Short Communication

The HER2 I655V Polymorphism and Risk of Breast Cancer in Women < Age 40 Years


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Abstract

The HER2 gene controls cellular function and has prognostic significance in breast cancer. The I655V polymorphism was associated with increased risk of breast cancer in Chinese women under the age of 45 years and in women with a first-degree family history of the disease. These associations, however, have not been confirmed in several studies of other women. We conducted a population-based case-control-family study of the I655V polymorphism using 409 Australian women with breast cancer diagnosed before the age of 40 years and 299 controls frequency matched for age. The I655V polymorphism was more common in cases (P = 0.01). A recessive model, in which homozygotes were associated with an adjusted odds ratio of 2.8 (95% confidence interval 1.3–6.2; P = 0.005), gave the best fit under parsimony. Although the biological role of the I655V polymorphism is not known, large independent studies of early onset breast cancer are warranted to attempt to replicate this finding.

Introduction

HER2 is a transmembrane glycoprotein with tyrosine kinase activity that has several functions, including the control of cellular proliferation. Amplification and/or overexpression of HER2, present in 30% of breast cancers, is associated with poor prognosis (1, 2). The use of a recombinant humanized monoclonal antibody that specifically targets HER2 may increase the clinical benefit of first-line chemotherapy in women with breast cancers that overexpress HER2 (3).

An isoleucine to valine polymorphism at codon 655 (I655V) was reported to be associated with an increased risk of breast cancer in a Chinese population (4). Of the six subsequent studies that investigated the risk of breast cancer associated with this HER2 I655V polymorphism, two reported a positive association (5, 6), whereas four found no association (7–10). It is difficult to interpret these studies given that the characteristics of the samples were different, and some lacked statistical power. Interestingly, in the two that reported a positive association, the only effect evident was in women diagnosed before age 45 years (4) or in women with a first-degree family history of breast cancer (5), groups in which inherited genetic effects on susceptibility are expected to be more pronounced. In the present study, we evaluated the association between the HER2 I655V polymorphism and breast cancer risk before the age of 40 years using Australian women.

Materials and Methods

Subjects. Subjects were drawn from the Australian Breast Cancer Family Study, a population-based, case-control-family study of early onset breast cancer carried out in Melbourne and Sydney during the period 1992 through 1995 that has been described in detail previously (11, 12). Briefly, women under the age of 40 at diagnosis of a first primary invasive breast cancer were identified through the Victorian and New South Wales cancer registries. Controls were selected from the electoral roll (registration for voting is compulsory in Australia) by use of stratified random sampling and were frequency matched for age. Response rates were 73% in both cases and controls (11). Case subjects, control subjects, and their relatives were administered the same questionnaire on risk factors (see Ref. 11 for characteristics of study participants). For each case and control, a detailed family history was recorded for all first- and second-degree relatives, and verification of all family cancers was sought through cancer registries, pathology reports, clinical records, and death certificates. Blood samples were collected from subjects at the time of interview. Written informed consent was obtained from all subjects, and approval of the study protocol was obtained from the relevant ethics committees.

Molecular Analysis. A total of 409 cases and 299 controls were genotyped for the HER2 I655V polymorphism using a dual color allele-specific PCR assay described previously (7). Briefly, PCR amplifications were performed using HEX- and FAM-labeled forward primers (5-CAGCCCTCTGAGTCATCA-3 and 5-CAGCCCTCTGAGTCCATCG-3) and a common reverse primer (5’-TTCTACGCTCCGTCTTCTTTC-3’). Ten percent of the genotyping was confirmed with a PCR
Table 1  Odds ratios and 95% CIs for breast cancer risk by HER2 genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Cases (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Controls (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>OR&lt;sup&gt;c&lt;/sup&gt; (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codominant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ile/Ile</td>
<td>240 (58.7)</td>
<td>196 (65.6)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Ile/Val</td>
<td>138 (33.7)</td>
<td>94 (31.4)</td>
<td>1.3 (0.9–1.8)</td>
</tr>
<tr>
<td>Val/Val</td>
<td>31 (7.6)</td>
<td>9 (3.0)</td>
<td>3.0 (1.4–6.8)</td>
</tr>
<tr>
<td>Dominant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ile/Ile</td>
<td>240 (58.7)</td>
<td>196 (65.6)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Val/Val or Ile/Val</td>
<td>169 (41.3)</td>
<td>103 (34.4)</td>
<td>1.4 (1.0–2.0)</td>
</tr>
<tr>
<td>Recessive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ile/Ile or Ile/Val</td>
<td>378 (92.4)</td>
<td>290 (97.0)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>Val/Val</td>
<td>31 (7.6)</td>
<td>9 (3.0)</td>
<td>2.8 (1.3–6.2)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Number and percentage of cases (n = 409) for the specified genotype.
<sup>b</sup>Number and percentage of controls (n = 299) for the specified genotype.
<sup>c</sup>Odds ratio (OR) and 95% CI, adjusted for study center (Melbourne/Sydney), demographic variables (study site, country of birth, education, marital status), reproductive, and lifestyle variables did not differ greatly from the crude estimates. There was evidence of an increased risk under dominant inheritance (P = 0.04), codominant inheritance (P = 0.01), and recessive inheritance (P = 0.005). The recessive model gave an increased risk of 2.8-fold (95% CI 1.3–6.2; P = 0.005) and provided the best fit under parsimony; the codominant model did not give an improved fit (P = 0.2), and the dominant model gave a worse fit for the same number of parameters (difference in log likelihood = 1.5). Stratification by body mass index, family history of cancer, alcohol consumption, or oral contraceptive use revealed no evidence for a modification of the recessive effect on breast cancer risk by these factors, albeit with limited power (data not shown).

Discussion

Our study, of women diagnosed before the age of 40 years, has demonstrated that homozygosity for the valine allele was associated with an increased risk of early onset breast cancer. This finding is consistent with the increased breast cancer risk observed by Xie et al. (4) among Chinese women diagnosed before age 45 years. Overexpression of HER2 is detected in a large proportion of breast cancers, indicating that activation of this gene is an important step in breast carcinogenesis. Consequently, it is plausible that functional polymorphisms in this gene that enhance HER2 activity may represent breast cancer predisposing alleles.

There is currently no direct information regarding any biological role of the I655V polymorphism, located in the transmembrane region of HER2. However, oncogene mutations have been reported in the transmembrane region of the related mouse gene neu (14) and an amino substitution at position 659 in HER2 has also been shown to increase transforming ability in NIH3T3 cells (15). It is possible, therefore, that the I655V polymorphism in HER2 may also have functional consequences. In light of our finding of a recessively inherited risk of early onset breast cancer associated with this polymorphism, investigations into the functional implications of the isoleucine to valine substitution, and attempts to replicate this association in independent and sufficiently large studies, are warranted.

References


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