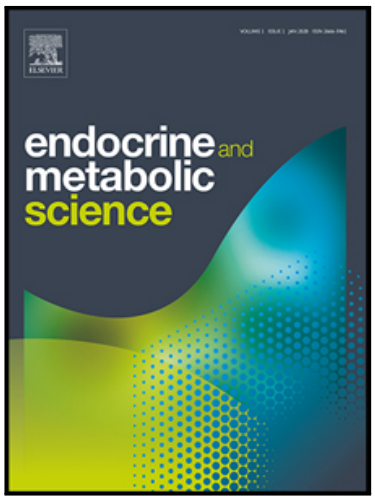

Obesity and Common Pathways of Cancer and Cardiovascular Disease

V Formica , C Morelli , S Riondino , N Renzi , D Nitti , N Di Daniele , M Roselli , M Tesauro

PII: S2666-3961(20)30019-4
DOI: https://doi.org/10.1016/j.endmts.2020.100065
Reference: ENDMTS 100065

To appear in: *Endocrine and Metabolic Science*

Received date: 25 September 2020
Revised date: 28 October 2020
Accepted date: 1 November 2020

Please cite this article as: V Formica , C Morelli , S Riondino , N Renzi , D Nitti , N Di Daniele , M Roselli , M Tesauro , Obesity and Common Pathways of Cancer and Cardiovascular Disease, *Endocrine and Metabolic Science* (2020), doi: https://doi.org/10.1016/j.endmts.2020.100065

Obesity and Common Pathways of Cancer and Cardiovascular Disease

Formica V*, Morelli C, Riondino S, Renzi N, Nitti D, Di Daniele N, Roselli M, Tesauro M

University of Rome Tor Vergata, Department of Systems Medicine, Italy

*Corresponding author. v.formica1@gmail.com

Highlights

- Obesity is increasing worldwide and recognized as pandemic.
- Cardiovascular complications and cancer are the two most fearsome long-term sequelae of obesity
- The present review summarize main common biological pathways linking obesity with cardiovascular diseases and cancer in order to suggest possible intervention strategies with double beneficial effect in terms of cancer prevention and cardiovascular risk reduction.

ABSTRACT

Obesity is constantly increasing worldwide due to the progressive globalization of sedentary lifestyle and diet rich in lipids and processed food. Cardiovascular complications and cancer are the two most fearsome long-term sequelae of obesity that justify the recent definition of this threaten as 'obesity epidemic'. Shared biological pathways can be recognized for obesity-induced cardiovascular and oncological complications that might prompt targeted interventions with potentially double beneficial effect. The present review aims at summarizing main common biological pathways linking obesity with cardiovascular diseases and cancer in order to provide a research framework within which therapeutic strategies might have at the same time cardiovascular-protective and cancer-preventive effects.

Keywords

Obesity; cancer; Cardiovascular Diseases

INTRODUCTION

In the last three decades, the impressive risk for the health associated with obesity has been increasingly recognized and the threat represented by the apparently unstoppable rise in obesity prevalence over the years has been labeled as the 'obesity pandemic'[1].

Obese and overweight subjects have approximately a 50% increase in the risk of dying compared to normal weight subjects[2]. Most of this excess mortality is due to cardiovascular disease (about 70%), while cancer is responsible for about 10% of these extra-deaths[3]. In obese cancer patients, a poor prognosis could also be related to a decreased response to treatment, either caused by adipocytes-promoted resistance to chemotherapy or to the occurrence of radioresistant phenotypes[4,5]

Based on the common link between obesity, cancer and cardiovascular complications, it is evident that effective interventions aiming at reducing body weight in high Body Mass Index (BMI) patients will have significant impact on both overall mortality and comorbidities burden.

The aim of the present review is to describe main physiological and biological changes triggered by obesity that might increase the risk of developing both cancer and cardiovascular diseases, in order to provide a mechanistic framework that might help develop fields of research on targeted interventions with double preventive effects: both cancer prevention and cardiovascular protection.

GENERAL MECHANICAL AND STRUCTURAL EFFECTS OF OBESITY

Accumulation of excess fatty acids derived from the diet and abnormal increase of adipose tissue is defined as obesity. Over-representation of the adipose tissue first determines well known hemodynamic and metabolic changes[6,7,8,9,10,11]

In order to meet the metabolic requests of enlarged tissues, an overall increase in total blood volume is generated as form of adaptation. This determines an increase in cardiac output (CO). High CO is accompanied by sympathetic hyperactivity which increases the peripheral vascular resistance and the heart rate. All these changes underlie the increased blood pressure seen in obese patients[12]

The above-described hemodynamic adaptations, if chronically persistent, lead to adverse structural modifications of the heart with left ventricular hypertrophy, left atrium enlargement, increased pulmonary artery systolic pressure, which ultimately determine dilated cardiomyopathy, heart failure and heart arrhythmias[13]. Interestingly, specific patterns of body fat distribution and composition seem to be more relevant than overall adipose tissue content for the occurrence of adverse cardiovascular adaptations. In a study by Park et al[14] of nearly 2000 subjects it was demonstrated that most harmful heart modifications were observed when visceral adipose tissue accumulation and muscle mass wasting in the limbs occurred synergistically.

Abnormal adipocyte proliferation may directly change and impair normal tissue composition by infiltrating and substituting structural cell components. In obese patients, myocardiocytes are progressively substituted by adipocytes and irregular bands of fat tissue that determine an overall adverse structural change of the heart with cardiac hyperthrophy and contractile dysfunction[15]

A number of studies demonstrated how in obese subjects subclinical changes in the structure of the heart may precede of several years overt dilated cardiomyopathy and heart failure[16].

CIRCULATING MEDIATORS INVOLVED IN THE SYSTEMIC CHANGES OF OBESITY

Apart from mechanical and structural effects caused by obesity, it is now widely recognized a real endocrine function of the adipose tissue, with direct synthesis and secretion from adipocytes of a number of bioactive substances, collectively named adipokines, that may significantly contribute to the systemic changes observed in obese patients[17]. A specific mention in terms of systemic effect of obesity merits the well characterized insulin-resistance and metabolic syndrome observed in obese and overweight subjects[18]. Authors summarize the systemic mediators involved in common pathways of oncological and cardiovascular complications of obesity in four groups

1. Hyperinsulinemia and insulin-resistance.
   A large body of literature is present about insulin-resistance during obesity. We will summarize findings regarding the double effect of insulin as cancer growth hormone and atherogenic mediator.
2. Sex-hormone alterations.
   Another systemic alteration frequently observed in obese patients is a significant sex hormone switch consisting of the combined estradiol increase and testosterone decrease. Estradiol, in particular, is recognized as a growth factor exerting protumoral effect potentially in all sex hormone-sensitive tissues such as gynecological organs, breast gland and prostate[19].
3. Systemic inflammatory mediators.
   Different patterns of adipokine secretion are observed in obese and normal weight subjects, thus prompting researchers to conclude that functional alterations accompany abnormal adipose tissue accumulation. Overall this dysfunction may be summarized as a state of chronic low grade inflammation which is present both locally within the adipose tissue and systemically.
   Adipose tissue enlargement is associated to both adipocyte hyperplasia with recruitment and proliferation of adipocyte precursors and adipocyte hypertrophy. This is concomitant to vascular rarefaction within the adipose tissue, mainly due to angiogenesis inhibition by dysfunctional fat. All these changes lead to a chronic state of localized ischemia with adipocyte necrosis and apoptosis that stimulate a persistent low grade inflammatory milieu mainly driven by resident macrophages. In this regard, adipose tissue can be considered as an highly active player of the innate immune response, in which adipocytes and macrophages are entwined in a paracrine loop and contribute to the systemic chronic low-grade inflammation that represents a favorable niche for tumor development and generalized cardiovascular

insult[20]. The low grade adipose tissue inflammation is reflected by an endocrine switch from anti-inflammatory mediators produced under normal conditions (e.g. adiponectin, transforming growth factor β (TGF-β), interleukin 10 (IL-10), secreted frizzled-related protein 5 (SFRP5), nitric oxide (NO)) to pro-inflammatory adipokines seen in obesity (e.g. leptin, c-reactive protein, angiotensin II, tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), interleukin 6 (IL-6), interleukin 18 (IL-18), resistin, retinol binding protein 4 (RBP-4), lipocalin 2, angiopoietin-like protein 2 (ANGPTL2)) [21,22]. Chronic inflammation also facilitates insulin resistance[,23]. In addition to driving systemic inflammation, many of these mediators bind directly to epithelial cell receptors and activate oncogenic downstream signaling thus further fueling the increased risk of both cardiovascular and oncological comorbidities.

4. Leptin increase and adiponectin decrease.
   Changes in leptin and adiponectin can be seen as part of the pro-inflammatory switch, however for their relevance they are treated separately in this review.

INSULIN PATHWAY IN OBESE PATIENTS AT THE CROSSROAD OF CANCER AND CARDIOVASCULAR COMPLICATIONS

A hallmark of obesity is the development of insulin-resistance and hyperinsulinemia. It is still debated whether the *primum movens* is the hyperinsulinemia occurring for the management of large quantity of metabolites in the context of over nutrition that chronically induces peripheral insulin-resistance, or whether, conversely, obesity initially causes peripheral changes of target tissues with reduced insulin sensitivity that subsequently determines a compensatory hyperinsulinemic state. In the latter case, it is hypothesized that insulin resistance is mainly due to activation of the PKC and TLR4 pathways in the target cells caused by circulating free fatty acids that are abundant in obese patients[24,25]. It is possible that both viewpoints are true and different obese subjects have different hyperinsulinemia etiologies which might potentially influence the risk of complications such as cardiovascular disease and cancer[26,27].

Insulin binds to a tetramer receptor and can act as growth factor. The insulin receptor is constituted of two extracellular subunits (alpha), which bind to insulin to activate the receptor function, and two transmembrane subunits (beta) with intracellular tyrosine kinase domain. Insulin-induced intracellular tyrosine phosphorylation is the first step to potentially modulate a myriad of downstream signaling that control cell growth and proliferation, apoptosis, differentiation, metabolic circuits.

Among the insulin-activated downstream pathways, two are well known as crucial in cancer growth, namely the RAS/RAF/MEK/ERK[28] pathway and the PI3K/AKT/mTOR pathway.

There are two isoforms of insulin receptor (IR), A and B. IR-B is mainly expressed by target tissues such as muscle, liver and adipose tissue, and regulates metabolic homeostasis. IR-B is an isoform 12 aminoacids longer than IR-A. IR-A is mainly expressed during embryonic development and is also expressed on tumor cells where may activate both RAS and PI3K. Physiologically, IR-A modulates cell proliferation and differentiation during the fetal development[29]. When abnormally expressed on cancer cells, it might contribute to stimulate cancer growth[30].

Interestingly, IR-A is also able to hetoridimerize with the receptor of the insulin-like growth factor (IGF), another well-known cancer-promoting factor, and hence respond to multiple ligands[31].

Breast cancer has been found as one of the cancers most clearly influenced by obesity and insulin pathway[32]. Insulin and IGF receptors are expressed in almost 90% of breast cancer cells[33] and hyperinsulinemia has been associated to both breast cancer development in healthy individuals and breast cancer relapse during follow-up in breast cancer patients initially radically resected for their disease[34].

Law et al. have investigated the impact of the expression of both total and phosphorylated IR and insulin-like growth factor receptor (IGF-R) by immunohistochemistry in over 400 cases of invasive breast cancer[35]. Amount of both phosphorylated and total IR/IGF-R were associated with significantly shorter survival (p values 0.05 and 0.009, respectively). Interestingly, phosphorylated IR/IGF-R were overexpressed in all the three principal subcategories of breast cancers (luminal, triple negative and HER2-positive subtypes) in a proportion ranging from 40 to 60% of cases, as compared to normal breast epithelial cells. In vitro, inhibitors of IR/IGF-R are able to reduce the receptor phosphorylation in breast cancer cell lines representative of the three breast cancer subtypes (MCF-7, SUM149, and AU565 lines) thus suppressing cancer cell growth. Clinical trials are underway to assess whether IR/IGF-R inhibitors might be confirmed as effective anti-cancer drugs in breast cancer patients. On the other hand, hyperinsulinemia and insulin-resistance can induce atheroma plaque formation and increased peripheral vascular resistance that ultimately may lead to cardiovascular complications.

Insulin exerts stimulating effect on vascular smooth muscle cell (VSMC) proliferation (a key component of the atherosclerotic plaque) via the RAS/RAF/MEK/ERK pathway and also determines direct peripheral vasoconstriction[36]. Finally, it is able to chronically and diffusely activate pathways in endothelial cells that substantially contribute to cardiovascular complications. Specifically, insulin-resistant endothelial cells reduce the production of Nitric Oxide (NO), which is essential in maintaining vasodilation. NO has also fundamental role in reducing platelet aggregation and local inflammation thus preventing the atherosclerotic disease[37].

Chapman et al reviewed competing causes of death in nearly 660 surgically resected breast cancer patients enrolled in a large phase III randomized trials of post-operative adjuvant therapy[38]. Of 170 recorded deaths, 55 (32.4%) were defined as non-breast cancer related, of which 24 due to other malignancies and 31 due to other causes (mainly cardiovascular deaths). Interestingly, high BMI and

high c-peptide level (the product of degradation of insulin) were both significantly associated with non-breast cancer deaths (p value 0.02)

OBESITY AND SEX HORMONE EFFECTS ON CANCER RISK AND CARDIOVASCULAR SYSTEM

It is well known that adipose tissue is a major source of estrogen production, and estradiol, the main estrogen hormone, is found at increased levels in obese patients[39]. Adipose tissue is rich in the enzyme aromatase that is responsible for the conversion of testosterone to estradiol. The overall increased amount of aromatase in obese patients is thought to be the main driver of hyperestrogenemia in females and hypogonadism in males[40].

Main data on the link between obesity-related sex hormones and cancer development have been produced for breast cancer, nonetheless other tumors, such as endometrial cancer and prostate cancer seem to be particularly influenced by adipose tissue-derived reproductive hormones.

Estradiol represents a main oncogenic stimulus for the epithelial cells of the breast tissue which physiologically express high levels of estrogen receptor and whose biology is almost totally regulated by the sex hormone homeostasis. The link between obesity, estradiol over-production and breast cancer risk has been extensively studied and consistently demonstrated in regard to *de novo* development of breast malignancy (incident breast cancer). The link between estradiol and breast cancer recurrence and outcomes in patients with early tumor or overall survival in patients with advanced disease is less well established.

In a recent analysis, Key et al. reviewed 18 prospective studies (over 7000 subjects) investigating the association of circulating levels of sex hormones (quantified using different essay methods) with BMI and breast cancer risk,[41]. Estradiol was significantly associated with breast cancer risk independently of the testing method (direct essay, mass spectroscopy or extraction method), with a nearly two-fold increase in the risk (Odds Ratio 2.15) when comparing the lowest versus the highest quintile of circulating estradiol level. The association of estradiol with prognosis in patients with an established diagnosis of breast cancer is less clear, with different studies showing conflicting results[42,43,44,45,46].

On the other hand, estradiol has long been thought to be protective for the cardiovascular system. The sex dimorphism in cardiovascular risk between men and premenopausal women has largely been explained by the higher circulating levels of estradiol observed in the latter group, and the raise in the incidence of cardiovascular complications seen with the menopausal transition is attributed to the remarkable drop in blood estradiol that accompanies that period of life[47]. However, the cardiovascular preventive effect of hormone supplementation in postmenopausal women studies has shown contradictory results, and evidence exists that prolonged exposition to estradiol may alter heart electrophysiology with QT interval prolongation, increased risk of *torsades de pointes* and cardiac sudden death[48].

OBESITY-INDUCED SYSTEMIC INFLAMMATION AS A RISK OF CANCER AND CARDIOVASCULAR COMPLICATIONS

A number of inflammatory mediators are increased following enlargement of dysfunctional adipose tissue.

Among the others, C reactive protein (CRP) is often increased during obesity, mainly due to the effect of IL-6 produced by adipose tissue-associated macrophages that directly stimulate CRP synthesis in the liver. CRP has been shown *in vitro* to exert prothrombotic and anti-fibrinolytic effects on endothelial cells by local induction of adhesion molecules, IL-6 and plasminogen activator inhibitor-1 (PAI-1)[49,50]

Moreover, CRP contributes to the activation of complement cascade within the atherosclerotic plaque that has potent prothrombotic effect[51]. Finally it has been found that CRP enhances plaque formation through generation of foam cells[52].

Another important inflammatory insult to arteries under obese condition is driven by an increase in toxic oxidants in the vessel wall caused by reduced HDL often seen in obese patients. It is well known, in fact, that HDL particles have important antioxidant and cardiovascular protective properties, and their reduction during obesity greatly contributes to the cardiovascular risk[53].

Other two obese-induced pathways foster inflammation in the atherosclerotic plaques. Hyperplastic adipocytes produce greater amount of angiotensin II that, apart from inducing hypertension, has direct effect on immune cells that inhabit atheromas. Indeed, atheroma immune cells express high amounts of angiotensin II type 1 receptor on their surface and angiotensin II may elicit a T helper I immune response in atherosclerotic plaque[54]. Finally, TNF-α and IL-6 produced by the adipose tissue bind directly to their receptors expressed on endothelial cells, where they activate downstream signaling that reduce, among the others, phosphorylation of the insulin receptor thus leading to enhanced insulin-resistance (see the above paragraph for discussion on the cardiovascular effect of insulin resistance) [55].

Most of the inflammatory mediators augmented during obesity and responsible for the increased cardiovascular risk also promote cancer growth by a double mechanism. A systemic oncogenic effect on a number of epithelial cells has been described for TNF-a, IL-1b, IL-6 and CRP during obesity, with a well-known process that associate chronically injured tissue, inflammation and tumor development[56,57,58]. Moreover a paracrine effect has been hypothesized in obese women for inflamed adipose tissue proximal to the breast gland. In the peri-mammary fat are often observed typical dysfunctional structures known as crown-like structures (CLS) constituted of necrotic adipocytes surrounded by macrophages which are highly productive of TNF-a and IL-1b that locally promote breast cancer via induction of the enzyme aromatase[59,60].

Apart from being oncogenic, obesity-associated IL-1b may also increase, in some cancer models, aggressiveness and resistance to chemotherapy by inducing enhanced peritumoral fibrotic reaction. Incio et al. demonstrated in a pancreatic cancer model that under obese conditions the pancreatic stromal cells known as pancreatic stellate cells (PSCs) are activated by IL-1b and angiotensin II produced by the adipose tissue. PSCs drive an intense desmoplastic reaction that favors cancer growth and, because of the lower blood perfusion of hyper-fibrotic tissue, induce cancer resistance to standard chemotherapy. The same is not observed in non-obese pancreatic cancer models. In mouse models, inhibition of obesity-associated IL-1b and angiotensin II with the use of losartan reverses pancreatic desmoplasia, restrains pancreatic tumor growth and improves response to chemotherapy[61].

ROLE OF LEPTIN AND ADIPONECTIN

Adipose tissue produces two adipokines, Adiponectin and Leptin, that were initially thought to be exclusively involved in appetite control, through binding to their hypothalamic receptors[62]. Obesity disrupts this balance, augmenting leptin release and reducing adiponectin. During obesity, a saturation of central leptin receptors is observed, leading to a condition known as leptin-resistance[63]. It is now known that increased leptin levels carry out peripheral and metabolic functions, justifying its potential role in tumor growth and cardiovascular diseases. Leptin promotes inflammatory reactions, oxidative stress and both atherogenic and thromboembolic processes, and leads to endothelial dysfunction, smooth muscle cell proliferation, arterial stiffness and development of vulnerable atherosclerotic plaques[64]. Clinical and preclinical studies demonstrated a direct correlation between leptin levels and onset and severity of coronary heart disease (CHD), heart failure (HF), stroke and carotid artery disease as well as hypertension and type 2 diabetes mellitus[65,66].

Leptin involvement in tumor growth takes place through the binding to its receptor Ob-R, expressed on neoplastic cell surface, followed by enablement of the Pi3K-AKT-mTOR pathway. An inverse correlation with survival between increased leptin and reduced adiponectin levels has been demonstrated in colorectal cancer patients suggesting that these two molecules might represent prognostic indicators in this disease. , Maintenance of higher levels of adiponectin might identify patients with longer survival as well as better response to treatment[67].

On the light of its key role in both pathologies, reducing leptin levels could positively influence prognosis in cancer and also be regarded as a form of cardiovascular prevention. Scientific attention has been focusing on metformin, a biguanide antidiabetic medication. Metformin is able to reduce leptin with subsequent reduction in reactive oxygen species and smooth muscle cell proliferation, thus reducing the risk of cardiovascular disease., Metformin also determines a drop in insulin and glucose levels which negatively regulate Pi3K-AKT-mTOR pathway and cancer growth risk.[68].

CONCLUSIONS

In the present review, we summarized pathways activated during obesity that simultaneously increase the risk of cancer and cardiovascular events (figure 1 and table 1). Weight-loss interventions and targeted pharmacological modulations in obese patients that particularly restrain hyperinsulinemia, estradiol secretion, CRP, TNF-α,IL-6 and leptin should be regarded as the most promising candidate to obtained double therapeutic effects against oncological and cardiovascular sequelae of obesity epidemic.

Declaration of Competing Interest

None.

REFERENCES

<BIBL>

[1] Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011; 378: 804-14.

[2] Xu H, Cupples LA, Stokes A, Liu CT. Association of Obesity With Mortality Over 24 Years of Weight History: Findings From the Framingham Heart Study [published correction appears in JAMA Netw Open. 2018 Dec 7;1(8):e186657]. *JAMA Netw Open*. 2018;1(7):e184587. Published 2018 Nov 2. doi:10.1001/jamanetworkopen.2018.4587.

[3] GBD 2015 Obesity Collaborators, Afshin A, Forouzanfar MH, et al. Health Effects of Overweight and Obesity in 195 Countries over 25 Years. N Engl J Med. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362.

[4] Duong MN, Geneste A, Fallone F, Li X, Dumontet C, Muller C. The fat and the bad: Mature adipocytes, key actors in tumor progression and resistance. Oncotarget. 2017 May 20;8(34):57622-57641. doi: 10.18632/oncotarget.18038. PMID: 28915700; PMCID: PMC5593672..

[5] Bochet L, Meulle A, Imbert S, Salles B, Valet P, Muller C. Cancer-associated adipocytes promotes breast tumor radioresistance. Biochem Biophys Res Commun. 2011 Jul 22; 411(1):102-6.

[6] Schinzari F, Tesauro M, Cardillo C. Endothelial and Perivascular Adipose Tissue Abnormalities in Obesity-Related Vascular Dysfunction: Novel Targets for Treatment. J Cardiovasc Pharmacol. 2017;69(6):360-368. doi:10.1097/FJC.0000000000000469.

[7] Schinzari F, Tesauro M, Veneziani A, Mores N, Di Daniele N, Cardillo C. Favorable Vascular Actions of Angiotensin-(1-7) in Human Obesity. Hypertension. 2018;71(1):185-191. doi:10.1161/HYPERTENSIONAHA.117.10280.

[8] Campia U, Tesauro M, Di Daniele N, Cardillo C. The vascular endothelin system in obesity and type 2 diabetes: pathophysiology and therapeutic implications. Life Sci. 2014;118(2):149-155. doi:10.1016/j.lfs.2014.02.028.

[9] Schinzari F, Tesauro M, Rovella V, et al. Generalized impairment of vasodilator reactivity during hyperinsulinemia in patients with obesity-related metabolic syndrome. Am J Physiol Endocrinol Metab. 2010;299(6):E947-E952. doi:10.1152/ajpendo.00426.2010.

[10] Schinzari F, Tesauro M, Cardillo C. Increased endothelin-1-mediated vasoconstrictor tone in human obesity: effects of gut hormones. Physiol Res. 2018;67(Suppl 1):S69-S81. doi:10.33549/physiolres.933821.

[11] Piro MC, Tesauro M, Lena AM, et al. Free-amino acid metabolic profiling of visceral adipose tissue from obese subjects. Amino Acids. 2020;52(8):1125-1137. doi:10.1007/s00726-020-02877-6.

[12] Alpert MA. Obesity cardiomyopathy: pathophysiology and evolution of the clinical syndrome. Am J Med Sci 2001;321:225–36.

[13] Koliaki C, Liatis S, Kokkinos A. Obesity and cardiovascular disease: revisiting an old relationship. Metabolism. 2019;92:98-107. doi:10.1016/j.metabol.2018.10.011.

[14] Park J, Kim NH, Kim SH, Kim JS, Kim YH, Lim HE, et al. Visceral adiposity and skeletal muscle mass are independently and synergistically associated with left ventricular structure and function: the Korean Genome and Epidemiology Study. Int J Cardiol 2014;176:951–5..

[15] Warnes CA, RobertsWC. The heart in massive (more than 300 pounds or 136 kilograms) obesity: analysis of 12 patients studied at necropsy. Am J Cardiol 1984;54: 1087–91.

[16] Wong CY, O'Moore-Sullivan T, Leano R, Byrne N, Beller E, Marwick TH. Alterations of left ventricular myocardial characteristics associated with obesity. Circulation 2004;110:3081–7..

[17] Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548–56.

[18] Candi E, Tesauro M, Cardillo C, et al. Metabolic profiling of visceral adipose tissue from obese subjects with or without metabolic syndrome. *Biochem J*. 2018;475(5):1019-1035. Published 2018 Mar 15. doi:10.1042/BCJ20170604.

[19] Michalakis K, Mintziori G, Kaprara A, Tarlatzis BC, Goulis DG. The complex interaction between obesity, metabolic syndrome and reproductive axis: a narrative review. Metabolism. 2013;62(4):457-478. doi:10.1016/j.metabol.2012.08.012

[20] Riondino S, Roselli M, Palmirotta R, Della-Morte D, Ferroni P, Guadagni F. Obesity and colorectal cancer: role of adipokines in tumor initiation and progression. World J Gastroenterol. 2014;20(18):5177-90.

[21] Tesauro M, Schinzari F, Rovella V, et al. Tumor necrosis factor-alpha antagonism improves vasodilation during hyperinsulinemia in metabolic syndrome. Diabetes Care. 2008;31(7):1439-1441. doi:10.2337/dc08-0219.

[22] Tesauro M, Rizza S, Iantorno M, et al. Vascular, metabolic, and inflammatory abnormalities in normoglycemic offspring of patients with type 2 diabetes mellitus. Metabolism. 2007;56(3):413-419. doi:10.1016/j.metabol.2006.10.026.

[23] Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175–84..

[24] Dresner A, Laurent D, Marcucci M, Griffin ME, Dufour S, Cline GW, Slezak LA, Andersen DK, Hundal RS, Rothman DL, et al. Effects of free fatty acids on glucose transport and IRS-1-associated phosphatidylinositol 3-kinase activity. J Clin Investig. 1999;103(2):253–9.

[25] Dong B, Qi D, Yang L, Huang Y, Xiao X, Tai N, Wen L, Wong FS. TLR4 regulates cardiac lipid accumulation and diabetic heart disease in the nonobese diabetic mouse model of type 1 diabetes. Am J Physiol Heart Circ Physiol. 2012;303(6):H732–42.

[26] Czech MP. Insulin action and resistance in obesity and type 2 diabetes. Nat Med. 2017;23(7):804-814. doi:10.1038/nm.4350.

[27] Tesauro M, Schinzari F, Adamo A, et al. Effects of GLP-1 on forearm vasodilator function and glucose disposal during hyperinsulinemia in the metabolic syndrome. Diabetes Care. 2013;36(3):683-689. doi:10.2337/dc12-0763.

[28] Skolnik EY, Batzer A, Li N, et al: The function of GRB2 in linking the insulin receptor to Ras signaling pathways. Science 260:1953-1955, 1993.

[29] Moller DE, Yokota A, Caro JF, et al: Tissuespecific expression of two alternatively spliced insulin

[30] Belfiore A,Malaguarnera R: Insulin receptor and cancer. Endocr Relat Cancer 18:R125-R147, 2011.

[31] Lawrence MC, McKern NM, Ward CW: Insulin receptor structure and its implications for the IGF-1 receptor. Curr Opin Struct Biol 17:699-705, 2007.

[32] Ferroni P, Riondino S, Buonomo O, Palmirotta R, Guadagni F, Roselli M. Type 2 Diabetes and Breast Cancer: The Interplay between Impaired Glucose Metabolism and Oxidant Stress. Oxid Med Cell Longev. 2015;2015:183928. doi: 10.1155/2015/183928. Epub 2015 Jun 11. PMID: 26171112; PMCID: PMC4480937..

[33] Mulligan AM, O'Malley FP, Ennis M, et al: Insulin receptor is an independent predictor of a favorable outcome in early stage breast cancer. Breast Cancer Res Treat 106:39-47, 2007.

[34] Formica V, Tesauro M, Cardillo C, Roselli M. Insulinemia and the risk of breast cancer and its relapse. Diabetes Obes Metab. 2012;14(12):1073-1080. doi:10.1111/j.1463-1326.2012.01614.x.

[35] Law JH, Habibi G, Hu K, et al: Phosphorylated insulin-like growth factor-i/insulin receptor is present in all breast cancer subtypes and is related to poor survival. Cancer Res 68:10238-10246, 2008.

[36] Wang CC, Gurevich I, Draznin B. Insulin affects vascular smooth muscle cell phenotype and migration via distinct signaling pathways. Diabetes. 2003;52(10):2562–9..

[37] Wu G, Meininger CJ. Nitric oxide and vascular insulin resistance. BioFactors (Oxford, England). 2009;35(1):21–7..

[38] Chapman JA, Pritchard KI, Goss PE, Ingle JN, Muss HB, Dent SF, Vandenberg TA, Findlay B, Gelmon KA, Wilson CF, Shepherd LE, Pollak MN. Competing risks of death in younger and older postmenopausal breast cancer patients. World J Clin Oncol. 2014 Dec 10;5(5):1088-96. doi: 10.5306/wjco.v5.i5.1088. PMID: 25493245; PMCID: PMC4259936..

[39] Ingram D, Nottage E, Ng S, Sparrow L, Roberts A, Willcox D. Obesity and breast disease. The role of the female sex hormones. Cancer. 1989;64(5):1049-1053. doi:10.1002/1097-0142(19890901)64:5<1049::aid-cncr2820640515>3.0.co;2-m.

[40] Siiteri PK. Adipose tissue as a source of hormones. Am J Clin Nutr. 1987;45(1 Suppl):277-282. doi:10.1093/ajcn/45.1.277.

[41] Key TJ, Appleby PN, Reeves GK, et al. Steroid hormone measurements from different types of assays in relation to body mass index and breast cancer risk in postmenopausal women: Reanalysis of eighteen prospective studies. Steroids. 2015;99(Pt A):49-55. doi:10.1016/j.steroids.2014.09.001.

[42] Lønning PE, Helle SI, Johannessen DC, et al: Influence of plasma estrogen levels on the length of the disease-free interval in postmenopausal women with breast cancer. Breast Cancer Res Treat 39: 335-341, 1996

[43] Holmberg L, Norde´ n T, Lindgren A, et al: Preoperative oestradiol levels - relation to survival in breast cancer. Eur J Surg Oncol 27:152-156, 2001 62. Micheli A, Meneghini E, Secreto G, et al: Plasma testosterone and prognosis of postmenopausal breast cancer patients. J Clin Oncol 25: 2685-2690, 2007

[44] Kim JY, Han W, Moon HG, et al: Prognostic effect of preoperative serum estradiol level in postmenopausal breast cancer. BMC Cancer 13:503, 2013

[45] Benn M, Voss SS, Holmegard HN, et al: Extreme concentrations of endogenous sex hormones, ischemic heart disease, and death in women. Arterioscler Thromb Vasc Biol 35:471-477, 2015

[46] Duggan C, Stanczyk F, Campbell K, et al: Associations of sex steroid hormones with mortality in women with breast cancer. Breast Cancer Res Treat 155:559-567, 2016.

[47] Dworatzek E, Mahmoodzadeh S. Targeted basic research to highlight the role of estrogen and estrogen receptors in the cardiovascular system. Pharmacol Res. 2017;119:27-35. doi:10.1016/j.phrs.2017.01.019.

[48] Salem JE, Alexandre J, Bachelot A, Funck-Brentano C. Influence of steroid hormones on ventricular repolarization. Pharmacol Ther. 2016;167:38-47. doi:10.1016/j.pharmthera.2016.07.005.

[49] Du Clos, T.W. & Mold, C. C-reactive protein: an activator of innate immunity and a modulator of adaptive immunity. Immunol. Res. 30, 261–277 (2004).

[50] Devaraj, S., Xu, D.Y. & Jialal, I. C-reactive protein increases plasminogen activator inhibitor-1 expression and activity in human aortic endothelial cells: implications for the metabolic syndrome and atherothrombosis. Circulation 107, 398–404 (2003)..

[51] Mathieu, P., Pibarot, P. & Després, J.P. Metabolic syndrome: the danger signal in atherosclerosis. Vasc. Health Risk Manag. 2, 285–302 (2006)..

[52] Mathieu P, Lemieux I, Després JP. Obesity, inflammation, and cardiovascular risk. Clin Pharmacol Ther. 2010;87(4):407-416. doi:10.1038/clpt.2009.311.

[53] Hansel, B. et al. Metabolic syndrome is associated with elevated oxidative stress and dysfunctional dense high-density lipoprotein particles displaying impaired antioxidative activity. J. Clin. Endocrinol. Metab. 89, 4963–4971 (2004)..

[54] Mazzolai, L. et al. Endogenous angiotensin II induces atherosclerotic plaque vulnerability and elicits a Th1 response in ApoE-/- mice. Hypertension 44, 277–282 (2004)..

[55] Karalis, K.P., Giannogonas, P., Kodela, E., Koutmani, Y., Zoumakis, M. & Teli, T. Mechanisms of obesity and related pathology: linking immune responses to metabolic stress. FEBS J. 276, 5747–5754 (2009).

[56] Bachelot T, Ray-Coquard I, Menetrier-Caux C, et al: Prognostic value of serum levels of interleukin 6 and of serum and plasma levels of vascular endothelial growth factor in hormone-refractory metastatic breast cancer patients. Br J Cancer 88:1721-1726, 2003

[57] Sicking I, Edlund K, Wesbuer E, et al: Prognostic influence of pre-operative C-reactive protein in node-negative breast cancer patients. PLoS One 9:e111306, 2014

[58] Allin KH, Bojesen SE, Nordestgaard BG: Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 27:2217-2224, 2009.

[59] Subbaramaiah K, Howe LR, Bhardwaj P, et al: Obesity is associatedwith inflammation and elevated aromatase expression in themousemammary gland. Cancer Prev Res (Phila) 4:329-346, 2011.

[60] Morris PG, Hudis CA, Giri D, et al: Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. Cancer Prev Res (Phila) 4:1021-1029, 2011.

[61] Incio J, Liu H, Suboj P, et al. Obesity-Induced Inflammation and Desmoplasia Promote Pancreatic Cancer Progression and Resistance to Chemotherapy. Cancer Discov. 2016;6(8):852-869. doi:10.1158/2159-8290.CD-15-1177.

[62] Trayhurn P, Bing C. Appetite and energy balance signals from adipocytes. Philos Trans R Soc Lond B Biol Sci. 2006 Jul 29;361(1471):1237-49. doi: 10.1098/rstb.2006.1859. PMID: 16815801; PMCID: PMC1642696.

[63] Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, Obesity, and Leptin Resistance: Where Are We 25 Years Later? Nutrients. 2019 Nov 8;11(11):2704. doi: 10.3390/nu11112704. PMID: 31717265; PMCID: PMC6893721..

[64] Schinzari F, Tesauro M, Rovella V, et al. Leptin stimulates both endothelin-1 and nitric oxide activity in lean subjects but not in patients with obesity-related metabolic syndrome. J Clin Endocrinol Metab. 2013;98(3):1235-1241. doi:10.1210/jc.2012-3424.

[65] Sweeney G. Cardiovascular effects of leptin. Nat Rev Cardiol. 2010 Jan;7(1):22-9. doi: 10.1038/nrcardio.2009.224. Epub 2009 Dec 1. PMID: 19949425..

[66] Unger RH, Roth MG. A new biology of diabetes revealed by leptin. Cell Metab. 2015 Jan 6;21(1):15-20. doi: 10.1016/j.cmet.2014.10.011. Epub 2014 Nov 20. Erratum in: Cell Metab. 2015 Apr 7;21(4):647. PMID: 25456738.

[67] Guadagni F, Roselli M, Martini F, Spila A, Riondino S, D'Alessandro R, Del Monte G, Formica V, Laudisi A, Portarena I, Palmirotta R, Ferroni P. Prognostic significance of serum adipokine levels in colorectal cancer patients. Anticancer Res. 2009;29(8):3321-7.

[68] Katsiki N, Mikhailidis DP, Banach M. Leptin, cardiovascular diseases and type 2 diabetes mellitus. Acta Pharmacol Sin. 2018;39(7):1176-1188. doi:10.1038/aps.2018.40.

</BIBL>

Figure 1 representation of main obesity-related factors that contribute concurrently to cancer and cardiovascular diseases

Table 1. Main mechanistic evidence relating obesity to cancer growth.

Cancer Type	**Obesity-related cancer promoting mechanisms**	**Reference**
Breast cancer	Hyperinsulinemia induces cell proliferation via direct activation of Insulin Receptors expressed on breast epithelial cells&&&Increased estradiol levels determine direct proliferative effect on breast epithelial cells&&&Brast-associated adipocytes locally stimulate breast cancer	38,39,40&&&&&&&&&45&&&&&63,64
Lung cancer	Increased c-reactive protein promotes lung cancer	62
Pancreatic cancer	Pancreatic adipocytes induce desmoplastic reaction with cancerogenic effect and resistance to anticancer drugs	65
Colorectal cancer	Leptin directly activate Pi3K-AKT-mTOR pathway with cancer promotion	71