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

Insulin resistance, a common feature of type 2 diabetes mellitus, is frequently associated with 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.

Epidemiologic evidences indicate that obesity (especially with upper body fat distribution) and type 2 diabetes mellitus are associated with an increased risk of several neoplastic hormone-dependent diseases. A 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 histologically 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/m² or larger.

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

Type 2 diabetes mellitus was defined by American Diabetes Association criteria.\(^1\)

Table IA. Collecting schedule

<table>
<thead>
<tr>
<th>Schedule no. _________</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BIRTH INFORMATIONS</strong></td>
</tr>
<tr>
<td>Name: ________________  Age: ________________  Clinical record no: ___________________________</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>FAMILY HISTORY OF DISEASES</th>
<th>Yes</th>
<th>No</th>
<th>Familiar relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoplastic diseases (type .......)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypertension was defined by Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure criteria. 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).

Differences between the latter categorical variables were tested with \( \chi^2 \). 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 concerning 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.
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 syndrome16.

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 resistance9.

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.

Hypothosis was raised that breast cancer risk is determined by cell proliferation in response to sex hormones, but also to polypeptide 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 origin16. 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 supra-physiologic insulin concentrations (as happens in metabolic syndrome) mediated through the IGF-1 and insulin receptors21.

There is a possibility that effect of BMI on breast cancer risk is mediated by both insulin resistance and estrogen metabolism4. 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 literature22.

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 whole23.

Vigorous physical activity was associated with reduced breast cancer risk in both Hispanic and non-Hispanic white women24. A nother study evidences the association between physical activity and breast cancer only for postmenopausal women25. 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.

### Table II.

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

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

References