Investigation of the association between metabolic syndrome and breast cancer patients

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Abstract

One of the most serious cancers among women is breast cancer. This disease is the first reason for the death of women due to cancer. Increasing breast cancer risk may associate with many factors including genetic, reproductive factors, people's lifestyle, metabolic syndrome (MS) and hormones. MS has been known as a risk factor for prostate, pancreatic, breast and colorectal cancers. The purpose of this review is to identify the relationship between MS components and breast cancer individually. This study was performed by researching electronic database references including PubMed, Google Scholar, CINAHL ProQuest, and web of science through 2019. The effect of MS with its components and breast cancer was reported in many studies. Nevertheless, a thorough understanding of the mechanisms involved remains a challenge. However, one can take several preventive measures, including a proper diet, which is one of the most important determinants of metabolic status. Also, general preventive recommendations are including reducing alcohol consumption, red meat and total fat in the diet. Moreover, increasing the consumption of vegetable and fruit reduce the proportion of MS patients to improve the outcome of breast cancer patients.

Key Words: Breast cancer, metabolic syndrome, electronic database, natural products.
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Breast cancer is one of the most serious diseases among women in the world. This disease is the first reason for the death of women due to cancer. Increasing breast cancer risk may be associated with many factors including genetic, reproductive and hormonal parameters, metabolic syndrome (MS) and people lifestyle.[1,2] MS is a cluster of metabolic abnormality that happens to people with disordered sensitivity to insulin.[3] It is described with the existence of factors including the increase of triglycerides in the blood, abdominal obesity, increasing fasting glucose and high pressure of blood.[4] MS is known as a danger for many cancers such as those of prostate, pancreas, breast and colorectal region.[5-10] Studies show that, in women age above 18 years, there is a mild positive dependency between breast cancer and MS.[11] Moreover, many of these studies indicate a positive relationship with diabetes, breast cancer,[12-18] and obesity.[2,19,20] Additionally, some studies show dyslipidemia and hypertension as danger agents in breast cancer.[11,21-24] Despite single MS components cannot be powerfully related to the advancement of breast cancer, their mixture can enhance the venture.[8,9] The main objective of this paper is to study relationship among the individual MS components and breast cancer.

Definition and Prevalence of Metabolic Syndrome

The definition of MS began from 2001,[25] then the concept of integrated definition has been fixed (Table 1).[4] For populations of Caucasian, in men and women 102 and 88 cm waist respectively, is generally chosen as an evidence of abdominal obesity. Diagnosis of MS complies when 3 of the 5 criteria exist.[4,25] The spread of MS in the west is among 20-25% of adult people, while in old people it ranges from 40 to 45%[26,27]. MS also increases risks of cardiovascular diseases.[28]

Association of breast cancer and diabetes

Many clinical studies showed diabetes and breast cancer correlation. In one study in the United States 1.2 million patients (588321 were women) were enrolled and studied

Table 1: *Criteria for Clinical Diagnosis of Metabolic Syndrome*[4]

Measure	Categorical cut points
Elevated waist circumference	**population- and country-specific definitions**
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	**≥150 mg/dL (1.7 mmol/L)**
Reduced HDL-cholesterol (drug treatment for reduced HDL- cholesterol is an alternate indicator)	**≤40 mg/dL (1.0 mmol/L) in males; ≤ 50 mg/dL (1.3 mmol/L) in females**
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	**Systolic ≥130 and/or diastolic ≥85 mm Hg**
Elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator)	**≥ 100 mg/dl**

for 6 years (1982- 1988). It was shown that diabetic women with breast cancer died more than women without diabetes.[29] Some meta-analyses have investigated this relation in details[13,30-32]. Much research confirmed the role of diabetes on breast cancer level, increasing hospitalization and decreasing illness-free duration.[33-35] Insulin resistance of Type 2 diabetes may cause hyperglycemia that support cell differentiation and proliferation. Hyperinsulinemia can increase mitogenicity. The increase of circulating estrogens may favor breast cancer development.[30] Insulin can have direct effects on epithelial cells and thus supporting tumorigenesis.[36,37] Insulin receptor is more concentrated in breast cancer tissue than in healthy tissue.[38] Insulin can act via an insulin-like growth factor (IGF) system that is a main breast cancer pathway. Increased of IGF-1 level and binding of insulin-like growth factor protein 3 (IGFBP3) level may increase risk of breast cancer.[39,40] Much research investigated the relationship between therapy for type 2 diabetes and breast cancer. Metformin is a biguanide medicine cause to decrease hyperinsulinemia and hyperglycemia by increasing muscle glucose absorption. It is thought metformin independent of insulin has a desirable effect on breast cancer prevention and treatment.[41,42] In 2018 Tang et al investigated 12 articles about metformin and breast cancer relationship in a systematic review. They showed non statistically significant improvement of T2D and breast cancer patients with metformin.[43] The multivariate investigation was performed by Bosco et al. showed metformin used for less than one year may decrease breast cancer incidence[42]. Research in 2018 evaluated the breast cancer risk for aged women treated with metformin or sulfonylureas. No reduction of breast cancer risk was showed adding metformin to the clinical alternative.[44] On the other hand, clinical trials show metformin efficacy when used before breast cancer surgery.[45] Recently, relation between PPAR γ (a nuclear hormone receptor) and breast cancer have been shown. Reducing PPAR γ expression causes higher tumor grade and development of the disease.[46] But in one study with 22 patients, a PPAR γ agonist didi not induced any reaction in patients.[47] In contrast, using long term of insulin glargine may increase breast cancer risk.[48] In summary, managements of diabetes can have the same impact as diabetes itself, thus randomized controlled trials are needed. In summary, published data demonstrate that type 2 diabetes increase breast cancer risk.[49] Better ndersatnding of the involved mechanisms may open the way to find new drugs that may be useful to establish stronger preventive measures.

Obesity and breast cancer

According to several epidemiological studies, obesity before menopause protects for breast cancer[50]. On the contrary, obesity after menopause may increase breast cancer risks[49,51].
In particular, triple-negative breast cancer.[52,53]
Indeed, adipokines and breast cancer relations have been studied. Leptin levels and obesity levels have positive effect on each other, while lower leptin levels are associated with increased obesity. One study has shown that leptin and its receptor expression in adipose tissue were similar to that of obesity in breast cancer.[54-56]

Breast cancer and hypertension

Recent studies have shown that increased blood pressure (hypertension) is a risk for breast cancer,[24,57,58] but there are contradictory findings.[56,58,59] One study found that diuretics increased breast cancer risk in hypertension.[60] In another study, Li CI et al. claims that there was low statistical correlation between these two events[61] High blood pressure during pregnancy or pre-eclampsia seem to be breast cancer risks, but another study found that that high blood pressure (pre-eclampsia) reduces the chance of breast cancer risk of 20-30%, through a lower concentration of insulin-like growth factor and estrogen and a higher amount of androgens and human chorionic gonadotropin in women with pre-eclampsia.[62] Anyhow, the relationship between hypertension, utilization of relevant drugs and breast cancer continues to be very controversial.

Breast cancer and dyslipidemia

Dyslipidemia is another widely discussed risk factor. Low HDL-cholesterol is a risk factor for cardiovascular

illness, but may cause cancer in other parts of the body,[63] but because of differences in the populations and methods of analysis, conclusions are mixed.[64-66] Kim et al. have shown that HDL has a protective effect on some postmenopausal women with breast cancer,[67] but Kucharska et al. in a prospective study of 15.792 men and women found that there was only a moderate dependence of breast cancer increased risk and low premenopausal HDL-cholesterol free, number of live births, race, age, age at menarche, smoking status and BMI.[68] All cancer cells need fatty acids (FA) to grow and survive and obstruction of de novo FA synthesis in rat models has resulted in anticancer effects.[56] In summary, lipids and lipoproteins have an impact on cardiovascular disease and may have also an impact in breast cancer being active molecules with high effects rather than idle means of energy storage. Changes in lifestyle, as advised for cardiovascular disease prevention, may be important to prevent also breast cancer deaths**.**

Breast cancer and Metabolic Syndrome

MS is a mixture of metabolic disturbances such as insulin resistance, dyslipidemia, hypertension, visceral obesity, and raised blood sugar. As a unique medical risk, MS has been studied with breast cancer.[56,69-71] The odds ratios of breast cancer after menopausal were 1.33 (95% CI 1.09-1.62) to diabetes, 1.19 (95% CI 1.07-1.33) to hypertension, 1.08 (95% CI 0.95-1.22) to hyperlipidemia, 1.26 (95% CI 1.11-1.44) to BMI ≥30 kg/m2, and 1.22 (95% CI 1.09-1.36) to waist perimeter ≥88 cm. In women with metabolic syndrome, the risk of breast cancer after menopausal is significantly increased (OR 1.75, 95% CI 1.37-2.22), which is higher at an older age (OR 3.04, 95% CI 1.75-5.29, at age ≥70 years).[5] Metabolic syndrome presents many changes in the body's metabolism. Below, we examine the possible mechanisms increasing the risk of breast cancer. One of the molecules presumed to mediated the metabolic syndrome risk is the plasminogen activator inhibitor-1 (PAI-1). This protein is known as a physiological inhibitor of urokinase (uPA). On the other hand, increased levels of PAI-1 are paradoxically associated with poor prognosis in breast cancer.[72] In fact, Stern introduced the hypothesis of a "common soil" affected by metabolic syndrome, defined as chronic inflammation and insulin resistance, that is suspected to be related to breast cancer.[73] Further evidence is presented in Figure 1.[27] The reason for high levels of insulin in cancer progression, as well as mortality, is that insulin appears to have mitogenic, anti-apoptotic and angiogenic properties.[74] Moreover, researchers have found insulin to incite the synthesis of insulin-like growth factor 1 (IGF-1) and to Poor link to the IGF-1 receptor. Commonly, insulin-IGF-1 signaling is up-regulated in tumor cells, as it is up-regulated in obesity, leading to activation of the oncogenic Ras-MAPK and PI3K-Akt pathways (MAPK - mitogen-activated protein kinase, PI3K - phosphoinositide 3-kinase). Additional, the Akt pathway

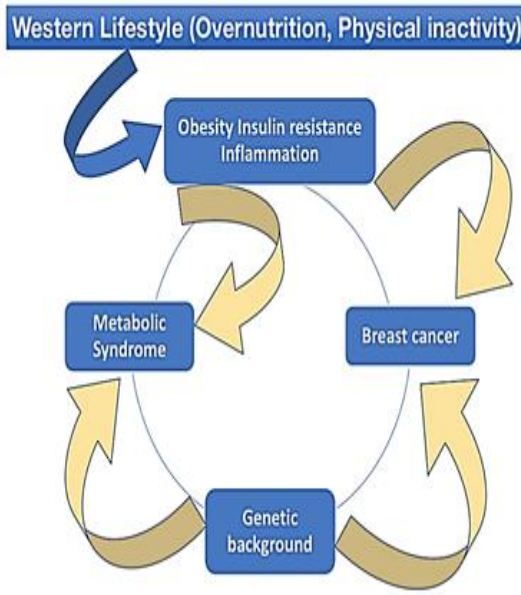

Fig 1. The diagram of the connection between metabolic syndrome and breast cancer[27]

stimulates the rapamycin mammalian target rapamycin (mTOR), all together known mechanisms of the tumor cell growth.[27,75] In breast cancer, adipose tissue is a major part of the tumor. Due to the interaction between cancer cells and the adipose surrounding fat, it is known as cancer-associated fat (CAA) that by its own secretion sustain tumor growth.[27] Direct contact of these two cells destroys differentiation markers and enhances expression of inflammatory cytokines including IL-6 and plasminogen activator type 1 inhibitor (PAI-1).[76] Reduction of fat tissue, especially visceral, may reduce MS features. So, weight loss obtained with regular exercise seems to decrease chronic inflammation and insulin resistance.[77] The achievement of these goals were recently investigated.[77] These studies show that weight loss decreases markers of cancer progression and the progression of the tumor.[27,78,79]

Another option for breast cancer prevention and for improvement of its prognosis is the Mediterranean diet.[80,81] Together with other food supplements, Mediterranean diet was reported to be effective also in pediatrics periods.[82-84]

Conclusion

In this short review, we examined the components of the metabolic syndrome in relation to breast cancer, as they are reported in many studies. Nevertheless, a thorough understanding of the mechanisms involved remains a challenge. Among a number of preventive measures, proper diet, that seems to be one of the most effectives determinants of metabolic status, ought to be considered. General preventive recommendations are to reduce

alcohol, red meat and total fat in the diet, while increasing consumption of vegetables and fruits. These measures will reduce thenumber of MS patients, thus improving outcomes of breast cancer.[53,56]

List of acronyms

MS - Metabolic syndrome
PPARγ - Peroxisome proliferator–activated receptor γ
FA - fatty acids
BMI - Body mass index
PAI-1 - Plasminogen activator inhibitor-1
MAPK - Mitogen-activated protein kinase
PI3K - Phosphoinositide 3-kinase
CAA - Cancer-Associated Adipocytes.

Authors contributions

DE, NKH, AGH, HS, AH drafted the manuscript and were responsible for literature review, participated in the conception and design of the work, and approved the final typescript.

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Conflict of Interest

The authors have no conflicts to disclose.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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