Evaluation of \textit{CYP17A1} and \textit{CYP1B1} polymorphisms in male breast cancer risk

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Abstract

Breast cancer in men is a rare and still poorly characterized disease. Inherited mutations in BRCA1, BRCA2 and PALB2 genes, as well as common polymorphisms, play a role in male breast cancer genetic predisposition. Male breast cancer is considered a hormone-dependent tumor specifically related to hyperestrogenism. Polymorphisms in genes involved in estrogen biosynthesis and metabolism pathways, such as CYP17A1 and CYP1B1, have been associated with breast cancer risk. Here, we aimed to investigate the role of CYP17A1 and CYP1B1 polymorphisms in male breast cancer risk.

A series of 597 male breast cancer cases and 1022 male controls, recruited within the Italian Multicenter Study on male breast cancer, was genotyped for CYP17A1 rs743572, CYP1B1 rs1056836 and rs1800440 polymorphisms by allelic discrimination real-time PCR with TaqMan probes. Associations with male breast cancer risk were estimated using logistic regression. No statistically significant associations between male breast cancer risk and the three analyzed polymorphisms emerged. Similar results were obtained also when BRCA1/2 mutational status was considered. No significant differences in the distribution of the genotypes according to estrogen receptor status emerged.

In conclusion, our study, based on a large series of male breast cancer cases, is likely to exclude a relevant role of CYP17A1 and CYP1B1 polymorphisms in male breast cancer predisposition. Overall, these results add new data to the increasing evidence that polymorphisms in these genes may not be associated with breast cancer risk.
INTRODUCTION

Male breast cancer (MBC) is a rare disease, representing about 1% of all breast cancers (BCs) and less than 1% of all cancers in men [1]. Germline pathogenic variants in BC genes, particularly BRCA1, BRCA2 and PALB2 genes, increase the risk of developing MBC [2-4]. Common polymorphisms may also contribute to MBC genetic predisposition and may have a modifying effect on BC risk for male BRCA1/2 mutation carriers, particularly through a polygenic inheritance model [5-7].

MBC is recognized as a hormone dependent malignancy and is widely considered as an estrogen-driven disease, specifically related to hyperestrogenism [1,8]. Notably, most of male breast tumors are estrogen receptor (ER) positive [1]. An increased level of circulating estradiol appears to be an important factor in the etiology of this disease and the mean total serum estradiol level is significantly increased in MBC patients compared with healthy males [8].

Polymorphisms in genes involved in estrogen biosynthesis and metabolism pathways, such as Cytochrome P450 family 17 subfamily A member 1 (CYP17A1) and Cytochrome P450 family 1 subfamily B member 1 (CYP1B1), may cause an increased risk of hormone-related cancers, such as BC, by altering the expression of steroid hormones, including estrogens [9-11].

CYP17A1 is an enzyme essential for the biosynthesis of estrogens and androgens [12]. A common polymorphism in the promoter of CYP17A1 (c.-34T>C; rs743572) has been associated with increased CYP17A1 expression, enhanced estrogen production and increased serum estradiol levels in post-menopausal women [12,13]. This polymorphism has been investigated in female BC (FBC) with controversial results [12,13]. To date, only two studies have analyzed a possible role of CYP17A1 rs743572 in MBC risk, with contrasting results [14,15]. A higher rs743572 CC genotype frequency among BRCA2 mutation carriers has been observed in a small MBC series, suggesting a possible effect of rs743572 polymorphism as a genetic modifier of BC risk [15].

CYP1B1 is a key enzyme in the initial catabolic step of estrogens metabolism. There are several common CYP1B1 polymorphisms known to affect its enzymatic efficiency, including CYP1B1
c.1294A>G (p.Leu432Val; rs1056836) and c.1358A>G (p.Asn453Ser; rs1800440) [9]. In particular, 
*CYP1B1* rs1056836 has been associated with increased CYP1B1 catalytic activity, whereas
*CYP1B1* rs1800440 has been associated with a decrease in protein expression due to degradation
[16,17]. These two *CYP1B1* polymorphisms have been widely investigated in female BC (FBC)
with contrasting results [18-23]. To date, the role of *CYP1B1* rs1056836 and rs1800440
polymorphisms in MBC risk has not been investigated.

In this study, we aimed to evaluate possible associations between *CYP17A1* rs743572, *CYP1B1*
rs1056836 and rs1800440 polymorphisms and MBC risk, analyzing a large series of MBC cases
characterized for *BRCA1/2* mutation status and ER status. Given that MBC is unencumbered by the
many confounding factors that exist in FBC (for example, reproductive factors and high frequency),
the investigation of *CYP17A1* and *CYP1B1* polymorphisms in men may be instrumental in giving
insight into the role these polymorphisms play in BC and to provide information that may be
inherent to the disease in both genders.
MATERIALS AND METHODS

Study population

A total of 597 MBC cases and 1022 male Italian (Caucasian) controls were included in the present study. MBC cases, together with information about BRCA1/2 mutation status and the main clinical-pathologic characteristics, were recruited in the frame of the ongoing Italian Multicenter Study on MBC, as previously described [24]. BRCA1 and BRCA2 mutation analysis was first performed in the frame of genetic counselling programs at the center of origin for all MBC cases, then BRCA1/2 mutation negative cases were retested using Next Generation Sequencing [4]. Overall, 89 out of 597 MBC cases (15%) were carriers of a pathogenic variant in BRCA1/2 genes (10 BRCA1; 79 BRCA2). Information on ER status was available for 448 MBCs; the majority of MBC cases were ER positive tumors (93.3%).

Of the 1022 male controls, 865 were male individuals without personal history of cancer (information about family history of cancer was not available), enrolled in hospital-based settings under research or clinical protocols at the same centers of MBC cases, or blood donors [5,24]. Of the 865 control individuals 260 (30%) were tested for BRCA1/2 mutations and resulted negative. The additional 157 controls were male carriers of BRCA1/2 mutations without personal history of cancer, recruited among hereditary breast and ovarian cancer families.

For each study participant, samples of blood or DNA from peripheral blood leukocytes were collected. DNA from blood samples was extracted and quantified as previously described [5]. The experimental protocol was approved by the Local Ethical Committee (Sapienza University of Rome, Number of Protocol 669/17). All procedures performed in the present study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all participants included in the study.
**Genotyping**

MBC cases and controls were genotyped by allelic discrimination real-time PCR with TaqMan probes in ABI 7500 fast real-time PCR instrument (Life Technologies, Carlsbad, California, USA) at CYP17A1 rs743572, CYP1B1 rs1056836 and rs1800440, by commercially available assays (Life Technologies), according to the manufacturer’s instruction. In each experiment, duplicates, positive (cases for which genotype was confirmed by Sanger Sequencing) and negative (water) controls were included [24].

**Statistical analysis**

Statistical analyses were performed as previously described [5,6,24]. The genotype frequencies for each polymorphism were evaluated in both cases and controls. The association between polymorphisms and MBC risk was estimated using logistic regression after adjustment for age of participants, center of enrolment and ascertainment (population- or clinic-based) and was measured by the odds ratio (OR) and its corresponding 95% confidence interval (CI). For each polymorphism, a specific model was used to evaluate separately the effect of the heterozygous and of the homozygous genotypes. We also evaluated MBC risk based on multiplicative codominant (per-allele) model. In each model, the common homozygote genotype in the control population was considered as the reference category. Considering a minor allele frequency of 20% (lower value in our control’s series) and a dominant model, with a case-control ratio of 1:1.7 (597 cases and 1022 controls), we could identify an OR of 1.45 with a power of 90% and alpha = 0.05. Chi-square test was performed in a case-case analysis in order to evaluate the potential associations between genotypes and ER status. A p-value <0.05 was considered statistically significant. All analyses were performed using STATA version 13.1 statistical program.
RESULTS

CYP17A1 rs743572, CYP1B1 rs1056836 and rs1800440 were genotyped in the whole series of 1619 individuals, including 597 MBC cases and 1022 male controls.

The distribution of genotype frequencies of CYP17A1 rs743572, CYP1B1 rs1056836 and rs1800440 polymorphisms in MBC cases and controls, and the risk estimates, are summarized in Table 1.

No statistically significant associations between MBC risk and the three analyzed polymorphisms emerged by logistic regression models. The same results were obtained when all affected and unaffected BRCA1/2 mutation carriers were excluded from the analyses (data not shown).

The analysis was then restricted to male BRCA1/2 mutation carriers comparing the 89 BRCA1/2-related MBC cases with the 157 unaffected male BRCA1/2 mutation carriers (Table 2). No statistically significant results emerged. The same results were obtained when only BRCA2 mutation carriers were considered (data not shown).

The distribution of the genotypes in MBC cases was further analyzed taking into account ER status. No significant differences in the distribution of the genotypes according to ER status emerged (Table 3).
DISCUSSION

Estrogens play a relevant role in MBC, thus genetic polymorphisms of genes involved in estrogen metabolism may impact on MBC susceptibility. The possible role of \textit{CYP17A1} rs743572 polymorphism in MBC risk has been analyzed by two studies both examining a limited number (from 39 to 76) of MBC cases, more than 15 years ago [14,15]. One study reported a significant association of this polymorphism with increased MBC risk [14] and the other study failed to replicate these findings [15]. Afterwards, no other study aimed to investigate this polymorphism in MBC, nevertheless, \textit{CYP17A1} is consistently reported as a putative genetic risk factor for MBC in reviews on the field [25-29]. Our results, based on the largest collection reported to date of MBC patients undergoing \textit{CYP17A1} genotyping, are likely to exclude, with a good confidence, a relevant contribution of \textit{CYP17A1} rs743572 polymorphism in MBC risk. Overall, in line with the most recent findings in FBC [30-32], our data further support the lack of association between \textit{CYP17A1} polymorphism and overall BC risk.

To our knowledge, at present there are no published data on the role of \textit{CYP1B1} polymorphisms in MBC; thus, our study is the first to investigate a possible association between the two most studied \textit{CYP1B1} common functional polymorphisms (\textit{CYP1B1} rs1056836 and rs1800440) and BC risk in men. Associations between these two \textit{CYP1B1} polymorphisms with BC risk in women has been reported in some populations [18-20], however, more recent meta-analyses showed that there is no overall effect on FBC risk [21-23]. In line with these meta-analysis studies, our study provides no evidence that \textit{CYP1B1} rs1056836 and rs1800440 may contribute to MBC risk.

Notably, loci for these two candidate genes have never emerged in any of the Genome Wide Association Studies (GWAS) on both female and male BC as reported in the GWAS Catalog [33], thus further proving for a marginal role, if any, in BC risk.

We also tested the hypothesis that \textit{CYP17A1} and \textit{CYP1B1} polymorphisms may modulate the risk of BC conferred by \textit{BRCA1/2} mutations in men, as previously suggested by a small study [15]. Results from our study, comparing \textit{BRCA1/2}-associated MBC cases with unaffected male \textit{BRCA1/2}
mutation carriers, showed no evidence for an association of \textit{CYP17A1} rs743572, \textit{CYP1B1} rs1056836 and rs1800440 polymorphisms with MBC risk, suggesting that these variants are not likely to modify BC risk in male \textit{BRCA1/2} mutation carriers.

To the best of our knowledge, our series, collected in the frame of the ongoing Italian Multicenter Study on MBC [24], represents one of the largest MBC series ever assembled in a single Country, for which \textit{BRCA1} and \textit{BRCA2} mutational status and clinical-pathologic data are available. In previous studies, this series allowed for the identification of genetic polymorphisms as low-penetrance susceptibility alleles in MBC [5,6,24]. Thus, the power of the present study is adequate to detect risk effects similar to those previously reported [14,18-20]. On the other hand, the power of our study may be insufficient to identify smaller risk effects. However, smaller effects may be of little clinical relevance, unless included in the frame of a polygenic risk model [7]. Large-scale collaborative studies are needed to investigate whether \textit{CYP17A1} and \textit{CYP1B1} genotypes may have a role in modulating anthropometric and epidemiologic risk factors in men.

In conclusion, our present findings, based on a large series of MBC cases and male controls, may exclude a relevant contribution of \textit{CYP17A1} and \textit{CYP1B1} polymorphisms in BC risk in men. Overall, these results add new data to the accumulating evidence that polymorphisms in these genes are not associated with BC risk in both genders.
Declaration of interest:

All authors declare that they have no conflict of interest.

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Author contribution:

Pi.R. and V.S. drafted the manuscript, performed genotyping and statistical analyses and interpreted the results; V.V., V.Z. and A.B. performed genotyping analysis; I.Z., S.B., M.G.T., A.R., L.V., G.T., B.B., J.A., S.M., A.C., G.G., L.C., A.V., M.M., P.P., Pa.R. and D.P. recruited samples and collected clinical-pathologic data; L.O. conceived, designed and coordinated the study. All authors reviewed, edited and approved the manuscript for publication.

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Table 1. Distribution of 597 MBC cases and 1022 male population controls according to genotype frequencies of *CYP17A1* rs743572, *CYP1B1* rs1056836 and rs1800440, and MBC risk estimates.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype</th>
<th>MBC cases (N=597)</th>
<th>Male controls (N=1022)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td><em>CYP17A1</em> c.-34T&gt;C</td>
<td>TT</td>
<td>190</td>
<td>31.8%</td>
<td>347</td>
<td>33.9%</td>
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<tr>
<td></td>
<td>TC</td>
<td>301</td>
<td>50.4%</td>
<td>489</td>
<td>47.9%</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>106</td>
<td>17.8%</td>
<td>186</td>
<td>18.2%</td>
</tr>
<tr>
<td>Co-dominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>CYP1B1</em> p.Leu432Val</td>
<td>GG</td>
<td>231</td>
<td>38.7%</td>
<td>385</td>
<td>37.7%</td>
</tr>
<tr>
<td>rs1056836</td>
<td>GC</td>
<td>290</td>
<td>48.6%</td>
<td>482</td>
<td>47.1%</td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>76</td>
<td>12.7%</td>
<td>155</td>
<td>15.2%</td>
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<tr>
<td>Co-dominant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>CYP1B1</em> p.Asn453Ser</td>
<td>AA</td>
<td>365</td>
<td>61.2%</td>
<td>654</td>
<td>64.0%</td>
</tr>
<tr>
<td>rs1800440</td>
<td>AG</td>
<td>208</td>
<td>34.8%</td>
<td>321</td>
<td>31.4%</td>
</tr>
<tr>
<td></td>
<td>GG</td>
<td>24</td>
<td>4.0%</td>
<td>47</td>
<td>4.6%</td>
</tr>
<tr>
<td>Co-dominant</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Table 2. Distribution of 89 *BRCA1/2*-associated MBC cases and 157 unaffected male *BRCA1/2* mutation carriers according to genotype frequencies of *CYP1A1* rs743572, *CYP1B1* rs1056836 and rs1800440, and MBC risk estimates.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype</th>
<th>BRCA1/2 MBC cases (N=89)</th>
<th>Unaffected male BRCA1/2 mutation carriers (N=157)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17A1 c.-34T&gt;C rs743572</td>
<td>TT</td>
<td>31</td>
<td>34.8%</td>
<td>57</td>
<td>36.3%</td>
</tr>
<tr>
<td></td>
<td>TC</td>
<td>48</td>
<td>53.9%</td>
<td>71</td>
<td>45.2%</td>
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<tr>
<td></td>
<td>CC</td>
<td>10</td>
<td>11.3%</td>
<td>29</td>
<td>18.5%</td>
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<tr>
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<td>Co-dominant</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CYP1B1 p.Leu432Val rs1056836</td>
<td>GG</td>
<td>34</td>
<td>38.2%</td>
<td>67</td>
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</tr>
<tr>
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<td>GC</td>
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<td>49.4%</td>
<td>70</td>
<td>44.6%</td>
</tr>
<tr>
<td></td>
<td>CC</td>
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<td>12.4%</td>
<td>20</td>
<td>12.7%</td>
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<td>Co-dominant</td>
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<td></td>
</tr>
<tr>
<td>CYP1B1 p.Asn453Ser rs1800440</td>
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<td>53</td>
<td>59.5%</td>
<td>96</td>
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</tr>
<tr>
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<td>55</td>
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</tr>
<tr>
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<td>GG</td>
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<td>4.5%</td>
<td>6</td>
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</tr>
<tr>
<td></td>
<td>Co-dominant</td>
<td></td>
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Table 3. Distribution of the three analyzed polymorphisms in the MBC case series according to ER status.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Genotype</th>
<th>ER positive MBC cases (N=418)</th>
<th>ER negative MBC cases (N=30)</th>
<th>Chi2 p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP17A1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.-34T&gt;C</td>
<td>TT</td>
<td>125</td>
<td>9</td>
<td>0.39</td>
</tr>
<tr>
<td>rs743572</td>
<td>TC</td>
<td>211</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CC</td>
<td>82</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>CYP1B1</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p.Leu432Val</td>
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<td>8</td>
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</tr>
<tr>
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<td>205</td>
<td>19</td>
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<tr>
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<td>CC</td>
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<td>rs1800440</td>
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<td>141</td>
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<td>GG</td>
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