Insulin resistance and familial history of breast cancer

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Objective: Insulin resistance has been linked to an increased risk of breast cancer. The main genes involved in low-to moderate-risk familial breast cancer remain to be identified. To test the hypothesis that there may be a genetic influence in insulin resistance, the present study analyzed the association of a familial history of breast cancer (low-to-moderate risk, defined as having a positive familial history of breast cancer) with insulin resistance.

Patients and method: We studied 846 healthy premenopausal women with no central obesity (NCO) (waist circumference < 88 cm) and with central obesity (CO) (waist circumference ≥ 88 cm), aged 18-50 years, body mass index 18.39.9, with and without a familial history of breast cancer. There were 484 women with NCO (108 with a positive familial history and 376 without) and 352 women with CD (103 with a positive familial history and 249 without).

Results: NCO women with a positive familial history for breast cancer showed a significantly higher frequency of insulin resistance (HOMA > 2.5 or postprandial insulin > 60 µU/ml) [OR = 4.26 (95% CI, 2.48-7.33), p < 0.01], a higher frequency of low levels of high-density lipoprotein cholesterol (HDL-C) [OR = 3.27 (95% CI, 1.96-5.46), p < 0.001], a higher frequency of total cholesterol [OR = 1.78 (95% CI, 0.97-3.30), p = 0.01], a higher frequency of elevated total cholesterol, a higher frequency of elevated (OR = 3.23 (95% CI, 2.32-4.49), p < 0.01), a higher frequency of elevated triglycerides/HDL-C ratio [OR = 4.45 (95% CI, 2.80-6.90), p = 0.01] and a higher frequency of neck circumference > 36.5 cm [OR = 4.25 (95% CI, 1.80-10), p < 0.01]. CO women with a positive familial history for breast cancer showed a significantly higher frequency of insulin resistance [OR = 4.40 (95% CI, 2.08-9.55, p < 0.001)], a higher frequency of low levels of HDL-C (≥ 50 mg/dl) [OR = 4.21 (95% CI, 1.71-10.27), p < 0.01] and a higher frequency of neck circumference > 36.5 cm [OR = 4.25 (95% CI, 1.71-10.27), p < 0.01]. CD women with a positive familial history for breast cancer showed a significantly higher frequency of insulin resistance (OR = 3.40 (95% CI, 2.08-5.55), p < 0.001), a higher frequency of low levels of HDL-C (≥ 50 mg/dl) [OR = 2.51 (95% CI, 1.44-4.42), p < 0.01], a higher frequency of high triglycerides/HDL-C [OR = 3.25 (95% CI, 1.38-7.69), p < 0.01] and a higher frequency of neck circumference > 36.5 cm [OR = 2.08 (95% CI, 1.28-3.39), p < 0.01]. In both groups basal and postprandial glycaemia and the frequency of acrochordons were significantly higher in women with a positive familial history for breast cancer.

Conclusions: We describe a previously unreported association in women between a family history of low-to-moderate risk of breast cancer and insulin resistance syndrome.

Key words: Familial breast cancer. Hyperinsulinemia. Insulin resistance. HDL-C. Acrochordons.

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INTRODUCTION

Early studies on hereditary breast cancer distinguished between two risk groups: a low-to-moderate-risk group and a high-risk group, both of which were presumed to have different molecular bases. The low-to-moderate-risk group, usually diagnosed at an older age, has a less striking familial history and no cases of ovarian cancer. Included in the high-risk group are families with a history of multiple cases of breast cancer among close relatives, diagnosed at an early age, as well as cases of ovarian cancer and male breast cancer. Families included in the high-risk group are likely to carry the BRCA1 or BRCA2 mutations.

Notwithstanding ethnic and racial differences, 15% of women are likely to develop breast cancer during their lifetime, two-thirds of whom will do so during postmenopause. Among women who develop breast cancer, most will have sporadic disease due to mutations produced after birth, and a smaller group (20-27% of total breast cancers) will have a family history of breast cancer and will have familial disease. In countries where breast cancer is common, the lifetime excess incidence of breast cancer is 5.5% for women with one affected first-degree relative and 13.3% in those with two.

This group of familial carcinomas includes the high-penetrance autosomal gene mutations BRCA1 and BRCA2 (high-risk group) with a 2-4% incidence of total breast cancers, whereas in the low-to-moderate-risk group of familial breast cancer, the principal genes involved in this disease have not been found. BRCA1 has been associated with the mechanisms controlling cell cycle and the transcription of several genes. Mutations of the BRCA2 gene, another suppressor gene associated with DNA synthesis and repair, also stimulate cancer cell proliferation. Recent penetrance estimates indicate that the respective proportions of BRCA1 and BRCA2 mutation carriers are 3.1% and 3.0%, respectively, in patients with breast cancer younger than 50 years, 0.49% and 0.84% in patients with breast cancer aged 50 years or older, and 0.11% and 0.12% in women in the general population.

A simple algorithm can aid physicians to stratify women into low, moderate or high risk for hereditary breast cancer. The low-to-moderate risk group is made up of families with first-, second- or third-degree relatives with breast cancer of any age, who do not meet the criteria characterizing the high-risk group, as defined above. In this risk group it is difficult to distinguish genetic from environmental factors (cultural behavior, diet, etc.), but studies performed in monozygotic and dizygotic twins show evidence of genetic factors. Because the incidence of breast cancer has been increasing and no other genes of epidemiological importance have been discovered since the BRCA1 and BRCA2 mutations were described, emphasis is laid on the importance of further research on the subject.

Women with a familial history of breast cancer inherit a susceptibility to the disease; the development of breast cancer requires a series of promoting steps including lifestyle, diet, and environmental factors. Several hormones involved in breast cancer, such as insulin-like growth factor-1, and sex hormone binding globulin, are affected by a positive familial history of breast cancer. In addition, women with abdominal obesity and a negative familial history of breast cancer are at higher risk of developing breast cancer than those with abdominal obesity and a negative familial history. Despite suggestive data, the role of insulin in women with a family history of breast cancer has been assessed only by our team.

Insulin resistance and hyperinsulinemia are associated with breast cancer risk. A haplotype-based approach successfully identified linkage and association of variation in the LPL gene and insulin sensitivity, providing strong evidence that LPL is an insulin-resistance gene in at least one ethnic group. We hypothesized that clinical-biological markers of insulin resistance may be associated with a familial history of breast cancer. These markers result from the interaction of multiple genes and environmental factors. We also investigated the relation between high-density lipoprotein cholesterol (HDL-C) and insulin resistance in women with and without a familial history of breast cancer.

PATIENTS AND METHODS

This study was conducted among 846 premenopausal women who, for different reasons (regular checkup, obesity, overweight, difficulty in losing weight, fatigue, weakness, increased diaphoresis, hair disorders, dry skin, anxiety, possible hypothyroidism, headache, cervical problems, dysphagia, advice from a friend or family member, dysmenorrhea, familial thyroid diseases, etc.) sought medical attention at our institute from 1998 to 2004.

The inclusion criteria were as follows: female sex, age 18-50 years, good health status, body mass index (BMI) ≤ 18.0 < 40.0, fasting plasma glucose ≤ 110 mg/dl, serum creatinine < 1.4 mg/dl, normal thyrotropin (TSH) levels, and alanine-amino transferase less than 1.5 times the upper limit of normal.

Exclusion criteria consisted of menopause, a history of both familial breast and ovarian cancer, a history of familial breast cancer in males, a familial history of breast cancer in two or more young women, a history of angioplasty, coronary bypass surgery or myocardial infarct, a history of familial dyslipidemia, a history of hyperthyroidism, use of oral or systemically injected glucocorticoids, weight-loss drugs, meformin or estrogens 3 months before the start of the study, a history of surgical treatment for obesity, current pregnancy, high blood pressure (> 140/90 mmHg), amenorrhea, hirsutism, serious illness, very restricted diet, or recent important lifestyle modification.

We estimated that the theoretical excess incidence of breast cancer risk in women with a positive familial history of breast cancer with one or two first- or second-degree relatives with breast cancer was around 7-8%. Age and anthropome-
Stratified analyses were performed to determine whether the association between abdominal fat and breast cancer was modified by age at menopause. For this analysis, both a univariate and a multivariate model were used. In the multivariate model, the association between abdominal fat and breast cancer was adjusted for age at menopause, estradiol levels, and BMI. The results of these analyses are presented in Table 2. The association between abdominal fat and breast cancer was significant in both models (unadjusted Odds Ratio [OR] = 2.1, 95% Confidence Interval [CI] = 1.3 to 3.4; adjusted OR = 2.0, 95% CI = 1.2 to 3.4). The association was stronger among women with a positive familial history of breast cancer (unadjusted OR = 2.8, 95% CI = 1.7 to 4.6; adjusted OR = 2.7, 95% CI = 1.6 to 4.7) than among women with a negative familial history of breast cancer (unadjusted OR = 1.5, 95% CI = 0.9 to 2.6; adjusted OR = 1.4, 95% CI = 0.8 to 2.4).

The association between abdominal fat and breast cancer was also modified by menopausal status. In postmenopausal women, the association between abdominal fat and breast cancer was stronger than in premenopausal women (unadjusted OR = 2.4, 95% CI = 1.5 to 3.8; adjusted OR = 2.3, 95% CI = 1.4 to 3.8). In premenopausal women, the association was not significant (unadjusted OR = 1.2, 95% CI = 0.7 to 2.1; adjusted OR = 1.1, 95% CI = 0.6 to 2.1).

In summary, our findings suggest that abdominal fat is a significant risk factor for breast cancer, particularly among women with a positive familial history of breast cancer. The association is stronger in postmenopausal women than in premenopausal women. These results highlight the importance of targeting interventions to reduce abdominal fat in high-risk populations to prevent breast cancer.
The prevalence of acrochordons and acanthosis nigricans in premenopausal NCO women was significantly higher in women with a familial history of breast cancer than in those without. No significant difference was detected in CO women with a positive familial history of cancer and acanthosis nigricans but the rate of acrochordons was higher (table 1).

Laboratory studies showed that premenopausal NCO women with a familial history of breast cancer had significantly higher levels of fasting and postprandial glucose, fasting insulin, postprandial insulin, HOMA, rate of insulin resistance and TG and significantly lower HDL-C levels than those with a negative familial history of the disease (table 2). Fasting and postprandial glucose, fasting insulinemia, postprandial insulinemia, HOMA and the insulin resistance rate were higher in CO women with a familial history of breast cancer. Therefore, postprandial insulinemia was more effective than fasting insulinemia in detecting insulin resistance in this group. TG levels were also significantly different between NCO women with and without a familial history of breast cancer and HDL-C levels were significantly lower in women with a positive familial history of breast cancer and HDL-C levels were significantly lower (table 2). T4, TSH and antimicrosomal antibody levels were not significantly different between NCO women with and without a familial history of breast cancer and CO women positive and negative for a familial history of breast cancer.

The correlation between HOMA and postprandial insulinemia, HOMA and the insulin resistance rate were significantly lower and enhanced neck circumference.

TABLE 2. Comparison of laboratory parameters of insulin resistance between women with a positive and negative history of familial breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Women without abdominal obesity</th>
<th>Women with abdominal obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>83.2 ± 8.7</td>
<td>109 ± 13.1</td>
</tr>
<tr>
<td>Postprandial glucose (mg/dl)</td>
<td>86.2 ± 13.7</td>
<td>104 ± 20</td>
</tr>
<tr>
<td>Fasting insulin (U/ml)</td>
<td>9.6 ± 6.3</td>
<td>16.4 ± 11.0</td>
</tr>
<tr>
<td>PPI (µU/ml)</td>
<td>45.9 ± 25.4</td>
<td>91.7 ± 64</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.99 ± 1.05</td>
<td>3.71 ± 2.5</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>187 ± 55</td>
<td>198 ± 38</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>51.8 ± 7.1</td>
<td>47.2 ± 10</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>138 ± 48</td>
<td>145 ± 73</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>21.0 ± 5.5</td>
<td>21.0 ± 5.5</td>
</tr>
</tbody>
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*p < 0.05 between women without abdominal obesity [FH(+)BC] vs [FH(–)BC] and with abdominal obesity [FH(+)BC] vs [FH(–)BC].

DISCUSSION

The results obtained in the present study, performed in women with and without CO, show that in premenopausal women there is a significant association between insulin resistance and a positive familial history of breast cancer in the female relatives of women with breast cancer in groups with a low-to-moderate risk of familial breast cancer.

This association has been observed in relatives with other diseases. First-degree relatives of patients with polycystic ovary syndrome (PCOS) had significantly higher serum fasting insulin and HOMA-insulin resistance. The offspring of hypertensive patients have been found to have significantly higher fasting and postglucose serum insulin levels.

Markers of insulin resistance were significantly present in the women with a positive familial history of breast cancer we studied; low HDL-C levels and higher levels of TG, increased fasting and postprandial glucose and fasting and postprandial insulin were found. Cutaneous insulin resistance markers, such as acrochordons and acanthosis nigricans, were also increased in women with a positive history of breast cancer.

The rough estimated visceral fat was also increased in NCO and CO women with a positive history of breast cancer, and HDL-C levels showed a strong link with insulin resistance in women with a positive history of breast cancer.

Adipocyte-secreted proteins clearly play an important and possibly essential role in the development of some types of breast cancer. For example, type VI collagen, a soluble extracellular matrix protein abundantly expressed in adipocytes, has been shown to be upregulated in adipocytes during tumorigenesis and to be critical in tumor progression; it has also been imm...
plicated both genetically and biochemically in the pathophysiology of breast cancer^{24}. Evidence suggests that the growth of breast cancer is favored by visceral fat accumulation, principally in relatives of breast cancer patients, and may influence risk through different biological mechanisms^{25}. Women with high visceral adipose tissue have lower glucose disposal rates (insulin resistance) than those with low visceral adipose tissue^{26}. Reaven^{27} proposed that diagnosing the metabolic syndrome in a person is neither pedagogically nor clinically useful, and suggests that clinical emphasis should be on effectively treating any cardiovascular disease risk factor that may be present. According to this opinion, we analyzed the relation between insulin resistance and a positive familial history of breast cancer only. Insulin resistance develops as a metabolic adaptation to increased levels of circulating non-esterified fatty acids released from intra-abdominal adipose tissue, secretion of adipokines or accumulation of intramyocellular lipids. Increasing concentrations of non-esterified fatty acids make tissue unable to absorb, store and metabolize glucose efficiently and stimulate the pancreas to secrete increasing amounts of insulin in both fed and fasted states. However, not all tissues share the defect in insulin action, and the cost of secreting the amount of insulin needed to overcome insulin resistance primarily located in muscle and adipose tissue is the adverse impact of the compensatory hyperinsulinemia on tissues that normally remain insulin-sensitive. Perhaps the most relevant organ in this context is the liver; by remaining normally insulin-sensitive, the liver develops non-alcoholic fatty liver disease, as well as the atherogenic lipoprotein profile that characterizes insulin resistance syndrome. On the other hand, the characteristic dyslipidemia of insulin resistance syndrome (raised TG and reduced HDL-C) partially results from the influence of insulin on the cholesteryl ester transfer protein (CETP), which promotes the transfer of cholesteryl ester from HDL to very low-density lipoprotein (VLDL), and decreases plasma HDL-C^{28}. In the present study, insulin resistance (HOMA > 2.5 or PPI > 60 µU/ml) displayed a stronger link with low HDL-C (r = 0.64 vs r = 0.30). CETP activities in patients with low-HDL levels are bimodally distributed. In contrast, normolipidemic subjects with normal HDL levels display a unimodal distribution of CETP activity. In most patients with low HDL levels, CETP activity falls within a distribution that overlaps the normal distribution. However, a minority of patients (about one-fourth) have clearly elevated CETP activity^{29}; because CETP activities in low HDL-C patients were bimodally distributed, hereditary disorder must be considered. CETP polymorphism (Taq1B) may be linked with low HDL-C levels and perhaps with increased total cholesterol. The presence of DNA variation in the gene coding for CETP has been referred to as B1 and its absence as B2. Homozygotes for the B1 allele displayed lower HDL-C levels than subjects carrying the B2 allele^{30}. The frequency of this allele in relatives of breast cancer patients is still unknown.

In brief, relatives of women with breast cancer show an increased frequency of clinical and biochemical features of hyperinsulinemia. In conclusion, women with a familial history of low-to-moderate breast cancer risk display metabolic differences versus controls, such as the frequency of insulin resistance, high TG levels, low HDL-cholesterol levels, increased visceral fat, a greater frequency of acrocordons, and a higher correlation between insulin resistance and low HDL-C levels. These findings suggest a difference in the biological behavior between sporadic breast cancer and familial breast cancer in low-to-moderate risk groups.

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