Germ-line HER-2 Variant and Breast Cancer Risk by Stage of Disease

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Abstract

HER-2 gene amplification and protein overexpression has been associated with increased risk of advanced-stage breast cancer and poor prognosis. Recently, a single missense point mutation (Ile655Val) in the transmembrane domain of the HER-2 gene was associated with a 40% increase in breast cancer risk among women 45 years of age and younger. In this analysis, we measured the association between the Ile655Val variant and postmenopausal breast cancer among women participating in the Hawaii and Los Angeles Multiethnic Cohort. Risk of localized breast cancer was significantly elevated among women with the HER-2 variant, but not among women with regional or metastatic disease. Women with at least one copy of the Valine variant were approximately one-half as likely to have high-stage as low-stage breast cancer (P = .02), and this effect was present across racial/ethnic groups.

Introduction

Many experimental and epidemiological studies have linked HER-2/neu gene amplification and protein overexpression to increased risk of advanced stage breast cancer and poor prognosis (1), indicating that this gene is an important predictor of disease progression. HER-2/neu is a proto-oncogene that codes for a tyrosine kinase growth factor receptor and normally functions as both a growth regulatory protein and cell motility factor (1). Although the only known mechanism of increased HER-2 activity in humans is through gene amplification and protein overexpression, experimental studies of rats show that a single missense point mutation (Val664Glu) in the transmembrane domain of the neu proto-oncogene (HER-2 human homologue) greatly increases its activity and cell transformation properties (2, 3). This point mutation has not been identified in cases of human cancer, however a recent publication (4) suggests that a germ-line missense variant in the transmembrane region of the HER-2 gene may influence breast cancer risk. Specifically, the authors found a 40% increase in risk (OR1.4; 95% CI, 1.0, 2.0) among women with a single bp variation (A > G or Ile655Val) within the coding region of the HER-2 gene. The effect was present exclusively among younger women (≤45 years of age, OR, 1.7; >45 years, OR, 1.0), and the authors concluded that the HER-2 variant may be an important susceptibility marker. We report here our findings for the HER-2 variant and breast cancer risk in a much larger sample of older women by stage of disease.

Materials and Methods

We measured this association among postmenopausal women participating in the Hawaii and Los Angeles Multiethnic Cohort. The cohort was designed to investigate diet and life-style characteristics in the etiology of cancer. At baseline, a total of 215,251 men and women, 45–75 years of age, were enrolled, including African Americans, Japanese, native Hawaiians, Latinos, non-Latino whites, and small numbers of other racial/ethnic groups. Women were considered postmenopausal if they indicated that their periods had stopped at the time of enrollment into the cohort and were at least 55 years of age at the time of blood draw. Incident case ascertainment was completed by computer linkage of the cohort with the Surveillance, Epidemiology, and End Results (SEER) cancer registries in Hawaii and Los Angeles, as well as with the California state cancer registry. The sample included all incident cases of localized (n = 508, excluding cases of ductal carcinoma in situ), regional, or metastatic breast cancer (n = 167) identified from the cohort, who agreed to provide a blood sample for analysis. Both cases and randomly selected, potential controls were contacted by phone and asked to provide a blood specimen. Approximately 80% of incident breast cancer cases and 76% of cohort controls from the four major racial/ethnic groups agreed to provide a blood specimen (5). Controls (n = 545) were randomly selected in approximately the same racial/ethnic distribution as the cases from postmenopausal, cohort women who had no history of breast, endometrial, or ovarian cancer. Additional details of the cohort have been published (6).

Alleles for the Ile655Val variant were identified using the fluorogenic 5′-nuclease assay (TaqMan; Ref. 7). PCR amplification was performed, a fluorescence profile of each well was measured, and the results were analyzed using Sequence Detection Software (Applied Biosystems). Experimental samples were compared with eight controls (six positive and two negative) to identify the three genotypes at this locus (AA, AG, and GG). Any samples that were outside the parameters defined by the controls were identified as noninformative. The percent of noninformative results was ~3% for both cases and controls.

Relative risks for breast cancer and the HER-2 variant were calculated using unconditional logistic regression adjusting for age (55–59, 60–64, 65–69, and 70+ years) and racial/ethnic group as categorical variables. Estimates were determined for all stages of disease combined, as well as for localized and regional or metastatic disease. Two-sided tests for trend were calculated scoring HER-2 genotypes as 0, 1, and 2 for the Ile655Val homozygous wild type, heterozygous variant, and homozygous variant respectively. The effect of HER-2 across stages of breast cancer was tested using a case analysis of high-stage versus low-stage breast cancer.

Results

We found a small increase in risk for all stages of breast cancer combined among women 55 years of age and older (Table 1). By stage of disease, we found the risk of localized breast cancer was significantly elevated among women with the HER-2 variant (Table 2). The relative risks for localized breast cancer were similar for women with one or two copies of the Valine allele (ORVal/Val = 1.00; ORVal/Val = 1.41; ORVal/Val = 1.45; trend test, P = 0.02), and this effect was present across racial/ethnic groups (ORAA = 1.7; OR1 = 1.3; OR1 = 1.7; and ORW = 1.1). In contrast, women with regional or metastatic breast cancer were ~20% less likely to have the Valine versus Isoleucine genotypes in our multiethnic population (ORVal/Val = 1.10; ORVal/Val = 0.87; ORVal/Val = 0.72; trend test, P = 0.49). The case-case analysis (high-stage versus low-stage breast cancer) showed that women with at least one copy of the Valine variant were approximately one-half as likely to have high-stage as low-stage breast cancer (P = .02), and this effect was present across racial ethnic groups (Table 2).

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The abbreviations used are: OR, odds ratio; CI, confidence interval; ER, estrogen receptor.
women in our study were postmenopausal and >45 years of age at the time of enrollment, we could not examine the effect of HER-2 on breast cancer risk for women <45 years of age, as previously published (4). However, our findings indicate the Ile655Val variant does have an effect in postmenopausal women, and that women with at least one copy of the Valine allele are more likely to be diagnosed with localized disease.

Cases and controls were similar with respect to mean age (cases, 65.8 years; controls, 66.2 years) and weight (cases, 151.7 pounds; controls, 150.0 pounds). The distribution of localized disease (75%) in our sample is similar to that in the cohort (72%) and higher than reported in SEER for localized breast cancer among women 45 years (65%; Ref. 8). The frequency of the Valine variant in our case-control populations was 14.1% and 11.7%, respectively. The frequency of the Valine variant in our sample is similar to that in the cohort (72%) and higher than reported in SEER for localized breast cancer among women ≥50 years (65%; Ref. 8). The frequency of the Valine variant in our case and control populations was 14.1% and 11.7%, respectively. The frequency in African-American controls (5%) was significantly lower than in the other three racial/ethnic groups (12% Japanese, 13% Latina, and 19% white) and lower than reported in a recent publication in the other three racial/ethnic groups (12% Japanese, 13% Latina, and 19% white).

Discussion

Our results agree with a previous finding that the germ-line Ile655Val variant confers a modest increase in breast cancer risk among women for all stages of disease combined (4). However, our findings suggest that women with germ-line Valine genotypes are more likely to develop localized disease and less likely or slower to progress to high-stage breast cancer than women with Isoleucine homozygous genotypes. This increase in risk for low-stage breast cancer without progression is like the pattern of diagnosis seen for estrogen replacement therapy and endometrial cancer. We hypothesize that this relationship could occur if the germ-line variant initially increases cellular proliferation, while subsequently decreasing the likelihood that the HER-2 gene will undergo amplification or protein overexpression. It is possible that a single base change in the transmembrane region of the HER-2 gene may be adequate to alter the binding site of the protein receptor given that a missense mutation in the same domain of the rat neu gene alters the tyrosine kinase phosphorylation site. The actual relationship between the HER-2 Ile655Val variant and HER-2 somatic activation is yet to be explored. To better understand this relationship, we are testing for the presence of HER-2 amplification among cases genotyped for the Ile655Val variant. When measured in combination, the germ-line and somatic variants may provide more information on breast cancer progression and treatment response than either alone. Similarly, it would be informative to test the association between the Ile655Val variant and other markers of progression, such as ER status. However, we did not have complete information on ER status in this data set, therefore we could not examine the relationship between ER status and the variant.

The lowest frequency of Valine genotypes was found among African-American women, who consistently present with an overall higher stage of breast cancer than white women (10, 11). Although there are other reasons for the racial/ethnic variation in breast cancer rates, differential expression of the Valine genotype may serve as one example of a genetic marker that may contribute to our understanding of breast cancer progression.

Although our sample size of localized and advanced stage breast cancer was reasonably large, testing of the relationship between the HER-2 variant and HER-2 amplification and protein overexpression by stage of disease is necessary to determine whether the germ-line variant provides more information than the somatic HER-2 variant alone.

References

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