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Metabolic syndrome and breast cancer risk

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Abstract. – **States of hyperinsulinemia with insulin resistance are frequently associated with proliferative tissue abnormalities, via stimulation of DNA synthesis and cell proliferation through the IGF-1 receptor. Such elements of metabolic syndrome (hyperinsulinemia/insulin-resistance, obesity, type 2 diabetes mellitus, hypertension, dyslipidemia) are explored in a population of 125 women (n. 50 with histologically confirmed diagnosis of breast cancer, Group A; n. 50 with benign breast pathology, Group B; n. 25 with no breast pathology, Group C, controls), affering to a Center for the prevention of breast cancer, in order to investigate for an eventual relationship between these pathologies.**

The prevalence of type 2 diabetes mellitus, hypertension, dyslipidemia, was higher in group of women affected by breast cancer vs. benign breast pathology and controls.

This finding is in agreement with the hypothesis of the interrelationship of hyperinsulinism/insulin resistance with the growth-related abnormalities of breast cancer.

Key Words:

Metabolic syndrome, Breast cancer.

Introduction

Insulin may be involved in the pathogenesis of growth-related abnormalities (endometrial, ovarian, prostate and breast cancer, i.e. hormone-dependent tumors)[1-4]. It is well known in fact that high insulin concentrations, despite of resistance to metabolic effects mediated through the insulin receptor, stimulate DNA synthesis and cell proliferation in vitro through the insulin-like growth factor I (IGF-I) receptor[5,6].

Moreover, the stimulation of DNA synthesis and cell growth may happen also via the insulin receptor, but only in certain cell types, particularly in cultured human breast cancer[7].

So, in addition to steroid hormones[4], polypeptide growth hormones (insulin-like factors and insulin itself) are thought to play an important role in regulation of breast tumor proliferation[8].

Insulin resistance, a common feature of type 2 diabetes mellitus, is frequently associated to hyperinsulinemia, hypertriglyceridemia, low HDL cholesterol, hypertension, hyperuricemia, abdominal obesity, increased levels of fibrinogen and PAI-1. The combination of these features with IGT or overt diabetes and microalbuminuria, is known as metabolic syndrome[9].

Epidemiologic evidences indicate that obesity (expecially with upper body fat distribution) and type 2 diabetes mellitus are associated with an increased risk of several neoplastic hormone-dependent diseases[10-13].

Aim of the present report is to analyze in a population of women who affer to a Center for the Prevention and Care of breast cancer, the prevalence of such metabolic abnormalities in breast pathology.

Materials and Methods

In order to evaluate the prevalence of such element of metabolic syndrome in neoplastic breast pathology, we recruited consecutively:

1. The first n. 50 subjects affected by hystologically confirmed breast cancer (mean age 59.05 ± 11.16 ys) (Group A).

2. The first n. 50 subjects affected by benign breast pathology (mean age 43.48 ± 6.55 ys) (Group B).
3. The first n. 25 subjects with no breast pathology (mean age 49.44 ± 10.44 ys) (Group C, controls).

These 125 outpatients attended the Department of Oncologic Surgery of our University Clinic.

Each patient was questioned (see schedule enclosed, Table IA and IB) about:

– anagraphic informations;
– family history of metabolic and neoplastic diseases;
– personal data on age at menarche and menopause, pregnancy history;
– personal history of cardiovascular and metabolic diseases.

Interviews were conducted in-person by the technician. Anthropometric measures (body weight, height, the waist and hip circumferences) were evaluated by a trainer anthropometrist.

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 the waist-to-hip circumference ratio (WHR).

Blood pressure was measured on the right arm with subjects lying to standing by means of mercury sphygmomanometer. The point of disappearance of the Korotkoff sounds (phase V) was recorded as diastolic blood pressure. The average of three measurements (made by the same operator) was taken as the subject blood pressure value. A large blood pressure cuff was used in obese subjects.

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

Upper-body fat distribution was defined as WHR > 0.8.

Type 2 diabetes mellitus was defined by American Diabetes Association criteria[14].

Table IA. Collecting schedule

Schedule no. _____

BIRTH INFORMATIONS

Name: _____ Age: _____ Clinical record no: _____

FAMILY HISTORY OF DISEASES

	Yes	No	Familiar relationship
Neoplastic diseases (type			_____
Type 2 diabetes mellitus			_____
Hypertension			_____
Cardiovascular diseases			_____
Obesity			_____
Dyslipidemia			_____
Hyperuricemia			_____

Table IB. Collecting schedule

PHYSIOLOGIC ANAMNESIS

Body weight: *at birth*: _____ *actually*: _____ *max:* _____

Age at menarche: _____ Menstrual cycle: _____

Pregnancy: _____ Abort: _____ Age at menopause: _____

Eating habits: _____

PERSONAL HISTORY OF DISEASES

Type 2 diabete mellitus	Yes	No
Age at onset: _____		
Hypertension	Yes	No
Age at onset: _____		
Cardiovascular diseases	Yes	No
Dyslipidemia	Yes	No

Other metabolic diseases _____

ANTHROPOMETRIC MEASURES

Body weight: _____ Height: _____ B.M.I.: _____ WHR: _____

Hypertension was defined by Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure criteria[15].

Dyslipidemia was considered when levels of triglycerides upper 180 mg/dl and total cholesterol upper of 200 mg/dl were referred.

History of type 2 diabetes mellitus, hypertension and dyslipidemia were based on interview data.

Statistical analysis was performed by t-test of Student-Newmann-Keuls (unpaired data) for the difference between means, calculated also considering two groups of age (> and < 50 years).

Difference between the latter categorical variables were tested with χ^2.

Two-tailed confidence limits at 95% level were calculated ($p < 0.05$).

Results

Results are listed in Table II.

The prevalence of obesity was similar in all the groups. No difference was found considering the prevalence of upper-body fat distribution.

The same behaviour was noted for the family history of type 2 diabetes mellitus.

The prevalence of personal type 2 diabetes mellitus was significantly higher in the group A than in the group B and in controls ($p < 0.005$).

Hypertension was significantly more prevalent in group A patients than in group B and C ($p < 0.0001$).

The mean age of group A was significantly higher than the B and C groups ($p < 0.0001$), but this significance failed if the duration of diabetes and hypertension was considered. In

Table II.

	Group A n. %	Group B n. %	Controls n. %	p
Obesity	16 (32)	1.0 (20)	11 (44)	n s.
Family diabetes	23 (46)	24 (48)	11 (44)	n.s.
Personal diabetes	13 (26)	3 (6)	1 (4)	0.004
Hypertension	24 (48)	7 (14)	5 (20)	0.000
Dyslipidemia	14 (28)	4 (8)	1 (4)	0.005
WHR > 0.8	15 (30)	29 (58)	14 (56)	n.s.
Family breast cancer	28 (56)	15 (30)	3 (12)	0.000

fact, subdividing the groups by age, the duration of diabetes and hypertension is significantly higher in subjects > 50 ys vs. subjects < 50 ys ($p < 0.001$) in each of them.

The prevalence of dyslipidemia was significantly higher in the group A vs. group B and C ($p < 0.005$).

Family history of breast cancer was more frequent in group A than in group B and C ($p < 0.0001$).

Discussion

The incidence of breast cancer in the Western world runs parallel to that of the major components of the insulin resistance syndrome: hyperinsulinemia, dyslipidemia, hypertension and atherosclerosis. Evidence is shown that the growth of breast cancer is favoured by specific dietary fatty acids, visceral fat accumulation and inadequate physical exercise; all of which are thought to interact in favouring the development of the insulin resistance syndrome[16].

Metabolic syndrome consists of conditions such as obesity, type 2 diabetes mellitus, hypertension, dyslipidemia, hyperuricemia, blood hypercoagulability and is characterized physiopathologically by the common feature of hyperinsulinemia/insulin resistance[9].

Our most important finding is the increased prevalence of personal type 2 diabetes mellitus, hypertension and dyslipidemia in subjects with documented breast cancer vs. controls and affected by benign breast pathology.

Hypothesis was raised that breast cancer risk is determined by cell proliferation in response to sex hormones, but also to polipeptide growth hormones (insulin-like growth factors and insulin itself)[17-20].

Clinical and epidemiological evidence suggests that both breast cancer and the metabolic disorders included in the insulin resistance syndrome are of polygenic and multifactorial origin[16]. Experimental evidence suggests that hyperinsulinemia and its features can increase the promotion of mammary carcinogenesis and the mechanism is likely related to increased bioactivity of insulin-like growth factor 1 (IGF-1)[16].

Therefore, our findings are consistent with insulin-stimulate growth promotion at supraphysiologic insulin concentrations (as happens in metabolic syndrome) mediated through the IGF-1 and insulin receptors[21].

There is a possibility that effect of BMI on breast cancer risk is mediated by both insulin resistance and estrogen metabolism[4].

In our study, obesity and upper body fat distribution are not related to the breast cancer probably because our subjects were affected by breast cancer at various degrees of pathology.

Finally, the higher prevalence of breast cancer in relatives of breast cancer patients is a confirmatory date of literature[22].

A family history of breast cancer is quite common in the general population, but preventive interventions targeted to women at risk of breast cancer because of family history will have limited impact on breast cancer morbidity as a whole[23].

Vigorous physical activity was associated with reduced breast cancer risk in both Hispanic and non-Hispanic white women[24]. Another study evidences the association between physical activity and breast cancer only for postmenopausal women[25]. So, nutrition and lifestyle modifications that improve insulin sensitivity may not only decrease a tendency to atherosclerosis but also reduce breast cancer risk in women.

Weight reduction combined with a program of regular physical exercise has been shown to reduce both estrogen and insulin concentrations in obese women and such a regimen might be tested in clinical trials for an effect on breast cancer risk in obese women[26].

Interventions to decrease breast cancer risk in first-degree relatives of breast cancer patients need to begin at an early age.

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