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Original Article

Metabolic Syndrome and Breast Cancer Risk

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Abstract

Objective: The study was meant to estimate the prevalence of metabolic syndrome in patients with breast cancer and to establish its role as an independent risk factor on occurrence of breast cancer. **Materials and Methods:** Fifty women aged between 40 and 80 years with breast cancer and fifty controls of similar age were assessed for metabolic syndrome prevalence and breast cancer risk factors, including age at menarche, reproductive status, live births, breastfeeding, and family history of breast cancer, age at diagnosis of breast cancer, body mass index, and metabolic syndrome parameters. **Results:** Metabolic syndrome prevalence was found in 40.0% of breast cancer patients, and 18.0% of those in control group (P = 0.02). An independent and positive association was seen between metabolic syndrome and breast cancer risk (odds ratio = 3.037; 95% confidence interval 1.214–7.597). **Conclusions:** Metabolic syndrome is more prevalent in breast cancer patients and is an independent risk factor for breast cancer.

Keywords: *Breast cancer, metabolic syndrome, risk factor*

Introduction

Metabolic syndrome (MS), variously called as insulin resistance syndrome or syndrome X or Reaven syndrome, consists of a constellation of metabolic abnormalities which include central obesity, hyperglycemia, hyperinsulinemia, hypertension, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterol, hyperuricemia, and increased levels of fibrinogen,[1] that confer increased risk of cardiovascular disease and diabetes mellitus.[2,3] MS has recently been proposed to play a part in breast carcinogenesis.[4] The metabolic syndrome could impact the risk of breast cancer through alterations in a number of interrelated hormonal pathways, including those involving insulin, estrogen, cytokines, and growth factors.[4,5]

Clinical and investigational evidence suggests that the increased breast cancer risk associated with greater abdominal visceral obesity may be related to anomalous insulin signaling through the insulin receptor substrate 1 pathway, leading to insulin resistance, hyperinsulinemia, and increased concentrations of endogenous estrogen and androgen.[6]

So far, many studies have analyzed the association of individual MS components with breast cancer risk, but only a few studied the role of MS *per se* in relation to breast cancer occurrence.[7-19] The present study was aimed to estimate the prevalence of metabolic syndrome in patients with breast cancer and to establish its role as an independent risk factor on occurrence of breast cancer.

Materials and Methods

The study was undertaken in the Departments of Medical Oncology, Endocrinology and Clinical Biochemistry, Sher-i-Kashmir Institute of Medical Sciences, Soura. The study was approved by Ethical Committee SKIMS. The study was conducted from October 2012 to September 2014.

Subjects

Patients affected by histologically confirmed breast cancer either pre- or post-menopausal were recruited for the study. An informed consent was taken from both individuals and their family members after detailed explanation of the procedure to them. Those who give informed consent were taken for the study.

Controls

Around 50 apparently healthy women both pre- and post-menopausal were taken as controls.

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Exclusion criteria

The individuals who had any history of systemic disease such as known diabetes, heart diseases, current pregnancy, lactation, history of drug intake such as steroids, androgens, oral contraceptives, drugs known to interfere in glucose, or lipid metabolism were excluded from the study.

Methods

Each of these participants was interviewed about:

1. Interview data
2. Detailed menstrual history including age of menarche, regularity, duration, and number of menstrual cycles per year
3. Detailed obstetric history including any infertility, drugs used for infertility, number of conceptions, any abortions, duration of lactation, and use of oral contraceptives
4. Personal history of metabolic and cardiovascular disease features of acne, any hair loss, or abnormal hair growth
5. Family history of metabolic and neoplastic diseases.

Physical examination

All females were subjected to assessment of anthropometric parameters such as measurement of body weight, height, and the waist and hip circumferences. Body weight was measured by electronic scale (Filizola) to the nearest 0.1 kg while individuals were barefoot and wearing light clothes. Height was determined by portable Seca stadiometer to nearest 01.0 cm, according to norms proposed by World Health Organization (1995). Measured weight and height were used to calculate the body mass index (BMI, weight in kilograms divided by height in meters squared). The smallest waist circumference and the largest hip circumference were used to calculate waist to hip circumference ratio (WHR).

Obesity was defined as BMI value of 27 kg/m^2 or larger.

Upper body fat distribution was defined as WHR >0.8.

Blood pressure (BP) was measured on the right arm with individuals lying to standing by means of mercury sphygmomanometer after the individual had been at rest for a minimum period of 5 minutes and the cuff involved 80% of the right arm's circumference. The point of disappearance of Korotkoff sounds (Phase V) was recorded as patient's diastolic BP. The average of three measurements will be taken as the individuals' BP value. Hypertension was defined by Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure Criteria.

Investigations

A sample of about 10 ml blood was taken from each female after overnight fasting ≥ 8h. The samples were sent for the following tests:

1. Fasting plasma glucose
2. Serum triglyceride levels
3. HDL levels
4. Low-density lipoprotein levels
5. Serum cholesterol levels.

Assays

1. Glucose was measured by the oxidize glucose method
2. Lipid profile, KFT was done by HITACHE.

These investigations were carried out at SKIMS Bio technology laboratory. Impaired glucose metabolism and type 2 Diabetes Mellitus were defined by American Diabetes Association criteria. Impaired fasting glucose was defined by fasting blood glucose levels = 100 mg/dl but <126 mg/dl and diabetes as fasting glucose ≥126 mg/dl.

Definition of the metabolic syndrome

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria will be employed for diagnosis of MS as per following criteria:

Presence of three or more of the following clinical criteria:

1. Waist circumference >88 cm
2. BP ≥135/85 mmHg
3. HDL cholesterol <50 mg/dl
4. Triglyceride level ≥150 mg/dl
5. Fasting plasma glucose ≥100 mg/dl.

Statistical analysis

Entire data were subjected to suitable standard statistical technique. Univariate analysis was done applying Chi-square test, *t*-test. The analyses were performed using SPSS statistical package 20 (SPSS Inc., IBM, Chicago, IL, USA).

Results and Observations

Table 1 shows the main results for the metabolic syndrome and its components. There was no statistically significant difference in number of individuals in various age groups between cases (mean age 54.28 ± 7.36 years) and controls (50.96 ± 9.94 years). Age, number of live births, and menopausal status did not seem to affect breast cancer risk. The prevalence of obesity was similar in both case and control groups. Significant difference was found considering the prevalence of upper body fat distribution. Family history of breast cancer was more frequent in cases than in controls ($P < 0.008$). The prevalence of the NCEP-ATP

Table 1: Metabolic syndrome components

Characteristics	Individuals, *n* (%)	Controls, *n* (%)	*P*
Obesity	18 (36.0)	13 (26.0)	0.387
Waist to hip circumference ratio >0.8	33 (66.0)	14 (28.0)	0.0001
Family breast cancer	12 (24.0)	2 (4.0)	0.008
Personal diabetes	15 (30.0)	3 (6.0)	0.003
Hypertension	20 (40.0)	5 (10.0)	0.001
Dyslipidemia	15 (30.0)	4 (8.0)	0.009

III-defined metabolic syndrome in this cohort of breast cancer patients was 40%, whereas it was 18% in the control group, representing a significant difference (P = 0.02). Metabolic syndrome was strongly associated with breast cancer risk. Relative to the control group, patients with metabolic syndrome were more than three times more likely to have breast cancer (odds ratio (OR) = 3.037; 95% confidence interval (CI) 1.214–7.597). Moreover, some of the individual components of the syndrome were associated with increased breast cancer risk, including higher waist circumference (OR = 4.992; 95% CI 2.132–11.685), BP levels (OR = 6.000; 95% CI 2.031–17.728) and serum triglyceride levels (OR = 4.929; 95% CI 1.503–16.157) and fasting glucose levels (OR = 6.714; 95% CI 1.803–24.998). However, low HDL levels did not seem to affect breast cancer risk as it did not achieve statistical significance between case and control groups [Table 1].

Discussion

Metabolic syndrome consists of constellations of metabolic abnormalities including obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, and is characterized physiopathologically by the common feature of hyperinsulinemia/insulin resistance.[1] Breast cancer risk is postulated to be driven by cell proliferation in response to sex hormones but also to polypeptide growth hormones (GHs) (insulin-like growth factors (IGFs) and insulin itself).[20-23] Studies suggest that hyperinsulinemia and its sequelae can increase the promotion of breast carcinogenesis, and the mechanism is likely related to increased bioactivity of IGF-1. In the present study, metabolic syndrome was identified by blood determinations to ensure the quality of metabolic syndrome diagnosis, toward estimating metabolic syndrome as a risk factor for breast cancer that possibly increases the risk prediction beyond what may already seem apparent by metabolic syndrome components. The present study reflected important finding of the increased prevalence of hypertension, personal type 2 diabetes mellitus, and dyslipidemia in individuals with documented breast cancer versus controls. Our observation exhibited higher prevalence of MS (40%) among women with breast cancer in postmenopausal compared to healthy women (18%).

Metabolic syndrome is an insulin resistance syndrome, and several studies have implicated insulin in breast cancer development.[24] C-peptide serum levels – indicator of pancreatic insulin production – is linked with increased breast cancer risk in postmenopausal women,[5] and in breast cancer patients, high serum insulin is associated with poorer outcome.[25] Insulin has a gonadotropic effect.[26] It promotes the ovarian stroma to produce androgens, whose peripheral aromatization is the main source of estrogens after menopause.[27,28] Insulin also augments aromatase activity.[29] Abdominal adipose, in particular, is an important source of both androgens and estrogens.[30] Obese women have high levels of estrogens, which are widely considered to facilitate the association of obesity with breast cancer risk.[31] In the present study, however, obesity was not associated with breast cancer risk, suggesting that metabolic syndrome has an effect that is independent of obesity.

Insulin also reduces liver production of sex hormone-binding globulin (SHBG), thereby increasing sex hormone bioavailability,[32] and metabolic syndrome is associated with increased levels of both total and free[33] testosterone.

A supplementary mechanism by which insulin may escalate breast cancer risk is through its effect on the bioavailability of IGF-I. Insulin declines hepatic production of two IGF-binding proteins, IGFBP1 and IGFBP2,[34,35] thereby increasing IGF-I bioavailability and enhances the synthesis of GH-receptor,[36,37] thus allowing GH to promote IGF-I synthesis. Both insulin[38] and IGF-I conjoin with estrogens to stimulate the proliferation of breast epithelium cells.[39] Many studies have examined the relationship of breast cancer with prediagnostic serum levels of IGF-I, with inconsistent results.[39] The initial studies found a positive association only in premenopausal women;[31,40,41] more recent studies on larger cohorts, however, did not endorse an association before menopause but emphasized a significant positive association after menopause.[42,43]

Metabolic syndrome is also associated with increasing levels of inflammatory cytokines[44] and leptin,[45] which can stimulate cell proliferation through various mechanisms,[46,47] and is inversely associated with adiponectin,[48] which downregulates tumor cell proliferation and upregulates apoptosis.[47]

Several studies have revealed that waist circumference is a significant predictor of breast cancer risk in postmenopausal women, and the positive link between abdominal obesity and breast cancer was found to be independent of BMI.[9,10] In the present study, abdominal obesity was associated with increased breast cancer risk. As the development of metabolic syndrome has been associated to obesity and physical inactivity, it is important to encourage increased physical activity and healthy dietary practices to diminish the prevalence of obesity in the population and the probable relationship between postmenopausal breast cancer and physical inactivity. Weight reduction combined with regular physical exercise has been displayed to decrease both estrogen and insulin concentrations in obese women, and such a regimen might be investigated in clinical trials for an effect on breast cancer risk in obese women.

Hypertension, which occurs as a single entity or as part of the metabolic syndrome, has been associated to be a risk factor for breast cancer.[49-51] The mechanisms underlying this association remain unclear, but breast cancer and hypertension may have common pathophysiologic means, including those involved in subclinical inflammation. In the

present study, hypertension had an adverse effect on breast cancer risk although BP could be elevated in the affected individuals purely because of the anxiety of attending an oncology consultation appointment.

Low serum HDL cholesterol has lately been associated with increased risk of breast cancer in overweight and obese women.[52] In the present study, however, HDL cholesterol did not seem to affect breast cancer risk. Elevated levels of plasma triglycerides are associated with increased risk of histologically documented premenopausal breast cancer. In this study, elevated serum triglyceride levels were found to be significantly associated with breast cancer risk. This association persevered after adjustment for age, body size, lipids, reproductive and familial risk factors, in keeping with an independent association of elevated triglycerides with breast cancer risk.

One exciting findings of the present study was the association of fasting glucose with breast cancer risk in both premenopausal and postmenopausal women. Schoen *et al.*[53] reported that fasting glucose was associated with colorectal cancer, another type of cancer of which the etiology has been related to impaired fasting glucose and hyperinsulinemic insulin resistance. Another prospective study, the Malmo Diet and Cancer Study, did not find an association between fasting glucose and breast cancer risk in premenopausal or postmenopausal women.[16] Fasting glucose levels, after an overnight fast, depend on the hepatic and renal gluconeogenesis.[54] Apart from decrease in insulin sensitivity or insulin secretion, which cause increased glucose production and decreased glucose utilization,[55] gluconeogenesis is stimulated by counterregulatory hormones such as adrenal hormones, androgens, and GHs.[56,57] These hormones are determinants of fasting glucose, and additional studies are needed to elucidate the potential etiological role of these hormones in breast cancer. On the other hand, one can hypothesize that increased serum glucose availability may offer a selective advantage to malignant cells with increased serum glucose requirement.[58] In addition, glucose itself may promote carcinogenic processes through the production of free radicals and the induction of oxidative injury to both DNA and to the enzymes concerned with the repair and processing of DNA.[59-62]

Limitations

There are important basic limitations of case–control studies. We tried to attenuate the effects of confounding factors by matching cases and controls for age, by enrolling cases and controls at the same time of the year and from the same institution. However, the controls seem to be younger than the affected patients. Although this is not statistically significant, it raises the question as to whether or not the age distribution of affected patients compared with controls could affect the overall results.

Conclusions

Our study adds evidence to the little understanding existing on the association of metabolic syndrome with breast cancer risk, confirming that metabolic syndrome is associated with breast cancer. Furthermore, the prevalence of metabolic syndrome is high and increasing with an increasing incidence of breast cancer worldwide. Multimodality actions involving nutrition, exercise, and stress reduction may be extremely important to control insulin resistance and improve cancer outcomes. Interventions to cut breast cancer risk in first-degree relatives of breast cancer patients need to be initiated at an early age.

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Conflicts of interest

There are no conflicts of interest.

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