Resistencia a la insulina e historia familiar de cáncer de mama

Objetivo: Analizar si la resistencia a la insulina (IR) se asocia a un riesgo incrementado de cáncer de mama (CM).

Se estudió a 846 mujeres sanas, premenopausias, con edades entre 18 y 50 años, IMC 18-39,9, sin NOC y con (OC) obesidad central (perímetro de cintura > 88 cm), con (AF-CM) y sin (AF-CM) antecedentes familiares de CM. De las 494 mujeres NOC, 108 tenían AF-CM y 386 no los tenían; y de 352 mujeres OC, 103 tenían AF-CM y 249 no los tenían.

Resultados: Las mujeres NOC con AF-CM presentaron mayor frecuencia de IR (HOMA > 2.5 o insulina posprandial > 60 μU/ml) (odds ratio [OR] = 4.26; intervalo de confianza [IC] del 95%, 2.04-8.83; p < 0.001), bajos cifras de colesterol de las lipoproteínas de alta densidad (cHDL < 50 mg/dl) [OR = 3.27; IC del 95%, 1.96-5.46; p < 0.001], colesterol total elevado (> 200 mg/dl) [OR = 1.78; IC del 95%, 1.09-2.90; p = 0.01), triglicéridos (TG) elevados (≥ 150 mg/dl) [OR = 2.33; IC del 95%, 2.32-4.49; p < 0.001), elevada razón triglicéridos/cHDL (> 3.2) [OR = 4.45; IC del 95%, 1.80-10.38; p < 0.05] y circunferencia de cuello > 36.5 cm [OR = 4.25; IC del 95%, 1.76-10.27; p < 0.001]. Las mujeres OC con AF-CM presentaron mayor frecuencia de IR [OR = 3.40; IC del 95%, 2.08-5.85; p < 0.001], cHDL bajo [OR = 2.51; IC del 95%, 1.44-4.25; p < 0.01], TG/cHDL elevado [OR = 2.25; IC del 95%, 1.38-3.69; p < 0.01] y circunferencia de cuello > 36.5 cm [OR = 2.08; IC del 95%, 1.28-3.39; p < 0.01]. En ambos grupos las glucemias basales y posprandiales y la frecuencia de acrocordones resultaron significativamente más elevadas en AF-CM.

Conclusiones: Describimos una asociación entre la historia familiar de CM de bajo y moderado riesgo y el síndrome de resistencia a la insulina hasta el momento no descrita.

Palabras clave: Cáncer de mama familiar. Hiperinsulinemia. Resistencia a la insulina. cHDL. Acrocordones.

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Insulin resistance and familial history of breast cancer

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Objetivo: 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 386 without) and 352 women with CO (163 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, 2.04-8.83; 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, 1.09-2.90; 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 < 0.001), a higher frequency of elevated triglycerides/HDL-C ratio [OR = 4.45 (95% CI, 1.80-10; p < 0.01) and a higher frequency of neck circumference > 36.5 cm (OR = 4.25 (95% CI, 1.76-10.27; p < 0.01). CO women with a positive familial history for breast cancer showed a significantly higher frequency of insulin resistance [OR = 3.40 (95% CI, 2.08-5.85; p < 0.001)], a higher frequency of low levels of HDL-C (≥ 50 mg/dl) [OR = 2.51 (95% CI, 1.44-4.25; p < 0.01), a higher frequency of high triglycerides/HDL-C [OR = 2.25 (95% CI, 1.38-3.69; 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 acrocordons were significantly higher in women with a positive familial history for breast cancer.

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

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

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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-penetration 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 positive 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 familial history of 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, metformin or estrogen ≤ 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-
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Tric parameters were assessed. The latter included body weight, height and BMI, abdominal circumference at the umbilical level to estimate subcutaneous abdominal and visceral fat (central obesity > 88 cm²), and neck circumference at the level of the superior border of the cricothyroid membrane for rough estimates of visceral fat (normal value, < 36.5 cm²). Office blood pressure was measured using an appropriate upper-arm cuff with an aneroid sphygmomanometer.

Cutaneous markers of insulin-resistance (the presence of acrochordons and acanthosis nigricans) were evaluated, and basal and 2-hour postprandial glycemia and insulinemia were measured after a standard mixed meal that was heavier than the usual glucose load. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C (normal value, < 50 mg/dl) and triglycerides (TG) were measured (TG/HDL-C normal value, < 5.2). Serum TSH and antinuclear antibodies were determined. Hyperinsulinaemia was defined as a homeostasis model assessment (HOMA) value higher than 2.5 or postprandial insulinemia (PPI) > 60 µU/ml.

HOMA is the product of fasting glucose (mg/180) times fasting insulin (µU/ml) divided by 22.5.

The following techniques were used. Insulin was measured using a two-site chemiluminescent enzyme immunoassay (INMULITE® INSULINA, Diagnostic Products Corporations, Los Angeles, USA), with 2-µU/ml sensitivity. Glycemia and TG were measured using the GOD/PAP automated method (SERA-PAK® Plus, Bayer Corporation, manufactured in Sés, Industrial Area, 61500 France). Spectrophotometer sensitivity at 505 nm is 0.03 mg/dl for glycaemia and 0.70 mg/dl for TG. Cholesterol was measured using the automated oxidase/peroxidase method (BioSystems, S.A., Costa Brava 30, Barcelona, Spain). Spectrophotometer sensitivity at 505 nm is 0.3 mg/dl. Micrinosomal antibodies were measured using the particle agglutination assay (SERODIA®, Fujirebio Inc., Tokyo, Japan) which considers titers below 1/100 dilution as negative. TSH was measured using an immunometric assay (Coat-A-Count TSH RMA, Diagnostic Products Corporation, Los Angeles, USA), with a sensitivity of 0.03 µU/ml (normal value, 0.30-4.5 µU/ml).

The patients were divided into two groups according to the pedigree under consideration:

**Group 1**: women with one or two first- or second-degree relatives with breast cancer. Twenty percent of this group had two first- or second-degree family members with breast cancer. We excluded women with a strong family history of breast cancer suspicious of a BRCA component (see above).

**Group 2**: women with a negative familial history of breast cancer.

The association between abdominal fat and breast cancer is controversial. In view of the importance of abdominal obesity in explaining the results, each group was then subdivided into two subgroups: women with central obesity (CO) (waist < 88 cm) and a familial history of breast cancer (n = 108) and those without a familial history of breast cancer (n = 386), and b) women with central obesity (CO) (waist ≥ 88 cm) and a positive familial history of breast cancer (n = 103) and those without a familial history of breast cancer (n = 249).

**Statistical analysis**

The results are expressed as mean ± SD. Between-group comparisons were made using Student’s t-test for independent samples in variables with normal distribution. The Wilcoxon rank-sum test was used for independent samples in variables with a non-normal distribution. The χ² test was used for nominal variables. The level of significance was set at p = 0.05. A statistically significant sample size was estimated according to Pita-Fernandez and Perea-Díaz. Odds ratios (OR) were estimated according to the UBC clinical significance calculator.

**RESULTS**

Anthropometric measurements showed that there were no significant differences in age, weight, BMI, blood pressure or waist circumference in premenopausal NCO women with and without a familial history of breast cancer. Neck circumference was significantly larger in NCO women with a familial history of breast cancer. There were no significant differences in age, weight, BMI, blood pressure or waist circumference among premenopausal CO women with and without a FH of breast cancer (table 1). Neck circumference was significantly larger in CO women with a familial history of breast cancer.

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**TABLE 1. Anthropometric parameters, age and signs of insulin resistance in 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></td>
<td>FHI−BC</td>
<td>FHI+BC</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>108</td>
<td>386</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>33.9 ± 9.9</td>
<td>33.1 ± 8.9</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>62.8 ± 7.2</td>
<td>64.4 ± 6.4</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>23.8 ± 2.7</td>
<td>24.2 ± 2.2</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg)</strong></td>
<td>108 ± 14</td>
<td>107 ± 14</td>
</tr>
<tr>
<td><strong>Diastolic blood pressure (mmHg)</strong></td>
<td>68 ± 11</td>
<td>68 ± 9</td>
</tr>
<tr>
<td><strong>Waist circumference (cm)</strong></td>
<td>76.2 ± 7.6</td>
<td>76.6 ± 6.8</td>
</tr>
<tr>
<td><strong>Neck circumference (cm)</strong></td>
<td>32.3 ± 1.8</td>
<td>31.2 ± 2.0</td>
</tr>
<tr>
<td><strong>Acanthosis nigricans (%)</strong></td>
<td>63.4</td>
<td>22.1</td>
</tr>
<tr>
<td><strong>Acrochordons (%)</strong></td>
<td>18.6</td>
<td>18.6</td>
</tr>
</tbody>
</table>

* p < 0.05 between women without abdominal obesity [FHI−BC] vs [FHI+BC] and with abdominal obesity [FHI−BC] vs [FHI+BC].

Abdominal obesity is defined as waist circumference ≥ 88 cm at the umbilical level. Data are mean ± SD or frequency.

BMI: body mass index; FHI−BC: women with a familial history of breast cancer; FHI+BC: women without a familial history of 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 insulinaemia, HOMA and the insulin resistance rate were higher in CO women with a familial history of breast cancer. Therefore, postprandial insulinaemia 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 CO women positively and negatively for a familial history of breast cancer.

The correlation between HOMA and postprandial insulin (0.26), postprandial glucose (0.28), TG (0.24), acrochordons (0.37) and visceral obesity (0.26), postprandial insulin (0.28), TG (0.24), acrochordons (0.37) and visceral obesity (0.26) were significant (p < 0.001).

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 im-

### TABLE 2. Comparison of laboratory parameters of insulin resistance between women with a positive and a 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></td>
<td>FH+BC</td>
<td>FH–BC</td>
</tr>
<tr>
<td>Number</td>
<td>108</td>
<td>249</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>83.2 ± 8.7</td>
<td>80.9 ± 9.0</td>
</tr>
<tr>
<td>Postprandial glucose (mg/dl)</td>
<td>86.2 ± 13.7</td>
<td>82.6 ± 13.3</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>9.6 ± 6.3</td>
<td>6.8 ± 5.5</td>
</tr>
<tr>
<td>PPI (µl/ml)</td>
<td>45.9 ± 25.4</td>
<td>29.3 ± 19.6</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.99 ± 1.05</td>
<td>1.43 ± 0.79</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>187 ± 55</td>
<td>175 ± 46</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>51.8 ± 7.1</td>
<td>55.9 ± 8.2</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>98.6 ± 25.9</td>
<td>99.1 ± 24.0</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>118 ± 48</td>
<td>88 ± 31</td>
</tr>
</tbody>
</table>

*p < 0.05 between women without abdominal obesity (FH+BC) vs FH–BC and with abdominal obesity (FH+BC) vs FH–BC

*HDL-C ≥ 50 mg/dl (%) | 45.7 | 20.4 | < 0.01* | 78.2 | 56.0 | < 0.01* |

Total cholesterol ≥ 200 mg/dl (%) | 35.0 | 23.3 | < 0.05* | 49.1 | 46.2 | NS |

**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 poly cystic 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 im-

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...plicated both genetically and biochemically in the pathophysiology of breast cancer. 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. Women with high visceral adipose tissue have lower glucose disposal rates (insulin resistance) than those with low visceral adipose tissue.

Reaven 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. In the present study, insulin resistance (HOMA > 2.5 or PPI > 60 µU/ml) displayed a stronger link with low HDL-C (≤ 50 mg/dl) in women with a positive history of breast cancer than in those without (z = 0.64 vs z = 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, because CETP activities in low HDL-C patients were bimodally distributed, in contrast to normal controls, such as the frequency of CETP activities in patients with 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.

REFERENCES