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Evidences for association of the CASP8 -652 6N del promoter polymorphism with age at diagnosis in familial breast cancer cases

Giovanna De Vecchi · Paolo Verderio · Sara Pizzamiglio · Siranoush Manoukian · Monica Barile · Stefano Fortuzzi · Fernando Ravagnani · Marco A. Pierotti · Paolo Radice · Paolo Peterlongo

To the Editor,

Recently, a study conducted in Chinese individuals reported that a 6-nucleotide deletion in the promoter of the CASP8 gene (the -652 6N del; rs3834129) was strongly associated with decreased cancer risk in several types of cancers including breast cancer (BC) [1]. Here, we studied the effect of this polymorphism in a series of 580 Italian familial BC index cases and 406 controls. The cases were originally ascertained through the Genetic Services of Fondazione IRCCS Istituto Nazionale Tumori (INT) or Istituto Oncologico Europeo (IEO) in Milan, as eligible for mutation analysis in BRCA genes based on criteria including family history and age at cancer diagnosis [2]. All the females affected with BC as the first diagnosed cancer (median age: 43; range: 21–80), who tested negative for BRCA disease-causing mutations, were included in this study. The controls were Italian female blood donors who were ≥45 years at the blood draw (median age, 54; range, 45–71) recruited at INT. The genotyping was performed comparing the length of PCR fragments of the normal and the deleted allele with a size marker using Denaturing High-Performance Liquid Chromatography (assay and primer sequences are available upon request).

In cases and controls, common homozygous (nor/nor), heterozygous (nor/del) and rare homozygous (del/del) were 162 (27.9%), 301 (51.9%) and 117 (20.2%); and 106 (26.1%), 206 (50.7%) and 94 (23.2%), respectively, consistent with Hardy-Weinberg equilibrium. By logistic regression analysis adjusted for age [3], we observed that the odds ratio (OR) for heterozygous and rare homozygous compared with common homozygous was 1.05 (95% confidence interval (CI) = 0.74–1.49) and 1.09 (95% CI = 0.71–1.67), respectively, and the per-allele OR was 0.96 (95% CI = 0.78–1.18). These results provided no evidence for association between the -652 6N del polymorphism and familial BC unlinked to BRCA genes, confirming the findings obtained in German, English and Polish individuals [4, 5]. We pursued the study of the -652 6N del polymorphism. Of interest was the investigation of the association between the polymorphism and age at BC diagnosis in cases. The three genotypes were collapsed into two: (del/del), and (nor/−·) by aggregating common homozygous and heterozygous cases; the age at diagnosis...
was categorized into four classes according to the pertinent age centiles (25th: 35; 50th: 43; 75th: 50). We assessed the associations between each age class and genotype by the logistic regression model considering as reference group the cases with younger age at diagnosis. We observed a statistically significant association between these two variables (Table 1). In particular, our results suggested an increasing trend of the del/del genotype with later age at BC diagnosis (trend test \( P \)-value = 0.01).

In conclusion, our results confirmed those obtained in previous Europeans studies. Nevertheless, we observed that the -652 6N del polymorphism of CASP8 was associated with age at diagnosis in familial BC cases. Thus, we suggest that this polymorphism may have an effect in postponing the BC onset in predisposed individuals. To our knowledge, this is the first study that investigated this latter aspect; consequently, our results should be taken with caution and further analyses are necessary to clarify the effect of this polymorphism on BC.

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References


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### Table 1

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>N</th>
<th>del/del (%)</th>
<th>nor/- (%)</th>
<th>OR ( b ) 95% CI ( c )</th>
<th>( P )-value</th>
</tr>
</thead>
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<tr>
<td>≤35 ( a )</td>
<td>173</td>
<td>22 (12.7)</td>
<td>151 (87.3)</td>
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<td>36–43</td>
<td>120</td>
<td>27 (22.5)</td>
<td>93 (77.5)</td>
<td>1.99 1.07–3.70</td>
<td>0.03</td>
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<tr>
<td>44–50</td>
<td>148</td>
<td>34 (23.0)</td>
<td>114 (77.0)</td>
<td>2.05 2.14–3.69</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;50</td>
<td>139</td>
<td>34 (24.5)</td>
<td>105 (75.5)</td>
<td>2.22 1.23–4.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\( a \) Reference group

\( b \) OR, Odds ratio

\( c \) CI, Confidence interval