Obesity and Cancer Risk: Emerging biological mechanisms and perspectives

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Abstract

Continuously rising trends in obesity-related malignancies render this disease spectrum a public health priority. Worldwide, the burden of cancer attributable to obesity, expressed as population attributable fraction, is 11.9% in men and 13.1% in women. There is convincing evidence that excess body weight is associated with an increased risk for cancer of at least 13 anatomic sites, including endometrial, esophageal, renal and pancreatic adenocarcinomas; hepatocellular carcinoma; gastric cardia cancer; meningioma; multiple myeloma; colorectal, postmenopausal breast, ovarian, gallbladder and thyroid cancers. We first synopsize current epidemiologic evidence; the obesity paradox in cancer risk and mortality; the role of weight gain and weight loss in the modulation of cancer risk; reliable somatometric indicators for obesity and cancer research; and gender differences in obesity related cancers. We critically summarize emerging biological mechanisms linking obesity to cancer encompassing insulin resistance and abnormalities of the IGF-I system and signaling; sex hormones biosynthesis and pathway; subclinical chronic low-grade inflammation and oxidative stress; alterations in adipokine pathophysiology; factors deriving from ectopic fat deposition; microenvironment and cellular perturbations including vascular perturbations, epithelial-mesenchymal transition, endoplasmic reticulum stress and migrating adipose progenitor cells; disruption of circadian rhythms; dietary nutrients; factors with potential significance such as the altered intestinal microbiome; and mechanic factors in obesity and cancer. Future perspectives regarding prevention, diagnosis and therapeutics are discussed. The aim of this review is to investigate how the interplay of these main potential mechanisms and risk factors, exerts their effects on target tissues provoking them to acquire a cancerous phenotype.

Key words: Adipokine; Adiponectin; Biomarker; Cancer; Inflammation; Microbiome; Obesity; Resistin; Visfatin

List of abbreviations

Akt: v-Akt murine thymoma viral oncogene homolog; AMPK: 5' AMP-activated protein kinase; APC: Adenomatous Polyposis Coli; BC: breast cancer; BMI: body mass index; CAA: Cancer-Associated Adipocyte; COX: Cyclooxygenase; CRC: Colorectal Cancer; CRP: C-Reactive Protein; CVD: Cardiovascular Disease; DCA: Deoxycholic Acid; DM: diabetes mellitus; DNA: Deoxyribonucleic Acid; EC: Endometrial Cancer; EHBCCG: Endogenous Hormones and Breast Cancer Collaborative Group; EMT: Epithelial-Mesenchymal Transition; EPIC: European Prospective Investigation into Cancer and Nutrition; ER: endoplasmic reticulum; ERK 1/2: extracellular signal-regulated kinase 1/ 2; FFA: Free Fatty Acid; GERD: Gastro-Esophageal Reflux; GLP: Glucagon Like Peptide; GSK3: Glycogen synthase kinase-3; HCC: Hepatocellular Cancer; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; HRT: Hormone Replacement Therapy; hsCRP: high sensitivity C-Reactive Protein; IARC: International Agency for Research on Cancer; IL: Interleukin; IGF: insulin-like growth factor; IGFBP: Insulin-like growth factor-binding protein; IR: Insulin Resistance; LES: Lower Esophageal Sphincter; LPS: Lipopolysaccharide; LTB-4: Leukotriene B4; MAPK: mitogen-activated protein kinase; MSC: Mesenchymal Cell; Mets: Metabolic Syndrome; MHO: Metabolically Healthy Obesity; MMP: matrix metalloproteinase; MRI: Magnetic Resonance Imaging; mTOR: mammalian target of rapamycin; MUO: Metabolically Unhealthy Obesity; NAFLD: Non-alcoholic Fatty Liver Disease; Nampt: Nicotinamide phosphoribosyltransferase; NASH: Non-Alcoholic SteatoHepatitis; NF-κB: nuclear factor-κB; NHANES: National Health and Nutrition Examination Survey; NLR: Nucleotide Oligomerization Domain-line Receptor; NSAIDs: Non-steroidal anti-inflammatory drugs; NSCLC: Non-Small Cell Lung Cancer; PAF: Population Attributable Fraction; PAK1: p21-activated kinase 1; PI3K: phosphatidylinositol 3-kinase; PPAR: Peroxisome Proliferator-Activated Receptors; PR: progesterone receptor; RCT: Randomized Controlled Trial; RNA: Ribonucleic

acid; ROS: Reactive oxygene species; SAT: Subcutaneous Adipose Tissue; STAT: Signal Transducer and Activator of Transcription; TLR: Toll-like receptor; TNF-α: tumor necrosis factor-α; Treg: Regulatory T cell; TZD: thiazolidinediones; VAT: Visceral Adipose Tissue; VEGF: vascular endothelial growth factor; WAT: White Adipose Tissue; WC: Waist Circumference; WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research; WHR: Waist-to-Hip Ratio

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1. Introduction

Cancer constitutes the second leading cause of death worldwide, with an estimated 14.1 million incident cases and 8.2 million deaths annually [1, 2]. Besides the well-established cancer risk factors such as genetic predisposition, ionizing radiation, tobacco use, infections, unhealthy diet, alcohol consumption, sedentary lifestyle and other environmental exposures, obesity is an established risk factor for several malignancies [3-5]. Cancer incidence will continue to grow due to the increase in the prevalence of risk factors, mainly obesity and metabolic syndrome (Mets) [6].

The prevalence of overweight and obesity has been expanded dramatically in almost all developing and developed countries, reaching pandemic levels of 60-70% of the adult population in industrialized countries, and being more frequent in females and in urban areas [7, 8]. The global prevalence of overweight and obesity has increased by 27% in adulthood and 47% in childhood during the last decades [9]. Obesity develops when exceeding energy consumption overtakes energy expenditure from metabolic and physical activity. As a consequence of excessive or abnormal fat tissue accumulation which exceeds genetically and epigenetically determined adipose tissue stores, fat gets deposited and accumulates as ectopic fat tissue leading to increased risk for many disease entities. Overweight and obesity are generally currently defined as a Body Mass Index (BMI) between 25-29.9 kg/m^2 and over 30 kg/m^2 respectively [10].

Obesity represents a risk factor for many chronic disease, most notably hypertension, dyslipidemia, Mets, diabetes mellitus (DM) type 2, cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), Alzheimer's disease including cancer [11, 12]. In the USA, overweight and obesity may cause 14% of cancer deaths in men and 20% in women [13]. Overweight/Obesity constitute major determinants of the increasing incidence and prevalence of cancer that could

surpass smoking as a significant preventable cause against cancer [14]. Tobacco cessation and reduction of overweight and obesity may represent the most important lifestyle changes impacting on human health and cancer in particular. Specifically, reduction of overweight/obesity may decrease the burden of postmenopausal breast cancer and colorectal cancer, which represent two of the most frequent malignancies at a global level. Ectopic fat deposition, which is described as the pathological expansion of white adipose tissue in areas that it should not be (e.g. intrahepatic, intra-abdominally, intramyocellular, etc), may cause through multiple pathways metabolic, inflammatory, and immunologic alterations affecting Deoxyribonucleic Acid (DNA) repair, gene function, cell mutation rate as well as epigenetic changes permitting malignant transformation and progression [3, 4].

In this review, we provide an overview of the association between excess body weight and cancer synopsizing the main biological mechanisms underpinning this association as well as highlighting recent developments that provide new insights on pathogenetic mechanisms. Furthermore, we give a special emphasis on: 1) current epidemiologic evidence; 2) the obesity paradox in cancer risk and mortality; 3) the role of weight gain or weight loss in the modulation of cancer risk; 4) reliable somatometric indicators for obesity and cancer research; and 5) gender difference in obesity-related cancer risk. Elucidating the association between obesity, adiposopathy and cancer is important for the development of preventive, diagnostic and therapeutic strategies against cancer.

2. Epidemiologic evidence linking obesity to cancer risk

As summarized in Table 1, based on the International Agency for Research on Cancer (IARC) Working Group, there is convincing evidence that excess body weight, is associated with an increased risk for cancer of at least 13 anatomic sites, including endometrial, esophageal, renal and pancreatic adenocarcinomas; hepatocellular carcinoma; gastric cardia cancer; meningioma;

multiple myeloma; colorectal, postmenopausal breast, ovarian, gallbladder and thyroid cancers [15]. Therefore, there is sufficient evidence ruling out bias, confounding and chance with confidence, to conclude that avoiding excess body weight reduces the risk of the abovementioned malignancies. For other anatomic sites, the IARC Committee cannot exclude confounding and bias in the observed positive associations. Based on a different classification of the strength of evidence for the link between overweight/obesity and cancer risk, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) found in common with the IARC working group convincing and sufficient evidence for cancers of endometrium, esophagus (adenocarcinoma), colon and rectum, liver, pancreas, postmenopausal breast and kidney (renal adenocarcinoma) [16]. In addition, the WCRF/AICR found some level of evidence of a probable protective effect, not addressed by the IARC Working Group, for premenopausal breast cancer, cervix, oral, oropharyngeal and larynx cancers. All these results were generally supported by a recent umbrella review of systematic reviews and 204 meta-analyses that have assessed the relationship between adiposity and cancer risk [17]. Although there is substantial uncertainty, the most valuable finding of this umbrella analysis was the strong evidence for the association between obesity and cancer, predominantly cancers of digestive organs and cancers of hormone sensitive organs in women [17].

Importantly, excess weight during adult life is not the unique driver of the association between obesity and cancer risk. Emerging data link higher body fatness in late adolescence and early adulthood with malignancy risk at an older age [18-20]. Excess body weight during childhood and early adulthood has been particularly associated with risks of pancreatic cancer independently from diabetes, colon cancer in women, and multiple myeloma [19, 21, 22]. Taking into account

the elevated rates of childhood obesity, this observation underscores the importance to prevent obesity in childhood and young adulthood.

Finally, another interesting epidemiologic aspect is the finding that excess body weight and its comorbidities have been increased in cancer survivors more rapidly compared with the general population [23]. In particular, colorectal and breast cancer survivors were identified as the more susceptible group for obesity risk [23].

3. The paradox between the association of obesity with cancer risk and mortality

Interestingly, recent epidemiological data support the hypothesis that obesity may be probably a protective factor for certain cancer types regarding their incidence and mortality. Indeed, obesity is associated with reduced risk of premenopausal breast cancer (BC), non-small cell lung cancer (NSCLC) and head and neck cancers, as suggested also by the WCRF/AICR working group (probable protective effect), while it is associated with improved survival in NSCLC, renal cell cancer and metastatic colorectal cancer (CRC) [24, 25]. This phenomenon, called "obesity paradox", is mainly analyzed in cardiovascular, renal, pulmonary, sepsis and metabolic studies, and is less estimated in cancer studies [26-31]. Potential explanations of the obesity paradox in cancer patients may include methodologic issues such as 1) the use of BMI as a measure of general adiposity; 2) study limitations including inadequate adjustment for confounding, selection, stratification and detection biases; 3) confounders such as age, smoking, physical activity, etc. Indeed, residual confounding by tobacco smoking, which is related with reduced weight, may account for the observed inversed association between obesity and smoking-related malignancies such as NSCLC, squamous cell esophageal and urinary bladder cancers [32]; 4) reverse causality where weight loss is associated with BMI at diagnosis due to cancer cachexia and biological

mechanisms such as i) differences in body composition and adiposity; ii) less aggressiveness of tumor biology in obesity; iii) nutritional reserve to face anti-cancer treatments [33, 34].

4. The role of weight gain and weight loss in the modulation of cancer risk

Weight gain as well as weight loss may modulate cancer risk. Adult weight gain, as a better metric indicator than BMI for determining the dynamic nature of adiposity throughout adulthood, is also associated with elevated cancer risk, particularly esophageal adenocarcinoma; colorectal (especially in men), pancreatic, liver, gallbladder (in women), renal, postmenopausal breast, endometrial, ovarian and advanced stage prostate cancers, as portrayed in Table 2 based on data of the WCRF project [35, 36]. A recent dose-response meta-analysis of 50 prospective observational studies found that adult weight gain was not associated with cancer risk of prostate, colorectal (in women), pancreas, thyroid and breast (in premenopausal and in postmenopausal Hormone Replacement Therapy/HRT users) [36]. In this meta-analysis, adult weight gain for breast cancer was significantly higher amid postmenopausal women and HRT users [36]. Although the assessment of weight gain relies on recall in most studies, weight gain represents a snapshot of the weight projection in adulthood signaling fat tissue accumulation in the majority of adults [35]. Because there is a correlation between BMI at later adulthood, captured as the baseline BMI in prospective studies, and weight gain, weight gain may not add more value than BMI per se [37]. However, as a preventive measure, avoidance of weight gain is a more drastic target than weight loss [36].

Intentional weight loss has been related with lower risk of cancer, particularly obesity associated cancers in women, underscoring the link between excess body weight and cancer risk [38-40]. However, the role of sustained weight loss needs to be further evaluated [40]. Moreover, there is evidence for a significant decline in cancer mortality after weight loss; however, trials presented

heterogeneity in terms of endpoints and design [40]. Recent meta-analyses of Randomized Controlled Trials (RCT) and non-RCTs have shown that bariatric surgery for weight loss has been associated with lower risk of obesity associated cancers and any type of cancer [41, 42]. However, the effect of such intervention in morbidly obese individuals may be seen in the long-term [37]. It is important to note that evidence regarding bariatric surgery and cancer risk from RCTs is limited due to lower statistical power, small sample sizes and short follow-up period, whereas the results from interventions employing medical nutrition therapy for obesity are eagerly awaited in the not so distant future.

5. Reliable Somatometric Indicators for Obesity and Cancer Research

BMI does not fully characterize the intricate biology and physiology of excess body fat, which is a heterogeneous condition associated with distinct cardiometabolic risk [37, 43]. Generally, BMI is inaccurate to evaluate: 1) the elderly population who may be losing height and/or developing sarcopenia due to ageing; 2) individuals of Asian descent; 3) individuals of extreme height; 4) very muscular individuals; and 5) fat individuals belonging to the normal-overweight range of BMI as evidenced by the National Health and Nutrition Examination Survey (NHANES) study [44]. Also, self-reported weight tends to underestimate BMI in heavy subjects. BMI cannot differentiate between adipose tissue and lean mass, which present high variability based on gender, age, ethnicity and race [35]. Finally, BMI may underestimate the prevalence of visceral obesity in the population, leading to misclassifications of visceral obesity status which result in potential biases of the association between obesity/overweight and cancer towards the null effect [39].

Visceral fat represents a key determinant of insulin resistance (IR), secreting a substantial amount of free fatty acids (FFAs), pro-inflammatory molecules, growth factors, locally synthesized estrogens, hormones and adipocytokines contributing to the development of diseases, including

cancer [4]. Besides its energy-storage and thermal buffering properties, white adipose tissue, particularly visceral fat, is a dynamic endocrine organ synthesizing a plethora of heterogeneous adipocytokines that modulate several physiologic and pathologic processes including insulin sensitivity, inflammation, appetite regulation, innate and adaptive immunity, hematopoiesis, and angiogenesis [45, 46]. To date, more than 15 adipocytokines have been linked to cancer while their list is still growing [3, 4, 47, 48].

Computed tomography represents the standard method for direct quantification of Visceral Adipose Tissue (VAT) but it is not feasible for population-based studies [39]. Somatometric measures surrogates of visceral adiposity in population-based research (Table 3), such as Weight Circumference (WC) and Waist-to Hip Ratio (WHR), may be better indicators for cancer risk, particularly colon and postmenopausal breast cancers, than BMI because they are associated more strongly with visceral fat than BMI [49-51]. However, the epidemiologic evidence is conflicting [37]. This is due to the fact that WC and WHR poorly approximate visceral adiposity, because they characterize both VAT and subcutaneous adipose tissue (SAT) at the waist level [37]. This may lead to potential misclassifications of visceral obesity status biasing the association between obesity and cancer [39]. Tables 2 and 3 synopsize the association between somatometric data and cancer risk.

6. Gender differences in obesity related cancer risk

Worldwide, the burden of cancer attributable to obesity, expressed as population attributable fraction (PAF), is 11.9% in men and 13.1% in women for all obesity-related malignancies with a substantial worldwide variation depending on the prevalence of obesity and the relative risk estimates [52]. In men, the largest PAF is usually observed for esophageal adenocarcinoma (≈33.3%) and in women the largest PAF is observed for endometrial cancer (≈34% and 47.8% in

North America) [52]. Overall, there is a striking association between obesity and gynecologic cancer (endometrial, postmenopausal breast and ovarian cancers), pointing to the role of female sex steroids in cancer pathogenesis. BMI and other somatometric parameters present differential associations by gender with risks for some cancers such as colon, rectal, gallbladder, renal and pancreatic cancers [17, 37]. For example, the relationship between BMI and colon cancer was supported by strong evidence in males and suggested evidence in females [17]. As men are more prone to visceral adiposity than women, this observation highlights the detrimental role of visceral adiposity and insulin resistance in colon cancer and the protective endogenous estrogenic effects against colon cancer in women [53, 54]. Interestingly, there was no association between BMI and rectal cancer in women [17]. In contrast, overweight/obesity in females at childhood has been associated with an elevated colon cancer risk at adulthood. This association presented a weaker evidence in males [21].

Finally, based on one prospective intervention trial, bariatric surgical procedures have been shown more effective at lowering cancer risk in women compared to men; however, the small mean follow-up period of ten years, which is not considered as adequate for cancer manifestation; the low statistical power; and the smaller sample size of men may account for the observed results [55].

7. Biological mechanisms linking Overweight/Obesity to Cancer

Recent data have underlined the contribution of the triad of overweight/obesity, IR and adipocytokines in cancer**.** Although the role of obesity in cancer etiopathogenesis is not fully elucidated, the main pathways linking obesity and adiposopathy to cancer comprise: 1) hyperinsulinemia/ IR and abnormalities of the insulin-like growth factor-I (IGF-I) system and signaling; 2) sex hormones biosynthesis and pathway; 3) subclinical chronic low-grade

inflammation and oxidative stress; 4) alterations in adipocytokine pathophysiology; 5) factors deriving from ectopic fat deposition; 6) microenvironment and cellular perturbations; 7) factors causing obesity and cancer such as disruption of circadian rhythms and dietary nutrients; 8) altered intestinal microbiome; and 9) mechanic factors in obesity. Figure 1 depicts the mechanisms associating obesity with cancer.

7.1 Abnormalities in the IGF-I axis and hyperinsulinemia/insulin resistance

Insulin-like growth factors (IGFs), synthesized by almost any tissue in the organism, constitute significant mediators of growth, development, and survival, being implicated in cancer pathogenesis [56]. The IGF system represents a complex system comprising two growth factors (IGF-I and IGF-II), six specific high-affinity binding proteins (IGFBP-1 to IGFBP-6), cell surface receptors (IGF-IR and IGF-IIR), proteases for Insulin-like growth factor-binding proteins (IGFBP), and many other IGFBP-interacting molecules that modulate and generate IGF actions in several tissues [56, 57]. Evidence from in vitro and animal studies underscored that IGFs overexpression by cancer or stromal cells as well as the specific type of IGF-I receptor by the cancer cells could exert neoplastic actions by promoting cell cycle progression and inhibition of apoptosis either directly or indirectly through interaction with established oncogenic systems, such as the steroid hormones and integrins [56]. Acromegaly, an endocrine disorder characterized by sustained hypersecretion of growth hormone and concomitant increase of IGF-I is associated with cancer risk, particularly colorectal cancer [58]. Epidemiologic evidence has highlighted that increased serum IGFs levels and/or altered circulating levels of their binding proteins are independently associated with an elevated risk for developing several malignancies, particularly prostate, colorectal and breast cancer [59-63]. However, overall these associations are modest and

vary between anatomic sites leading to conflicting results for some obesity associated cancers like pancreatic and ovarian cancer [64-66].

Type 2 DM has been shown to cause a consistent elevation in the risk of pancreatic, biliary tract, and esophageal cancer in men; breast and endometrial cancer (EC) in women; and kidney, liver and CRC in both genders [67]. Moreover, patients with DM present greater cancer mortality in a variety of malignancies when compared with non-diabetic controls [67]. Obesity is associated with increased adipose tissue inflammation manifested as the secretion of pro-inflammatory cytokines and alterations in the pattern of adipokine secretion. IR in metabolically active tissues increases as a consequence of these changes, demanding more insulin from the pancreatic islets to maintain normal glucose levels. In practice, IR is reflected in elevated HbA1C and C-peptide serum levels, the latter being a more sensitive indicator of early phases, when HbA1C is still in the normal range. C-peptide levels have been associated with the risk of CRC in the New York University Women's Health Study, and have been replicated within the European Prospective Investigation into Cancer and Nutrition (EPIC) study [68, 69].

Insulin is thought to promote carcinogenesis directly and indirectly; target cell stimulation occurs via the insulin receptor or IGF mediation [70, 71]. Insulin reduces the circulating levels of IGFBP1 and IGFBP2 and as a result, circulating IGF is increased. Insulin and IGF induce a multitude of tumor-promoting mechanisms on target cells, implicated in proliferation, anti-apoptosis, angiogenesis and lymphangiogenesis [72]. These effects are the result of a series of cellular events, starting with membrane receptors and downstream transduction through the phosphatidylinositol 3-kinase (PI3K)–AKT– mammalian target of rapamycin (mTOR) pathway regulating cell growth and differentiation, and the Ras–Raf–MEK– Mitogen-Activated Protein Kinase (MAPK) pathway that induces proliferation [7]. In more detail, stimulation of the insulin receptor or the IGF-1R,

both receptors with intrinsic tyrosine kinase activity, induces the production of lipid messengers by PI3K that, in turn, activates the v-Akt murine thymoma viral oncogene homolog (Akt) cascade. The cascade culminates with mTOR activation, which regulates cell growth, proliferation and death through various other mediators [73]. Stimulation of mTOR is common in tumors and many normal tissues from obese and/or diabetic mice, and mTOR inhibitors hinder obesity-induced tumor progression in mouse models [74-76]. IGF as well as IGF receptors are highly expressed in many types of cancers [67].

Many tumors, including breast, colon, lung, prostate, ovary, and thyroid cancers, express the insulin receptor in high levels [77, 78]. Insulin receptor exists in two splice variants, Insulin Receptor-A (IR-A) and IR-B. In tumors, aberrant signaling leads to changes in the expression of splicing factors, leading to an increase in IR-A expression, and this is speculated to be responsible for at least part of the effects of hyperinsulinemia on oncogenesis [77]. Insulin upregulates the metabolic activity of the cell, leading to increased levels of oxidative stress that cause DNA damage either in the form of double strand breaks or mutations. These events have been displayed in colon cancer cell lines as well as in intestinal epithelium cells and lymphocytes of rats in vivo [79].

Cancer cells rely upon aerobic metabolism for their energy demands; they also synthesize fatty acids, proteins and nucleotides. As a result, they are in a constant need of increased glucose supply that has been proposed to be supported by diabetes associated hyperglycemia. High dietary glycemic load in patients with higher BMI, who likely present Mets or DM type 2, may induce hyperglycemia, providing the tumor with more glucose that facilitates its growth and progression, leading to decreased survival [80]. High levels of HbA1c that reflect the levels of hyperglycemia have been positively associated with various malignancies; breast, colorectal, gastric, pancreatic,

and hepatocellular cancer [81]. However, when the effect of hyperglycemia alone (without hyperinsulinemia) was investigated in streptozotocin-induced diabetes in mice, no positive associations of glucose levels with tumor growth were observed [82-85]. Interestingly, data on patients with type 1 DM are inconsistent, showing a weak, if any, association of type 1 DM with cancer risk or mortality, adding to the hypothesis that hyperglycemia-the common theme of type 1 and 2 DM- should not be a principal contributor of tumor promotion [67].

The pharmacotherapy of diabetes has an interesting interplay with the risk of cancer development. On the one hand, insulin as well as insulin secretagogue therapy have been associated with an increased risk of cancer development in human and animal studies [86, 87] but these associations may not reflect causality. On the other hand, patients who receive metformin seem to have a lower risk in cancer development [67]. Metformin induces hepatic gluconeogenesis and reduces IR of peripheral tissues resulting in lower insulin and IGF1 levels. Moreover, it leads to activation of 5' AMP-activated protein kinase (AMPK) affecting the mTOR pathway that is crucial for cell proliferation [67].

7. 2 Sex hormones biosynthesis and pathway

The peripheral adipose tissue is responsible for the process of steroid aromatization. Androgens and androgenic precursors are converted to estradiol by the enzyme aromatase. In the context of obesity and excess adipose tissue, aromatase increased activity leads to higher conversion rates resulting in higher levels of estrogens [88].

Higher concentrations of circulating sex hormones including dehydroepiandrosterone, dehydroepiandrosterone sulfate, Δ4-androstenedione, testosterone, oestrone and total estradiol, and decreased concentrations of sex hormone-binding globulin (SHBG) were associated with increased risk of breast cancer in postmenopausal women in the Endogenous Hormones and Breast

Cancer Collaborative Group (EHBCCG) and EPIC studies [89, 90]. Increased estrogen levels in women with higher BMI accounted almost exclusively for the association of BMI with postmenopausal BC risk [89]. The higher risk of obesity-associated BC in postmenopausal women is mainly observed in hormone receptor positive (ER+/PR+) disease, without any history of hormone replacement therapy, a fact that supports the hypothesis of the essential role of estrogen [91]. The reduced risk for BC in obese premenopausal women is hypothesized to be mediated by reduced mammary tissue progesterone exposure caused by ovarian hyperandrogenism [91].

Testosterone has displayed a bimodal correlation with BMI when subjects are grouped by gender. It has been shown to be elevated in obese women and decreased in obese men. Elevated blood concentrations of androgens have been associated with increased risk of BC in women regardless of menopausal status [89, 90]. However, basic research has been inconclusive on the testosterone effect on mammary tissue [88].

Obesity is associated with a 2.6-fold higher risk of EC compared to normal weight [92]. Estrogen promotes tumorigenesis in endometrial tissue by stimulation of cell proliferation and inhibition of apoptosis [92]. These effects are mediated by the induction of IGF1 production in endometrial tissue which then acts on the endometrium in a paracrine manner [92]. Progesterone, on the other hand, opposes estrogen effects mainly by stimulating the production of IGF1 binding protein which, in turn, inhibits IGF1 [93]. IGF2 mediates the effects of progesterone in the luteinizing phase of the menstrual cycle and is important in endometrial differentiation and in endometrial interactions with the fetus [94]. Unopposed estrogen effect is the main sex-hormone hypothesis for EC. Ovarian hyperandrogenism is another proposed mechanism linking obesity sex-hormone dysregulation and EC [93].

Although androgens occupy a central role in prostate cancer pathogenesis, there is no clear correlation of serum sex hormone levels and risk of malignancy development [37]. As previously stated, obese men tend to have lower testosterone levels when compared to normal weight individuals. This low testosterone environment seems to promote the development of a less differentiated, aggressive cancer phenotype [95]. Men treated with finasteride, a 5a-reductase inhibitor that decreases dihydrotestosterone levels, displayed an increased risk for high-grade and decreased risk for well-differentiated prostate cancer [96]. Low serum testosterone was associated with a higher risk of poorly differentiated prostate cancer, albeit BMI was not considered in the data analysis [97, 98].

7.3 Subclinical chronic low-grade inflammation and oxidative stress

Obesity is a state of chronic inflammation [99] which constitutes an established mediator of cancer development and progression as many inflammatory components reside in the tumor microenvironment and promote a cancerous phenotype [100]. When comparing obese subjects with or without adipose inflammation and metabolic dysfunction, the former exhibit elevated cancer and CVD risk [101].

Adipose tissue, an active endocrine organ, releases a variety of adipocytokines in the bloodstream, the more important being adiponectin and leptin [48]. Visceral obesity and excessive ectopic fat distribution are strongly associated with hypoadiponectinemia [102]. Adiponectin is a hormone synthesized by adipose tissue presenting anti-inflammatory as well as insulin-sensitizing properties [102]. Adiponectinemia has an inverse correlation with inflammatory cytokines which are elevated in obesity, such as tumor necrosis factor-α (TNF-a) and interleukin (IL)-6; it can also attenuate nuclear factor-κB (NF-kB) activation [103]. Leptin levels positively correlate with BMI and adipose tissue mass [104]. Contrary to adiponectin, leptin exerts pro-inflammatory actions

stimulating the production of IL-1, IL-6, IL-12, TNF-α, Leukotriene B4 (LTB-4) and Cyclooxygenase 2 (COX2) [105]. Moreover, it promotes T cell proliferation and TH1 phenotype whereas it suppresses Regulatory T (Treg) cells [105].

Hypoadiponectinemia has been observed in a multitude of malignancies, confirming its tumor suppressive role; epidemiological data for leptin levels relative to cancer has been inconclusive in contrast to many experimental studies where supraphysiologic levels of leptin were employed [4, 48, 104, 106-110].

Obesity presents a causal relation with IR, which, in turn, potentially promotes inflammation as hinted by recent data [111]. Beside their direct effect on tissues, inflammatory adipocytokines influence the sex hormone mechanism of tumorigenesis via stimulation of estrogen production by aromatase (separately addressed).

A recent study by Lee et al attempted to elucidate the effect of systemic inflammation on all-cause and cancer-related mortality [112]. Increased mortality rates in individuals with elevated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and/or high sensitivity C-reactive protein (hsCRP) levels were observed [112]. Interestingly, the effect of systemic inflammation in cancer-related mortality was found to be more pronounced. Tumor progression in obesity-related malignancies implicates IR, inflammation and tumor infiltration with immune cells [113].

The inflammatory environment of obesity has been proven reducible following weight loss. Ziccardi et al showed an attenuation of endothelial dysfunction in women that lost weight [114]. Reduction of subcutaneous adipose tissue inflammation has been observed in patients that have achieved a decrease in their BMI by bariatric surgery [115]. Although, holistic lifestyle modifications for weight loss as investigated in the Look Ahead study have a positive effect on

cardiometabolic factors, the potential benefits in cancer risk reduction are much awaited [116]. Contributing to the above, an array of drugs used to treat several factors of metabolic syndrome such as thiazolidinediones, angiotensin receptor blockers and statins can raise adiponectin levels contributing to the much desired reduction of inflammation [99].

Malignant cells can induce adjacent adipocytes to alter their phenotype; reducing their lipid content and release of adipokines and secreting tumor-promoting substances such as matrix metalloproteinases [117].

Reactive oxygene species (ROS) production, which has been associated with obesity, contributes to tumor promotion [118]. Hyperglycemia along with elevated free fatty acid levels induce ROS production and the secretion of pro-inflammatory cytokines that additively provoke mitochondrial and DNA damage [119].

The effect of inflammation-combating medication on obesity-related cancer is an ongoing research question. Non-steroid anti-inflammatory medication has been associated with reduced cancer risk in obesity-related malignancies [120-122].

7.4 Alterations in adipocytokine pathophysiology

White adipose tissue (WAT), a major component of the adipose tissue is considered to be a metabolically active endocrine and secretory organ [123]. It produces a plethora of cytokines and adipokines [123]. In obesity, adipose tissue hypoxia ensues and results in chronic inflammatory state [124]. This condition, triggers alterations of normal leptin and adiponectin levels, which in combination with the co-occurrence of other changes, including infiltration of macrophages, mitochondrial dysfunction and increased endoplasmic reticulum (ER) stress response, may be associated with promotion of cancers such as CRC in obese individuals [125-127]. In a recent review, our group described the multiple and complex associations of a dozen of different

adipocytokines (both classic and novel) with various cancers and the possible therapeutic approaches which target those adipocytokines [48].

Peritumoral adipocytes may augment tumor growth [128]. In BC, adipocytes of tumor-stromal interface [cancer-associated adipocytes (CAAs)] acquire a fibroblast-like phenotype which is associated with greater invasiveness through secretion of various proteases and cytokines [117, 129]. Regarding ovarian cancer, CAAs, found in omentum, secrete cytokines (IL-6 and IL-8), which result in increased migration and invasiveness of cancerous ovarian cells [130]. Other mechanisms of "cross-talk" between cancer and peritumoral adipocytes include increased lipolysis, which provides an energy source to cancerous cells, as observed in ovarian cancer, and chemokine secretion, as detected in prostatic cancer [131].

7.5 Factors deriving from ectopic fat deposition

Ectopic local adipose tissue might be a more important risk factor for site-specific cancers. Data from the Framingham Heart Study indicate that the risk for malignancies could be elevated for metabolically unhealthy obesity (MUO) older individuals than metabolically healthy obesity (MHO) adults [101]. MHO individuals present with less local ectopic adipose tissue surrounding organs and blood vessels [132]. Emerging data from epidemiologic and translational research studies have indicated that the local ectopic fat tissue, such as breast, bone marrow, intrahepatic and intrapancreatic adipose tissues, presents toxic and carcinogenic effects for the development of breast, hematopoietic, liver and pancreatic cancers [37, 133, 134]. Local ectopic adipose tissue is associated with a more pronounced inflammatory milieu influencing tumor promotion and progression [135, 136].

Adiponectin, the most abundant adipokine in blood, is the first hormone that gets dysregulated (hypoadiponectinemia) due to intrabdominal and ectopic fat distribution leading to dysregulation

of IGFs, inflammation, estrogen/progesterone imbalance, and finally to neoplastic transformation [4, 137].

Although adiponectin is primarily produced in fat tissue, circulating concentrations of adiponectin are paradoxically decreased in obese subjects. Besides its intimate implication in the regulation of metabolism, in vitro studies have been shown that adiponectin inhibits the proliferation of several cancer-derived cells such as endometrial, breast, prostate and colorectal cancer. Adiponectin has been shown to inhibit tumor development and growth by affecting several intracellular signaling pathways including AMPK, mTOR, PI3K/ Akt, MAPK, Signal Transducer and Activator of Transcription (STAT) 3, NFκB and the sphingolipid metabolic pathway [4, 138]. Importantly, adiponectin seems to exhibit its strongest effect under the high-fat diet i.e. a condition directly related with insulin resistance and pro-inflammatory state, a fact with significant implications in anti-neoplastic therapy [138]. Adiponectin exhibits also indirect anti-tumor action through an insulin-sensitizing and anti-inflammatory effect. Consistent with *in vitro* and animal studies, several epidemiological studies conducted to date link hypoadiponectinemia to the risk of obesity-associated cancers including but not limited to breast, endometrial, prostate, colon, pancreatic cancers, and hematologic malignancies [4, 107, 109, 110, 133, 139-146]. Current evidence has highlighted the role of adiponectin as a novel risk factor (hypoadiponectinemia) and potential diagnostic and prognostic biomarker in cancer.

7.6 Microenvironment and cellular perturbations

7.6.1 Vascular perturbations

Obesity is linked to chronic low grade inflammation, described as lipo-inflammation [147]. It is also known that inflammation contributes to carcinogenesis [148]. “Angiogenic switch”, a process during which many different tumor-associated immune cells promote angiogenesis, is a main

pathway through which inflammation promotes carcinogenesis [149, 150]. On the other hand, cancer cells *per se* produce pro-angiogenic factors which, in turn, activate endothelial cells [151]. Activated endothelial cells give rise to tumor-associated vasculature which is essential for cancer progression and dissemination [152].

7.6.2 Epithelial-Mesenchymal Transition (EMT)

Epithelial-mesenchymal transition (EMT) is a process of epithelial cell differentiation to a mesenchymal phenotype. This change decreases cell adhesion to other cells and matrix, increasing cell motility [153]. EMT is normally implicated in embryogenesis allowing controlled cell migration and differentiation [153].

In diet-induced obesity animal models, there is formation of a microenvironment appropriate for tumorigenesis [154]. Such a microenvironment is the result of changes in hormones, growth factors, cytokines, adipocytes and alterations in EMT [154]. In contrast, calorie restriction presents opposite effects; these include prevention of intra-tumoral adipocytes infiltration, decrease in various hormones, growth factors and cytokines and attenuation of EMT [154]. EMT components may represent novel targets for cancer prevention or therapy, particularly in obese individuals [154].

7.6.3 Endoplasmic reticulum (ER) stress

ER is involved in the process of protein folding. Increased FFAs levels are found in obese individuals and are associated with ER stress in adipocytes [155]. Specifically, FFAs induce formation of ROS that oxidize proteins and, thus increase the number of unfolded proteins in ER [128]. The accumulation of unfolded proteins elicits an inflammatory response [128]. The cytokines involved in this process have been linked to colon cancer [156]. The identification of

ER stress as a factor related to cancer cell proliferation and survival, has led to the idea that "unfolded protein response'", could possibly be a target for antitumor therapies [157]. However, one should necessarily bear in mind that cellular response to ER stress is not always oncogenic; meaning that this pathway needs further investigation [157].

7.6.4 Migrating adipose progenitor cells

The stroma of tumors contains mesenchymal cells (MSCs) that serve as important progenitor cells which, in turn, play an important role in carcinogenesis [37]. Such an example is neovascularization by endothelial cells derived from MSCs [37]. MSCs are initially found in circulation and are recruited in tumor sites under the influence of necessary signals (inflammation or hypoxia) [158]. In the past, bone marrow was considered the major site of production of such cells [158]. However, it has been shown that WAT, found in abundance in obese individuals, is another possible site of MSCs production [158].

7.7 Factors causing obesity and cancer

7.7.1 Disruption of circadian rhythms

Circadian rhythm dysregulation is linked to both obesity and cancer [159]. Decreased sleep quantity and quality can result in altered glucose regulation and energy balance including obesity [160]. For example, obesity is associated with the development of Hepatocellular Cancer (HCC) through obesity-induced steatosis [160]. Disruption of circadian rhythms may be associated with HCC due to metabolic and obesity-related factors.

It has also been shown that hepatic hormones function in a circadian-rhythm fashion and an alteration of this rhythm has been linked to the development of cirrhosis and HCC [161]. Of interest, it was found that certain drugs against HCC are better administered in a circadian-modulated rhythm [162]. Thus, circadian rhythm may also be taken into consideration in anti-

cancer treatments [160]. Lately, the theory that electric light exposure during night may be associated with BC, has been investigated epidemiologically; consequently, the link between cancer and circadian rhythm disruption will probably be a promising field of future investigation [163].

7.7.2 Dietary nutrients and cancer

Since the Hippocratic "Let food be thy medicine and medicine be thy food", it has been known that diet can both increase the risk for cancer and also be used therapeutically in cancer [164]. Red and processed meat consumption, which is common among obese people, is strongly associated with stomach, colon and rectal cancer [165, 166]. In contrast, high fiber consumption (vegetables and fruits), not usually consumed by obese people, decreases the risk of developing CRC [167, 168]

Regarding BC, findings from a meta-analysis showed that increased fat intake is probably associated with increased risk for the disease [169]. However, the effect of meat and fruit/vegetable consumption on BC was not clear [169]. Mediterranean diet, which is associated with lower obesity rates, consists of food items rich in antioxidants, fibers and unsaturated fatty acids, being associated with a lower risk for EC [170]. Regarding ovarian cancer, no clear associations with dietary habits have been identified so far [171]. For renal cancer, there is a higher risk among those who frequently eat red or processed meats but no association was found among those ingesting low fiber [172, 173]. Interestingly, consumption of sweetened carbonated beverages, which is a common habit of obese people, is not associated with an increased risk for any type of cancer [174]. However, these results need further validation [174].

In the micronutrient level, B-complex vitamins, vitamin D and magnesium are associated with decreased risk for CRC [175-177]. B vitamins are also protective against lung cancer [178]. In

addition, vitamin C and carotenoids decrease the risk for gastric malignancy [179]. Antioxidant intake is possibly associated with a low risk for EC but these results need further confirmation by cohort studies [180]. Regarding ovarian cancer, no specific association has been identified with any antioxidant or dietary element, in recent systematic reviews [171]. Of dietary supplements, calcium and multivitamins are associated with reduced CRC, while for the rest supplement types, the associations are inconsistent [181].

7.8 Altered intestinal microbiome, obesity and cancer

One potential factor in the association between cancer and obesity may be the altered intestinal microbiome. The intestinal microbiota harbour a very large number of genes, which outnumber human genome by about 100 times [182]. These genes provide them with elaborate tools that enable them to utilize gut substances, adapt to host defences and form a stunning network of symbiosis. Bacteria metabolize a vast variety of substances, among which are prebiotics, fibers, aminoacids and drugs. The products of these reactions may be utilized by other species; the big picture consists of a highly complex system with many relations of interdependence. The host organism through an evolutionary maintained, albeit, complex system of innate immunity, epithelial cells and a spectrum of other factors, functions to prevent invasion, i.e. maintaining a well-functioning gut barrier.

The human gut microbiome consists of four phyla: Bacteroidetes and Probacteria which are Gram negative; Acenetobacteria and Firmicutes which are Gram positive [183]. Bacteroidetes and Firmicutes comprise over 90% of the microbiome, whereas their relationship and prevalence is determined by diet, BMI and other environmental factors [183]. Gut microbiome has an active role in the intestinal metabolism of digested nutrients, influencing their availability for absorption and, consequently participates in the pathogenesis of metabolic disorders such as DM, obesity, CVD

but also cancer [184]. Obese mice, either genetically predisposed or diet-induced, tend to display an increase in Firmicutes and a decrease in Bacteriodetes [185-189]. Specifically, in diet-induced obesity, Mollicutes, a subclass of Firmicutes seems to be particularly favored [189]. These bacteria are associated with higher levels of lactate, acetate and butyrate; all three being substrates for fatty acid synthesis [189]. Obesity can be induced through alteration in the microbiome; it is unlikely that altered microbiome is a consequence of obesity. When the microflora of diet-induced obese mice was transferred to normal weight, low-fat fed mice, the latter acquired the phenotype of the former [189]. Weight loss and bariatric surgery in humans has been shown to decrease Firmicutes abundance [190]. The vital role of microbiota in humans was demonstrated in a study where researchers transferred fecal content of twins that had different phenotype regarding obesity, to microflora-free mice [191]. Interestingly, the rodents adopted the respective phenotype of the human donors.

The potential mechanisms that link microbiota, obesity and cancer can be classified in two overlapping groups: promotion of inflammation and production of cancer-promoting substances [69].

The intestine displays a highly complex, interconnected immunologic response to the inhabitant microflora. Pattern recognition receptors sense the profile of microorganisms which they process downstream as an innate inflammatory response. Alterations in this interaction are proposed as a strong component of the obesity-inflammation-cancer trio.

Obesity-associated inflammation originates in the intestinal lumen. Endotoxinemia, a term coined for the leakage of bacteria derived substances in the bloodstream, is currently considered pivotal for the initiation of inflammation [192]. Bacterial death releases LPS that binds to a Toll-like receptor (TLR)4 molecule, activating NF-kB and promoting the secretion of inflammatory

cytokines as IL-1, IL-6 and TNF-a. NF-kB is a central player in the initiation of liver and intestinal tumorigenesis; its inhibition promoted apoptosis in cells carrying malignant potential [193-195]. Whereas under normal conditions the gut barrier allows only a minimal amount of Lipopolysaccharide (LPS) to enter circulation, LPS levels in obesity are at least doubled [192]. The elevation in serum LPS of mice fed with a high fat diet was attributed to decreased ZO-1 expression of tight junction molecules on intestinal epithelial cells [196]. The effects of TLR2, TLR4 and TLR family members exhibit global cancer promoting properties in the colon, liver and pancreas [197]. Apart from TLRs, Nucleotide Oligomerization Domain-line Receptor (NLR)1 and 2, which are also receptors for bacterial molecules, function against gut inflammation and tumorigenesis in the context of obesity [198]. Taken together, obesity leads to gut barrier dysfunction, mediated by a variety of pathways, eventually, favoring carcinogenesis. This context is thought to be pivotal in the association of ulcerative colitis and CRC [197, 199]. The gut barrier dysfunction seems to be conditionally reversible; prebiotic induced alteration of gut bacteria, stimulated the secretion of Glucagon Like Peptide (GLP)1, PYY and GLP2 that led to reduced food intake, and enhanced glycemic indices as well as gut barrier function reducing local inflammation [192].

An interesting display of the role of bacteria induced inflammation in cancer promotion is derived from studies in HCC [200]. Obesity favors the manifestation of NAFLD that progresses to non-alcoholic steatohepatitis (NASH) associated with HCC [200]. Gut barrier dysfunction is considered as the main trigger of NASH. Microbe-associated Molecular Patterns such as LPS translocation through a defective intestinal barrier and, subsequent TLR, NF-kB signaling and upregulation of mitogenic factors are thought to be central in the sequence of liver cancer pathophysiology [201].

Fusobacteria, species of particular focus regarding oncogenesis, have been found elevated in the saliva and the intestine of obese individuals [202, 203]. It has been shown that they provoke activation of NF-kB and other proinflammatory components such as IL-1, IL-6, IL-8, TNF-a, matrix metalloproteinase (MMP)3 and COX2, that are associated with intestinal carcinogenesis [7]. Other possible mediators of Fusobacteria cancer promotion are β-catenin, TLR4 and p21-activated kinase (PAK)1 signaling [202, 203]. Adenomatous Polyposis Coli (APC) deficient mice fed with Fusobacteria exhibited higher number of tumors and a more rapid intestinal tumor progression compared to controls fed with Streptococci [7, 204, 205].

The effects of the microbiome on body weight and HCC cancer risk may be transmitted along generations [206]. Gut content of high-fat diet fed mice transferred to germ-free mice, increased the risk of obesity and liver cancer in their offsprings as well [206].

The second main theme of microbiota-related cancer promotion is the generation of toxic metabolites. Obesity and high-fat diet associated changes in intestinal microbiome have been associated with altered bile acid metabolism, with increased production of deoxycholic acid (DCA) being of particular importance. High fat diet fed mice exhibit higher levels of serum DCA, a phenomenon attributed to Clostiridia that used primary bile acids as substrates [207]. DCA suppresses p53 by enhancing its degradation by the proteasome system [208]. Moreover, DCA causes DNA damage through ROS formation [209]. The cancer promoting environment created by DCA, in conjunction with cytokines secreted from senescent cells have been demonstrated to favor HCC genesis and progression [207]. When researchers suppressed Clostiridia populations with antibiotics, DCA levels were diminished and HCCs were reduced in size and number [207].

Last but not least, gut microflora has been shown to have the ability to affect the human epigenome. Butyrate, an abundant bacterial metabolite, inhibits deacetylation of histones whereas certain species of bacteria can alter the non-coding RNA profile of host cells [210-212].

7.9 Mechanic factors in obesity and cancer

Esophageal adenocarcinoma represents a paradigm where obesity increases the risk of cancer indirectly through a "mechanic" way [213]. Specifically, obesity increases abdominal pressure resulting in relaxation of the lower esophageal sphincter (LES) [214]. Due to relaxation of the LES, esophageal mucosa is exposed to gastric contents resulting in gastro-esophageal reflux (GERD), a phenomenon strongly associated with Barett's esophagus and esophageal adenocarcinoma [214]. Obesity is also associated with increased occurrence of hiatal hernia, which also plays a role in the pathogenesis of GERD and, consequently, esophageal cancer in obese people [215].

8. Perspectives and future directions

A significant percentage of cancer cases may be preventable through quitting smoking, maintaining a healthy weight, following a diet with nuts, fruits, vegetables and olive oil, increasing physical exercise and decreasing alcohol intake [5]. The American Society of Clinical Oncology has stressed that obesity is one of the most important determinant of cancer mortality [14]. From a public health aspect, tackling obesity offers the opportunity to prevent an important number of chronic non-communicable diseases, including CVD and DM, with the same panel of public health interventions.

The most important preventive measures for obesity associated cancers are based on lifestyle modification, diets leading to weight loss, medical nutrition therapy and bariatric surgery. Intentional weight loss has been reported to decrease cancer incidence in women, specifically

postmenopausal breast and endometrial cancers [216, 217]. Hypocaloric diet is the most effective way to induce weight loss [218]. However, it is difficult to keep long-term caloric restriction. During adulthood, there is a weight gain at a rate of 0.5 kg per year observed in all BMI ranges [219]. In contrast to weight loss and its maintenance over time, avoidance of further weight gain may be a better preventive and effective goal to achieve, which confers protection against obesity associated cancers, particularly among women [36]. Incorporation of physical exercise into daily practice may be an effective preventive strategy to tackle with weight gain [36].

Ketogenic (low-carbohydrate) diets may be options for weight loss and cancer prevention as they adjust systemic metabolic signalling by reducing blood glucose and insulinemia and improving insulin sensitivity in murine models and humans [220-222]. Although the available evidence is only preliminary, a ketogenic diet may decelerate the progression of certain cancer types [138, 223]. Dietary patterns rich in vegetables, fruits, nuts, olive oil, fibre and wholegrains, and low in processed food and animal products full of saturated fatty acids and cholesterol are associated with decreased cancer incidence and mortality [224-226]. Dietary ω3-polyunsaturated fatty acids, which share anti-inflammatory and anti-neoplastic properties, could diminish the risk of several cancers [7, 227]. Some nutraceuticals such as curcumin, a polyphenol derived from turmeric, may regulate the mRNA and protein levels of pro-inflammatory adipocytokines: resistin and visfatin/Nampt [228].

Bariatric surgery provides long-term weight loss for morbidly obese individuals along with resolution of comorbidities [229]. Nowadays, laparoscopic sleeve gastrectomy provides excellent weight loss with low complication rates and technical simplicity [230]. More importantly, bariatric surgery has been shown to reduce the incidence of many cancers such as endometrial, breast, colorectal, non-Hodgkin lymphoma and melanoma [55, 231, 232]. Overall, bariatric surgery

causing weight loss has been shown to decrease obesity associated cancers with a 40-50% reduction in cancer-specific mortality across cancer types, highlighting that weight loss could be an effective preventive measure in obese subjects [39, 233]. In MUO, bariatric surgery improved insulin sensitivity and intestinal microbiota profile, restored inflammatory adipocytokines and decreased tissue inflammation [3, 47, 234-236].

Glycemic control with metformin or Peroxisome Proliferator-Activated Receptors (PPAR)-γ agonists can restore adipocytokines concentrations, increasing adiponectin and decreasing pro-inflammatory adipocytokine levels in both humans and mice being at the forefront of therapeutic strategies for obesity-related malignancies [3, 47, 237, 238]. Metformin is a chemopreventive agent against a plethora of cancers restricting tumor growth through insulin-independent mechanisms involving the activation of the AMPK, which is critical in cell proliferation [239]. Whilst evidence from preclinical and population-based studies suggests an anticancer role for metformin, this is challenged by the fact that higher metformin doses are used in mechanistic studies and animal studies, exceeding standard treatment doses in humans [240]. Since direct tumor uptake of metformin relies on the expression of elevated levels of organic cation transporters which vary in cancers, it seems that metformin's actions in lowering insulin levels account for the decrease in cancer risk observed in epidemiologic studies [241, 242]. Emerging evidence from human studies have shown that metformin is a cancer chemotherapeutic agent. Despite several conflicting results, meta-analyses have shown an overall decrease in cancer risk of about 30% throughout all malignancies, particularly in pancreatic and hepatocellular cancers [243, 244]. Clinical trials using metformin alone or in combination with standard therapy in a variety of malignancies, either as a preventive or therapeutic strategy are ongoing [245]. Currently, 322 trials on metformin in cancer can be identified in Clinicaltrials.gov (retrieved on October 6, 2018).

Overall, the data is strongest regarding treatment against gynecologic (endometrial and breast), colorectal, prostate cancers where there is some evidence of positive biomarker modulation [246-248]. However, the design of most trials has been questioned due the insufficient underlying molecular rationale and the wide inclusion criteria [249]. Long-term phase II-III clinical trials are strongly warranted to further explore metformin activity in malignancies [250]. Whether metformin should be utilized as a chemopreventive agent in obese subjects without DM or insulin resistance is a matter of debate. Generally, metformin is a well-tolerated drug with mild side effects including gastrointestinal disturbances, such as abdominal discomfort, anorexia, nausea and diarrhea [248].

Activation of PPAR-γ by thiazolidinediones (TZDs) or other agonists could restrict cell proliferation by decreasing insulin and influencing key pathways of the Insulin/IGF axis, such as MAPK, PI3K/mTOR and Glycogen synthase kinase (GSK)3-β/Wnt/β-catenin cascades, which modulate tumor cell survival and differentiation [251]. Nevertheless, the use of PPAR-γ agonists as antineoplastic agents have reached conflicting results in clinical trials [251].

Lipid-lowering drugs, calcium-channel blockers, vitamin C and D supplementation, folic acid and oleic acid could significantly restore adipocytokine levels impacting on cancer risk. In particular, long-term statin use (≥ 4 years) is associated with lower overall cancer mortality [7, 252]. Acetylsalicylic acid may be beneficial in treating the systemic or local implications of white adipose tissue inflammation decreasing the incidence and mortality of certain obesity-related cancers, particularly colorectal and endometrial cancers [128, 253]. Since obesity is related to elevated levels of cyclooxygenase-2 and elevated prostaglandin signaling and synthesis, non-steroidal anti-inflammatory drugs (NSAIDs) may play a role in obesity associated cancers through COX inhibition and decrease of prostaglandin levels [254]. The strongest evidence for an anti-

neoplastic role of chemoprevention with NSAIDs is observed in colorectal adenoma and cancer [255]. Antimicrobial treatment modulating gut microbial populations could be a useful approach for the management of obesity and metabolic conditions including cancer [128, 253].

In pre-clinical studies, pegylated leptin-receptor antagonist 2 has been reported to diminish the proliferation and angiogenesis of BC cells [256, 257]. Also, ADP355, a peptide-based adiponectin receptor agonist, has been shown to restrict the proliferation of adiponectin receptor-positive cancer cell lines [258, 259]. Targeting the inhibition of pro-inflammatory adipocytokines such as resistin and visfatin could be an effective strategy in cancer therapeutics, particularly in depleting the tumor inflammatory microenvironment [3, 47]. Combination treatment of chemotherapeutics drugs or radiation with Nicotinamide phosphoribosyltransferase (Nampt) inhibitors could represent an emerging strategy potentiating the efficacy of existing chemotherapeutic agents [3].

A critical research goal is to include serum or plasma biomarkers reflecting adipose inflammation that would allow wider studies of associations between obesity and malignancies, providing surrogate markers of intervention efficacy in obesity-related cancers. Adipocytokines, particularly adiponectin, may be useful diagnostic and prognostic biomarkers, reflecting stage, prognosis and inflammatory state in cancer [3, 47, 260-263]. However, more prospective and longitudinal studies are needed to investigate the diagnostic and prognostic potential of classic and novel adipocytokines as cancer biomarkers. Also, there is need to develop more reliable and practical automated laboratory techniques with standardization of immunoassay procedures to explore the pathophysiological relevance of adipocytokines. Finally, high throughput technologies such as proteomics and metabolomics will discover novel adipocytokines and obesity-related biomarkers. More detailed methods of adipose tissue distribution in large epidemiological studies are required to better discriminate and quantify different body fat composition (VAT and SAT) and ectopic fat

deposition, and their role in cancer, such as ^{1}H magnetic resonance spectroscopy and Magnetic Resonance Imaging (MRI) [37, 264].

In summary, there is evidence for a strong connection between obesity-driven chronic inflammation, IR, adipokines, altered microbiome and cancer. Further research in basic and translational research is essential to delineate the ontological role of adipocytokines and their interplay in obesity-related cancer pathogenesis. More prospective and longitudinal studies are expected to determine a broad spectrum of obesity-related biomarkers and evaluate their clinical utility in cancer prognosis and monitoring. Reversing obesity-associated dysfunction and inflammation of the adipose tissue by lifestyle interventions such as weight loss, physical activity and dietary modifications as well as bariatric surgery could present a public health relevant contribution to decrease cancer risk or progression. Finally, novel more effective and adipocytokine-oriented therapeutic interventions could pave the way for targeted oncotherapy.

Table 1. Epidemiologic evidence associating overweight/obesity and cancer risk by level of evidence and strength of Relative Risk increase for overweight/obesity in comparison to normal-range body mass index (18.5-24.9 kg/m^2) defined by the WHO as synopsized by the IARC Working group in 2017.

Evidence level	**Strength of Relative Risk Increase for Obesity and Cancer Risk**		
Convincing/Sufficient	**High (RR increase≥3)**	**Modest (RR increase: 1.50-2.99)**	**Little (RR increase: 1.00-1.49)**
	Endometrial adenocarcinoma	Renal adenocarcinoma	Colorectal cancer
	Esophageal adenocarcinoma	Hepatocellular cancer	Postmenopausal breast cancer
		Pancreatic adenocarcinoma	Gall bladder cancer
		Gastric cardia cancer	Ovarian Cancer
		Multiple myeloma	Thyroid Cancer
		Meningioma	
Limited			
		Advanced stage prostate cancer	
		Male breast cancer	
		Diffuse large B-cell lymphoma	

Table 2. Associations of weight gain per 5 kg per m^2 increase of BMI with cancer risk by anatomic site. Associations with somatometric data and overall level of evidence for the association of BMI with cancer risk by cancer type based on the WCRF project.

Refs	Strength of evidence	Anatomic site	Histologic type	Summary risk estimate per 5 kg per m^2 BMI increase (95% CI)	BMI	WC	WHR	Adult attained height
[1], [4]	Convincing	Esophageal	Adeno-carcinoma	Men 1.52 (1.33, 1.74) Women 1.51 (1.31, 1.74)	+ +			
[1], [5]	Probable	Gastric	Adeno-carcinoma	Men 0.97 (0.88, 1.06) Women 1.04 (0.90, 1.20)	+			
[1], [6]	Convincing	Colorectal	Adeno-carcinoma	Colon *men* 1.24 (1.20, 1.28) *Women* 1.09 (1.05, 1.13) Rectum *Men* 1.09 (1.06, 1.12) *Women* 1.02 (1.00, 1.05)	+ +	+ +	+ +	+ +
[1], [7]	Probable	Gallbladder	Adeno-carcinoma	Men 1.09 (0.99, 1.21) women 1.59 (1.02, 2.47)	+			
[2], [8]	Convincing	Pancreatic	Adeno-carcinoma	Men 1.13 (1.04, 1.22) Women 1.10 (1.04, 1.16)	+ +	+ +	+ +	+
[3], [9]	Convincing	Liver	HCC	Men 1.19 (1.09, 1.29) Women 1.12 (1.03, 1.22)	+ +			
[1], [10]	Convincing	Renal	Not investigated	Men 1.24 (1.15, 1.34) Women 1.34 (1.25, 1.43)	+ +	+ +	+ +	+
[1], [11]	Convincing	Postmenopausal breast	Not investigated	Women 1.12 (1.08, 1.16)	+ +			+ +
[1], [12]	Convincing	Endometrial	Not investigated	Women 1.59 (1.50, 1.68)	+ +	+		
[13]	Probable	Ovarian	Not	Women	+			+ +

			investigated	1.06 (1.00, 1.12)				
[14]	Probable	Advanced prostate	Not investigated	Men 1.08 (1.04, 1.12)	+	+	+	
+ + convincing increased risk; + probable increased risk: BMI, Body Mass Index; WC, Waist Circumference; WHR, Waist-Hip ratio; WCRF, World Cancer Research Fund								

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Table 3. Somatometric data related to obesity and cancer risk		
Factors	**Classifications**	**Comments**
BMI (kg/m^2)	Underweight: <18.5 Normal weight: 18.5–24.9 Overweight: 25.0–29.9 Obese I: 30.0–34.9 Obese II: 35.0–39.9 Obese III: ≥40.0	✓ BMI is not a good marker of adiposity as it cannot differentiate between adipose tissue and lean mass. This may partially explain the "obesity paradox" in cancer patients. ✓ BMI is inaccurate to evaluate obesity in elderly subjects; individuals at extreme height; very muscular individuals and fat subjects in the normal-range BMI. ✓ BMI may underestimate visceral obesity status biasing the association between obesity and cancer risk towards the null ✓ At the same BMI, women tend to present higher fat percentage than men ✓ Self-reported weight tends to underestimate BMI in heavy subjects
WC (cm)	M: >102 W: >88	✓ WC is associated more strongly with visceral fat than BMI ✓ WC is a better indicator for cancer risk than BMI
WHR	M: >0.90 W: >0.85	✓ WHR is associated more strongly with visceral fat than BMI; ✓ WHR is a better indicator for cancer risk than BMI. ✓ WHR better mirrors weight changes in men
HC	-	✓ Lower HC is associated with increased cancer mortality and increased risk of CVD
Fat distribution	Abdominal adiposity as SAT and VAT	✓ There is evidence that the association between obesity and cancer is mediated by VAT. ✓ CT is the standard method for quantification of VAT but is not feasible for population-based studies ✓ WC and WHR are surrogates of visceral obesity in population-based studies but they may not distinguish VAT and SAT at the waist level
NAFLD	Steatosis, NASH, inflammation, injury, fibrosis	✓ NAFLD is considered the hepatic manifestation of metabolic syndrome. ✓ NAFLD is a key predictor of insulin resistance

BMI, body mass index; CT: Computed Tomography; CVD: Cardiovascular Disease; HC, hip circumference; M, men; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; W, women; WC, waist circumference; WHR, waist/hip ratio.		

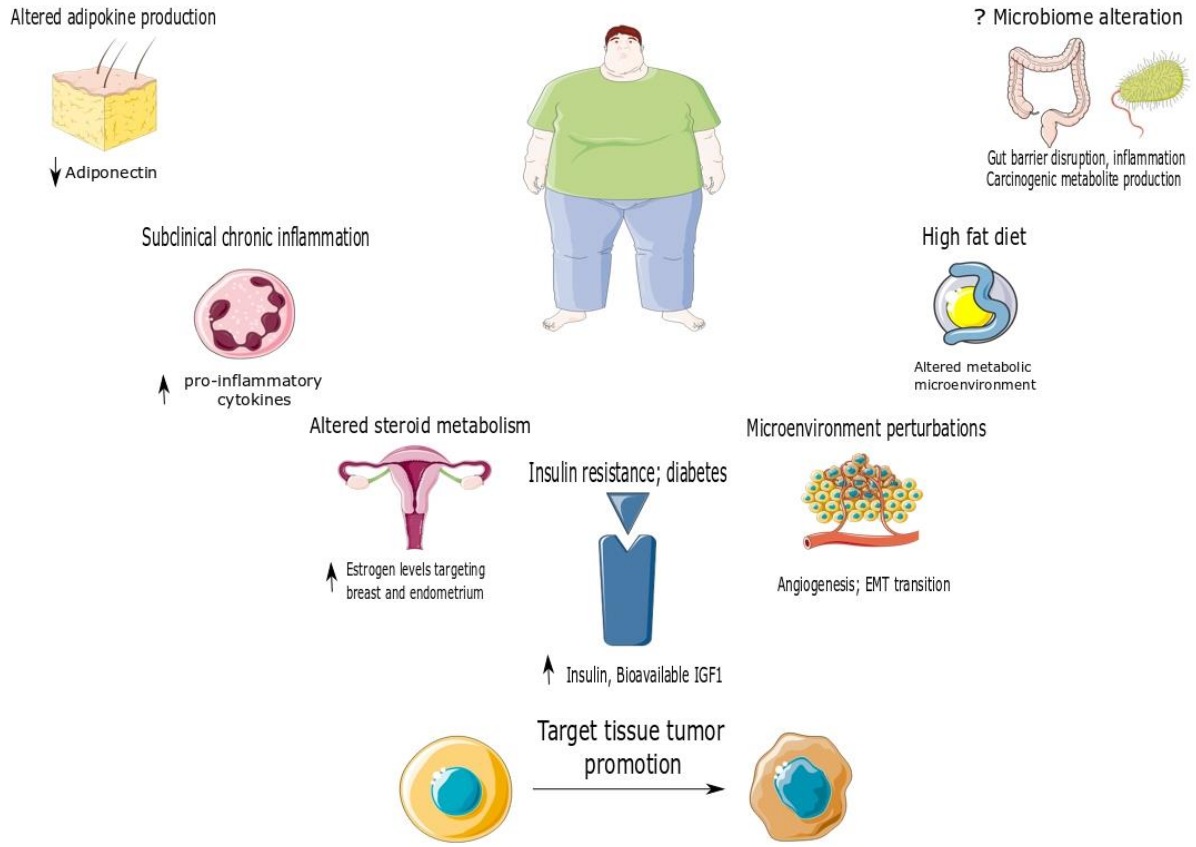

Figure legend Main mechanisms associating obesity and cancer

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Konstantinos I Avgerinos performed literature search, wrote section 7 and created Tables and Figure.

Nikolaos Spyrou performed literature search, wrote section 7 and created Tables and Figure.

Christos S Mantzoros supervised, edited and reviewed the manuscript.

Maria Dalamaga designed the review and its sections, performed literature search, wrote sections 1-6 and 8, edited and reviewed the manuscript.

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