Review

Turk J Endocrinol Metab 2018;22:244-253

Obesity and Breast Cancer: Adipose Tissue, Adipocytokines, Chronic Inflammation, and Hypoxia

Obezite ve Meme Kanseri: Yağ Dokusu, Adipositokinler, Kronik İnflamasyon ve Hipoksi

Ilgın Yıldırım Şimşir, Utku Erdem Soyaltın, Candeğer Yılmaz*

Ege University Faculty of Medicine, Division of Endocrinology and Metabolism Disorders, İzmir, Turkey
*Ege University Faculty of Medicine, Division of Endocrinology and Metabolism Disorders (Retired Lecturer), İzmir, Turkey

Abstract

Obesity that has represented defense and warfare in the stone age and beauty, success, authority, and welfare in the middle ages, has now turned into a chronic and undesirable low-grade inflammatory disease that adversely affects the lifespan and quality of life. It results in serious complications such as Type 2 diabetes, cardiovascular disease, and cancer and is considered a pandemic all over the world. Chronic inflammation in obesity is attributed to an increase in the release of pro-inflammatory factors. This makes it a risk factor for many types of cancers, such as colon, gastric, breast, and prostate carcinomas, suggesting a cause and effect relationship between obesity and cancer. These pro-inflammatory factors act as signal transducers for tumor growth and progression. In recent years, animal studies have shown that adipocyte hypoxia can result in tumor growth in adipocytes and stromal vascular tissue. However, the mechanisms associated with obesity and cancer are still not completely understood. In the present study, we discussed the relationship between inflamed adipose tissue and cancer in obese patients, together with the contribution of interaction between hormones, cytokines, growth factors, and angiogenesis.

Keywords: Obesity; breast cancer; inflammation; cytokines; adipose tissue

Özet

Taş devrinde savunma, mücadele gücü, kuvveti, orta çağda güzellik, başarı, otorite, iktidar ve zenginliği simgeleyen obezite; günümüzde yaşam süresini ve yaşam kalitesini olumsuz etkileyen kronik ve istenmeyen düşük dereceli inflamatuar bir hastalığa dönüşmüştür. Tip 2 diyabet, kardiyovasküler hastalık ve kanser gibi ciddi komplikasyonlara neden olmakta ve tüm dünyada bir pandemi olarak kabul edilmektedir. Obezitede kronik inflamasyon, proinflamatuar faktörlerin salınımındaki artışla ilişkilendirilmektedir. Bu; kolon, mide, meme ve prostat karsinomları gibi birçok kanser türü için bir risk faktörüdür ve obezite ile kanser arasında neden ve sonuç ilişkisi olduğunu düşündürmektedir. Bu proinflamatuar faktörler, tümör büyümesi ve ilerlemesi için sinyal transdüseri görevi görmektedir. Son yıllarda, hayvan çalışmaları adiposit hipoksisinin adipositlerde ve stromal vasküler dokuda tümör büyümesi ile sonuçlanabileceğini göstermiştir. Bununla birlikte, obezite ve kanser ile ilişkili mekanizmalar hâlâ tam olarak anlaşılamamıştır. Bu çalışmada, obez hastalarda inflame adipoz doku ve kanser arasındaki ilişkinin; hormonlar, sitokinler, büyüme faktörleri ve anjiyogenez arasındaki etkileşimin katkısıyla birlikte tartışılması amaçlanmıştır.

Anahtar kelimeler: Obezite; meme kanseri; inflamasyon; sitokinler, adipoz doku

Introduction

Obesity, an increasing pandemic in the world, is defined as an abnormal or excessive accumulation of fat to the extent that it impairs human health. According to the 2014 report of World Health Organization (WHO), more than 1.9 billion adults are overweight (39%) and over 600 million adults are obese (13%) worldwide (1). In the United States alone, this rate has been reported to be 69% and 35%, respectively (2). Obesity leads to increased health problems, thereby reducing life expectancy (3). According to a recent study, association of

Address for Correspondence: Ilgın Yıldırım Şimşir, Ege University Faculty of Medicine, Division of Endocrinology and Metabolism Disorders, Izmir, Turkey
Phone: +90532 512 69 17 **E-mail:** ilginyildirim@hotmail.com **Received:** 13/09/2017 **Accepted:** 24/11/2017

DOI: 10.25179/tjem.2017-57808

body mass index (BMI) with death due to all causes has increased from 23.7 kg/m2 in the cohort that was evaluated from 1976 to 1978 to 27.0 kg/m2 in the cohort that was evaluated form 2003 to 2013 (4).

Obesity, which is the second leading cause of preventable deaths after cigarette smoking, is a multifactorial disease (5). Genetic factors have a penetrance of 25 to 40% in obesity, whereas environmental factors, such as low the level of physical activity due to sedentary lifestyle and consumption of foods rich in simple carbohydrates and oil, are also involved. Earlier studies report that obesity increases the susceptibility to cardiovascular disease, type 2 diabetes mellitus (DM), obstructive sleep apnea, osteoarthritis, and many types of cancers (3, 6-10). According to "The Turkish Diabetes Epidemiology Study (TURDEP-II)," obesity increased by 44% in Turkey in 12 years. Interestingly, the average age of the adult population has also increased by four years in the 12-year period since TURDEP-I. The average male and female height increased by 1 cm each, whereas the body weight increased by 8 kg in men and 6 kg in women, waist circumference by 7 cm in men and 6 cm in women, the hip circumference by 2 cm in men and 7 cm in women. According to the TURDEP-II study, obesity prevalence was 32% in Turkey (11, 12). These results indicate that obesity and its consequences are important social health problems all over the world and more research is required in this regard.

Obesity involves an excessive accumulation of fat in adipocytes and is accompanied by a low-grade chronic inflammation. Recent studies indicate that fat tissue functions as an endocrine organ (13) and has a heterogeneous structure, consisting of preadipocytes, fibroblasts, endothelial cells, nerve cells, and macrophages around mature adipocytes (7). Majority of cells found in fat tissue are brown, white, and beige adipocytes (14). White fat tissue acts as the primary endocrine organ with metabolically active secretions. For this reason, adipocytes behave differently with different physiologic reactions in lipid and glucose metabolism, and during blood pressure regulation, angiogenesis, and homeostasis. Accumulation of fat beyond the threshold limit leads to hypoxia and necrosis, which, in turn, initiate chronic subclinical inflammation and metabolic disorders, as well as changes in carcinogenesis, tumor progression, and formation of metastases (9).

Fat tissue is known as the largest endocrine organ of the body owing to the secretion of many cytokines and hormones. An increase in adipose tissue leads to an increase in the synthesis of leptin, also known as the starvation hormone. Chronic inflammation in enlarged adipose tissue augments the secretion of IL-6 and TNF. Since increased levels of these cytokines, along with leptin, are also reported in cancer patients, obesity is considered to be a cause of cancer development, growth, progression, and metastasis (15).

Obesity is characterized by fat tissue hypoxia associated with chronic type 1 inflammation, decrease in adiponectin, increase in leptin, death of adipocytes, mitochondrial dysfunction, and cancer development as a result of insulin resistance, increased proinflammatory cytokines (IL-1, IL-6, TNF-α, and PAI-1), and infiltration of macrophages. Hypoxia-induced factor-1α (HIF-1α), released during hypoxia, regulates the transcription of the genes associated with carcinogenesis and is associated with increased formation of metastases (10, 16-19). The relationship between inflammation and cancer was first described by Virchow more than 100 years ago, who observed that leukocytes were increased in the neoplastic tissue (20-22).

Together with the relationship between chronic inflammation and cancer, these findings reveal many common mechanisms for the association between obesity and cancer.

Relationship Between Breast Cancer and Obesity

Although breast cancer has not yet acquired a pandemic aspect as obesity, it is the most common type of cancer in women worldwide, and the leading cause of death by cancer (23). The development of breast cancer in the premenopausal or postmenopausal period is important in terms of assessing the risk factors. Various factors, including genetic, hormonal, and environmental factors, influence the development of the malignant tumor. Weight gain and obesity pose a po-

tential risk for breast cancer. Several studies exist that have investigated the relationship between obesity and breast cancer. However, the results of these studies are not consistent. Some researchers advocate that the risk of breast cancer increases in both premenopausal and postmenopausal periods if BMI is greater than 30 kg/m^2 (24-27). While some researchers indicate that obesity decreases breast cancer risk in the premenopausal period but increases the risk in the postmenopausal period (28-32). In "Nurses' Health Study," which included 87,143 women in menopause period followed up for a long time, it was reported that women who gained 10 kg or more weight after menopause had a higher risk of breast cancer than those who maintained their weight (33). In studies reporting premenopausal obesity to be protective against breast cancer, pathogenesis has not yet been completely elucidated. However, breast cancer in the premenopausal period was positively associated with estrogen and androgen levels in the circulatory system (34). Estrogen, estrogen receptor (ER), leptin, and adiponectin play a pivotal role in this mechanism. It has been shown that estrogen, a potent mitogen for breast cells, is involved in the development of breast tumors. Estrogen is synthesized primarily in ovarium and placenta with the aromatase activity in the premenopausal period. Its aromatase activity in the fat tissue and epidermis is more effective after menopause that increases the conversion of androgens to estrogen. Therefore, fat tissue in the breast is an important source of local estrogen production (18).

Breast is a modified apocrine gland that produces milk after delivery. After menopause, adipose tissue is the only source of estrogen production through the aromatization of androstenedione, which is a 19-carbon steroid. Increased aromatase activity and androstenedione production in obesity lead to a larger total estrogen pool in obese women (35). Thus, anti-estrogenic compounds and aromatase inhibitors are the methods used to treat breast cancer (36).

Obesity is also considered a risk factor in relapse of breast cancer and poor survival (37-39). A meta-analysis published in 2011 reported that the lifestyle changes are the foremost step in the prevention and treatment of obesity. These lifestyle changes can decrease breast cancer progression and increase overall survival (40).

Earlier studies have indicated that high levels of leptin in blood have a mitogenic effect, which might be attributed to leptin resistance associated with obesity (41, 42). Leptin, when binds to its receptor, can result in breast cancer cell proliferation and angiogenesis; it also stimulates the estrogen receptor pathway by increasing aromatization (43). Adiponectin, with antagonistic effects to leptin, has anti-proliferative, pro-apoptotic, and anti-estrogen effects and its low levels play a role in the progression of breast cancer (44, 45). Recently, different studies have reported the relationship between adiponectin and leptin and breast cancer (46-48).

In addition, hyperinsulinemia and hyperglycemia that develop with obesity affect breast cancer development and progression (49). Insulin directly stimulates cell proliferation in breast cancer cell lines and reduces sex hormone-binding globulin (SHBG) levels, thereby increasing free estradiol. Some researchers suggest that insulin-like growth factor-1 (IGF-1) levels, which rise in premenopausal women, are associated with the risk of developing breast cancer. Increased level of insulin is one of the reasons for breast cancer recurrence and death in breast cancer survivors. Therefore, targeting insulin as a therapeutic modality in breast cancer could be an option in the adjuvant treatment of breast cancer. It seems that insulin may trigger the activation of a cascade of proliferative and anti-apoptotic events in the cancer cells. Metformin, an oral anti-diabetic known for 50 years, may also have direct effects on cancer cells. Metformin causes Her-2 suppression through inhibition of mTOR in breast cancer cells. Yurekli et al. reported the use of metformin as an adjuvant therapy in breast cancer patients to target insulin reduction and alter Her-2 oncogene-based molecular pathogenetic steps in breast cancer (50).

A nutritious, energy balanced diet with macronutrients and physical activity are the main determinants of IGF-1 levels. The changes in IGF-1 axis due to nutritional and lifestyle changes can mediate the develop-

ment and progression of cancer (18, 51). Metabolic changes due to insulin resistance and cytokines produced from adipose tissue play a significant role in making the tumors more aggressive. Insulin acts through its receptors found in normal cells and cancer cells and stimulates cell growth by allowing glucose and amino acids to enter the cells. Insulin and IGF-1 stimulate estrogen synthesis and the tyrosine kinase signaling pathway. Binding of insulin to IGF-1 receptor leads to mitogenicity and transformation, reduction in the synthesis of IGF-binding proteins (IGFBP-1 and IGFBP-2), and increased free IGF-1 levels. The PI3K-Akt signaling pathway, the main pathway of insulin and IGF-1 effect, upon activation by high levels of insulin and IGF-1 transduces the signal to the nucleus and inhibits p27 function by phosphorylation, thereby inhibiting cell growth.

HER-2/neu (c-erbB-2) is an oncogene that encodes the tyrosine kinase receptor involved in the pathogenesis of breast cancer. Insulin, IGF-1, and estrogen stimulate proliferation of breast cancer cells via a signaling pathway activated by HER-2/neu. Increased IGF-1 receptor stimulation has been shown to play an important role in the development of resistance against monoclonal antibody called trastuzumab, developed against HER-2/neu (52).

The anti-estrogenic drug, tamoxifen, is one of the strongest medications used in the treatment of breast cancer and has been shown to reduce IGF-1 levels. The main reason for its ineffectiveness is its insufficiency to block estrogen receptor due to high levels of insulin. This explains why patients with postmenopausal diabetic breast cancer are desensitized to its effects. Metformin that has shown to break insulin resistance in cell culture studies reduces the growth of breast cancer cells that are resistant to tamoxifen (53-55). It is also used in the treatment of type 2 diabetes and has been shown by multiple studies to prolong the survival in breast cancer by decreasing AMP kinase pathway and insulin levels. Again, metformin reduces the cardiotoxic effect of trastuzumab in HER-2-positive patients. This effect is seen not only in patients who have type 2 diabetes but also in patients without type 2 diabetes (55).

Breast cancer, as a result of direct effect of insulin or indirectly by increasing IGF-1 receptor levels, may develop resistance to treatment by increasing the aggressiveness of tumor cells.

Cell proliferation and angiogenesis are stimulated by proinflammatory cytokines, such as IL-6, IL-1β, tumor necrosis factor-α (TNF-α), C reactive protein (CRP), and PAI-1, that are released during chronic low-grade inflammation in insulin resistance.

One of the problems encountered in the treatment of patients with breast cancer is weight gain during or after treatment. It affects the treatment negatively through the mechanisms described below.

Insulin resistance and high levels of insulin or IGF-1 can be controlled by simple, easily applicable, and harmless approaches, such as exercise and nutritional regulation. Metabolic changes caused by reduced activity and high caloric diet are involved both in the pathogenesis of breast cancer and negative prognosis of breast cancer. Since the mechanisms involved in pathogenesis could be improved with exercise and medical nutrition treatments, it is important that patients diagnosed with breast cancer do not gain weight. Additionally, those who are overweight during the diagnosis must lose weight in a controlled manner. In this way, protection against breast cancer becomes possible and the chances of successful treatment could be increased.

Obesity-Related Comorbid Conditions Affect Breast Cancer Development and Surveillance

Dyslipidemia

Hyperlipidemia, which often accompanies type 2 diabetes and obesity, is an important metabolic problem. In addition, dyslipidemia and hypercholesterolemia are found to be associated with aggressive breast cancer growth. In particular, it affects the ER ligand, thus contributing to the growth of ER-positive tumors. Many studies have demonstrated the role of statins in the treatment of hyperlipidemia to prolong the survival in breast cancer patients. One of the most recent studies in this regard is the observational BIG 1-98 study (56), in which statin added to the adjuvant endocrine therapy, as

a part of the treatment of ER-positive breast cancer, reduced total cholesterol, thus decreasing the cholesterol metabolite 27-hydroxycholesterol (27HC). 27HC is a molecule that acts as an estrogen receptor ligand and its elevated levels in blood accelerate the tumor growth (57). In the BIG 1-98 study, 318 ER-positive patients in the postmenopausal period were evaluated after treatment with letrozole, 106 patients with tamoxifen, 189 patients initially with tamoxifen followed by letrozole, and 176 patients initially with letrozole followed by tamoxifen. The hazard ratio (HR) for only endocrine therapy before statin was added to the treatment was 0.82 for disease-free survival, 0.83 for disease relapse, and 0.81 for disease survival without distant. The addition of statin to treatment protocol improved the parameters; HR ratios were 0.79, 0.76, and 0.74, respectively (56). However, apart from this observational study, there is an absolute need for randomized, controlled studies to reach a final and foolproof conclusion.

Nonsteroidal Anti-Inflammatory Drugs

The recent surge in the incidence of osteoarthritis is attributed to mechanical load on joints in obese patients and increases the frequency of the use of nonsteroidal anti-inflammatory drugs (NSAIDs). A study has reported NSAIDs to have a protective effect against breast cancer and may even reduce mortality in patients with breast cancer (58). Potential mechanisms include the ability of NSAIDs to inhibit prostaglandin synthesis, while prostaglandins increase the estrogen level by increasing aromatase gene expression. In breast cancer, studies have reported an increased expression of COX-2 and prostaglandin levels, with COX-2 gene responsible for angiogenesis and apoptosis (59-62). The animal studies have shown elevated nitric oxide levels after aspirin use to have an inhibitory effect on tumor cell growth (63). A meta-analysis involving 6 cohorts and 8 case-control studies published in 2001 reported that NSAIDs could slightly reduce the risk of breast cancer (64). In another meta-analysis of 3,133 patients published in the same year, a 24% reduction in the risk was observed with NSAID use for more than two months, especially when used more than eight years (65).

However, a cohort study comprising 28,695 patients, published in 2008, where patients were observed for 7.5 years, 847 breast cancer cases were found to have a higher NSAID use; the relation was not causal but coincidental. There was no relationship between NSAID use frequency and dose and breast cancer. The decrease in breast cancer incidence with NSAID use, detected in previous studies, could not be demonstrated in this study (66).

The Vitamin and Lifestyle (VITAL) study consisting of 35,323 postmenopausal patients reported that the use of NSAIDs increases breast cancer risk, and the HR was 1.26 (67). To conclude, even if NSAIDs have been considered protective against breast cancer, the dose and duration of the use of these drugs remain to be resolved.

Can Weight Loss Reduce the Incidence of Breast Cancer?

The risk of cancer increases with the increase in body weight. However, the question remains whether a loss in body weight is associated with a reduction in cancer incidence. Many diseases can be prevented with a reduction in weight; however, whether this is also true for breast cancer is still not known. In a study of 67,000 postmenopausal women, no reduction in breast cancer incidence was observed after weight loss. In this study, a linear relationship was found between BMI and breast cancer. Patients with BMI 35 kg/m^2 and above, when compared to patients with BMI less than 25 kg/m^2, had a 60% increased risk of invasive breast cancer (HR: 1.58). These patients also had cancer detected in more advanced stages (tumor size HR: 2.12, lymph node positivity HR: 1.89, local or distant metastasis HR: 1.89), and had a higher level of mortality in the obese patients (HR: 2.25, BMI: 30-35 kg/m^2; HR:1.37, BMI: 35 kg/m^2; and above HR: 2.11). The same study also demonstrated that the incidence of ER and progesterone receptor (PR)-negative breast cancer was not increased in patients who developed breast cancer. The patients, who were followed up throughout the study and had BMI of 25 kg/m^2 at the beginning of the study, reported an increased breast cancer risk with a 5% weight gain (HR: 1.36). However, patients with an

initial high BMI did not report a significant reduction in breast cancer after weight loss. From these studies, the following can be deduced: obese patients should be advised to lose weight; even after weight loss, these patients should be followed up owing to the increased risk of developing malignancy. From the above study, it appeared that increased white fat tissue in the postmenopausal period increases estrogen receptors in the breast tissue, leading to an increase in the breast cancer incidence (68). On the other hand, Schauer et al. showed that in patients with severe obesity, bariatric surgery was associated with a lower risk of cancer, particularly obesity-associated cancers, such as postmenopausal breast cancer, endometrial cancer, and colon cancer (69).

One of the key points in the pathogenesis of the relationship between obesity and breast cancer is an interaction between the stromal microenvironment and normal epithelial cells. The stromal microenvironment includes adipose stromal cells and adipose stem cells (ASC). Increased accumulation of ASCs in obesity leads to increased adipogenesis and angiogenesis, which, in turn, accelerates cancer growth. Studies have demonstrated that ASCs obtained from patients with BMI above 30 kg/m^2 enhanced tumorigenesis and led to a change in the genetic profile of breast cancer cells. Another study reported increased secretion of leptin by ASCs in patients with BMI over 30 kg/m^{2}as compared to those with BMI under 25 kg/m^2 (70).

Leptin is the most important weight controlling adipokine in white fat tissue and thus has a key role in the relationship between obesity and cancer. It is reported to affect survival, migration, and growth of cancer cells by increasing the expression of anti-apoptotic proteins; estrogen; pro-inflammatory cytokines, such as TNF-α and IL-6; and angiogenic factors, such as VEGF and hypoxia-induced factors (HIF-1α) (18, 19, 71-74). In a cell culture study that investigated the effect of leptin on breast cancer, leptin (obASC) from obese patients led to increased proliferation of ER-positive breast cancer cells, whereas no such effect was observed in case of leptin (InASC) from patients with BMI less than 25 kg/m^2. Increased epithelial-mesenchymal transformation and enhanced expression of metastatic genes (SERPINE1, MMP-2, and IL-6) were detected in the breast cancer cell culture performed with obASC. An absence of leptin decreased the tumor size and number of metastatic lesions (70). Previous studies have shown that leptin enhanced the tumor survival by altering various signaling pathways in tumor cells, including MAP-kinase, JAK2-STAT3, and PI3K-AKT pathways (75). The relationship between leptin and breast cancer is also related to menopause with an inverse relationship between increased leptin levels and cancer development in premenopausal patients. However, the level of leptin in postmenopausal patients increases the risk of breast cancer (76).

In a meta-analysis performed by Niu et al., patients with different breast diseases were evaluated. In 23 studies, 2,058 patients with breast cancer, 2,078 healthy controls, and 285 controls with light breast problem were included. Leptin levels in circulation were the lowest in healthy controls. The ranking for all groups was as follows: healthy control, control with light breast disease, patients with breast cancer, and patients with lymph node metastasis. Serum leptin levels in postmenopausal ER-positive breast cancer patients were found to be the lowest in clinical and pathologic classifications (72, 73, 76).

Increased ectopic lipoaccumulation in obesity leads to tissue hypoxia, inflammation, and reactive angiogenesis, leading to changes in tumorigenesis and tumor characteristics (metastasis, invasion) (77).

Adiponectin is one of the major adipokines secreted by the adipose tissue, with a potent anti-inflammatory activity. Adiponectin increases insulin sensitivity, allows regulation of many growth factors at the receptor level, and inhibits angiogenesis. Its decreased levels in obese people lead to increased activity of growth factors at the receptor level, thereby causing tumorigenesis (78, 79). The effect of adiponectin on breast cancer is closely related to the condition of menopause with different results. One study found a close association between low adiponectin and premenopausal breast cancer (80), whereas another study, which included 4,249 patients, no such as-

sociation was reported (81). In postmenopausal patients, however, the relationship between low adiponectin and breast cancer incidence has been clearly demonstrated (79, 82). In postmenopausal patients, the relationship between obesity and breast cancer can be simply explained as a consequence of the relationship between many metabolic factors, endocrines, receptors, inflammation, stromal cells, and tumor microenvironment, which are triggered by increased adipose tissue. Furthermore, in vitro studies have clearly demonstrated the antitumor and apoptosis-inducing effects of adiponectin; these effects are independent of ER and PR positivity (83).

Conclusion

In conclusion, increased adipose tissue mass and adipose inflammation lead to increased risk of tumor growth and progression through the involvement of many complex and intertwined pathways. In this regard, healthy lifestyle and nutrition are the first steps in prevention.

Source of Finance: During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest: No conflicts of interest between the authors and/or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Candeğer Yılmaz; Design: Ilgın Yıldırım Şimşir; Control/Supervision: Candeğer Yılmaz; Data Collection and/or Processing: Ilgın Yıldırım Şimşir, Utku Erdem Soyaltın; Analysis and/or Interpretation: Candeğer Yılmaz, Ilgın Yıldırım Şimşir, Utku Erdem Soyaltın; Literature Review: Candeğer Yılmaz, Ilgın Yıldırım Şimşir, Utku Erdem Soyaltın; Writing the Article: Ilgın Yıldırım Şimşir, Utku Erdem Soyaltın, Candeğer Yılmaz; Critical Review: Candeğer Yılmaz; References and Fundings: Ilgın Yıldırım Şimşir, Utku Erdem Soyaltın; Materials: Ilgın Yıldırım Şimşir, Utku Erdem Soyaltın.

References

1. World Health Organization (WHO). Obesity and Overweight. Genova: WHO Media Centre; 2015. http://who.int/mediacentre/factsheets/fs311/en.
2. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311:806-814.
3. Haslam DW, James WP. Obesity. Lancet. 2005;366: 1197-1209.
4. Afzal S, Tybjærg-Hansen A, Jensen GB, Nordestgaard BG. Change in body mass index associated with lowest mortality in Denmark, 1976-2013. JAMA. 2016;315:1989-1996.
5. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA. 2004;291:1238-1245.
6. Widschwendter P, Friedl TW, Schwentner L, DeGregorio N, Jaeger B, Schramm A, Bekes I, Deniz M, Lato K, Weissenbacher T, Kost B, Andergassen U, Jueckstock J, Neugebauer J, Trapp E, Fasching PA, Beckmann MW, Schneeweiss A, Schrader I, Rack B, Janni W, Scholz C. The influence of obesity on survival in early, high-risk breast cancer: results from the randomized SUCCESS A trial. Breast Cancer Res. 2015;17:129.
7. Zhang Y, Bellows CF, Kolonin MG. Adipose tissue-derived progenitor cells and cancer. World J Stem Cells. 2010;2:103-113.
8. Laforest S, Labrecque J, Michaud A, Cianflone K, Tchernof A. Adipocyte size as a determinant of metabolic disease and adipose tissue dysfunction. Crit Rev Clin Lab Sci. 2015;52:301-313.
9. Nieman KM, Romero IL, Van Houten B, Lengyel E. Adipocyte tissue and adipocytes supports tumorogenesis and metastasis. Biochim Biophys Acta. 2013;1831:1533-1541.
10. Matafome P, Santos-Silva D, Sena CM, Seiça R. Common mechanisms of dysfunctional adipose tissue and obesity-related cancers. Diabetes Metab Res Rev. 2013;29:285-295.
11. Satman I, Yilmaz T, Sengül A, Salman S, Salman F, Uygur S, Bastar I, Tütüncü Y, Sargin M, Dinççag N, Karsidag K, Kalaça S, Ozcan C, King H. Population-based study of diabetes and risk characteristics in Turkey: results of the turkish diabetes epidemiology study (TURDEP). Diabetes Care. 2002;25:1551-1556.
12. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J; TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol. 2013;28:169-180.
13. Poulos SP, Hausman DB, Hausman GJ. The development and endocrine dysfunctions of adipose tissue. Mol Cell Endocrinol. 2010;323:20-34.
14. Brestoff JR, Artis D. Immun regulation of metabolic homeostasis in health and disease. Cell. 2015;161: 146-160.

15. Raucci R, Rusolo F, Sharma A, Colonna G, Castello G, Costantini S. Functional and structural features of adipokine family. Cytokine. 2013;61:1-14.
16. Diedrich I, Gusky HC, Podgorski I. Adipose tissue dysfunction and its effects on tumor metabolism. Horm Mol Biol Clin Investig. 2015;21:17-41.
17. Divella R, De Luca R, Abbate I, Neglieri E, Daniele A. Obesity and cancer: the role of adipose tissue and adipo-cytokines-induced chronic inflammation. J Cancer. 2016;7:2346-2359.
18. Iyengar NM, Hudis CA, Dannenberg AJ. Obesity and cancer: local and systemic mechanisms. Ann Rev Med. 2015;66:297-309.
19. Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. Horm Mol Biol Clin Investig. 2015;21:57-74.
20. Rogers CJ, Prabhu KS, Vijay-Kumar M. The microbiome and obesity-an established risk for certain types of cancer. Cancer J. 2014;20:176-180.
21. Balkwill F, Mantovani A. Inflamation and cancer: back to Virchow? Lancet. 2001;357:539-545.
22. Strong AL, Burow ME, Gimble JM, Bunnell BA. Concise review: the obesity cancer paradigm: exploration of the interactions and crosstalk with adipose stem cell. Stem Cells. 2015;33:318-326.
23. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. Lancet Oncol. 2012;13:790-801.
24. Barlow WE, White E, Ballard-Barbash R, Vacek PM, Titus-Ernstoff L, Carney PA, Tice JA, Buist DS, Geller BM, Rosenberg R, Yankaskas BC, Kerlikowske K. Prospective breast cancer risk prediction model for women undergoing screening mammography. J Natl Cancer Inst. 2006;98:1204-1214.
25. Sonnenschein E, Toniolo P, Terry MB, Bruning PF, Kato I, Koenig KL, Shore RE. Body fat distribution and obesity in pre- and postmenopausal breast cancer. Int J Epidemiol. 1999;28:1026-1031.
26. Tehard B, Clavel-Chapelon F. Several anthropometric measurements and breast cancer risk: results of the E3N cohort study. Int J Obes (Lond). 2006;30:156-163.
27. Tian YF, Chu CH, Wu MH, Chang CL, Yang T, Chou YC, Hsu GC, Yu CP, Yu JC, Sun CA. Anthropometric measures, plasma adiponectin, and breast cancer risk. Endocr Relat Cancer. 2007;14:669-677.
28. Mathew A, Gajalakshmi V, Rajan B, Kanimozhi V, Brennan P, Mathew BS, Boffetta P. Anthropometric factors and breast cancer risk among urban and rural women in South India: a multicentric case-control study. Br J Cancer. 2008;99:207-213.
29. Montazeri A, Sadighi J, Farzadi F, Maftoon F, Vahdaninia M, Ansari M, Sajadian A, Ebrahimi M, Haghighat S, Harirchi I. Weight, height, body mass index and risk of breast cancer in postmenopausal women: a case-control study. BMC Cancer. 2008;8:278.
30. Palmer JR, Adams-Campbell LL, Boggs DA, Wise LA, Rosenberg L. A prospective study of body size and breast cancer in black women. Cancer Epidemiol Biomarkers Prev. 2007;16:1795-1802.
31. Loi S, Milne RL, Friedlander ML, McCredie MR, Giles GG, Hopper JL, Phillips KA. Obesity and outcomes in premenopausal and postmenopausal breast cancer. Cancer Epidemiol Biomarkers Prev. 2005;14:1686-1691.
32. Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. PLoS One. 2012;7: e51446.
33. Eliassen AH, Colditz GA, Rosner B, Willett WC, Hankinson SE. Adult weight change and risk of postmenopausal breast cancer. JAMA. 2006;296: 193-201.
34. Eliassen AH, Missmer SA, Tworoger SS, Spiegelman D, Barbieri RL, Dowsett M, Hankinson SE. Endogenous steroid hormone concentrations and risk of breast cancer among premenopausal women. J Natl Cancer Inst. 2006;98:1406-1415.
35. Kosova F, Arı Z. Adipositokinler ve meme kanseri. FÜ Sağ Bil Tıp Derg. 2008;22:377-384.
36. Stephenson GD, Rose DP. Breast cancer and obesity: an update. Nutr Cancer. 2003;45:1-16.
37. Niraula S, Ocana A, Ennis M, Goodwin PJ. Body size and breast cancer prognosis in relation to hormone receptor and menopausal status: a meta-analysis. Breast Cancer Res Treat. 2012;134:769-781.
38. Protani M, Coory M, Martin JH. Effect of obesity on survival of women with breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat. 2010;123:627-635.
39. Ligibel J. Obesity and breast cancer. Oncology (Williston Park). 2011;25:994-1000.
40. Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. Acta Oncol. 2011;50:167-178.
41. Karaduman M, Bilici A, Ozet A, Sengul A, Musabak U, Alomeroglu M. Tissue leptin levels in patients with breast cancer. J BUON. 2010;15:369-372.
42. Xu P, Ye W, Jen R, Lin SH, Kuo CT, Lin YC. Mitogenic activity of zeranol in human breast cancer cells is enhanced by leptin and suppressed by gossypol. Anticancer Res. 2009;29:4621-4628.
43. Nalabolu MR, Palasamudram K, Jamil K. Adiponectin and leptin molecular actions and clinical significance in breast cancer. Int J Hematol Oncol Stem Cell Res. 2014;8:31-40.
44. Maiti B, Kundranda MN, Spiro TP, Daw HA. The association of metabolic syndrome with triple-negative breast cancer. Breast Cancer Res Treat. 2010;121:479-483.
45. Gulcelik MA, Colakoglu K, Dincer H, Dogan L, Yenidogan E, Gucelik NE. Associations between adiponectin and two different cancers: breast and colon. Asian Pac J Cancer Prev. 2012;13:395-398.
46. Rose DP, Komninou D, Stephenson GD. Obesity, adipocytokines, and insulin resistance in breast cancer. Obes Rev. 2004;5:153-165.
47. Matsubara M, Maruoka S, Katayose S. Inverse relationship between plasma adiponectin and leptin concentrations in normal-weight and obese women. Eur J Endocrinol. 2002;147:173-180.
48. Grossmann ME, Ray A, Nkhata KJ, Malakhov DA, Rogozina OP, Dogan S, Cleary MP. Obesity and breast cancer: status of leptin and adiponectin in pathological processes. Cancer Metastasis Rev. 2010;29:641-653.
49. Ryu TY, Park J, Scherer PE. Hyperglycemia as a risk factor for cancer progression. Diabetes Metab J. 2014;38:330-336.

50. Yurekli BS, Karaca B, Cetinkalp S, Uslu R. Is it the time for metformin to take place in adjuvant treatment of Her-2 positive breast cancer? Teaching new tricks to old dogs. Med Hypotheses. 2009;73:606-607.
51. Zielinska HA, Bahl A, Holly JM, Perks CM. Epithelial-to-mesenchymal transition in breast cancer: a role for insulin-like growth factor I and insulin-like growth factor-binding protein 3? Breast Cancer (Dove Med Press). 2015;7:9-19.
52. Nahta R. Deciphering the role of insulin-like growth factor-I receptor in trastuzumab resistance. Chemother Res Pract. 2012;2012:648965.
53. Jang SY, Kim A, Kim JK, Kim C, Cho YH, Kim JH, Kim CH, Lee JY. Metformin inhibits tumor cell migration via down-regulation of MMP9 in tamoxifen-resistant breast cancer cells. Anticancer Res. 2014;34:4127-4134.
54. Berstein LM, Yue W, Wang JP, Santen RJ. Isolated and combined action of tamoxifen and metformin in wild-type, tamoxifen-resistant, and estrogen-deprived MCF-7 cells. Breast Cancer Res Treat. 2011;128:109-117.
55. Camacho L, Dasgupta A, Jiralerspong S. Metformin in breast cancer-an evolving mystery. Breast Cancer Res. 2015;17:88.
56. Borgquist S, Giobbie-Hurder A, Ahern TP, Garber JE, Colleoni M, Láng I, Debled M, Ejlertsen B, von Moos R, Smith I, Coates AS, Goldhirsch A, Rabaglio M, Price KN, Gelber RD, Regan MM, Thürlimann B. Cholesterol, cholesterol-lowering medication use, and breast cancer outcome in the BIG 1-98 study. J Clin Oncol. 2017;35:1179-1188.
57. Nelson ER, Wardell SE, Jasper JS, Park S, Suchindran S, Howe MK, Carver NJ, Pillai RV, Sullivan PM, Sondhi V, Umetani M, Geradts J, McDonnell DP. 27-hydroxycholesterol links hypercholesterolemia and breast cancer pathophysiology. Science. 2013;342:1094-1098.
58. Cui Y, Deming-Halverson SL, Shrubsole MJ, Beeghly-Fadiel A, Cai H, Fair AM, Shu XO, Zheng W. Use of nonsteroidal anti-inflammatory drugs and reduced breast cancer risk among overweight women. Breast Cancer Res Treat. 2014;146:439-446.
59. Davies G, Martin LA, Sacks N, Dowsett M. Cyclooxygenase-2 (COX-2), aromatase and breast cancer: a possible role for COX-2 inhibitors in breast cancer chemoprevention. Ann Oncol. 2002;13:669-678.
60. Davies G, Salter J, Hills M, Martin LA, Sacks N, Dowsett M. Correlation between cyclooxygenase-2 expression and angiogenesis in human breast cancer. Clin Cancer Res. 2003;9:2651-2656.
61. Bennett A, Berstock DA, Carroll MA, Stamford IF, Wilson AJ. Breast cancer, its recurrence, and patient survival in relation to tumour prostaglandins. Adv Prostaglandin Thromboxane Leukot Res. 1983;12:299-302.
62. Harris RE, Chlebowski RT, Jackson RD, Frid DJ, Ascenseo JL, Anderson G, Loar A, Rodabough RJ, White E, McTiernan A; Women's Health Initiative. Breast cancer and nonsteroidal anti-inflammatory drugs: prospective results from the Women's Health Initiative. Cancer Res. 2003;63:6096-6101.
63. Girish GV, Sinha N, Chakraborty K, Bhattacharya G, Kahn NN, Sinha AK. Restoration by aspirin of impaired plasma maspin level in human breast cancer. Acta Oncol. 2006;45:184-187.
64. Khuder SA, Mutgi AB. Breast cancer and NSAID use: a meta-analysis. Br J Cancer. 2001;84:1188-1192.
65. Cotterchio M, Kreiger N, Sloan M, Steingart A. Nonsteroidal anti-inflammatory drug use and breast cancer risk. Cancer Epidemiol Biomarkers Prev. 2001;10:1213-1217.
66. Friis S, Thomassen L, Sørensen HT, Tjønneland A, Overvad K, Cronin-Fenton DP, Vogel U, McLaughlin JK, Blot WJ, Olsen JH. Nonsteroidal anti-inflammatory drug use and breast cancer risk: a Danish cohort study. Eur J Cancer Prev. 2008;17:88-96.
67. Ready A, Velicer CM, McTiernan A, White E. NSAID use and breast cancer risk in the VITAL cohort. Breast Cancer Res Treat. 2008;109:533-543.
68. Neuhouser ML, Aragaki AK, Prentice RL, Manson JE, Chlebowski R, Carty CL, Ochs-Balcom HM, Thomson CA, Caan BJ, Tinker LF, Urrutia RP, Knudtson J, Anderson GL. Overweight, obesity, and postmenopausal invasive breast cancer risk: a secondary analysis of the women's health initiative randomized clinical trials. JAMA Oncol. 2015;1:611-621.
69. Schauer DP, Feigelson HS, Koebnick C, Caan B, Weinmann S, Leonard AC, Powers JD, Yenumula PR, Arterburn DE. Bariatric surgery and the risk of cancer in a large multisite cohort. Ann Surg. 2017 Sep 21. Doi: 10.1097/SLA.0000000000002525. [Epub ahead of print].
70. Strong AL, Ohlstein JF, Biagas BA, Rhodes LV, Pei DT, Tucker HA, Llamas C, Bowles AC, Dutreil MF, Zhang S, Gimble JM, Burow ME, Bunnell BA. Leptin produced by obese adipose stromal/stem cells enhances proliferation and metastasis of estrogen receptor positive breast cancers. Breast Cancer Res. 2015;17:112.
71. Strong AL, Strong TA, Rhodes LV, Semon JA, Zhang X, Shi Z, Zhang S, Gimble JM, Burow ME, Bunnell BA. Obesity associated alterations in the biology of adipose stem cells mediate enhanced tumorigenesis by estrogen dependent pathways. Breast Cancer Res. 2013;15:R102.
72. Newman G, Gonzales-Perez RR. Leptin-cytokine crosstalk in breast cancer. Mol Cell Endocrinol. 2014;382:570-582.
73. Saxena NK, Sharma D. Multifaceted leptin network: the molecular connection between obesity and breast cancer. J Mammary Gland Biol Neoplasia. 2013;18:309-320.
74. Macciò A, Madeddu C, Gramignano G, Mulas C, Floris C, Massa D, Astara G, Chessa P, Mantovani G. Correlation of body mass index and leptin with tumor size and stage of disease in hormone-dependent postmenapausal breast cancer: preliminary results and therapeutic implications. J Mol Med (Berl). 2010;88:677-686.
75. Frühbeck G. Intracellular signalling pathways activated by leptin. Biochem J. 2006;393:7-20.
76. Niu J, Jiang L, Guo W, Shao L, Liu Y, Wang L. The Association between leptin level and breast cancer: a meta-analysis. PLoS One. 2013;8:e67349.

77. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer--mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol. 2014;10:455-465.
78. Hui X, Lam KS, Vanhoutte PM, Xu A. Adiponectin and cardiovascular health: an update. Br J Pharmacol. 2012;165:574-590.
79. Surmacz E. Leptin and adiponectin: emerging therapeutic targets in breast cancer. J Mammary Gland Biol Neoplasia. 2013;18:321-332.
80. Macis D, Gandini S, Guerrieri-Gonzaga A, Johansson H, Magni P, Ruscica M, Lazzeroni M, Serrano D, Cazzaniga M, Mora S, Feroce I, Pizzamiglio M, Sandri MT, Gulisano M, Bonanni B, Decensi A. Prognostic effect of circulating adiponectin in a randomized 2x2 trial of low-dose tamoxifen and fenretinide in premenopausal women at risk for breast cancer. J Clin Oncol. 2012;30:151-157.
81. Macis D, Guerrieri-Gonzaga A, Gandini S. Circulating adiponectin and breast cancer risk: a systematic review and meta-analysis. Int J Epidemiol. 2014;43:1226-1236.
82. Liu LY, Wang M, Ma ZB, Yu LX, Zhang Q, Gao DZ, Wang F, Yu ZG. The role of adiponectin in breast cancer: a meta-analysis. PLoS One. 2013;8:e73183.
83. Wang Y, Lam JB, Lam KS, Liu J, Lam MC, Hoo RL, Wu D, Cooper GJ, Xu A. Adiponectin modulates the glycogen synthase kinase-3beta/beta-catenin signaling pathway and attenuates mammary tumorigenesis of MDA-MB-231 cells in nude mice. Cancer Res. 2006;66:11462-11470.