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Energy homeostasis genes and breast cancer risk: The influence of ancestry, body size, and menopausal status, the breast cancer health disparities study

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ABSTRACT

Background: Obesity and breast cancer risk is multifaceted and genes associated with energy homeostasis may modify this relationship.
Methods: We evaluated 10 genes that have been associated with obesity and energy homeostasis to determine their association with breast cancer risk in Hispanic/Native American (2111 cases, 2597 controls) and non-Hispanic white (1481 cases, 1585 controls) women.
Results: Cholecystokinin (*CCK*) rs747455 and proopiomelanocortin (*POMC*) rs6713532 and rs7565877 (for low Indigenous American (IA) ancestry); *CCK* rs8192472 and neuropeptide Y (*NYP*) rs16141 and rs14129 (intermediate IA ancestry); and leptin receptor (*LEPR*) rs11585329 (high IA ancestry) were strongly associated with multiple indicators of body size. There were no significant associations with breast cancer risk between genes and SNPs overall. However, *LEPR* was significantly associated with breast cancer risk among women with low IA ancestry ($P_{ARTP} = 0.024$); *POMC* was significantly associated with breast cancer risk among women with intermediate ($P_{ARTP} = 0.015$) and high ($P_{ARTP} = 0.012$) IA ancestry. The overall pathway was statistically significant for pre-menopausal women with low IA ancestry ($P_{ARTP} = 0.05$), as was cocaine and amphetamine regulated transcript protein (*CARTPT*) ($P_{ARTP} = 0.014$) and ghrelin (*GHRL*) ($P_{ARTP} = 0.007$). *POMC* was significantly associated with breast cancer risk among post-menopausal women with higher IA ancestry ($P_{ARTP} = 0.005$). Three SNPs in *LEPR* (rs6704167, rs17412175, and rs7626141), and adiponectin (*ADIPOQ*); rs822391) showed significant 4-way interactions (GxExMenopausexAncestry) for multiple indicators of body size among pre-menopausal women.
Conclusions: Energy homeostasis genes were associated with breast cancer risk; menopausal status, body size, and genetic ancestry influenced this relationship.

1. Introduction

The association between obesity and risk of breast cancer is complex, with differences in associations being reported by menopausal status, hormone receptor status of tumor, and ethnicity [1–4]. Studies that have included Hispanic women suggest significant inverse associations with BMI among pre-menopausal women, and either no association or an inverse association between BMI and breast cancer risk among post-menopausal women, but a positive association with weight gain, particularly among those who were lean in young adulthood. These findings suggest that the associations between obesity and breast cancer risk are multifaceted and may be influenced by genetic makeup. Considerable evidence from both human and animal

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studies suggests that genes play an important role in regulating obesity and energy homeostasis [5,6].

We hypothesize that genetic variation in genes that are associated with obesity, energy homeostasis, and satiety may help explain differences observed for breast cancer associations between pre- and post-menopause and indicators of body size. Additionally, genetic variation in energy homeostasis genes may help explain the influence of race and ethnicity on breast cancer risk. We examine 10 genes, including adiponectin (*ADIPOQ*), cocaine and amphetamine regulated transcript protein (*CARTPT*), cholecystokinin (*CCK*), ghrelin/obestatin prepropeptide (*GHRL*), leptin (*LEP*), leptin receptor (*LEPR*), Membrane bound *O*-acyltransferase domain containing 4 (*MBOAT4*), melanocortin 4 receptor (*MC4R*), neuropeptide Y (*NPY*), and proopiomelanocortin (*POMC*), and evaluate their associations with body size measures and with breast cancer risk. Both adiponectin and leptin are adipokines that are secreted by adipocytes [7]. Leptin has been directly associated with obesity, while adiponectin has been inversely associated with obesity and visceral fat accumulation [8]. Among these genes, *LEP* and *LEPR* have been studied the most with breast cancer and have been associated with obesity [9]. Several studies have evaluated polymorphisms in these genes with breast cancer, with conflicting results [10–16]. However, consideration of level of obesity as a component of risk has generally not been done, although the study by Llanos suggested that BMI level may influence risk associated with both leptin and adiponectin [9]. Several of our target genes including, *CARTPT*, *CCK*, *MC4R*, *NPY*, and *POMC*, are neuropeptides involved in the regulation of appetite and satiety. *GHRL* is involved in energy homeostasis and regulation of body weight through its influence on satiety. Polymorphisms in *GHRL* have been linked to breast cancer risk as well as to obesity and insulin levels [17]. *MBOAT4* codes the ghrelin *O*-acyltransferase (GOAT) enzyme that acrylates ghrelin to enable its endocrine actions [18].

In this study, we focus on energy homeostasis genes to evaluate associated breast cancer risk in an ethnically diverse population. In this hypothesis-driven study, we evaluate pre- and post-menopausal breast cancer risk separately given differences in reported association with BMI for these groups. Additionally we consider Indigenous American (IA) ancestry to better understand the contribution of the underlying genetic ancestry in this ethnically diverse population that may be modifying breast cancer risk associated with these energy homeostasis genes. Our hypothesis is that the energy homeostasis pathway will be associated with breast cancer risk and associations will vary by IA ancestry as well as by menopausal status.

2. Methods

Data from the Breast Cancer Health Disparities Study that includes participants from three population-based case-control studies [19], the 4-Corners Breast Cancer Study (4-CBCS) [1], the Mexico Breast Cancer Study (MBCS), and the San Francisco Bay Area Breast Cancer Study (SFBCS) [2,20,21] who completed an in-person interview and who had a blood or mouthwash sample available for DNA extraction were used. In the 4-CBCS, participants were between 25 and 79 years; participants from the MBCS were between 28 and 74 years; the SFBCS included women aged 35–79 years. The 4-CBCS consisted of population-based breast cancer cases and controls from Arizona, Colorado, New Mexico and Utah who were diagnosed between October 1999 and May 2004. Of cases contacted, 852 Hispanic, 22 American Indian, and 1683 NHW women participated. Of controls contacted, 913 Hispanic, 23 American Indian, and 1669 NHW women participated. Blood was collected and DNA extracted for 76% of participants in Arizona, 71% of participants in Colorado, 75% of participants in New Mexico, and 94% of participants in Utah. Of participants contacted, 63% of Hispanic and 71% of NHW cases participated; for controls these numbers were 36% and 47% respectively. For the MBCS, cases were diagnosed between January 2004 and December 2007. A total of 1000 cases and 1074 controls were recruited, and blood was collected and DNA extracted from 85% and 96% of women, respectively. The SFBCS included breast cancer cases diagnosed between April 1997 and April 2002. DNA was available for 93% of cases and 92% of controls interviewed, including 1105 cases (793 Hispanics, 312 NHW) and 1318 controls (998 Hispanics, 320 NHW). Participation was 89% for cases and 92% for controls contacted. All participants signed informed written consent prior to participation and the Institutional Review Board for Human Subjects approved the study at each institution.

3. Data harmonization

Data were harmonized across all study centers and questionnaires as previously described [19]. In the United States, women were ask to self-report their race/ethnicity and were classified as non-Hispanic white (NHW) if they reported no Hispanic or Native American (NA) ancestry. Women who reported any Hispanic or NA ancestry were classified accordingly. Women also were classified as either pre-menopausal or post-menopausal based on responses to questions on menstrual history. Women who reported still having periods during the referent year (defined as the year before diagnosis for cases or before selection into the study for controls) were classified as pre-menopausal. Women were classified as post-menopausal if they reported either a natural or surgically-induced menopause or if they reported taking hormone therapy (HT) and were still having periods or were at or above the 95th percentile of age for those who reported having a natural menopause (i.e., $\geq$12 months since their last period). Women were categorized as having a positive family history of breast cancer if they reported having a first-degree relative with breast cancer.

Body size indicators used were body mass index (BMI) of weight (kg)/height (m)^2, weight gain since young adult, waist circumference (an indicator of central obesity), hip circumference, waist-to-hip ratio (WHR) as a measure of body fat distribution, and waist-to-height ratio (WHtR) as an indicator of visceral adiposity independent of height. These indicators were chosen given previous associations with breast cancer [4]. Weight was based on self-reported weight during the reference year or weight measured at interview if weight during the reference year was not available. Height was based on measured height at interview or self-reported height if the measurement was declined. Categories of BMI were normal BMI ($<$25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese ($\geq$30 kg/m^2). In the SFBCS, young-adult BMI was based on self-reported weight at age 25–30 years for cases diagnosed from 1995 to 1998 and their matched controls, or on self-reported weight at age 20–29 years for cases diagnosed from 1998 to 2002 and their matched controls. In the 4-CBCS and MCBCS, young-adult BMI was based on the average weight reported at ages 15 years and 30 years. Weight gain (in kg) was calculated as the difference between self-reported young-adult weight and self-reported weight in the reference year (or measured weight at interview if self-reported weight was not available). Women who lost weight were excluded from weight gain analyses. Current BMI was categorized as underweight to normal weight ($<$25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese ($\geq$30.0 kg/m^2). All other body size variables were categorized according to the tertile distribution among controls.

4. Genetic data

DNA was extracted from either whole blood (n = 7287) or mouthwash (n = 634) samples. Whole genome amplification