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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 494 women with NCO (108 with a positive familial history and 386 without) and 352 women with CO (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 μUI/ml) [OR = 4.26 (95% CI, 2.04-8.83), p < 0.001], 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 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, 2.08-5.55, 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 glycemia 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.

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). No se ha encontrado hasta el momento los principales genes de CM familiar de bajo a moderado riesgo. Nuestra hipótesis es que se relacionan con la IR. Para evaluarla estudiamos la relación de la IR con la historia familiar de CM de bajo a moderado riesgo (AF+CM).
Pacientes y método: Se estudió a 846 mujeres sanas, premenopáusicas, 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 μUI/ml) (*odds ratio* [OR] = 4,26; intervalo de confianza [IC] del 95%, 2,04-8,83; p < 0,001), bajas 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 = 3,23; IC del 95%, 2,32-4,49; p < 0,001), elevada razón triglicéridos cHDL (> 3,2) (OR = 4,45; IC del 95%, 1,80-10,98; p < 0,01) y circunferencia de cuello > 36,5 cm (OR = 4,25; IC del 95%, 1,76-10,27; p < 0,01). Las mujeres OC con AF+CM presentaron mayor frecuencia de IR (OR = 3,40; IC del 95%, 2,08-5,55; 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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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 BCRA1 or BRCA2 mutations.

Notwithstanding ethnic and racial differences, 15% of women are likely to develop breast cancer during their lifetime[1], 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)[2,3] 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[4].

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[5], whereas in the low-to-moderate-risk group of familial breast cancer, the principal genes involved in this disease have not been found[5]. BRCA1 has been associated[6] with the mechanisms controlling cell cycle and the transcription of several genes. Mutations of the BRCA2 gene, another suppressor gene[7] 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[5].

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[8]. 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[5].

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[9-11].

Insulin resistance and hyperinsulinemia are associated with breast cancer risk[12]. 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[13]. 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, metformin 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%[4]. Age and anthropome-