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Original article

Metabolic syndrome and breast cancer: a dangerous association for postmenopausal women. A postmenopausal women prevention study

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Abstract. *Background:*Breast cancer(BC) is the most common cancer in women worldwide, the relationship between metabolic syndrome(MetS) and BC needs to be better clarified. Today the early diagnosis of breast cancer(BC) is yet a challenging problem in clinical practice, so the evidence that a well identified population of postmenopausal women, affected by MetS, presents a high risk, of breast cancer occurrence, is useful for breast cancer prevention. Our study aims to assess the prevalence of metabolic syndrome, diagnosed according to current guidelines, in postmenopausal women with breast cancer, and its role as an independent risk factor. *Results:* MetS rate was significantly higher among women affected by BC:10.1%, 33 women, than CG:5.4%, 18 women, Chi-squared4.8,Odds ratio1.94,c.i.95%,p<0.02. *Metabolic cardiomyopathy rate was significantly higher among women affected by BC:5.8%, 18 women, than CG:1.8%, 6 women,* Chi-squared6.5,Odds ratio3.2,c.i.95%,p<0.01. *Otherwise MetS rate without cardiomyopathy was higher among women affected by BC:4.8%, 15 women, than CG:3.4%, 11 women, but in a not statistically significant way,* Chi-squared0.8,Odds ratio1.35,c.i.95%,p<0.36. *Conclusion:* There was a significant relationship, in our population, between MetS and BC, adding evidence to this controversial association, the relationship was even tighter, when restricted to women affected by metabolic cardiomyopathy; otherwise it, restricted to women affected by MetS, without metabolic cardiomyopathy, was not statistically significant. Since the prevalence of MetS is increasing worldwide, just like the incidence of BC, an intervention is needed to improve physical activity and weight reduction to decrease the MetS rate.

Key words: metabolic syndrome, breast cancer, cardiomyopathy

Introduction

The metabolic syndrome(MetS) is a cluster of cardiovascular risk factors, including central obesity, hyperglycemia, hyperinsulinemia, hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, all these conditions interact increasing the risk of cardiovascular events. We diagnose MetS, according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III definition. For this assessment we need of three or more of the following five criteria: waist circumference over 35 inches, blood pressure over 130/85 mmHg, fasting triglyceride level over 150 mg/dl, fasting high-density lipoprotein (HDL) cholesterol level less than 50 mg/dl and fasting blood sugar over 100 mg/dl (1), (Figure. 1). Breast cancer(BC) is a very common malignancy among postmenopausal women and despite advances in the treatment strategies in recent decades (2,3), its mortality remains high (4,5). We perform diagnosis of BC by clinical examination, associated with imaging and confirmed by pathological assessment. Final diagnosis

is made according to the World Health Organization (WHO) classification (6) and the eight edition of the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) staging system (7). This staging system includes anatomical information and prognostic information related to biology of the cancer as grading, presence of estrogen receptors, progesterone receptors, human epidermal growth factor receptors 2 (HER2) and gene expression data.

MetS seems to play a role in determining of BC (8), because of it impacts on hormonal pathways that involve: insulin, estrogen, cytokines, and growth factors (9). There is an important correlation between obesity and BC risk due to the insulin resistance, hyperinsulinemia, and increased levels of endogenous estrogen and androgen (10,11). MetS is also associated with increased risk of breast cancer mortality, especially among post-menopausal women (12). Pathologically, patients with MetS are characterized by chronic inflammation and oxidative stress, which is involved in the carcinogenesis (13,14), (Figure. 2). The role of single metabolic factor in the pathogenesis of BV remains unclear and therefore strategies for primary prevention of BC, targeting the modifiable metabolic factors, have been unsuccessful (15,16).

We know that there many studies that evaluated the association of BC risk with every single factor of the above mentioned cluster, i.e. abdominal visceral adiposity(17–20), serum lipid levels (21,22), insulin and glucose levels (23–25), while only few studies tried to consider multiple items of the cluster (26,27). Today the early diagnosis of BC is yet a challenging problem in clinical practice, so the evidence that a well identified population of postmenopausal women, affected by MetS, presents a high risk of occurrence is useful, for BC prevention. Our study aims to assess the prevalence of metabolic syndrome, diagnosed according to current guidelines, in postmenopausal women with breast cancer, and its role as an independent risk factor.

National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III

3 or more criteria:

Obesità viscerale	Maschi: circonferenza vita ≥102 cm Femmine: circonferenza alla vita ≥88 cm
Trigliceridi	≥150 mg/dl
Colesterolo HDL	Maschi: <40 mg/dl Femmine: <50 mg/dl
Pressione arteriosa	≥130/85 mmHg
Glicemia a digiuno	≥110 mg/dl

Figure 1. National Cholesterol Education Program Adult Treatment Panel III Criteria

Patients and Methods

755 consecutive postmenopausal women, referred to our Hearth Station for cardiac evaluation because their breast cancer, histologically confirmed, aged between 48 and 67 years, were enrolled. All women gave informed consent for participating in the study. We collected the demographics of all of them: age, height, weight, body mass index (BMI) and symptom duration, then all women underwent to electrocardiographic and echocardiographic evaluation. We enrolled a control group (CG) of 750 consecutive women without breast cancer, aged between 48 and 67 years. Exclusion criteria were thyroid disorders, all cardiovascular diseases, including mitral disease with moderate or severe mitral regurgitation and known coronary arteries diseases, malignancies, neurological disabilities such as paraplegia and hemiplegia, psychotic disorders.

A detailed personal history of metabolic and cardiovascular disease, family history of metabolic and neoplastic diseases was collected together with

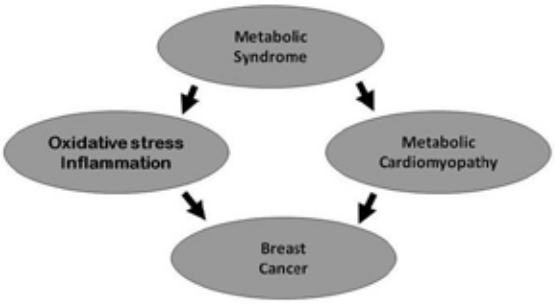

Figure 2. Metabolic Syndrome and Breast Cancer, a dangerous association for Postmenopausal Women

anthropometric parameters such as measurement of body weight, height, and the waist and hip circumferences. Weight and height were used to assess body mass index (BMI): ratio between weight in kilograms and height in squared meters. Obesity was defined as BMI value of 30 kg/m^2 or greater, according to 2020 WHO recommendations. Blood pressure (BP) was performed to upper arm with sphygmomanometer after at least 5 minutes rest and the cuff involved 80% of the upper arm circumference. The average of three measurements was taken as the individuals' BP value. Hypertension was defined by Eigth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Criteria(28). TransToracicEchocardiography (TTE), performed with patient in left lateral decubitus, after 10 minutes of resting, with the exam table elevated by 30°. The exam was carried out with 3.5 MHz probe, with ECG trigger. We used echo-Doppler system equipped with a multifrequency transducer, Philips, Epiq 7, Utrasound System for Cardiology, Healthcare, viale Sarca 235, Milan (Italy). We assessed: intraventricular septum thickness in diastole and in systole, left ventricular end-diastolic and end-systolic diameter, left ventricular posterior wall thickness during diastole and systole, ejection fraction and fractional shortening. Peak velocities of early, E wave, and late, A wave, trans-mitral flow and deceleration time (DT) were determined; E' wave and A' wave by tissue Doppler imaging were determined at mitral annulus level. E/A ratio, E'/A' ratio and E/E' ratio were calculated. LV mass was determined according to the formula by Devereux et al (29) and indexed by body surface area (BSA) to obtain LV mass index, normal values of the above parameters according to the American Society of Echocardiography. LV Diastolic Dysfunction was diagnosed following the current guidelines (30), by PW Doppler of mitral inflow and Doppler Tissue Imaging of the mitral annulus. All LVDD subjects had abnormal diastole for all different degrees of severity. Cardiomyopathy diagnosis was formulated according to well established criteria (31).

Table 1. Women affected by Breast Cancer and Metabolic Syndrome

	BC		CG	
All women	755		750	
Women affected by MetS	78	10.3%	42	5.6%
Women MetS free	677	89.7%	708	94.4%

BC: breast cancer; MetS: metabolic syndrome; CG: control group

Statistical analysis

We performed using SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA). We checked normality for each variable and applied Chi-square test for categorical variables. The odds ratio (OR) for MVP, its standard error, and 95 % confidence interval (CI) were calculated. Results with p values less than 0.05 were statistically significant.

Results

There was no statistically significant difference in number and age of individuals between the two groups, age range was between 48 and 67 years for both. MetS rate was significantly higher among women affected by breast cancer: 10.3%, 78 women; compared to CG: 5.6%, 42 women, *Chi-squared 12, Odds ratio 1.97, c.i.95%, p<0.005*, therefore metabolic syndrome was strongly associated with breast cancer, compared to the control group, patients with metabolic syndrome were two times more likely to have breast cancer, (Table. 1).

Metabolic cardiomyopathy rate was significantly higher among women affected by breast cancer: 6.8%, 51 women, compared to CG: 2.9%, 22 women, *Chi-squared 12.1, Odds ratio 2.41, c.i.95%, p<0.005*, metabolic cardiomyopathy was strongly associated with BC risk, compared to control group, patients with

Table 2. Women affected by Breast Cancer and Metabolic Cardiomyopathy

	BC		CG	
All women	755		750	
Women affected by MetC	51	6.8%	22	2.9%
Women MetS free	704	93.2%	728	97.1%

BC: breast cancer; MetC: metabolic cardiomyopathy; CG: control group

metabolic cardiomyopathy were two times and half more likely to have breast cancer, (Table. 2).

Otherwise MetS rate without cardiomyopathy was higher among women affected by breast cancer: 3.5%, 27 women, than in CG: 2.6%, 20 women, but this datum is not statistically significant, *Chi-squared 1, Odds ratio 1.35, c.i.95%, p<0.31.*

Discussion

The main finding of our study is that MetS is relatively common in postmenopausal women affected by BC; women with MetS have a double chance to be affected by this type of cancer. Women with metabolic cardiomyopathy have a chance even greater to be affected by breast cancer, otherwise MetS rate without cardiomyopathy was higher among women affected by breast cancer, but not statistically significant. Breast cancer risk increased by a factor of 1·050 for every year older at menopause, a little less in women with increased adiposity, but this increase is not influenced by women's year of birth, ethnic origin, childbearing history, smoking, alcohol consumption, or hormonal contraceptive use (32). MetS consists of a cluster of metabolic disorders: obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, and is characterized by alteration in insulin metabolism (17). BC is a cell proliferation that occurs in response to sex hormones stimulus, but not only. Others stimulating factors are: polypeptide growth hormones, insulin-like growth factors (IGFs) and insulin itself (31,33) high serum insulin is associated with poorer outcome (34). C-peptide serum levels, indicator of pancreatic insulin production, is linked with increased BC risk in postmenopausal women (9), and in BC patients. Insulin has a gonadotropic effect (35), stimulating ovaries to produce androgens, their aromatization is the main source of estrogens after menopause (26,36), aromatase activity is increased by insulin (37). Obesity increases the occurrence of breast cancer in post-menopausal women and negatively affects prognosis independently of menopausal status, because of a chronic sub-inflammatory state of cancer cells and the surrounding mammary adipose tissue, that amplifies the tumor progression (38). Abdominal fat is an important source of both androgens and estrogens (37), high levels of estrogens, drive the association of obesity with BC risk (39); however often obesity is not associated with BC risk, suggesting that metabolic syndrome has an effect not depending by obesity. Insulin and IGF-I cooperate with estrogens stimulating the proliferation of breast epithelium cells, however a significant association between BC and serum levels of IGF-I was found only in postmenopausal women (40,41). Postmenopausal women affected by metabolic syndrome presented increased levels of inflammatory cytokines (42) and leptin (43), just like low levels of adiponectin with adverse effects on the proliferation of breast epithelium cells (44,45). Several studies witness that abdominal obesity is related with BC risk in postmenopausal women (46,47) with metabolic syndrome, all conditions linked to physical inactivity. An important contribution to BC prevention in postmenopausal women includes prescription of a dietary regimen and increased physical activity, in order to reduce the prevalence of obesity in this population and to decrease both estrogen and insulin concentrations in obese women. Hypertension is often present in the cluster of metabolic syndrome and is linked to breast cancer (48–50), because of a common status of subclinical inflammation, but however the exact underlying mechanism MetS is still unclear, the same for low levels of HDL cholesterol and high levels of triglycerides (51). The Malmo Diet and Cancer Study, did not find an association between fasting glucose and BC risk in postmenopausal women, while the same associations was found il this other study (52,53)**,** but the real weight of these observation need to be clarified. Anyhow MetS is a risk factor for BC for itself, beyond the role that can play every single component. Our observation exhibited higher prevalence of MetS among women with BC in postmenopausal age compared to women without cancer, even more in women affected by metabolic cardiomyopathy, because the correlation increases when the metabolic disease is in an advanced stage. Limitation of the study: we did not discuss the single components of the metabolic syndrome (i.e. hypertension), in determining breast cancer, due to the number of patients. Moreover metabolic syndrome has been defined as a cluster of disease and we aim to evaluate the impact of the cluster more than

the impact of the single disease. We need to improve the prevention of cancer through a strict monitoring of women with MetS, and the attempt to correct all MetS cluster factors in every single women, even more in this pandemic time we need to implement strategies to increase home-based physical activity and to encourage adherence to a healthy diet, for a good lifestyle routine (54).

Conclusions

A significant relationship was found in our population between MetS and BC over the entire sample, adding evidence to this controversial association, that was even tighter when restricted to women affected by metabolic cardiomyopathy; otherwise the relationship, restricted to women affected by MetS, without metabolic cardiomyopathy, was not statistically significant. Since the prevalence of metabolic syndrome is increasing worldwide, just like the incidence of breast cancer, an intervention is needed to improve physical activity and weight reduction, so decreasing the metabolic syndrome rate.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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