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A weighty problem: metabolic perturbations and the obesity-cancer link

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Abstract

Obesity is an established risk factor for several cancers, including breast, colon, endometrial, ovarian, gastric, pancreatic and liver, and is increasingly a public health concern. Obese cancer patients often have poorer prognoses, reduced response to standard treatments, and are more likely to develop metastatic disease than normo-weight individuals. Many of the pathologic features of obesity promote tumor growth, such as metabolic perturbations, hormonal and growth factor imbalances, and chronic inflammation. Although obesity exacerbates tumor development, the interconnected relationship between the two conditions presents opportunities for new treatment approaches, some of which may be more successful in obese cohorts. Here, we discuss the many ways in which excess adiposity can impact cancer development and progression and address potential preventive and therapeutic strategies to reduce the burden of obesity-related cancers.

Keywords

adipose tissue; cancer; inflammation; obesity; risk factors

Introduction

In the past three decades, the prevalence of obesity has dramatically increased, with nearly 40% of adults and 20% of children in the USA currently classified as obese, defined as a body mass index (BMI) of ≥ 30 kg/m² [1]. It is estimated that more than 600 million adults are obese and 2.1 billion are overweight worldwide [2]. Aside from biophysical problems such as overexertion of cardiovascular, skeletal, muscular, and respiratory systems, obesity poses as a major risk factor for a plethora of diseases and comorbidities [3], including type II diabetes, cardiovascular disease, hypertension, chronic inflammation, and, the focus of this review, cancer.

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In the USA, obesity has surpassed tobacco use as the leading preventable cause of cancer. Obese individuals are at a higher risk of developing a number of different cancers including breast (post-menopausal), ovarian, liver, colon, pancreatic, gastric, and endometrial [4]. More than 40,000 new cancer diagnoses in the USA each year are attributed to obesity, and obesity is implicated in ~20% of all cancer-related mortalities [5]. In addition to a higher cancer risk, obese individuals are also more likely to have a poorer cancer prognosis, to develop metastases, and have a reduced response to anti-cancer therapies [6]. These statistics make the obesity-cancer link a major public health concern and highlight the necessity for new strategies to prevent and treat obesity-related cancers. Here we characterize the mechanisms by which adiposity can influence normal tissue homeostasis, cancer development and progression, including metabolic perturbations, hormonal and inflammatory alterations, and interactions with the vasculature. We will also highlight potential cancer prevention and treatment strategies for obese individuals.

Metabolic syndrome

Obesity is intrinsically linked with metabolic syndrome, characterized by insulin resistance, hyperglycemia, hypertension, and dyslipidemia. In both obesity and metabolic syndrome, alterations occur in circulating levels of insulin and insulin-like growth factor (IGF-1), adipokines (e.g. leptin, adiponectin, monocyte chemotactic factor), inflammatory factors, and vascular-associated factors (e.g. vascular endothelial growth factor [VEGF], plasminogen activator inhibitor [PAI] 1) [7, 8], all of which have known roles in the development and progression of cancer, as well as a number of other chronic diseases [7, 8] including cardiovascular disease and type II diabetes.

A major hallmark of cancer is metabolic reprogramming to facilitate proliferation [9]. Specifically, cancer cells preferentially metabolize through glycolysis rather than oxidative phosphorylation, even in the presence of O₂ [9-11]. Citric acid cycle intermediates are thus not used for ATP production and are shuttled out of the mitochondria, providing precursors for nucleotide, amino acid, and lipid synthesis pathways for the dividing cell [11]. In this way, cancer cells readily take up and metabolize glucose to provide substrate for daughter cell production, with glucose transporters and glycolytic enzymes (e.g. hexokinase II) being elevated in most cancers [12]. Insulin resistance and hyperglycemia resulting from obesity and metabolic syndrome are therefore key risk factors for development of cancer and are tumor promoting once a cancer has been established. Pre-clinical and early-phase clinical studies show that metformin, an anti-diabetes drug that regulates blood glucose levels, may be an effective anti-cancer drug in a wide variety of cancers, including breast [13], pancreatic [14, 15], and liver, and inhibits obesity-driven pancreatic [14] and ovarian cancers [16] in mouse models.

Not all obese individuals develop metabolic dysregulation, and these “metabolically healthy obese” individuals apparently do not have elevated cancer risk, at least initially. Some 30% of obese individuals in the USA are metabolically healthy [17, 18]. Conversely, some non-obese individuals can develop metabolic perturbations usually associated with obesity and are generally more prone to chronic diseases, including cancer. This suggests that is not

necessarily dietary components or increased adiposity per se, but instead, the obesity-related metabolic changes that are at the crux of the relationship between obesity and cancer.

Adipose tissue

White adipose tissue (WAT) is composed mainly of adipocytes, which serve to store neutralized triacylglycerides for use during low energy levels. This is in contrast to brown adipose tissue, which generates body heat, particularly in neonate infants [19]. Also contained in WAT are a number of stromal cells, including pre-adipocytes, vascular cells, fibroblasts, and a host of immune cells such as adipose tissue macrophages (ATMs) [20]. While the main function of WAT is storage of energy, it is also recognized as a major endocrine organ, producing a number of hormones, adipokines, and cytokines, including estrogen, resistin, leptin, adiponectin, and tumor necrosis factor α (TNF- α), which enter the circulation and interact with distal tissues and organs [21, 22].

Stored triacylglycerides undergo lipolysis within the cytoplasm of adipocytes and are released into the bloodstream as free fatty acids during times of low substrate availability or heightened energy requirements [23]. Once in the circulation, free fatty acids can then be used for β -oxidation by peripheral tissues to provide intermediates for both the citric acid cycle and the oxidative phosphorylation to generate energy. In a diseased state such as metabolic syndrome or type II diabetes, WAT does not respond appropriately to energy requirement changes, resulting in altered metabolic signaling characterized by elevated adipokine and cytokine production [24]. Cancer cells undergo a massive metabolic reprogramming in order to adapt to changing energy needs and to fuel proliferation [9, 11]. In particular, there is a high demand for fatty acids for the formation of lipid bilayers in dividing cells. Excess WAT therefore promotes tumor cell proliferation through the provision of circulating fatty acids [25].

In obese individuals, excess energy consumption results in increased adipocyte size (hypertrophy) and enhanced adipocyte proliferation (hyperplasia). Adipocyte hypertrophy strongly correlates with both insulin resistance and secretion of pro-inflammatory cytokines, such as interleukin (IL) 6 and TNF- α [26]. Release of inflammatory mediators and insulin resistance in obese patients can have drastic effects on peripheral tissue function and can even lead to tissue atrophy, particularly in skeletal muscle [27]. Moreover, WAT distribution also determines risk for metabolic diseases. Increased visceral WAT (adipocytes surrounding internal organs) is positively associated with insulin resistance, likely due to a highly active metabolism, releasing more free fatty acids into the bloodstream than other adipose depots [28]. Distinct from visceral WAT, subcutaneous WAT does not appear to pose such a high risk for chronic disease and can in some contexts be protective, in particular by reducing visceral WAT deposits. Reduction of subcutaneous WAT either surgically or via liposuction provides no metabolic benefit, while visceral WAT removal results in improved sensitivity to insulin, reduced blood glucose, and decreased pro-inflammatory mediators [29]. Therefore, body fat distribution should be considered when determining cancer risk and treatment in obese individuals.

When lipid storage capacity in adipose tissue is exceeded, surplus lipids often accumulate within muscle, liver, and pancreatic tissue [30]. As a consequence, hepatic and pancreatic steatosis (PS) can develop; both have been positively associated with insulin resistance and ultimately lead to impairment of lipid processing and clearance within these tissues [30]. As a result of lipotoxic and inflammation-mediated adipocyte dysfunction, the liver and pancreas are unable to cope with the overflow of lipids and lipotoxic effects of free fatty acids [31]. Consequently, lipid intermediates impair function of cellular organelles and cause release of cytokines, which foster insulin resistance by activating intracellular kinases, thus impairing the cell's ability to respond to insulin. Pancreatic adipocyte infiltration and fat accumulation appears to be an early event in obesity-associated pancreatic endocrine dysfunction and can trigger PS, non-alcoholic fatty pancreatic disease (NAFPD), and pancreatitis [32, 33]. In addition, "fatty pancreas" has been positively associated with visceral WAT mass and systemic insulin resistance [32, 33]. Together, PS and NAFPD contribute to the already complex metabolic and inflammatory perturbations associated with obesity and metabolic syndrome, and obesity-associated pancreatic lipid infiltration is a risk factor for pre-cancerous pancreatic lesions [34].

Insulin and IGF-1

Insulin, a peptide hormone produced by pancreatic β -cells, is released in response to elevated blood glucose. Hyperglycemia is a hallmark of metabolic syndrome and is associated with insulin resistance, aberrant glucose metabolism, chronic inflammation, and the production of other metabolic hormones such as IGF-1, leptin, and adiponectin [35]. IGF-1 is a peptide growth factor produced primarily by the liver following stimulation by growth hormone (GH). IGF-1 regulates growth and development of many tissues, particularly during embryonic development [36]. IGF-1 in circulation is typically bound to IGF binding proteins (IGFBPs), which regulate the amount of free IGF-1 bioavailable to bind to the IGF-1 receptor (IGF-1R) to induce growth or survival signaling [37]. In metabolic syndrome, the amount of bioavailable IGF-1 increases via hyperglycemia-induced suppression of IGFBP synthesis and/or hyperinsulinemia-induced promotion of hepatic GH receptor expression and IGF-1 synthesis [35]. Elevated circulating IGF-1 is an established risk factor for many cancer types [37].

Downstream of both the insulin receptor and the IGF-R, is the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, one of the most commonly altered pathways in epithelial cancers [38]. This pathway integrates intracellular and environmental cues, such as growth factor concentrations and nutrient availability, to regulate cellular survival, proliferation, protein translation, and metabolism. Activation of receptor tyrosine kinases, such as the insulin receptor or IGF-1R, stimulates PI3K to produce lipid messengers that facilitate activation of the Akt cascade [38]. Akt regulates the mammalian target of rapamycin (mTOR) [39], which regulates cell growth, cell proliferation, and survival through downstream mediators. mTOR activation is inhibited by increased AMP-activated kinase (AMPK) under low-nutrient conditions [40]. Increased activation of mTOR is common in tumors and many normal tissues from obese and/or diabetic mice [41], and specific mTOR inhibitors block the tumor-enhancing effects of obesity in mouse models [14, 42, 43]. Furthermore, both rapamycin (mTORC1 inhibitor) and metformin (AMPK activator) have been shown to block tumor

formation in multiple animal models [44-48]. Interestingly, in some model systems, rapamycin has also been shown to block inflammation associated with tumor formation [49].

Adipokines

Leptin, a peptide hormone produced by adipocytes, is positively correlated with adipose storage and nutritional status and functions as an energy sensor. Leptin release from adipocytes signals to the brain to reduce appetite. In an obese state, WAT overproduces leptin, and the brain becomes desensitized to the signal [50]. Leptin release is stimulated by a number of hormones and signaling factors, including insulin, glucocorticoids, TNF- α , and estrogen [51]. Leptin directly interacts with peripheral tissues, indirectly interacts with hypothalamic pathways, and modulates immune function, cytokine production, angiogenesis, carcinogenesis, and many other biological processes [51]. The leptin receptor is structurally and functionally similar to class I cytokine receptors, including their ability to signal through the signal transducer and activator of transcription (STAT) family of transcription factors. STATs induce transcription programs for a number of cellular processes, including cell growth, proliferation, survival, migration, and differentiation, and their activity is commonly deregulated in cancer [52].

Adiponectin is the most abundant hormone secreted from WAT. In contrast with leptin, levels of adiponectin correlate negatively with adiposity. Adiponectin functions to counter the metabolic alterations associated with obesity and hyperleptinemia through modulation of glucose metabolism, increasing fatty acid oxidation and insulin sensitivity [53], and reducing IGF-1/mTOR signaling through AMPK activation. Adiponectin can also reduce pro-inflammatory cytokine expression and induce anti-inflammatory cytokine expression via inhibition of the nuclear factor κ light-chain enhancer of B cells (NF- κ B) [54]. Owing to the anti-tumorigenic function of adiponectin, drugs mimicking its action are now coming to the fore as anti-cancer drugs and may pave the way in helping to treat obesity-related cancers [55]. While leptin levels correlate with poor cancer prognosis and adiponectin levels correlate with favorable prognosis, it is the ratio of these two adipokines that may be important for cancer, rather than their absolute individual concentrations [56].

Sex hormones

Abnormalities in sex hormone levels have long been associated with obesity [57]. BMI positively correlates with estrone, estradiol, and free estradiol in post-menopausal women [58]. Increased estrogens are also observed in obese men [57, 59], while testosterone is significantly decreased [60]. Changes in sex hormones can have profound effects on the body including menstrual disturbances, hirsutism, hypertension, erectile dysfunction, gynecomastia, and increased adiposity [57]. Moreover, high estrogen levels bear a significant risk of breast [57, 58, 61], ovarian [62], and endometrial cancers [63].

In pre-menopausal women, estrogen is mainly synthesized in the ovaries, whereas in post-menopausal women, endogenous estrogen is produced at peripheral sites. In obese post-menopausal women, adipose tissue is the main source of estrogen biosynthesis [58]. Circulating estrogens bind to either of the cytoplasmic estrogen receptors, ER- α and ER- β ,

resulting in receptor dimerization and recruitment to the nucleus. ER- α and ER- β can bind directly to DNA or to other transcription factors to induce expression of genes involved in a variety of cellular processes including growth, proliferation, and differentiation [64]. The two receptors have opposing roles in cancer, with ER- α being mitogenic and ER- β being tumor suppressive [65]. Obese post-menopausal cohorts are more consistently associated with increased risk of receptor-positive than receptor-negative breast cancers [66]. The increase in circulating estrogens and a greater risk of ER-positive breast cancer in obese women has led to a number of trials investigating the effectiveness of adjuvant therapy with aromatase inhibitors and estrogen-receptor antagonists (e.g. tamoxifen) in obese breast cancer patients [67]. Obesity also plays a significant role in development of male breast cancer, as aromatase in adipocytes converts androgens to estrogens. More than 90% of male breast cancer is ER-positive and tamoxifen is part of the standard care [68].

Inflammation

A major feature of both obesity and metabolic syndrome is a state of chronic inflammation, heightened by increased circulating free fatty acids and recruitment of immune cells, in particular macrophages [69-71]. These effects are further amplified by the release of inflammatory cytokines from adipocytes including IL-1 β , IL-6, TNF- α , and monocyte chemoattractant protein 1 (MCP-1) [72]. Adipocytes can swell past the point of effective oxygen diffusion, resulting in hypoxia and eventually necrosis. Free fatty acids leak from the engorged/necrotic adipocytes and migrate to other tissues, impairing their function and promoting inflammation, insulin resistance and diabetes [73], hypertension [74], and fatty liver disease. They also activate signaling molecules involved in epithelial carcinogenesis, such as NF- κ B [75]. NF- κ B is a major transcription factor that is activated in response to bacterial and viral stimuli, growth factors, and inflammatory molecules (e.g. TNF- α , IL-6, IL-1 β) and is responsible for inducing gene expression associated with a vast array of cellular functions including cell proliferation, apoptosis, inflammation, metastasis, and angiogenesis [76]. Activation of NF- κ B is a common characteristic of many tumors and is associated with insulin resistance and elevated circulating levels of leptin and insulin [77, 78].

Chronic inflammation has long been associated with cancer, at least since Rudolph Virchow first observed leukocytic infiltrations in neoplastic tissues [79]. Inflammation is now regarded as a key hallmark of cancer cells [9], with growing evidence continuing to show that chronic inflammation is a major risk factor for many cancers [80-82]. The progression of a number of cancers from preceding inflammatory lesions is well established, including gastritis leading to gastric cancer [83], inflammatory bowel disease (IBD) leading to colon cancer [84], pancreatitis leading to pancreatic cancer [85], and hepatitis leading to liver cancer [86]. Obesity is associated with each of these diseases, and the chronic inflammation seen in obesity is likely a contributing factor in their development. Early detection and management of these preceding inflammatory lesions via lifestyle changes or pharmaceutical interventions such as non-steroidal anti-inflammatory drugs (NSAIDs) or certain phytochemicals may prevent the progression to neoplastic disease [87].

The tumor microenvironment is the main mediator of local, tumor-associated inflammation and contains fibroblasts, mast cells, and a variety of immune cells [88, 89]. Of note, tumors are infiltrated by tumor-associated macrophages, which are activated and circulate in the blood in an obese state, maintaining an inflammatory state within the tumor microenvironment through NF- κ B-dependent cytokine production and angiogenic mediators [90]. Cyclooxygenase 2 (COX-2) is another key cancer-related inflammatory mediator, which catalyzes the synthesis of the potent inflammatory lipid metabolite, prostaglandin E₂ [91]. COX-2 is upregulated in most tumors, and its over-expression is an indicator of poor prognosis in multiple cancer types [92]. COX-2 activation is also involved in obesity-associated inflammation, contributing to the development of insulin resistance and fatty liver in obese rats [93, 94]. A wealth of evidence shows that use of NSAIDs such as aspirin and ibuprofen, which inhibit COX-2 and COX-1, can prevent the development of or improve prognosis of many cancers, including breast, colon, gastric, and pancreatic, highlighting the role of inflammation in these diseases.

While some malignancies progress from pre-existing inflammatory lesions, others develop prior to the inflammatory microenvironment [81]. Cancers can therefore be initiated or exacerbated by inflammation, and inflammatory mediators may be a cause and/or consequence of cancer [81, 82]. Whether cause or effect, the inflammatory microenvironment exerts tumor-promoting effects, with deregulated inflammatory pathways driving cell proliferation, survival, angiogenesis, and metastasis associated with cancer [80, 82, 95].

Liver disease

In Western populations, obesity is the most common cause of non-alcoholic fatty liver disease (NAFLD), a spectrum of diseases including variable degrees of simple steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis [96]. Simple steatosis is benign, whereas NASH is characterized by hepatocyte injury, inflammation, and/ or fibrosis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma [97]. NAFLD is diagnosed when liver fat content is >5%–10% by weight in the absence of alcohol use or other liver disease [98]. Eighty percent of cryptogenic cirrhosis cases present with NASH, and 0.5% of these patients will progress to hepatocellular carcinoma, a figure that increases significantly with hepatitis C-associated cirrhosis [99]. NAFLD is one of the most common chronic diseases [100, 101], with the incidence in both adults and children rising rapidly [101, 102]. Furthermore, prevalence of fatty liver disease has increased concomitantly with the increase in childhood obesity over the past 30 years [102]. NAFLD is a multifactorial disorder linked to hypertriglyceridemia, obesity, and insulin resistance, similar to patients with metabolic syndrome [98]. Ultimately, hepatic steatosis leads to impairment of lipid processing and clearance in the liver. Lipotoxic and inflammation-mediated mechanisms have been suggested to be responsible for adipocyte dysfunction and remodeling of peripheral lipid storage capacities, resulting in release of free fatty acids and increased hepatic lipid burden [103]. In NAFLD, the liver is overwhelmed with excess lipids. The lipotoxic effects of free fatty acids and lipid intermediates impair function of liver cell organelles by mechanisms that involve production of reactive oxygen species, endoplasmic reticular stress, activation of pro-inflammatory programs, and eventually death of hepatic cells [104]. The accumulation

of toxic lipids and release of pro-inflammatory cytokines cause insulin resistance by activating JNK, PKC, and other kinases, thereby impairing insulin signaling [105]. Disturbed insulin signaling contributes to diminished fatty acid oxidation and assembly and secretion of very-low-density lipids through inadequate regulation of peroxisome proliferator-activated receptor (PPAR- α and PPAR- γ) [106]. Activation of cellular defense programs, specifically activation of NF- κ B, is an important determinant for disease progression from steatosis to NASH [107]. Although those at risk of hepatocellular carcinoma currently form a small cohort, this cohort will become a more significant public health concern as the prevalence of obesity and type II diabetes continues to rise.

Angiogenesis

As adipose tissue grows, so does the need for new blood vessels. Angiogenesis is the outgrowth of new blood vessels from existing blood vessels. It is mediated by factors such as VEGF, which can be produced and secreted by both adipocytes and tumor cells. VEGF is angiogenic and mitogenic and has vascular permeability-enhancing activities specific for endothelial cells [108]. Circulating levels of VEGF are increased in obese individuals, and expression of VEGF is associated with poor prognosis in several obesity-related cancers [109]. While secretion of angiogenic factors induces local blood vessel development through interactions with proximal endothelial cells, VEGF released into the circulation can interact with peripheral tissues and may also facilitate angiogenesis at tumor sites. In addition to providing adequate oxygen and nutrients to cells within the primary tumor mass, newly forming blood vessels presumably provide a route into the circulation for cells, which will metastasize to distal sites in the body. Excess VEGF may complicate treatment options for obese patients, as anti-VEGF therapies (e.g. bevacizumab) have reduced efficacy in obese colon cancer patients compared to non-obese individuals [110]. Another angiogenic factor, PAI-1 is a serine protease inhibitor produced by endothelial cells, stromal cells, and adipocytes in visceral WAT [111]. Increased circulating PAI-1 levels, frequently found in obese subjects, are associated with increased risk of atherosclerosis and cardiovascular disease, diabetes, and several cancers [111]. PAI-1, through its inhibition of plasminogen activators, regulates fibrinolysis and integrity of the extracellular matrix [112]. Remodeling of the extracellular matrix is a key feature of invasive cancers and is involved in the development of metastatic disease [113]. Therefore, PAI-1 is a potential anti-angiogenic target in some obese populations. However, caution should also be taken when administering such treatments in obese patients, as the application of an anti-angiogenic therapy will induce hypoxia in the primary tumor and may encourage cells to metastasize, already a concern in obese patients.

Microbiome

An emerging field of research is the influence of the microbiome, the community of commensal, symbiotic, and pathogenic microorganisms that inhabit an individual, on adiposopathy and related chronic diseases. In both humans and mice, two divisions of bacteria, the *Bacteroidetes* and *Firmicutes*, represent >90% of all phylogenetic types in the gut, although there are large differences between individuals at the species level [114]. The relative ratio of these two divisions is significantly altered with obesity, with decreased

Bacteroidetes and a corresponding increase in *Firmicutes*, resulting in a microbiome with an enhanced ability to harvest dietary energy. This increased metabolic potential is transmissible between subjects, such that colonization of a germ-free mouse with the microbiota of an obese (vs. lean) mouse leads to significantly greater fat mass gain, independent of calorie consumption [115]. Obesity is also associated with an overall reduction in gut bacterial diversity [116], and decreased bacterial richness has been linked to elevated systemic inflammation, measured by plasma C-reactive protein (CRP) and white blood cell counts [117]. Furthermore, weight loss does not significantly improve CRP levels in obese subjects with low microbiome richness [118], suggesting that resistance to the inflammation-reducing effects of weight loss may be mediated by differences in microbiome richness. Others have demonstrated that high-fat feeding is accompanied by impairments in gut barrier function, including decreased gene expression for tight junction proteins and higher plasma levels of lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria [119]. LPS has previously been shown to induce metabolic endotoxemia, characterized in part by elevated ATM infiltration and pro-inflammatory cytokine expression [120]. Increased systemic inflammation is also apparent in high-fat fed mice, and these diet effects can be completely prevented by treatment with a broad-spectrum antibiotic [119]. Therefore, gut microbial dysbiosis and impaired barrier function associated with obesity can induce chronic systemic and adipose tissue inflammation. Given the known role this type of inflammation plays in the progression of many cancers [121], it is highly probable that obesity-induced perturbations of the gut microbiota are a contributing factor in the obesity-cancer link.

Concluding remarks

Obesity is fast becoming the leading preventable cause of cancer, impacting almost all facets of cancer biology. Poorer prognosis, reduced response to anti-cancer therapy, and increased metastasis all contribute to the high mortality rates observed in obese cancer populations. However, the multitudinous ways in which obesity impacts cancer development and progression (illustrated in Figure 1) present as opportunities for intervention and prevention. An obvious treatment strategy to break the obesity-cancer link and to prevent NAFLD is obesity reversal, although the proportion of visceral/subcutaneous WAT should be considered to ensure benefit from weight loss. Furthermore, dietary composition can impact whether adipose tissue reduction is of any benefit to the cancer patient, as low-fat/high-carbohydrate diets are likely to provide cancer cells with adequate glucose and promote systemic inflammation. In this way, high-fat/low-carbohydrate diets have proved fruitful both in obesity reversal and in inhibiting the growth of some cancers [122-126]. Altered hormonal and growth factor balance may make obese individuals more responsive to anti-cancer therapies targeting these factors than non-obese subjects. Furthermore, given that obesity drives chronic inflammation and alters microbiome composition, modulation of these factors may be key in treating obese cancer patients.

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Figure 1.

Obesity directly impacts a multitude of systems that are involved in tumor development and progression. Obesity causes many metabolic disturbances including excess blood glucose, insulin, and lipid levels, which can provide fuel and molecular precursors for synthetic pathways in proliferating tumor cells, and obesity is strongly correlated to insulin resistance. Excess adipose tissue can result in fatty acid deposits in both the liver and pancreas, causing NAFLD and NAFPD, both of which are significant risk factors for hepatocellular carcinoma and pancreatic cancer, respectively. Excess adipose tissue alters production of many hormones including increased levels of leptin, insulin, and estrogen, all of which can promote cancer development and decreased adiponectin, which is tumor suppressive. Obesity results in increased IGF-1, a major tumor promoter, activating a broad spectrum of intracellular signals associated with cancer cell growth, proliferation, survival, and migration. VEGF and PAI-1, key angiogenic factors, are also increased in the obese state. As in metabolic syndrome, obesity is characterized by a chronic, low level of inflammation,

both locally (as macrophages recruited to necrotic adipocytes) and systemically (as dying adipocytes releasing free fatty acids and immune modulators such as TNF- α , IL-6, and MCP-1 into the circulation). Fatty acid deposits and an inflammatory microenvironment can cause several inflammatory lesions such as pancreatitis, gastritis, hepatitis, and IBD that lead to cancer development. A chronic state of inflammation will also promote tumor progression in cancers driven by other mechanisms. Obesity is linked with alterations in the intestinal microbiome, decreasing bacterial diversity, impairing gut barrier function, and increasing local inflammation.