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REVIEW

Novel perspectives on the link between obesity and cancer risk: from mechanisms to clinical implications

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Abstract **Existing epidemiologic and clinical studies have demonstrated that obesity is associated with the risk of a variety of cancers. In recent years, an increasing number of experimental and clinical studies have unraveled the complex relationship between obesity and cancer risk and the underlying mechanisms. Obesity-induced abnormalities in immunity and biochemical metabolism, including chronic inflammation, hormonal disorders, dysregulation of adipokines, and microbial dysbiosis, may be important contributors to cancer development and progression. These contributors play different roles in cancer development and progression at different sites. Lifestyle changes, weight loss medications, and bariatric surgery are key approaches for weight-centered, obesity-related cancer prevention. Treatment of obesity-related inflammation and hormonal or metabolic dysregulation with medications has also shown promise in preventing obesity-related cancers. In this review, we summarize the mechanisms through which obesity affects the risk of cancer at different sites and explore intervention strategies for the prevention of obesity-associated cancers, concluding with unresolved questions and future directions regarding the link between obesity and cancer. The aim is to provide valuable theoretical foundations and insights for the in-depth exploration of the complex relationship between obesity and cancer risk and its clinical applications.**

Keywords obesity; obesity-associated cancers; cancer risk; carcinogenesis; cancer prevention

Introduction

Obesity is a common and complex disease as well as a growing health problem [1,2]. The World Health Organization defines obesity as an excessive accumulation of fat that may impair health [3]. Obesity has been reported to be a risk factor for many diseases, such as coronary heart disease, diabetes, and hepatitis [4,5]. Several studies have shown that obesity is associated with the risk of several cancers [6–11]. For example, overweight and obesity can increase the risk of non-Hodgkin's lymphoma by 7% and 20% [10] and the risk of liver cancer by 17% and 89% [12], respectively; overweight or obesity increases the risk of colorectal cancer in men by 37% and the risk of endometrial cancer

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by 62% [9,13] while reducing the risk of lung cancer by approximately 20% [14].

In recent years, the effect of obesity on cancer risk has become one of the hotspots in the field of cancer research [15–17]. According to the current understanding, the possible factors through which obesity affects cancer development mainly include inflammation, adipokines, hormones, and gut microorganisms [18–20]. Current reviews on the mechanisms of obesity and cancer risk focus on site-specific cancer or a certain mechanism [21–27]. Obesity may affect the risk of cancer at different sites to varying degrees through the same mechanism, which may be attributed to the heterogeneity of the role of the mechanism in the development of cancer at different sites [28,29]. For example, when estrogen is expressed at high levels in endometrial cells as a result of obesity, it activate oncogenic pathways upon binding to the corresponding receptors, further promoting cancer development; however, when estrogen is expressed at high levels in colorectal cells as a result of obesity, it appears to exert anti-inflammatory and anticancer effects, thereby inhibiting colorectal carcinogenesis [28,29]. In addition, within the same site, obesity may affect the development of cancer through different mechanisms, and there may be differences in this effect [18,29–32]. For example, as described above, obesity-induced high estrogen levels may exert a protective effect against colorectal carcinogenesis, but obesity may promote colorectal carcinogenesis through molecular mechanisms such as promoting intestinal inflammation, inducing gut microbial dysbiosis, and increasing leptin secretion [18,29,30,32]. However, there is a lack of systematic discussion of the mechanisms by which obesity affects the risk of different cancer types and the differences between the mechanisms.

Therefore, in this article, we focus on how obesity affects the risk of cancer at different sites and provide a comprehensive and systematic review of the specific mechanisms and the differences between the mechanisms. Moreover, based on these mechanisms, we explore possible ways to prevent the occurrence of obesity-related cancers. This study aims to provide theoretical support and propose future directions for elucidating the mechanisms of obesity-related cancer and developing personalized cancer prevention and treatment strategies for obese patients.

Mechanisms by which obesity affects cancer risk

The main mechanisms by which obesity affects carcinogenesis include (1) inflammation initiation, (2) hormonal disturbances, (3) microbial dysregulation, (4) dysregulation of adipokine levels, and (5) generation of physical stimuli and other biochemical factors (Fig. 1). Low-grade chronic inflammation is one of the main characteristics of obesity, as obesity disrupts the normal balance between proinflammatory and anti-inflammatory states in adipose tissue, and the anti-inflammatory state dominates [33–35]. In addition, metabolic disturbances may occur in obese patients, mainly involving hormones and adipokines. Disturbances in hormone secretion include elevated levels of estrogen, insulin, and cholecystokinin as well as decreased levels of progesterone and ghrelin [36–40]. Adipose tissue is actually an endocrine tissue that secretes a variety of adipokines, including leptin, adiponectin, resistin, chemerin, visfatin, fatty acid binding protein 4 (FABP4), retinol binding protein 4 (RBP4), and others, whose levels are abnormally elevated or decreased in obese patients [41–45]. Obesity may also induce physical and biochemical changes such as increased abdominal pressure, promotion of extracellular matrix (ECM) fibrosis, and lipid accumulation [46–48]. These abnormal obesity-induced changes may play an important role in the process of cancer development.

Inflammation initiation

Obesity causes low-grade chronic inflammation

Low-grade chronic inflammation of adipose tissue in obese patients is characterized by increased infiltration of proinflammatory immune cells, massive release of cytokines, and the formation of crown-like structures [49–52] (Fig. 2A). M1 macrophages are a major component of the proinflammatory adipose tissue microenvironment [53,54]. In obese patients, blood monocytes are recruited to adipose tissue and differentiate into M1 macrophages [49]. M1 macrophages release many molecules, including COX2, IL-1, TNF-α, MCP-1, and CSF-1, which in turn activate the M1 polarization of macrophages [49,50]. MCP-1 secreted by adipocytes themselves also promotes the M1 polarization of macrophages [50]. The proinflammatory adipose tissue microenvironment also features increased infiltration of neutrophils, Th1 cells, mast cells, and mature B cells, as well as an increase in the levels of cytokines secreted by these proinflammatory cells (e.g., IFN-γ, IL-8) [51,55]. In contrast, a decrease in the infiltration of anti-inflammatory cells (e.g., M2 macrophages, Treg, Th2 cells, and iNKT cells), along with a concomitant decrease in the levels of anti-inflammatory cytokines secreted by these cells (e.g., IL-4, IL-10), contributes to the formation of a proinflammatory microenvironment in adipose tissue [51]. In addition, the formation of crown-like structures is one of the hallmarks of the formation of a proinflammatory microenvironment in adipose tissue, which is manifested by many macrophages encircling dead adipocytes [52,56].

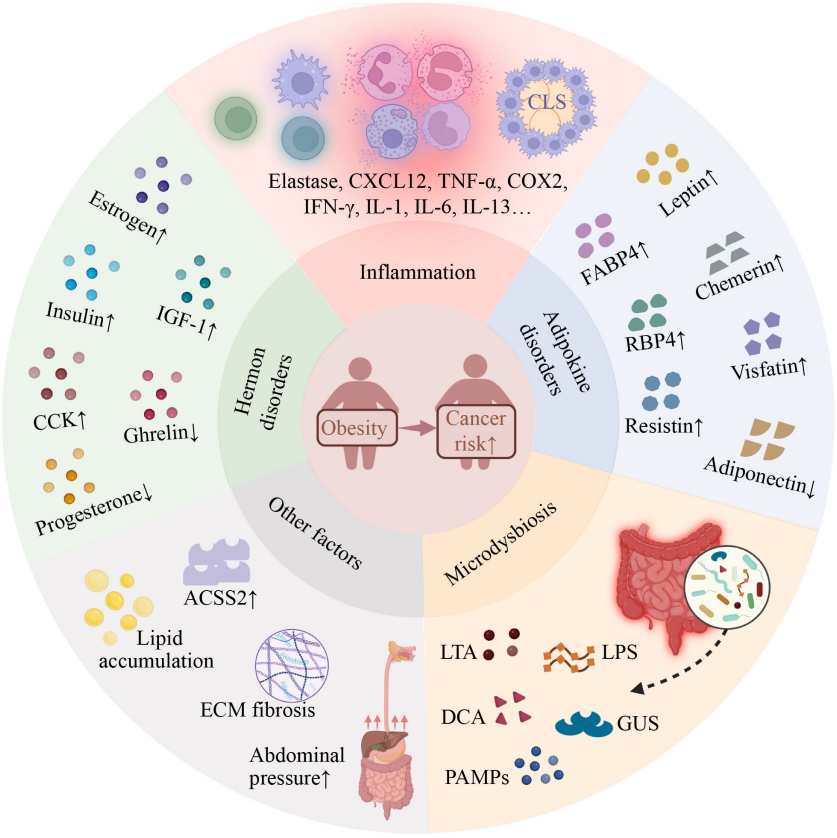

Fig. 1 Overview of the mechanisms linking obesity and cancer risk. Abbreviations: IGF-1, insulin-like growth factor 1; FABP4, fatty acid binding protein 4; RBP4, retinol binding protein 4; LTA, lipoteichoic acid; LPS, lipopolysaccharide; DCA, deoxycholic acid; GUS, β-glucuronidase; PAMPs, pathogen-associated molecular patterns; ACSS2, acetate-dependent acetyl-CoA synthetase 2; ECM, extracellular matrix. This figure was created based on the tools provided by Biorender.com.

The development of low-grade chronic inflammation may be associated with hypoxia and adipocyte death [57–59]. Inadequate oxygen and blood supply caused by adipose tissue hyperplasia in obese patients leads to tissue fibrosis as well as an increase in the number of degenerated and dead adipocytes, the latter of which contribute to the M1 polarization of macrophages by releasing free DNA and damage-associated molecular patterns [57,58,60–62]. In addition, fatty acids produced by lipolysis are phagocytosed by adipose tissue macrophages and deposited in the cells [63]. Excess accumulation of lipids in adipose tissue macrophages may promote M1 macrophage polarization and trigger inflammation [64]. In addition, lipopolysaccharide enters adipose tissue through the intestinal mucosa upon obesity-induced damage, further promoting cytokine release from M1 macrophages [65,66].

Obesity-related inflammation promotes carcinogenesis

Localized inflammation in adipose tissue may be one of the factors linking obesity to cancer development [18,67,68]. Different cytokines in adipose tissue mediate carcinogenesis at different sites by activating corresponding signaling pathways (Fig. 2B).

In obesity-associated hepatocarcinogenesis, IL-1, IL-6, and VEGF may play an important promotional role [67,69,70]. Elevated serum IL-6 levels were observed in mice with diet-induced obesity or hereditary obesity [67]. When the level of IL-6 is elevated, it binds to receptors on the surface of hepatocytes and activates the STAT3 signaling pathway, which further promotes cell proliferation and inhibits apoptosis, thereby promoting hepatocarcinogenesis [67,71]. In addition, IL-6, through trans-signaling, inhibits P53 to suppress apoptosis and simultaneously promotes endothelial cell proliferation and VEGF secretion to promote angiogenesis, which also contributes to liver cancer development [70,72]. Inflammation-induced reactive oxygen species production and hepatocyte death may contribute to the increase in IL-1 levels, which can stimulate the production of IL-6, indirectly promoting hepatocarcinogenesis [35,69].

TNF-α and IL-13 are mainly associated with the development of obesity-associated colorectal cancer [18,73]. Elevated levels of inflammatory factors, such as TNF-α and IL-13, were observed in diet-induced obese

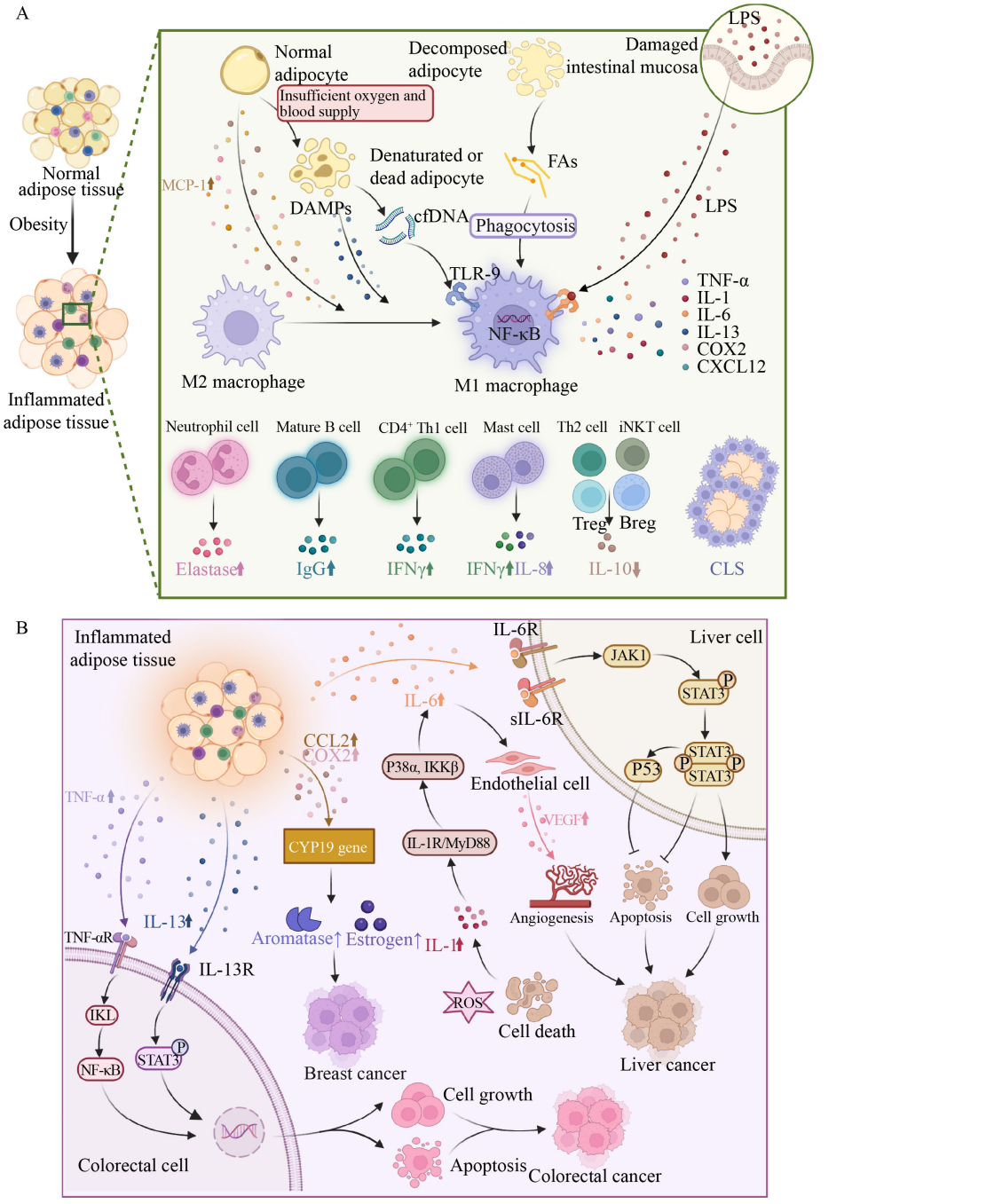

Fig. 2 The potential mechanism by which inflammation links obesity and cancer risk. (A) Adipose tissue from patients with obesity is in a state of low-grade chronic inflammation. When obesity-induced adipocyte hyperplasia and hypertrophy lead to insufficient oxygen and blood supply to adipose tissue, the number of adipocytes undergoing degeneration and death increases, and the amount of FAs produced by lipolysis increases; moreover, obesity-induced damage to the intestinal mucosa allows LPS to enter the blood circulation. These changes induce M1 macrophage polarization to recruit more immune cells and activate them, resulting in the release of many inflammatory factors. Adipocytes surround adipose macrophages to form crown-like structures, which are one of the hallmarks of the proinflammatory microenvironment in adipose tissue. (B) Inflammatory factors mediate carcinogenesis. When the level of IL-6 is increased, STAT3 signaling is activated, which promotes cell proliferation and inhibits apoptosis; furthermore, IL-6 promotes angiogenesis, which is conducive to the development of hepatocellular carcinomas. Increased ROS levels and hepatocellular cell death indirectly contribute to the increase in IL-6 expression. Obesity-associated colorectal carcinogenesis mainly involves IL-13-mediated activation of STAT6 signaling and TNF-α-mediated activation of the Wnt pathway. When CCL2 and COX2 are upregulated, they promote aromatase and estrogen synthesis by activating the CYP19 gene, which ultimately promotes breast cancer growth. Abbreviations: MCP-1, monocyte chemoattractant protein-1; DAMPs, damage-associated molecular pattern molecules; cfDNA, circulating cell-free DNA; FAs, fatty acids; TLR-9, Toll-like receptor 9; LPS, lipopolysaccharide; CLS, crown-like structures; sIL-6R, soluble IL-6R. This figure was created based on the tools provided by Biorender.com.

mice, and this alteration was mainly mediated by obesity-related processes [74]. TNF-α and IL-13 bind to TNF-αR and IL-13R on the surface of colorectal cells, respectively, and accordingly activate the WNT signaling pathway and STAT6 signaling pathway, which increase the proliferation of intestinal epithelial cells and intestinal mucosal cells, thus promoting colorectal carcinogenesis [18,73]. In an experimental study by Li *et al*., knocking down TNF-α attenuated inflammation and reduced the risk of obesity-associated intestinal cancer development [75].

Molecules such as CCL2 and COX2 may be pivotal factors involved in the increase in risk of developing postmenopausal obesity in patients with breast cancer. In breast tissue under obesity conditions, CCL2 secreted by adipocytes and macrophages contributes to the exacerbation of local inflammation; at the same time, CCL2 promotes the transcription of the CPY19 gene, leading to elevated local aromatase and estrogen levels, which in turn stimulate breast cell proliferation [76]. Experiments on a diet-induced obesity animal model showed that COX2 is involved in the formation of an inflammatory microenvironment in adipose tissue and increases aromatase and estrogen synthesis, which plays an important role in breast carcinogenesis [77].

Obesity also promotes the development of acute lymphoblastic leukemia, which may be related to CXCL12 [78]. CXCL12 secreted by adipocytes and MIP-1α secreted by NK cells are chemokines for leukemia cells [78]. Moreover, factors such as TGF-β and VEGF secreted by adipose stromal cells can promote the proliferation of lymphoblastoid cells to induce cancer development [78–80].

Hormonal disturbances

Estrogen

The increase in estrogen levels in obese patients may be one of the important mechanisms mediating the development of cancer [26]. In obese patients, circulating or local tissue levels of estrogen are elevated [36]. This is because obesity-induced chronic inflammation increases aromatase activity, resulting in the conversion of more androgens to estrogens in germ cells, and obesity reduces sex hormone binding globulin (SHBG) expression, resulting in less estrogen bound to SHBG and more free estrogen [26,81,82]. In obese postmenopausal women, this process occurs primarily in adipose tissue [26]. In contrast, a randomized controlled trial of a weight loss intervention in postmenopausal women resulted in weight loss favoring a decrease in body estrogen levels [83]. Obesity-induced elevation of estrogen levels increases the risk of cancer of the endometrium, ovaries, and breast in postmenopausal women (Fig. 3A). Large amounts of estrogen bind to estrogen receptor alpha (ER-α) in normal breast, endometrial, and ovarian cells and activate related oncogenic pathways, such as the PI3K/AKT and MAPK signaling pathways, which promote cell proliferation and, consequently, the development of cancers of the female reproductive system [28,84,85]. Increased estrogen levels also promote the harmful accumulation of quinone, an estrogen metabolite, which can cause DNA damage to induce carcinogenesis [86,87].

In addition to promoting carcinogenesis, high levels of estrogen in obese patients may be one of the most important factors underlying the inhibition of cancer development [88]. For example, elevated estrogen levels may have a protective effect against colorectal and prostate cancers (Fig. 3A). Unlike in cells of the female reproductive organs, estrogen receptor beta (ER-β) is the predominant estrogen receptor in normal colorectal cells [89]. Large amounts of estrogen combined with ER-β in colorectal cells activate specific pathways that downregulate IL-6 expression and promote DNA repair to reduce the risk of cancer [29,90]. In addition, estrogen supplementation was found to help reduce inflammation in prostate tissue induced by high-fat diet consumption in a recent experimental animal study and may reduce the risk of prostate carcinogenesis [91].

Progesterone

Decreased levels of progesterone in obese patients may promote endometrial cancer [91] (Fig. 3B). Progesterone is a progestin that counteracts the pro-proliferative effects of estrogen under normal conditions [92]. Progesterone inhibits carcinogenesis by exerting an anti-inflammatory effect, as evidenced by a reduction in dendritic cell infiltration and macrophage polarization to the M2 phenotype [93]. However, obesity can lead to an estrogen/progesterone imbalance, which decreases progesterone levels; this leads to diminished antiestrogenic and inflammatory effects and is thought to be possibly related to endometrial carcinogenesis [40]. In addition, treatment with progesterone inhibits the development of precancerous endometrial lesions [94]. The evidence mentioned above suggests that a decline in progesterone levels may be one of the mechanisms by which obesity promotes the development of endometrial cancer.

Insulin/IGF axis

Insulin resistance and insulin/insulin-like growth factor (IGF) axis abnormalities often occur in obese patients [37]. Obesity-induced elevation of the levels of free fatty acids, TNF-α, etc., leads to the development of insulin resistance in obese patients, which is manifested by hyperinsulinaemia along with the upregulation of IGF expression [37,95,96].

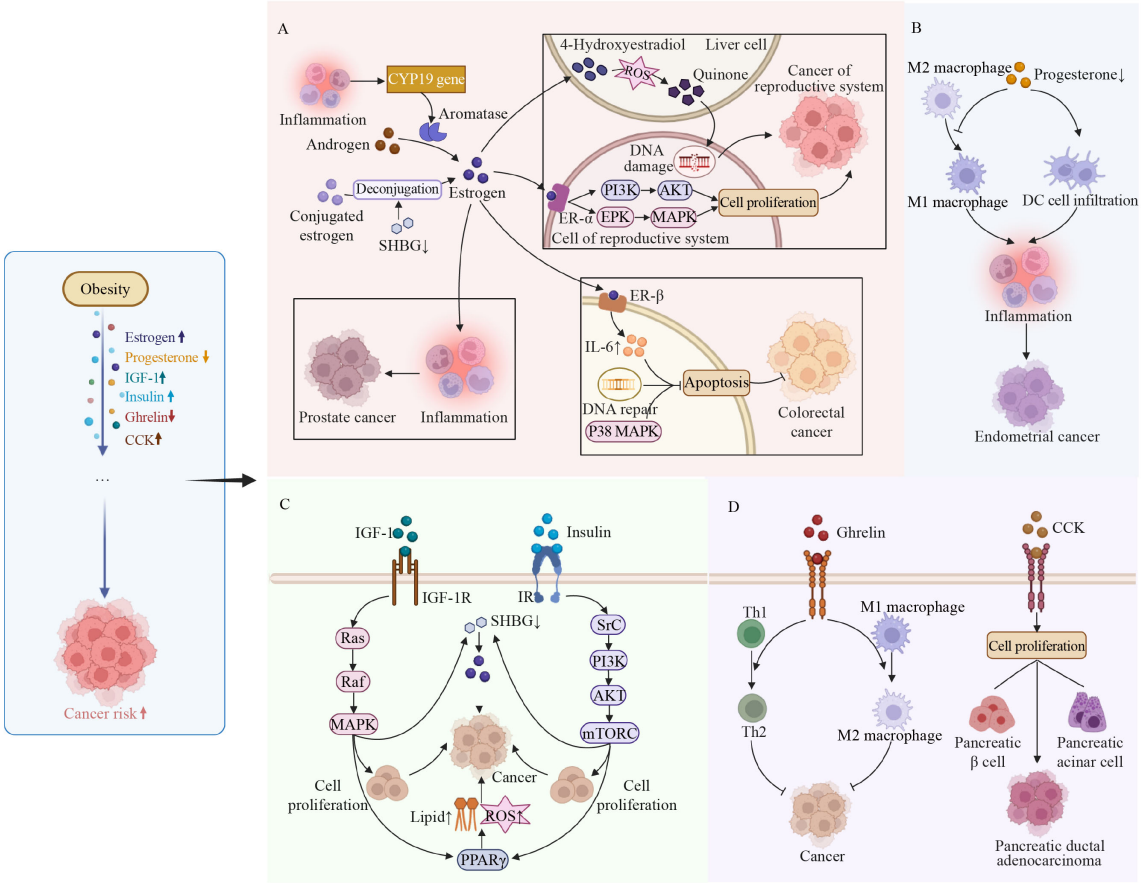

Fig. 3 Mechanisms by which obesity-induced hormone disruption promotes carcinogenesis. (A) Mechanisms by which increased estrogen levels play a role in the development of obesity-associated female-specific neoplasms and colorectal and prostate cancers. The obesity-induced increase in estrogen levels affects the risk of different obesity-associated cancers by transmitting cell proliferation- or apoptosis-associated signals, reducing tissue inflammation, and increasing metabolism. (B) Decreased luteinizing hormone levels affect endometrial carcinogenesis. The obesity-induced reduction in luteinizing hormone levels attenuates the suppression of inflammation and is associated with an increased risk of endometrial cancer. (C) Mechanisms by which insulin resistance is associated with the development of multiple cancers. Multiple factors stimulate the development of insulin resistance in obesity, and insulin and IGF-1 promote procancer events by activating procancer pathways after binding to their receptors, thus inducing colorectal cancer, hepatocellular carcinoma, and acute lymphoblastic leukemia development. (D) Abnormalities in intestinal hormone levels are associated with intestinal tumorigenesis. Obesity induces a decrease in growth hormone-releasing peptide levels, which attenuates the inhibition of inflammation to increase the risk of cancer. Obesity also induces an increase in CCK levels, which promotes the proliferation of pancreatic cells to promote pancreatic carcinogenesis. Abbreviations: IGF-1, insulin-like growth factor 1; CCK, cholecystokinin; SHBG, sex hormone binding globulin; ER-α, estrogen receptor alpha; ER-β, estrogen receptor beta; IR, insulin receptor. This figure was created based on the tools provided by Biorender.com.

Obesity-induced abnormalities in the insulin/IGF axis may be associated with the development of cancers such as obesity-associated colorectal cancer, liver cancer, and acute lymphoblastic leukemia [78,97] (Fig. 3C). Both insulin and IGF activate the Src/PI3K/Akt signaling pathway upon binding to the corresponding receptors IR and IGF-R, respectively, and IGF also activates the Ras/Raf/MAPK pathway to promote cell proliferation and inhibit apoptosis, which ultimately mediates the development of tissue carcinogenesis [78,97–99]. The activated Src/PI3K/Akt and Ras/Raf/MAPK signaling pathways may further activate PPARγ to promote adipogenesis and oxidative stress, which plays an important role in nonalcoholic fatty liver-induced hepatocarcinogenesis [99]. Elevated insulin and IGF levels can also indirectly affect levels of estrogen by decreasing SHBG levels, which may promote the development of obesity-related estrogen-related cancers [100,101]. Thus, insulin resistance and the insulin/IGF axis play an integral role in the development of cancer in obese patients.

Gastrointestinal hormones

The levels of gastrointestinal hormones such as ghrelin and cholecystokinin (CCK) are altered in obese patients, and this change may underlie the increased risk of digestive cancers [102] (Fig. 3D). Ghrelin is a peptide

secreted in the stomach that produces hunger [103]. CCK is a hormone synthesized and secreted by small intestinal cells that induces satiety and promotes pancreatic secretion [104]. In obese patients, ghrelin levels decrease, and CCK levels increase [38,39,105,106]. Ghrelin binds to its receptor and promotes the M2 polarization of macrophages and activation of Th2 cells, exerting an anti-inflammatory effect [107]. Therefore, the obesity-induced decrease in the level of ghrelin may inhibit its anti-inflammatory effects and increase the risk of cancer [108]. In a mouse model of inflammation-associated colorectal cancer, ghrelin treatment was shown to inhibit cancer growth [102]. In addition, obesity induces localized elevation of CCK levels in pancreatic tissues, which promotes the abnormal proliferation of pancreatic islet β-cells and pancreatic acinar cells, which in turn promotes hyperplasia and carcinoma in pancreatic ductal glands [38].

Microbial dysregulation

Dysregulation of the gut microbiota in obese patients is characterized by an increased proportion of LPS-producing bacteria and a decreased proportion of short-chain fatty acid-producing bacteria, especially butyrate producers and *Bifidobacterium* spp., which have a protective effect on the intestinal barrier [109–112]. Butyrate is a cancer-inhibiting metabolite produced by intestinal bacteria that ferments dietary fiber and has a role in modulating the body's immune function [113]. Dysregulation of the gut microbiota can trigger inflammation and disruption of gut barrier function, leading to LPS leakage, causing metabolic endotoxaemia and exacerbating inflammation [111,114]. Treatment of high-fat diet-induced obese mice with probiotics normalizes LPS levels and ameliorates endotoxaemia [114].

Obesity-induced gut microbial dysbiosis promotes colorectal cancer development by promoting intestinal inflammation [30,115] (Fig. 4). Some gut microbes, such as *Bacteroides fragilis*, produce enterotoxins that cause DNA damage in intestinal cells and promote intestinal inflammation [116,117]. A recent randomized controlled trial demonstrated that lifestyle interventions targeting the gut microbiota (a Mediterranean diet and weight loss) reduced the risk of colorectal cancer in obese patients [118].

Obesity-induced production of substances associated with gut microbes may also increase the risk of liver cancer (Fig. 4) [16,119]. Obesity promotes increased production of lipoteichoic acid, a gut microbial component, and secondary bile acids, a metabolite of Gram-positive bacteria, which enter the liver through the hepato-intestinal circulation, activate cellular senescence-associated secretory phenotypes, and promote secretion of inflammatory factors, contributing to hepatocarcino-

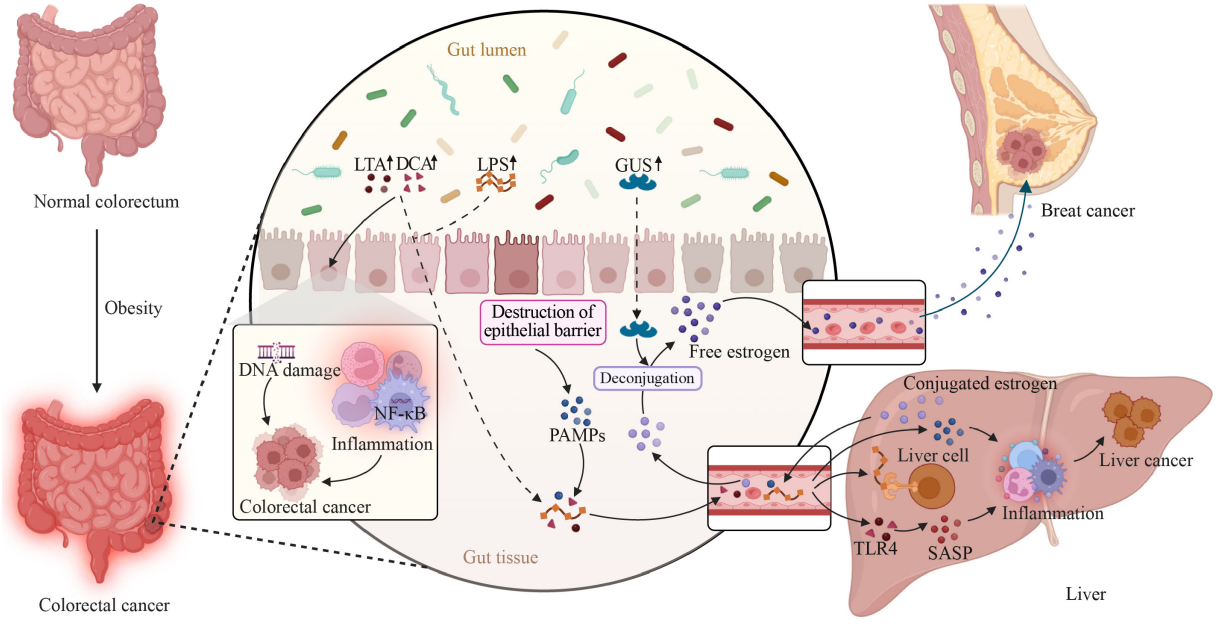

Fig. 4 Mechanisms by which gut microbiota dysbiosis promotes obesity-related carcinogenesis. Obese patients are prone to dysregulation of the gut microbiota environment, which is mainly characterized by increased production of LPS, LTA, DCA, and β-glucuronidase. These substances further cause DNA damage, inflammation, release of PAMPs, and estrogen metabolism, which play a role in the development of different obesity-associated tumors (colorectal, liver, and breast cancers). Abbreviations: LTA, lipoteichoic acid; LPS, lipopolysaccharide; DCA, deoxycholic acid; GUS, β-glucuronidase; PAMPs, pathogen-associated molecular patterns; TLR-4, Toll-like receptor 4; SASP, senescence-associated secretory phenotype. This figure was created based on the tools provided by Biorender.com.

genesis [16,120,121]. On the other hand, endotoxins released by Gram-negative bacteria in the intestinal tract also enter the liver through the hepato-intestinal circulation, exacerbating localized inflammation of the liver in obese organisms and thus promoting carcinogenesis [119,122].

Obesity-induced gut microbial dysbiosis may also cause abnormalities in estrogen levels, indirectly affecting the risk of breast cancer [123] (Fig. 4). Increased production of β-glucuronidase by gut bacteria promotes the deconjugation of bound estrogen to free estrogen in the gut [123,124]. When the level of free estrogen is increased in this way, estrogen reaches the mammary glands via the bloodstream and, as mentioned earlier, has a role in promoting breast cancer.

Dysregulation of adipokine levels

Leptin

Leptin is an important adipokine secreted by adipose tissue and has a role in regulating energy balance in the body [125]. In obesity, leptin gene expression is upregulated, causing an increase in leptin levels, which is associated with the development of obesity-related cancers [31,126,127] (Fig. 5).

Leptin binds to the leptin receptor and activates multiple signaling pathways to promote cell proliferation and inhibit apoptosis, which in turn promotes the development of colon, lung, endometrial, and kidney cancers [19,31,128]. Leptin promotes colorectal cancer development by increasing the PKC/MAPK, JAK/STAT3, and PI3K/AKT/mTOR signaling pathway activity [31]. Endo *et al*. found that the normal colon epithelium of obese mice showed active proliferation, whereas the growth of colon cancer was inhibited in leptin-deficient and leptin-receptor-deficient obese mice; moreover, they found that leptin-induced promotion of cancer growth was also mediated through STAT3 signaling [32]. This finding reflects the important role of leptin in colorectal carcinogenesis [32]. In a high-fat diet-induced obese mouse model, leptin promoted lung carcinogenesis through activation of PI3K/AKT/mTOR/STAT3 [19]. A recent study revealed that obese endometrial cancer patients express high levels of leptin and that this high level of leptin secreted by adipocytes activates the JAK2/STAT3 signaling pathway, which enhances cancer cell activity and promotes cancer growth and progression [129]. In addition, renal precancerous lesions in obese rats were also associated with leptin-induced activation of STAT3 signaling [128].

By affecting estrogen-related metabolic and signaling pathways, leptin may promote breast and prostate carcinogenesis [130–132]. After activation of the PKC/MAPK signaling pathway and downregulation of P53 expression by leptin, the expression of aromatase in mammary tissues is upregulated, thereby promoting estrogen production, which in turn may promote obesity-associated breast cancer development [131–133]. In addition, leptin directly activates ER-α and amplifies estrogen signaling in breast cells, which may promote obesity-associated breast cancer development [131]. Christine *et al*. found that leptin increases ER-α expression and decreases ER-β expression in prostate cancer cells, suggesting that leptin may play a promotional role in prostate carcinogenesis [130].

Adiponectin

Adiponectin is also one of the possible factors by which obesity affects the risk of cancer [134]. Adiponectin is another adipokine secreted by adipose tissue that has a role in maintaining homeostasis in the body [135]. The levels of adiponectin are decreased in obese patients, which may be associated with increased secretion of TNF-α by adipose tissue [136].

Decreased levels of adiponectin may promote the development of obesity-related cancers including colorectal, cervical, liver, and pancreatic cancers. Normally, adiponectin inhibits colorectal cancer cell growth through AMPK/mTOR. In addition, adiponectin inhibits cervical cancer development by altering the expression of the cell cycle regulators cyclin D1 and c-myc [137]. By activating AMPK/JNK/caspase3 and AMPK/TSC2/mTOR, adiponectin also inhibits hepatocarcinogenesis [138]. The role of decreased adiponectin in patients with obesity in increasing risk of pancreatic cancer has been characterized [139,140]. GSK-3β-mediated degradation of β-catenin is promoted in cancer cells in response to lipocalin, while the expression of TCF7L2 (a β-catenin-related transcription factor) is downregulated, resulting in disruption of the transcription of the β-catenin gene, which inhibits pancreatic cancer cell growth [140]. Therefore, obesity-induced decreases in adiponectin levels may increase the risk of these cancers by suppressing the anticancer effects of adiponectin [141] (Fig. 5).

Resistin

Obesity-induced increases in resistin levels in adipose tissue may also be associated with obesity-induced carcinogenesis [142]. Increased adipocyte infiltration in the obese state may result in elevated secretion of resistin [143]. Resistin binds to Toll-like receptor 4 (TLR4) and exerts proinflammatory effects, which may be one of the mechanisms by which obesity promotes cancer [144,145]. In addition, resistin binding to TLR4 increases NF-κB and STAT3 signaling to promote epithelial-to-mesenchymal transition and stemness and thus

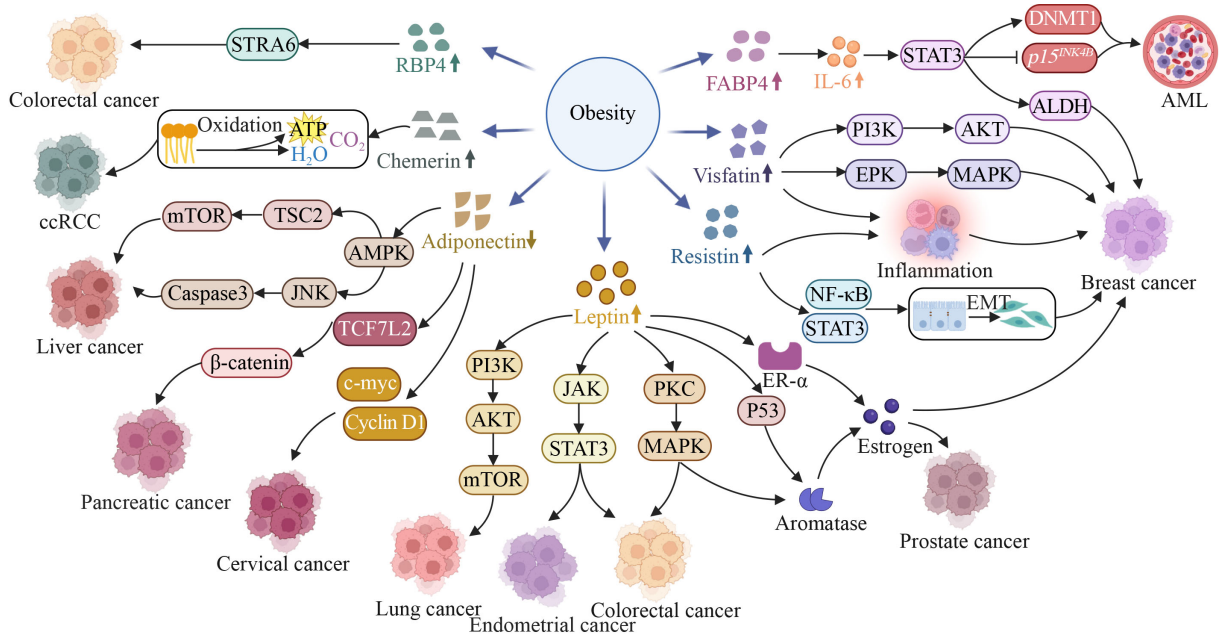

Fig. 5 Mechanisms by which adipokines promote obesity-related carcinogenesis. Obesity promotes the release of adipokines such as leptin, lipocalin, resistin, visfatin, chemerin, RBP4, and FABP4. These adipokines contribute to the development of various cancers (colorectal, clear renal cell, liver, cervical, lung, prostate, and breast cancers as well as ccRCC and AML) by increasing or decreasing cancer-related signaling pathway activity, affecting estrogen metabolism, and promoting inflammation. Abbreviations: FABP4, fatty acid binding protein 4; RBP4, retinol binding protein 4; ER-α, estrogen receptor alpha; EMT, epithelial-mesenchymal transition; ccRCC, clear cell renal cell carcinoma; AML, acute myeloid leukemia. This figure was created based on the tools provided by Biorender.com.

carcinogenesis of breast cancer cells [146]. In a study on a high-fat diet-induced obese mouse model, Gao *et al.* found that increased adipose tissue TAZ expression may promote resistin secretion and further promote breast carcinogenesis [147] (Fig. 5).

Novel adipokines

Chemerin, visfatin, FABP4, and RBP4 are novel adipokines that have been identified in recent years and may also be some of the factors linking obesity and cancer development [148–153]. Chemerin levels are elevated in obesity [149]. Increased chemerin levels inhibit fatty acid oxidation to resist iron death, which in turn promotes the development of clear cell renal cell carcinoma (ccRCC) [149]. Visfatin may be associated with the development of obesity-related breast cancer [150]. *In vitro* cellular experiments revealed that visfatin promotes breast cancer cell proliferation through activation of AKT/PIK3 and ERP/MAPK while inhibiting apoptosis to promote breast carcinogenesis [154]. FABP4 is an adipokine associated with fatty acid metabolism, and its circulating levels are positively correlated with body mass index [153]. Clinical studies have found circulating FABP levels to be elevated in obese breast cancer patients [155]. Circulating FABP4 has a role in promoting the breast cancer stem cell phenotype and cancer development, which is associated with its activation of the IL-6/STAT3/ALDH1 pathway [152,155]. Increased intracellular FABP4 expression activates NF-κB and promotes IL-6 signaling in macrophages, which may play a role in breast carcinogenesis [152]. In addition, FABP4 expression is similarly elevated in obese acute myeloid leukemia (AML) patients [156]. By promoting the expression of IL-6 and phosphorylation of STAT3, FABP4 upregulates the expression of the DNMT1 gene and inhibits the expression of the p15INK4B tumor suppressor to promote AML cell proliferation [156]. RBP4, a transporter protein for vitamin A, may also be implicated in obesity-associated cancer development [151]. In animal experiments, researchers found that RBP4 levels were elevated in colon cancer tissues compared to normal colon tissues [157]. RBP4 was found to mediate colon carcinogenesis through activation of the STRA6 pathway in a high-fat diet-induced obese mouse model [157]. Other previous studies have reached similar conclusions [158,159] (Fig. 5).

Physical stimuli and other biochemical factors

Abdominal pressure

Increased abdominal pressure due to abdominal obesity increases the incidence of gastresophageal reflux, which in turn may be associated with an increased risk of obesity-related esophageal cancer [160]. Obesity-induced

increases in abdominal pressure relax the esophageal sphincter, which can easily lead to the occurrence of gastresophageal reflux [161]. Prolonged irritation of the esophageal mucosa by gastric contents is likely to cause mucosal abnormalities and promote the development of esophageal cancer [160,162].

Interstitial fibrosis

Obesity promotes interstitial fibrosis in breast tissue, which may be an additional mechanism linking obesity to an increased risk of breast cancer [163]. Obesity-induced increases in ECM stiffness were observed to promote mammary epithelial cell carcinogenesis in an obese mouse model [164]. In obese patients, adipose tissue is exposed to a hypoxic environment, which activates fibrosis-related pathways and fibrosis of the adipose tissue ECM [165]. Fibrosis of the ECM also causes local inflammation, which in turn promotes cancer [47].

Lipid accumulation and peroxidation

One mechanism by which obesity increases the risk of clear cell carcinoma may be lipid accumulation and peroxidation [166]. In obesity, circulating fatty acid levels may increase, causing an increase in fatty acid uptake by proximal tubular cells, which in turn causes lipid accumulation in the kidney [166,167]. Accumulation of a large amount of lipids leads to increased lipid β-oxidation and a subsequent increase in local reactive oxygen species production, causing oxidative stress, which in turn induces renal clear cell carcinoma [166].

ACSS2

Obesity-induced increases in acetyl coenzyme A synthase 2 (ACSS2) expression may promote myeloma [168]. ACSS2 is an important regulatory substance in lipid metabolism [169]. In obesity, the secretion of angiotensin II by adipocytes is increased, and adipocytes can promote the expression of ACSS2 in myeloid cells [168]. When the expression of ACSS2 is increased, its binding to interferon regulatory factor 4 (IRF4), which has an inhibitory effect on hematologic malignant cancers, is reduced, thus possibly promoting myeloma development [168].

Potential prevention strategies for obesity-related cancers

Obesity is associated with increased risk of various cancers; thus, it is important to develop cancer prevention strategies for obese patients [6–9]. Obesity interventions are traditional strategies for preventing cancer development, including dietary interventions, increasing physical activity, taking weight loss medications, and bariatric surgery, which have become popular in recent years. In addition, developing preventive strategies that target the links between obesity and carcinogenesis rather than directly alleviate obesity is a potential future direction (Fig. 6).

Diet and physical activity

Dietary interventions, which can include changes in the foods consumed or the timing of meals, are one of the simple and low-cost ways to prevent cancer development in obese patients. Meta-analysis results suggest that *ad libitum* low-fat diets contribute to weight loss [170]. In addition, the risk of pancreatic cancer in overweight and obese women on low-fat diets (reduced fat intake and increased intake of vegetables, fruits, and grains) was significantly reduced by 29% [171]. A prospective cohort study showed a 55% reduction in liver cancer risk in patients consuming a low-fat diet [172]. A low-carbohydrate diet was shown to reduce pancreatic cancer risk by 39% [173]. In addition, a significant negative correlation between the composite dietary antioxidant index and colorectal cancer risk has been reported [174]. An observational meta-analysis by Parohan *et al*. yielded similar results: dietary antioxidant capacity was found to be negatively correlated with the risk of several cancers (composite effect values: 0.82 for colorectal cancer, 0.63 for gastric cancer, and 0.78 for endometrial cancer) [175]. Therefore, foods with high antioxidant activity, such as green tea, ginger, soybeans, tomatoes, and cabbage, which reduce body weight and oxidative stress in obese patients, may be beneficial in reducing the risk of cancer [176]. The Mediterranean diet comprises unprocessed, naturally sourced, and high-fiber foods and has been shown to help reduce cancer risk, which may be related to its ability to ameliorate inflammation and oxidative stress as well as modulate gut microbiota composition [177–181]. Studies have shown that adherence to the Mediterranean diet reduces the risk of lung cancer by approximately 15%, breast cancer by 6%, colorectal cancer by 14%, and prostate cancer by 4% [177,179,182]. Time-restricted eating, proposed in recent years, has been shown to reduce body weight, fat mass, and body mass index, making it one of the new strategies to fight obesity, with a potential role in preventing cancer development [182,183].

Maintaining a certain level of physical activity is another simple and low-cost strategy to prevent the development of obesity and cancer. Routine physical activity reduces the risk of common malignant cancers such as breast, endometrial, colon, and stomach cancers by 10%–20% in obese patients [184,185]. This may be because aerobic exercise normalizes immune metabolism and alleviates chronic inflammation in obese patients

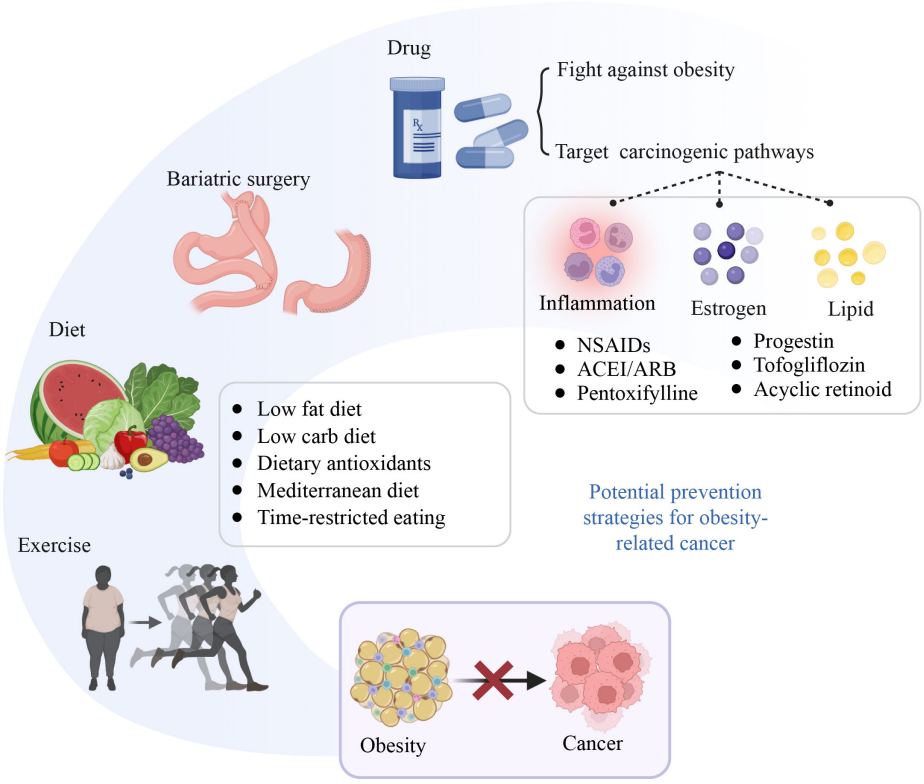

Fig. 6 Potential prevention strategies for obesity-related cancers. Strategies for preventing obesity-related cancers include four broad categories: exercise, dietary interventions, bariatric surgery, and medications. Exercise, dietary interventions, and bariatric surgery focus on reducing the risk of cancer through weight loss. Drugs include weight loss drugs and drugs that target oncogenic pathways. Weight loss drugs also work primarily to reduce body weight. Drugs targeting oncogenic pathways directly target obesity-related oncogenic pathways, and the current main research targets are inflammation, estrogen, and lipids. This figure was created based on the tools provided by Biorender.com.

[186]. In a clinical controlled trial, a physical activity intervention was observed to reduce serum estrogen levels in postmenopausal women, which may be another mechanism by which increased physical activity reduces breast cancer risk [187]. A recent study has shown that exercise testing parameters are significant predictors of the risk of death from noncardiovascular diseases, including cancer, in a primary prevention population [188]. A high exercise heart rate reflects better cardiorespiratory fitness and is a protective factor in terms of the risk of mortality from noncardiovascular diseases (including cancer) [188,189]. Thus, physical activity may play an important interventional and protective role in the development of cancer in patients with obesity.

Bariatric surgery

Bariatric surgery, which has become particularly popular in recent years, is a strategy that indirectly prevents cancer development by treating obesity [190,191]. The results of several clinical studies and meta-analyses have shown that undergoing bariatric surgery is associated with a reduced risk of cancer, particularly malignant cancers of the reproductive system and digestive tract in women [192–198]. Specifically, obese patients who underwent bariatric surgery had a 38% reduction in the risk of overall cancer, a 49% to 62% reduction in the risk of breast cancer, a 53% to 55% reduction in the risk of ovarian cancer, a 60% to 67% reduction in the risk of endometrial cancer, a 40% reduction in the risk of esophageal and gastric cancer, a 48% reduction in the risk of pancreatic cancer, a 65% reduction in the risk of hepatocellular carcinoma, a 59% reduction in the risk of gallbladder cancer and a 19% to 44% reduction in the risk of colorectal cancer [192–198].

Drug treatment

Weight loss medication

Similar to bariatric surgery, taking weight loss medications to reduce weight is also a strategy to prevent the development of obesity-related cancers [199]. Specific weight loss medications include oseltamivir, phentermine, topiramate, naltrexone, and bupropion, which have been shown to be associated with reduced cancer risk in clinical studies [199].

Targeting obesity-related oncogenic pathways

Unlike weight loss drugs, drugs that target obesity-related mechanisms of carcinogenesis rather than directly affecting body weight may be emerging options for preventing carcinogenesis. Although weight loss is the simplest and most direct method for preventing cancer, some obese patients have poor compliance and often have difficulty with long-term adherence to diet and exercise [200]. In addition, the adverse effects of weight loss drugs are also a concern; for example, the reported rate of gastrointestinal-related adverse events for the widely used drug simethicone is 84.1% [201]. Bariatric surgery may also be rejected by some patients due to its invasiveness and high cost. Moreover, weight recurrence may occur after the implementation of weight loss [202,203]. Therefore, targeting obesity-related oncogenic pathway strategies has become an emerging strategy to prevent cancer development in obese patients.

Inhibiting inflammation and modulating oxidative stress

Drugs that inhibit inflammation and modulate oxidative stress include pentoxifylline, ACEIs, ARBs, nonsteroidal anti-inflammatory drugs (NSAIDs), and acyclic retinoids. Pentoxifylline is a drug that improves blood circulation and has been found to exert cancer-preventive effects by inhibiting inflammation in recent years [204–206]. In an obese mouse model, after inducing the development of precancerous colorectal lesions using carcinogens, administration of pentoxifylline was found to reduce TNF-α levels in the colon and inhibit the development of colon carcinogenesis [205]. These results were also confirmed in another animal study [204]. ACEIs/ARBs, widely known drugs for treating high blood pressure, may also be promising drugs for cancer prevention [207]. By reducing inflammation and oxidative stress, captopril and telmisartan significantly reduce colon carcinogenesis in obese mice [207]. NSAIDs exert their anti-inflammatory effects by inhibiting Cox-2, although their reported effect on breast cancer risk varies slightly from study to study [208,209]. Studies have shown that NSAIDs reduce the risk of breast cancer in women and that this relationship does not change according to ER, PR, or HER2 status or breast cancer subtype [209]. However, a recent cohort study based on a Norwegian female population demonstrated that low-dose aspirin use reduced the risk of ER^+ breast cancer in women ⩾ 65 years of age and a body mass index ⩾ 25, while having no effect on ER^- breast cancer risk [208]. In addition, as a nutraceutical, acyclic retinoids have been shown to ameliorate obesity-related inflammation and metabolic disorders and thus have a preventive effect against the development of liver cancer [210,211].

Targeting estrogen

Progesterone/levonorgestrel intrauterine system, a female contraceptive that targets estrogen, may also reduce the risk of endometrial cancer [212]. Clinical trials have shown that a levonorgestrel intrauterine system significantly reduces endometrial cancer risk in grade III obese women [212]. The levonorgestrel intrauterine system releases progesterone to counteract the cancer-promoting effects of estrogen produced as a result of obesity [212].

Reducing lipid levels and inflammation

Tofogliflozin is a common hypoglycaemic agent, and the results of experimental studies suggest that it may also have cancer-preventive properties [213–215]. Tofogliflozin was observed to reduce serum free fatty acid levels in obese mice with precancerous lesions, in turn ameliorating hepatic fat accumulation and thereby preventing hepatocellular carcinoma [214]. In a mouse model of precancerous colorectal lesions, a decreased risk of colorectal cancer was observed in the group administered tofogliflozin, which was associated with its effect on inflammation [213].

Discussion

Obesity causes complex changes in the body and is associated with increased cancer risk. By promoting inflammation formation, hormonal disorders, microbial dysbiosis, abnormal adipokine levels, and other alterations in physical and biochemical factors, obesity influences cancer development at different sites. Diet, exercise, bariatric surgery, and weight loss medications are commonly used to prevent cancer development by reducing body weight. Targeting obesity-associated oncogenic mechanisms, including inflammation, estrogen production, and fat metabolism, is likely efficacious in preventing obesity-associated cancer development. Therefore, exploring the mechanisms linking obesity and cancer risk is important for the development and clinical application of preventive interventions for obesity-related cancers. However, there are still many directions for further research on the mechanisms of and intervention strategies for obesity-related cancers.

Are the cancer-promoting effects of acquired and hereditary obesity distinct?

Obesity can be categorized as hereditary obesity or acquired obesity [216]. Currently, most of the studies on the mechanism by which obesity promotes carcinogenesis are based on high-fat diet-induced obese animal models [19,67,74,114,147]. First, does hereditary obesity affect

cancer development? In a study by Park *et al*., both high-fat diet-induced obesity and leptin-deficient hereditary obesity (spontaneous development of obesity despite consumption of a normal diet) were found to promote diethylnitrosoamine-induced hepatocarcinogenesis in mice [67]. This study demonstrates that the "promoter" of cancer is obesity itself and not the high-fat diet [67]. Pfalzer *et al*. showed that obesity can promote cancer in the absence of a high-fat diet [217]. In addition, in a Mendelian randomization study based on the UKB database cohort, researchers found that genetics-related increases in body weight were associated with a reduced risk of breast and prostate cancer [218]. These studies seem to suggest that similar to acquired obesity, hereditary obesity may also influence the risk of developing cancer. Second, do different dietary interventions, such as low-fat, normal-fat, and high-fat diets, modify the effect of hereditary obesity on cancer risk? Third, are the effects of diet-induced obesity and hereditary obesity on the risk of cancer development synergistic, do they counteract each other, or are they mutually exclusive? Many animal experiments as well as population-based cohort studies are needed to answer these questions. In addition, more and larger population-based cohorts are needed to validate the mechanisms by which obesity affects cancer development.

Does aging affect the cancer-promoting effects of obesity?

It is well known that the risk of many cancers increases with age, and aging seems to play a particularly important role in the increased risk of cancer [219]. Aging promotes reprogramming of the body's metabolism [220] and increased lactate production in the body, making it easier for cancer cells to evade immune surveillance and cause DNA damage [220]. In addition, aging increases the body's basal level of inflammation and promotes immunosuppression, i.e., weakening of innate and adaptive immunity, as evidenced by decreased numbers of NK cells and naïve T cells, depletion of memory T cells, and decreased dendritic cell function [221]. Aging also alters the composition of the gut microbiota, resulting in the production of single-chain fatty acids, thereby impairing anticancer immunity [222,223]. This set of changes results in a reduced ability to fight cancer with aging, which may lead to an increased risk of cancer development. Therefore, we ask the following question: do aging-induced changes in an organism affect the cancer-promoting effects of obesity, and do they enhance, counteract, or attenuate these effects? It is necessary to conduct large-scale epidemiologic studies to explore the relationship between obesity and cancer risk in patients of different ages, as well as animal experiments or cohort studies to further investigate the specific mechanisms involved.

Is there a vicious cycle between worsening obesity, gut microbiota dysbiosis, and cancer promotion?

Currently, the consensus among researchers is that obesity may cause gut microbiota dysbiosis, which in turn promotes cancer [30,115,123]. However, the specific relationship between worsening obesity, gut microbiota dysbiosis, and cancer promotion is unclear and warrants further investigation. Several studies have suggested that dysregulation of the gut microbiota may promote the development of obesity, and the mechanism may involve dysregulation of the gut microbiota to promote the absorption of food and influence the cerebral-gut axis, which in turn regulates appetite and increases food intake, as well as excessive accumulation of fatty acids due to the metabolism of some intestinal flora [224–226]. Currently, there are still numerous questions that have not been fully answered, including (1) whether dysregulation of the gut microbiome in the context of obesity and cancer development may worsen obesity and thus promote cancer progression and (2) whether obesity and gut microbiota dysbiosis are further exacerbated by cancer, which may promote cancer progression, creating a vicious cycle.

The gut microbiota is one of the research hotspots in the field of cancer therapy. Faecal bacteria transplantation is a treatment for dysbiosis [227]. Faecal bacteria transplantation refers to the transplantation of functional flora from the faeces of a healthy person into the intestines of a patient to establish a new gut microbiota and restore intestinal ecology to treat diseases associated with an abnormal gut microbiota composition [227]. Many studies have demonstrated the ability of gut microbes to enhance the clinical response to immune checkpoint inhibitors against cancer, including gastrointestinal cancers, epithelial cancers, and metastatic melanoma [228–232]. In a study conducted by Riquelme *et al*., faecal bacteria transplantation delayed the progression of pancreatic cancer in a mouse model, primarily by altering the cancer-related microbiome and thereby affecting cancer growth, increasing tumor immune cell infiltration, and promoting $CD8^+$ T cell activation and thus the anticancer immune response [233]. Bifidobacteria and *B. fragilis* are common intestinal microorganisms [234,235]. Studies have shown that bifidobacteria primarily promote DC activation, which in turn promotes $CD8^+$ T cell responses [236]. *B. fragilis* induces M1 macrophage polarization, increases macrophage phagocytosis, and upregulates CD80 and CD86 to promote innate immunity [237]. In addition, in a phase 2 clinical trial, researchers found that faecal bacterial transplantation was beneficial in treating obesity by increasing insulin sensitivity and promoting

metabolism in obese patients [238]. This series of findings suggests that faecal bacteria transplantation will hopefully become a new strategy for preventing obesity-related cancers.

Therefore, there is a need to delve into the specific role of the gut microbiota in obesity-associated cancers and whether it can be applied as a therapeutic target. In the future, changes in body weight as well as changes in the gut microbiota of obese mice after cancer development could be observed to explore whether body weight and gut microbiota dysbiosis further increase in mice with cancer. In addition, the gut microbiota of healthy animals could be transplanted into obese animals with precancerous lesions, and whether cancer growth is inhibited could be assessed to determine the role of gut microbiota in obese individuals with precancerous lesions. Metagenomic techniques may also allow exploration of the specific role of each gut microbe in cancer development in obese mice.

In addition to gut microbes, non-gut-related microorganisms are also present in various organs and tissues in normal organisms. In the healthy state, non-gut-related microbes are seen in tissues such as the lungs, pancreas, and mammary glands, and their levels may become abnormal in the obese state [239,240]. Abnormalities in non-gut-related microbe levels have the potential to promote cancer development by creating a proinflammatory environment [240,241]. Researchers observed in a mouse model that microbiota dysbiosis in the lungs induced the formation of a pro-cancer inflammatory environment [241]. When they treated the mice with antibiotics, they observed that the lung tumors in the mice decreased in size or even disappeared [241]. Thus, it remains to be investigated whether abnormalities in non-gut-related microbe levels could be the mechanism linking obesity to the risk of cancer development.

Are there differences in the effect of different intervention strategies in preventing obesity-induced cancers?

Dietary interventions may help to ameliorate obesity or prevent the development of obesity-related cancers [172,175]. As mentioned above, low-fat, low-carbohydrate diets with high antioxidant levels and the Mediterranean diet are beneficial in reducing the risk of obesity-related cancers [171–177,179,182]. However, it is unclear whether the preventive effects of dietary interventions differ for different cancers, whether the type of diets influences its effects on cancer risk depending on the type of cancer, and whether certain diets exert preventive and suppressive effects on only a subset of cancer types.

Drugs that target obesity-related oncogenic pathways also have a potential effect on cancer development [205,242]. Progesterone-based drugs that inhibit the action of estrogen have been shown to prevent endometrial cancer in obese patients, but their preventive effect against other cancers is unknown [242,243]. The inflammation-suppressing drug pentoxifylline has been shown to decrease the risk of obesity-induced colon cancer in animal studies, but it is not clear whether it has a similar effect in obese patients [204,205]. Moreover, in addition to preventing obesity-associated colon cancer, is pentoxifylline associated with the risk of other obesity-associated cancers? Similarly, most of the current research suggests that NSAIDs, which inhibit inflammation, have a stronger preventive effect against breast cancer, but their specific effects on other obesity-related cancers is unclear. Therefore, studies on whether there are differences in the preventive effects of different drugs targeting obesity-related oncogenic pathways against diverse cancers are being performed.

Individual and combined intervention strategies appear to have different effects on the risk of cancer development. In Istfan's retrospective study, bariatric surgery combined with postoperative weight loss drug administration was effective in reducing postoperative weight gain [244]. Using a mouse model of obesity, Hsu *et al*. observed that exercise in combination with probiotics decreased mouse body weight to a greater extent than exercise or probiotics alone [245]. Therefore, whether any combined intervention strategies more strongly reduce cancer risk remains unclear. It would also be interesting to study the effects of different combinations of dietary intervention, exercise, bariatric surgery, and weight loss drugs on the risk of obesity-related cancer development.

Therefore, it is necessary to design further experiments to explore the preventive effects of different intervention strategies on obesity-induced cancer development in the future. For individual strategies such as diets and drugs, specific stratification analyses can also be performed to obtain more precise results. If there are significant differences in the preventive effects of different diets, different drugs, and different combination approaches against different cancers, it may be possible to recommend more effective interventions for obese patients who already have risk factors for a particular cancer. Research on these issues could be instructive in optimizing personalized intervention strategies for obese patients.

With this comprehensive review, we aimed to delineate the intricate connections between obesity and cancer risk, highlighting specific mechanisms and clinical implications. First, this article presents a more comprehensive and systematic review of the mechanisms through which obesity influences cancer risk. For each category of mechanism, the potential mechanisms by which obesity impacts cancer risk across various types of

cancer are described in detail and summarized in a comparative manner. Second, this article systematically summarizes potential interventions for obesity-associated cancers, including direct interventions targeting obesity or related oncogenic pathways. This summary provides a framework for the future development of personalized and diverse interventions for obesity-related cancers. Finally, this article proposes intriguing and significant avenues for future research, such as exploring the roles of hereditary and acquired obesity, aging, and gut microbiota in the development of obesity-associated cancers, as well as investigating the differential effects of various interventions.

However, we acknowledge certain limitations within our scope of discussion that merit attention. First, because there are still many research gaps on the causes and mechanisms of the increased risk of certain cancers due to obesity, especially because of the lack of preclinical experimental studies and clinical evidence, we only summarized the results of the existing experimental and clinical studies, but other mechanisms may exist, so further study is needed. Second, our review provides a mechanistic overview of obesity and cancer risk at the macroscopic level, but our description may not reflect the subtle and complex molecular aspects of these processes, which need to be explored in more detail in the future to fully understand the complex relationship between obesity and cancer risk. Third, our discussion of intervention strategies to reduce obesity-associated cancer risk is based on current clinical practice and the literature, and some intervention strategies are still in experimental animal studies and have not yet been translated into human clinical trials. The effectiveness of implementing these intervention strategies in obese populations still needs to be validated and discussed in many future studies.

Conclusions

In this study, we summarize the specific mechanisms by which obesity affects the risk of different cancers, as well as potential prevention strategies for obesity-related cancers. This review lays a theoretical foundation and provides directions for further research on the mechanism of obesity-related cancers and the development of better, more personalized, and more precise intervention strategies for obese patients in the future, greatly contributing to reducing the incidence of obesity-related cancers.

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Compliance with ethics guidelines

Xiaoye Shi, Aimin Jiang, Zhengang Qiu, Anqi Lin, Zaoqu Liu, Lingxuan Zhu, Weiming Mou, Quan Cheng, Jian Zhang, Kai Miao, and Peng Luo declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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