptit hormonu leptinin kanserin başlaması ve ilerlemesindeki rolünü, özellikle kolorektal kanser (CRC) üzerinde yoğunlaşarak değerlendirmeyi amaçlamaktadır. 2020 ve 2025 yılları arasında yayınlanmış ilgili çalışmaları belirlemek için Google Akademik ve PubMed veri tabanları kullanılarak kapsamlı bir literatür araştırması yürütülmüştür. Leptinin ve reseptörlerinin kanser gelişimi ve ilerlemesi, özellikle de CRC üzerindeki etkisini araştıran makaleler dil kısıtlaması olmaksızın dahil edilmiştir. Bu derleme makalesi, leptinin kemoterapötik ajanların etkinliğini ortadan kaldırarak kanser ilerlemesini desteklediğini vurgulamaktadır. Ayrıca, incelenen makalelerden bazı çalışmalar leptin ve CRC arasında nedensel bir korelasyon olmadığını ve leptin ve CRC arasında istatistiksel olarak anlamlı bir ilişki olmadığını bildirmiştir. Bazı makaleler leptinin ve reseptörünün kanser gelişimi ve ilerlemesi ile bir ilişkisi olmadığını bildirmesine rağmen, makalelerin çoğu leptinin kanser gelişimi ve ilerlemesinde, özellikle CRC'de rol oynadığını belirtmektedir. Bu tutarsızlıklar nedeniyle, potansiyel karıştırıcı faktörleri ortadan kaldırmak için daha titizlikle tasarlanmış standartlaştırılmış metodolojiler ve titiz kontrol önlemleri içeren daha fazla çalışmaya acil ihtiyaç vardır. Bu çelişkili bulgular, çalışma tasarımlarındaki farklılıklar ve obezite gibi karıştırıcı faktörlerin varlığı ile açıklanabilir. Obezite, çeşitli kanser türleri için önemli bir risk faktörüdür ve mitokondriyal disfonksiyon gibi hücresel değişikliklere neden olarak CRC'yi tetikleyebilir. Bu gibi durumlarda, artan leptin seviyeleri doğrudan leptinin CRC'ye neden olduğu anlamına gelmeyebilir. Kanıtlar, CRC'nin gelişimi ve ilerlemesinde leptinin potansiyel bir rolü olduğunu gösterse de, literatürdeki tutarsızlıklar daha fazla araştırmaya ihtiyaç olduğunu vurgulamaktadır. Gelecekteki çalışmalar, leptinin kolorektal karsinogenezdeki mekanistik ve klinik önemini açıklığa kavuşturmak için standartlaştırılmış metodolojiler ve karıştırıcı faktörlerin titiz kontrolünü kullanmalıdır.

Anahtar Sözcükler: Leptin, leptin ve kolorektal kanser, leptin ve kanser, leptin ve kanser önleyici ilaçlar, kolorektal kanser

Cite this article as: Akanbong EA, Şenol A, Duru Ö, Çınar M, Öcal H. Leptin as a biomarker of cancer prognosis: a friend of colorectal cancer. Gazi Med J. [Epub Ahead of Print].

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Received/Geliş Tarihi: 23.06.2025
Accepted/Kabul Tarihi: 17.09.2025
Epub: 08.12.2025

INTRODUCTION

Leptin, a 16 kDa peptide hormone composed of 167 amino acids and expressed mainly by adipocytes, was discovered in 1994 in leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice. This hormone, which was later referred to as a product of the obese (ob) gene in vertebrates, shows structural differences in its primary amino acid sequence, but secondary and tertiary structures are the same and similar to the long-chain helical cytokines, including interleukin (IL) 6, IL-11, and IL-12 (1). The leptin hormone plays a crucial role in regulating body weight and energy expenditure. Circulating leptin levels reflect the amount of energy stored in adipose tissue and correlate with the occurrence and degree of obesity. In other words, a higher circulating leptin level indicates greater energy storage (Figure 1) (2). Although it is expressed primarily in adipose tissue, it has also been found in other tissues, such as muscle, the brain, and the gastrointestinal system. Its expression is regulated by IL-1β during inflammation, insulin, and cortisol (1).

Aside from the pivotal role of leptin in obesity by regulating food intake and basal metabolism, its influence extends to various tissues and systems, including its interactions with the immune system and implications for cancer initiation and progression. The hormone leptin has been implicated in the initiation and progression of many types of cancer. However, evidence has suggested that leptin has a beneficial and possibly antitumoral role. The first anticancer effect of leptin treatment in human cancer cell lines was reported in the Michigan Adenocarcinoma Pancreatic Cancer-2 and Pancreatic Carcinoma-1 pancreatic cancer cell lines. Low serum leptin levels have been correlated with pancreatic cancer, and high expression of leptin has been associated with better survival in patients with colorectal cancer (CRC) (1). Nonetheless, due to the paradoxical effect of leptin, pre-exposure of colon cancer cells to leptin inhibited tumour necrosis factor alpha (TNF-α)-induced apoptosis. However, its knockdown enhanced TNF-α-induced apoptosis by upregulating the p53-upregulated modulator of apoptosis (PUMA). That is, the expression of functional leptin and/or leptin receptors inhibits TNF-α-induced apoptosis in colon cancer cells (3). Excessive systemic and pulmonary leptin levels have also been linked to an increased risk of lung cancer (4).

Since leptin is produced in adipose tissue, understanding its relationship with adipose tissue mass is essential for exploring its potential correlation with the risk of colon cancer (3). With more than 1 million new cases diagnosed annually, CRC is the third most prevalent cancer in men, the second most prevalent cancer in women, and the primary cause of cancer-related mortality (5). While its risk factors include germline mutations, alcohol, and tobacco, obesity is also a significant risk factor for CRC (3). Considering the role of leptin in the initiation and progression of cancer, as well as its significant impact in mitigating obesity, a primary risk factor for colon cancer, this review aims to determine whether leptin is a friend or foe of colon cancer by examining publications from 2020 to date using Google Scholar and PubMed databases.

Literature Search

This review was conducted by searching the Google Scholar and PubMed electronic databases for relevant literature using keywords such as leptin, colon cancer, leptin and colon cancer, and leptin and cancer. Of the articles obtained, only those published in 2020 or later were considered in this work. Considering the topics discussed in this review, Research articles, meta-analyses, and reviews that did not pertain to the topics of this review were considered irrelevant and excluded from the study. No language limitation was applied in the literature search. Moreover, the reference lists of review papers were further searched to identify potentially more relevant research articles.

Leptin and Cancer

Leptin exhibits proliferative activity in tumour cells of various cancer types (Figure 2), such as breast, gastric, endometrial, and prostate cancers. In vitro experiments have shown that leptin, through the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3), and extracellular signal-regulated kinase 1 and 2 (ERK1/2) signalling pathways, can exert its proliferative effect in cancer cells (7). Leptin does not influence carcinogenesis via proliferation alone; it may also influence carcinogenesis by suppressing apoptosis in cancer cells. This may be achieved by upregulating the expression of anti-apoptotic genes such as B-cell lymphoma-x-long (Bcl-xl), B-cell lymphoma 2 (Bcl-2), and survivin. According to Ayed et al. (7), leptin has been reported to reduce apoptosis in cancer cells by inhibiting the expression of many pro-apoptotic genes, including TNFR1, FADD, Caspase 3, 6, 7, 9, and 10, CAD, ICAD, BAX, BAD, BAK1, BID, BOK, APAF1, TRAF-interacting protein, TRAIL, IGF1R, and TRADD.

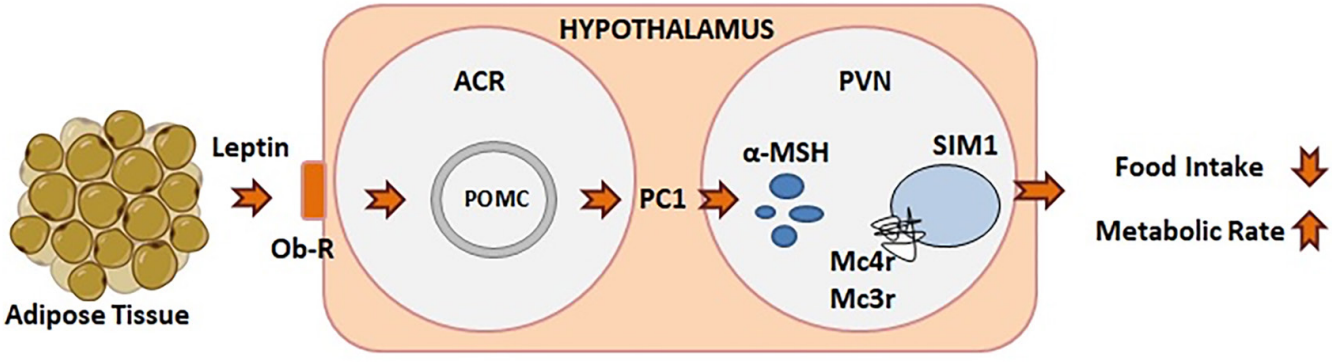

Figure 1. Adipose tissue responds to higher energy levels by producing leptin. This was adapted from Reference 6.

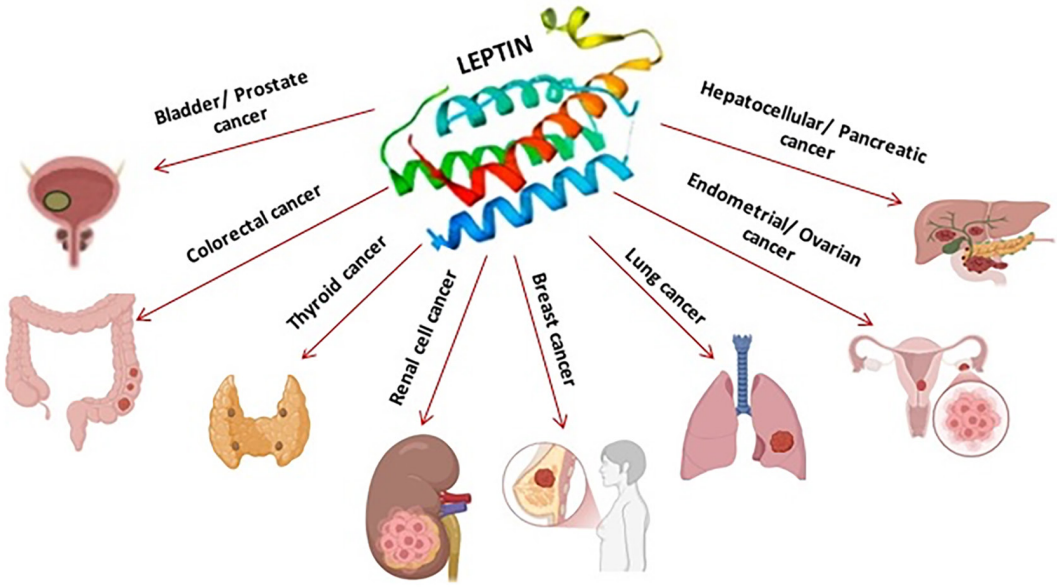

Figure 2. Leptin is associated with various types of tumours. This was adapted from Reference 1.

Chronically elevated leptin levels (hyperleptinemia), characteristic of obesity, may increase cancer susceptibility and progression, as the antitumor immune response is impaired in such cases. For instance, it may result in complete paralysis of the cellular metabolism and cytotoxic machinery in natural killer (NK) cells, driven by lipid accumulation (7).

Leptin and Breast Cancer

Studies on leptin and cancer have shown that leptin is involved in the occurrence and progression of breast cancer. Leptin and its receptor can be used in the diagnosis and prognosis of breast cancer (8). According to Ayed et al. (7), leptin promotes cell cycle progression in cancer cells by upregulating the cell cycle progression genes CCND1, CCNA2, PCNA, and E2F3, and downregulating the cell cycle inhibitor genes p21WAF1/CIP1, p27KIP1, and GADD45A. Leptin enhances fatty acid synthesis and oxidation in oestrogen receptor-positive breast cancer cells. These metabolic changes, which are necessary for leptin-stimulated tumour growth, are caused by activation of autophagy and of the sterol regulatory element-binding protein 1 (SREBP-1) (9).

Leptin and Gastric Cancer

Leptin facilitates the metastasis and invasion of cancer cells. In a previous study, leptin induced migration and invasion of gastric cancer cells by activating AKT and andextracellular signal-regulated kinase (ERK) pathways and upregulating vascular endothelial growth factor (VEGF) (10).

Leptin and Endometrial Cancer

Endometrial cancer is not excluded from the influence of leptin. Leptin plays a role in invasion and distant metastasis of endometrial cancer and, in fact, is responsible for its proliferation (11). In a study conducted among 30 endometrial cancer patients, it was reported that leptin and its receptors were overexpressed and that the elevated levels of leptin and its receptors were the potential reason for the progression of endometrial cancer (12).

Leptin and Prostate Cancer

The expressions of leptin and its receptors could also serve as potential biomarkers for assessing the risk and severity of prostate cancer. In a study, it was reported that leptin and its receptors were overexpressed in patients with prostate cancer, with higher expression in the severe and metastatic group than in patients with confined tumours (13).

Leptin and Gall bladder Cancer

Exosomes derived from gallbladder cancer cells have been shown to polarize macrophages toward the M2 phenotype via activation of the STAT pathway. The study also reported that leptin was present in exosomes produced by gallbladder cancer cells and that increased leptin levels facilitated the invasion and migration of gallbladder cancer cells. The researchers indicated that blocking leptin reduces the polarization effect (14).

Leptin and Anticancer Drugs

In a study, a drug was designed, and its anticancer and cytotoxic effects were evaluated. According to the researchers, the drug suppressed the expression of leptin and its receptor genes and could significantly increase the efficiency of targeted drug delivery in cancer treatment (4). Increasing evidence suggests that obesity, aside from being a major predisposing factor for cancer, is associated with resistance to anticancer chemotherapy, and this is probably driven by leptin. Inferring from obesity's role in chemoresistance, recent studies have further reported on leptin's specific roles in various cancers. Ayed et al. (7) reported that a study found patients with pancreatic adenocarcinoma who did not respond to gemcitabine-based chemotherapy had significantly higher serum leptin levels compared to those who were responsive. This lack of responsiveness to chemotherapy may be linked to elevated leptin levels, which are associated with obesity.

A study investigating survival and chemoresistance in patients with estrogen-receptor-negative breast cancer reported that the expression of the leptin receptor and leptin-targeted genes is associated with poorer survival. In addition, increased expression of these genes (*ABCB1, WNT4, ADHFE1, TBC1D3, LL22NC03, RDH5*, and *ITGB3*), which are chemoresistance-related genes, was associated with tumorigenesis and chemotherapeutic failure. Thus, targeting leptin receptor signalling during chemotherapy could improve chemotherapeutic efficacy (15), and this has been demonstrated in a study in which metformin and silibinin synergistically suppressed lung cancer growth, possibly through regulation of the gene expression of leptin and its receptor. In the study, the synergistic effect of metformin and silibinin considerably reduced the expression of leptin and of its receptor gene, thereby providing a more promising and safer treatment strategy for cancer, especially lung cancer (16).

In addition, leptin's influence on chemoresistance in mesenchymal cells has been demonstrated in a study in which a leptin-conditioned medium from human mesenchymal cells promoted resistance to cisplatin in cultured human osteosarcoma cells. According to the study, leptin upregulated transforming growth factor-β (TGF-β) expression in mesenchymal cells, an effect that was suppressed by knockdown of the leptin receptor. The suppression of TGF-β expression in the mesenchymal cells due to leptin receptor knockdown also ameliorated the chemoresistance of osteosarcoma cells to cisplatin (17). Additionally, leptin has been suggested to influence the growth and drug resistance of cancer cells; however, its mechanism by which it induces drug resistance in gallbladder cancer cells has not been fully elucidated. Given this, leptin-induced drug resistance in gallbladder cancer cells was investigated in vivo. The study found that leptin reduced the efficacy of gemcitabine by activating myeloid cell leukaemia 1 (MCL-1), thereby promoting resistance to gemcitabine. Upon treatment with leptin, a chain reaction was observed in which activated pSTAT3, in turn, activated the transcription factor CEBPD, which subsequently increased MCL1 levels, thereby contributing to drug resistance in gallbladder cancer cells. In other words, targeting the pSTAT3/CEBPD/MCL1 axis could help improve the efficacy of gemcitabine in cancer patients, specifically gallbladder cancer patients (18). Leptin increases AXL expression by inhibiting the AMPK pathway, thereby increasing activation and nuclear translocation of yes-associated protein. This process ultimately increased resistance to the chemotherapy drug 5-fluorouracil (5-FU) in the CRC tumours from mice fed a high-fat diet. However, when leptin levels were neutralised, the sensitivity of CRC tumours to 5-FU was restored (19). This further demonstrates leptin's interference with chemotherapy in favour of cancer cells.

Overall, the gene expression of leptin and its receptor could affect the success of cancer therapy by promoting drug resistance or reducing the efficacy of therapeutic agents. The reviewed studies consistently demonstrate that leptin contributes to chemoresistance in various cancers by affecting gene expression and signalling pathways. Therefore, targeting either these leptin-mediated mechanisms or leptin and its receptor gene expression could enhance chemotherapy outcomes.

Leptin and Colon Cancer

Leptin's Influence and Biochemical Mechanisms in Colorectal Cancer

CRC is associated with obesity, and available data suggest that CRC is positively correlated with many factors, including metabolic syndrome and serum leptin levels (1,20). Leptin is thought to be involved in the development and progression of CRC (21). Some studies have reported no association between circulating or high serum leptin levels and CRC (1,18). The majority of studies have reported that the overexpression of leptin and its receptor is correlated with tumour progression (1,22,23). Colectomy has been reported to decrease serum leptin levels, supporting the correlation between leptin and CRC. Thus, targeting leptin and its receptor is essential for the prevention and treatment of CRC (1).

Singh et al. (3) also demonstrated that TNF-α induces p53-independent apoptosis of colon cancer cells through the upregulation of PUMA. However, pre-exposure of the colon cancer cells to leptin inhibited TNF-α–induced PUMA. In other words, it can be inferred that leptin promotes the growth of colon cancer cells by inhibiting apoptosis. Because of leptin's mitogenic, antiapoptotic, and tumorigenic effects, significantly higher leptin levels observed in 32 CRC patients were associated with an increased risk of CRC (23). In addition, leptin was considered a candidate gene for further analysis after assessing The Cancer Genome Atlas (TCGA) to identify expressed genes with prognostic value in CRC. The researchers then investigated its expression in 206 CRC patients without liver metastasis and 201 CRC patients with liver metastasis. Based on TCGA data, they concluded that leptin overexpression indicates a poorer overall survival prognosis in CRC patients. It was also reported that leptin expression is significantly correlated with the stage of metastasis and is a valuable marker for predicting outcomes in CRC patients (22). Erkasap et al. (24) noted that leptin could play a significant role in the initiation and/or development of CRC. Their research revealed significantly increased mRNA expression of leptin, its receptor, Notch, and IL-1 in human CRC specimens.

Leptin may also contribute to the survival and progression of CRC by reducing the efficacy of colorectal anticancer drugs. Leptin, by inhibiting the AMPK pathway, increased AXL expression, subsequently increasing YAP activation and nuclear translocation, culminating in increased resistance to 5-FU in CRC cells in high-fat-fed mice; when leptin levels were neutralised, the sensitivity of CRC cells to the chemotherapy drug 5-FU was restored (19). This illustrates the chemoresistant and antiapoptotic nature of leptin in promoting CRC cell survival.

CRC Therapeutic Approaches

Due to leptin's role in CRC progression, there is a critical need for interventions, and this could be addressed by leveraging its relevance. To further demonstrate that leptin and its receptors are essential in the development and progression of CRC and play a role in CRC chemoresistance, leptin's unique ability to target its receptor was leveraged to enhance drug delivery in CRC. PEGylated liposomal doxorubicin was functionalized with a leptin-derived peptide (Lp31), resulting in improved uptake and cytotoxicity in C26 colon cancer cells. The study found that doxorubicin inhibited tumour growth

in a concentration-dependent manner (25). Similarly, the leptin-derived peptide was used to suppress tumour growth in a tumour-bearing mouse model of colon carcinoma (26). The suppression of tumour growth and angiogenesis, promotion of apoptosis, in a human colon cancer cell subcutaneous xenograft mouse model by Weichang'an Formula (WCAF), a traditional Chinese medicine (herbal preparation), through decreased leptin mRNA expression, was attributed to leptin/STAT3 signal transduction (27).

Epidemiological Evidence

Epidemiologically, studies exploring a related factor, such as adipose tissue, have reported that adipose tissue mass, especially visceral adipose tissue mass, is directly correlated with the risk of colon adenoma and cancer. In the case of excess adipose tissue mass (obesity), the functional roles of adipose tissue are disrupted, which could cause inflammation and altered secretion of pro- and anti-inflammatory cytokines. Additionally, excess adipose tissue mass leads to increased levels of leptin, which have been associated with an increased risk of colon cancer (3).

Contrasting Views and Future Directions

Although leptin is implicated and reported to be essential in CRC progression, a case-control study involving 955 CRC patients, 497 colon adenoma patients, and 911 healthy individuals that investigated the causal association between circulating leptin levels and the risk of colon adenoma, CRC, and the progression of colon adenoma to CRC reported otherwise. According to the case-control study, circulating leptin levels probably correlate with the risk of colon adenoma, CRC, and progression from colon adenoma to CRC. However, the Mendelian randomisation analysis found no evidence of a causal association between circulating leptin levels and the risk of colon adenoma, CRC, and progression from colon adenoma to CRC (28). The expression levels of leptin and its receptor were evaluated in 46 healthy individuals and 44 CRC patients. No statistically significant differences were observed between the normal group and the CRC group in the expression of leptin and its receptor. Thus, leptin and its receptor would not be useful biomarkers for CRC. However, according to the study, the CRC cases showed an insignificantly higher expression of the leptin receptor (29).

Overall, leptin and its receptors are involved in the initiation and progression of CRC. However, investigating the mRNA expression of leptin and its receptor within in vivo CRC-induced model-based studies, independent of obesity, would provide further essential data on its role. Moreover, the prognosis of CRC treatment could be improved by leveraging the leptin signalling pathway or its derived peptides in a case of CRC.

CONCLUSION

Based on the reviewed papers from 2020 to date, leptin may be involved in the development and progression of CRC. Additionally, targeting leptin and its receptor during chemotherapy could contribute to a favorable prognosis, as it has the potential to induce chemoresistance. However, other studies have reported neither a causal correlation between leptin and colorectal cancer nor a statistically significant association. Given these discrepancies, there is an urgent need for additional studies with more meticulously designed, standardised methods and rigorous control measures to eliminate potential confounding factors. For instance, obesity, the major risk factor for various forms of cancer, causes several changes, including mitochondrial dysfunction, which can also induce CRC. Thus, the increased level of leptin in such circumstances may not necessarily indicate that leptin is the cause of CRC. This review also highlights the necessity for additional clarification of and research into the mechanisms and clinical implications of leptin's effects on CRC.

Footnotes

Authorship Contributions: Concept: E.A.A., A.Ş., Ö.D., M.Ç., Design: E.A.A., A.Ş., Data Collection or Processing: E.A.A., Literature Search: E.A.A., A.Ş., H.Ö., Writing: E.A.A., A.Ş., Ö.D., M.Ç., H.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Acknowledgements

The authors acknowledge that the figures used in this paper were created using BioRender.com.

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