The V89L Polymorphism in the 5-α-Reductase Type 2 Gene and Risk of Breast Cancer

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Abstract

Women with high androgen levels appear to be at increased risk for breast cancer. The 5-α-reductase type 2 enzyme (SRD5A2) is an important mediator of local androgen actions. The SRD5A2 gene contains a polymorphism leading to a valine to leucine change in codon 89 (V89L). The Leu allele has been associated with lower SRD5A2 activity and might be protective for breast cancer. At the same time, among breast cancer patients, the Leu allele has been associated with lower prostate-specific antigen expression, indicating poor prognosis.

Within a cohort of breast cancer screening participants in the Netherlands (DOM-cohort) we examined whether the V89L polymorphism is associated with the risk and prognosis of breast cancer. We studied 295 postmenopausal breast cancer cases and a randomly selected reference group from the baseline cohort (postmenopausal breast cancer cases and a randomly selected reference group from the baseline cohort). The genotype distribution in the reference group was: VV 52%; VL 40%; and LL 8%. Compared with women with the VV genotype, adjusted breast cancer rate ratios for women with VL and LL genotypes were 1.5 (95% confidence interval = 1.0–2.2) and 1.1 (95% confidence interval = 0.5–2.1), respectively. Compared with breast cancer patients with VV or VL genotypes, those with the LL genotype showed larger tumors (proportion with size > 2 cm is 26 versus 55%, respectively; P = 0.07), a higher frequency of positive lymph nodes (28 versus 55%, respectively; P = 0.04), and a higher tumor-node-metastasis stage (proportion with stage III/IV: 6 versus 25%, respectively; P = 0.09), and a higher tumor-node-metastasis stage (proportion with stage III/IV: 6 versus 25%, respectively; P = 0.09). The LL genotype is also associated with shorter survival compared with the VV and VL genotypes (P = 0.10). In conclusion, our findings do not provide evidence for an important role of the V89L polymorphism in the etiology of breast cancer.

However, in breast cancer patients, the LL genotype may be associated with unfavorable prognosis.

Introduction

There is evidence that postmenopausal women with increased androgen levels have a higher risk of breast cancer (1–9). Androgens may influence breast cancer risk indirectly through their conversion to estrogens, mediated by aromatase (10, 11), but also directly by stimulating the growth and division of breast cells (12, 13).

The enzyme 5-α-reductase is an important regulator of local actions of androgens. It reduces testosterone into the biologically more active and nonaromatizable DHT (14). DHT binds to the AR with greater affinity than testosterone and the DHT-AR complex transactivates a number of genes with AR-responsive elements. In addition, DHT has been shown to act through the estrogen receptor α as well, leading to cell proliferation without conversion to estrogens (15). Two isoforms of 5-α-reductase are known, encoded for by different genes: SRD5A1 (chromosome 5p15) and SRD5A2 (chromosome 2p23). Both genes are restricted in their expression patterns, the SRD5A1 gene being primarily expressed in liver and skin and the SRD5A2 gene in liver, prostate, and epididymis (16). Until now, no results have been published on the expression of these genes in normal breast tissue, but there is evidence that both type I and type II enzymes are expressed in human breast carcinoma tissues (17). Also, enzymatic activity of 5-α-reductase has been demonstrated in normal breast tissue (18) and in higher concentrations in breast cancer cell lines (19) and breast cancer tissue (18).

Thus far, no polymorphisms have been reported for the SRD5A1 gene. For the SRD5A2 gene, however, a considerable number of naturally occurring single nucleotide polymorphisms and other variants have been characterized and described previously (20). Many of these have been found to influence enzyme activity, but they occur rarely with allele frequencies being <2% (20). The following genetic polymorphisms are the most frequent and have been described repeatedly, mostly in relation to prostate cancer risk: a variable number of TA-repeat polymorphism in the 3'-untranslated region (14); an alanine (ala) to threonine (thr) change in codon 49 (A49T; Ref. 21); and a valine (val) to leucine (leu) change in codon 89 (V89L; Ref. 14). No functional effects are known for the TA-repeat polymorphism in the SRD5A2 gene. The A49T polymorphism, on the other hand, appears to result in a strongly increased enzymatic activity in vitro, but this polymorphism is also relatively
rare, with the frequency of the Thr allele being <4% (22). For the V89L polymorphism, some effects have been reported as well: the Leu allele appears to be related to lower levels of 5α-androstane-3α,17β-diol-17β-glucuronide (AAD), a metabolite of DHT, which is commonly used as an in vivo measure of 5α-reductase activity (21, 23). The V89L polymorphism is fairly common with the Leu allele frequency in Caucasian control populations being ~30% (21, 23, 24). This polymorphism has been examined in relation to breast cancer risk in only one study (25), reporting a decreased risk for Japanese women with two Leu alleles. Another study examined this polymorphism in relation to breast cancer prognosis (26) and showed that the Leu allele was associated with lower breast tumor extract concentrations of PSA, an earlier onset of breast cancer and a shorter disease-free and overall survival (26).

On the basis of the increasing evidence that androgens may have a direct effect in the development and growth of breast cancer, we hypothesize that the V89L polymorphism in the SRD5A2 gene may be related to breast cancer risk and prognosis.

Materials and Methods

Participants. The study population was selected from participants in a population-based screening program for the early detection of breast cancer, the so-called DOM project that has been described earlier (27). During the period 1974–1986, women born between 1911 and 1945 who lived in the city of Utrecht, the Netherlands, were invited to participate in this screening program. A total of 27,718 women attended the screening program. In this period, >95% of the women in this age group living in Utrecht and the surrounding areas had the Dutch ethnicity, i.e., Caucasian (28, 29). At the start of the screening, program participants provided an overnight urine sample, which was stored at −20°C, and they filled out a questionnaire on health status and lifestyle.

Up to 1996, 942 breast cancer cases had been identified by the regional cancer registry (Comprehensive Cancer Center Middle Netherlands). To be eligible for this study, breast cancer cases had to meet the following criteria: (a) postmenopausal (natural menopause) at the time of urine collection; and (b) no breast cancer at the start of the screening program. We excluded 397 women who were premenopausal at the time of urine collection, 147 who had ovariectomy and/or hysterectomy, and 47 who already appeared to have breast cancer at the start of the screening program. Eventually, 351 incident breast cancer cases were eligible. As a reference, 421 women were randomly selected from the total of 9349 participants in the DOM baseline cohort who were fulfilling the same criteria as the cases (sampling fraction subcohort = 4.5%). The study was approved by the Institutional Review Board for human studies of the University Medical Center Utrecht.

Information on follow-up after diagnosis was available for those breast cancer patients who lived in the city of Utrecht and belong to the first birth cohort that was invited to the screening program (birth years 1911–1925; n = 270). Follow-up data on death and migration were obtained from municipal registries. Cause of death was inquired from the women’s general practitioners. Follow-up data had been completed up to January 1, 1996. Follow-up time was the time between the date of diagnosis and the date of death, migration, or January 1, 1996, whichever came first. Follow-up time after diagnosis varied from 1 month to ~20 years, with a median follow-up of 6 years. By January 1, 1996, 38 women had died of breast cancer, 40 from other causes, 14 were lost to follow-up, and the remainder were withdrawn alive.

Questionnaire Data. At the initial screening examination, all participants filled out a questionnaire on lifestyle and health. Included were questions on family history of breast cancer, smoking habits, drug use, and reproductive characteristics such as parity, age at first childbirth, and age at menopause. In addition, the participants’ height and weight were measured.

Laboratory Analysis. DNA was isolated from 100-ml urine samples as described earlier (30). A 58-bp fragment containing the V89L polymorphism was amplified with the PCR using the forward primer 5′-CACCCTGGACGCTTTCTCTTG-3′ and the reverse primer 5′-AAACGCTACCTTGGAAAGTAA-3′. PCR reactions were carried out in a final volume of 25 μl containing 1X Perkin-Elmer Buffer Gold (PE Biosystems), 0.5 mM of each nucleotide (dATP, dCTP, dGTP, and dTTP), 1.5 mM MgCl2, 1 μM of each primer, 1.0 unit of AmpliTaq Gold polymerase (PE Biosystems), and 2 μl of DNA. Amplification conditions were 95°C for 9 min, followed by 35 cycles of 94°C for 30 s, 55°C for 45 s, 65°C for 20 s, and a final step at 65°C for 10 min on a Hybaid PCR Express Thermal Cycler (Thermo Hybaid).

The V89L polymorphism is caused by a G (Val) to C (Leu) transversion. Genotypes were determined with an ASO hybridization method (31). ASO hybridization is a classical and widely used technique for the detection of genetic mutations and polymorphisms (32). It has been used for the detection of mutations in the HLA, CTRF, factor V, prothrombin, MTHFR, and many other genes (33–35). The ASO used to detect the G (Val) allele was: 5′-GGCTTTCTCTTGAGACAACTG-3′ (ASO-VAL); and the ASO for the C (Leu) allele: 5′-GGCTTTCTCTTGACTACA-3′ (ASO-LEU). The allele specific washing temperature was 59°C for ASO-VAL and 55°C for ASO-LEU. The robustness of this assay was tested by comparing results from ASO hybridization with those from a RFLP-PCR method that has been described earlier (23). Comparisons were made using 47 DNA samples obtained from blood from healthy persons. The genotypes of 41 samples were in agreement. In 2 samples, ASO hybridization had not succeeded, and in 4 samples, the RFLP genotype could not be read unambiguously.

All genotypes were assessed by two separate researchers, blinded to case-cohort status. In case of sample failure or if there was disagreement between the observers and they could not reach a consensus, the experiments were repeated, and a final genotype was assessed. After repeated efforts, genotyping did not succeed in samples of 56 breast cancer cases and 39 subcohort participants, probably because of low amounts of DNA (30), leaving 295 cases and 382 subcohort participants for analysis.

Statistical Analysis. First, to get some idea of potential confounders in our study, we explored whether among subjects at the start of follow-up (subcohort), known breast cancer risk factors were related to genotype. Breast cancer risk factors included age at recruitment (years), height (m), weight (kg), BMI (kg/m2), use of oral contraceptives (ever/never), smoking cigarettes (ever/never), parity (nulliparous/parous), age at first full-term pregnancy (years), age at menopause (years), first-degree family history of breast cancer (yes/no), and regular use of HRT (yes/no). Associations were assessed using one-way ANOVA for continuous variables and χ2 tests for categorical variables. Fisher’s exact test was used when expected numbers in the contingency tables were too low to perform a valid χ2 test, i.e., when >20% of the expected frequencies were <5. In these cases, the Val/Val and Val/Leu genotypes were pooled. All statistical tests were two-sided.
Within the case group and the subcohort, we assessed allele frequencies and computed 95% CIs. Deviations from Hardy-Weinberg equilibrium were assessed using a goodness-of-fit $\chi^2$ test with one degree of freedom. For estimating the association between V89L genotype and breast cancer risk, the case-cohort data were analyzed according to the method of Barlow et al. (36). Cox proportional hazards models with robust variance adjustment were used to calculate breast cancer IRRs for the different genotypes. For this purpose, we used a SAS program (version 9.0) was used for all statistical analyses, except for the case-cohort analyses, where SAS (version 6.12) was used.

### Results

In Table 1 known breast cancer risk factors are presented by SRD5A2 V89L genotype for the subcohort sample. The V89L genotype was not related to age at recruitment, height, weight, BMI, smoking behavior, parity, age at first full-time pregnancy, age at menopause, or first degree family history of breast cancer. Among the women with the Val/Leu genotype, there was a higher proportion of women who were ever oral contraceptive users and a higher proportion of women who had regularly used HRT in the 12 months before recruitment into the study.

The Val and Leu allele frequencies in the cases and the subcohort are shown in Table 2. The frequency of the Leu allele in cases is 29.3% (95% CI, 24.1–34.5) and in the subcohort 28.1% (95% CI, 23.6–32.6). The distribution of genotypes in the subcohort is in Hardy-Weinberg equilibrium ($df = 1; P = 0.84$). In the same table, breast cancer IRRs are presented for each genotype. No consistent relationship was observed between number of Leu alleles and breast cancer risk. Compared with women with the Val/Val genotype, those with the Val/Leu genotypes showed a breast cancer IRR of 1.5 (95% CI, 1.0–2.2), whereas those with the Leu/Leu genotype showed an IRR of 1.1 (95% CI, 0.5–2.1). These estimates were adjusted for the breast cancer risk factors mentioned in the preceding paragraph.

The relationship between genotype and breast cancer risk did not vary across strata of age at recruitment, height, weight, BMI, and age at menopause (all dichotomized based on median values) or between ever- and never-smokers, nulliparous and parous women, ever and never oral contraceptive users, women with or without a first-degree family history of breast cancer, and women who did or did not regularly used HRT in the 12 months before recruitment (data not shown).

Table 3 shows the relationship between the V89L genotype and clinical/pathological breast cancer features mentioned above.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Val/Val (n = 198)</th>
<th>Val/Leu (n = 153)</th>
<th>Leu/Leu (n = 31)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in yrs) at recruitment, mean (SD)</td>
<td>58.0 (4.7)</td>
<td>57.7 (4.5)</td>
<td>58.1 (4.5)</td>
<td>0.85</td>
</tr>
<tr>
<td>Height (cm), mean (SD)</td>
<td>161.8 (6.0)</td>
<td>162.0 (6.0)</td>
<td>162.1 (6.5)</td>
<td>0.94</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>68.9 (12.3)</td>
<td>67.3 (9.3)</td>
<td>67.7 (8.8)</td>
<td>0.38</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>26.3 (4.8)</td>
<td>25.6 (3.4)</td>
<td>25.8 (2.7)</td>
<td>0.30</td>
</tr>
<tr>
<td>Ever-smokers, %</td>
<td>27.3%</td>
<td>27.5%</td>
<td>16.1%</td>
<td>0.40</td>
</tr>
<tr>
<td>Nulliparous women, %</td>
<td>22.2%</td>
<td>19.6%</td>
<td>19.4%</td>
<td>0.82</td>
</tr>
<tr>
<td>Age at first full-term pregnancy, mean (SD)</td>
<td>26.9 (4.4)</td>
<td>27.4 (4.8)</td>
<td>27.8 (4.5)</td>
<td>0.58</td>
</tr>
<tr>
<td>Ever oral contraceptive users, %</td>
<td>1.6%</td>
<td>5.3%</td>
<td>12.9%</td>
<td>0.03*</td>
</tr>
<tr>
<td>Age (in yrs) at menopause, mean (SD)</td>
<td>49.5 (4.2)</td>
<td>49.6 (3.9)</td>
<td>50.5 (2.5)</td>
<td>0.49</td>
</tr>
<tr>
<td>Positive family history of breast cancer (first grade), %</td>
<td>8.7%</td>
<td>6.0%</td>
<td>3.3%</td>
<td>0.71*</td>
</tr>
<tr>
<td>Regular HRT users in past 12 months, %</td>
<td>7.7%</td>
<td>8.5%</td>
<td>19.4%</td>
<td>0.05*</td>
</tr>
</tbody>
</table>

* $p$ computed using one-way ANOVA for continuous variables and $\chi^2$ tests for categorical variables.

**Parous women only.**

* Expected numbers in cells were too small to calculate a valid $\chi^2$ value, therefore, Fisher exact test was performed for the categories (Val/Val + Val/Leu) versus (Leu/Leu).
Table 2  Breast cancer incidence rate ratios (IRRs) in relation to SRD5A2 V89L genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>No. of breast cancer cases (%)</th>
<th>No. of women in subcohort (%)</th>
<th>IRR unadjusted (95% CI)</th>
<th>IRR adjusted (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Val/Val</td>
<td>140 (47)</td>
<td>198 (52)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Val/Leu</td>
<td>137 (46)</td>
<td>153 (40)</td>
<td>1.3 (1.0–1.9)</td>
<td>1.5 (1.0–2.2)</td>
</tr>
<tr>
<td>Leu/Leu</td>
<td>18 (6)</td>
<td>31 (8)</td>
<td>0.8 (0.5–1.3)</td>
<td>1.1 (0.5–2.1)</td>
</tr>
<tr>
<td>Total</td>
<td>295 (100)</td>
<td>382 (100)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for: age at recruitment, height, weight, smoking (ever/never), parity/age at first full-term pregnancy (nulliparous/≤25 years/26–29 years/≥30 years), oral contraceptive use (ever/never), age at menopause, family history of breast cancer, and regular HRT use in past 12 months (yes/no).

and clinical/pathological tumor features. The genotype was not related to age at diagnosis, but breast cancer patients with the Leu/Leu genotype, compared with those with the Val/Val or Val/Leu genotypes, showed more often large tumor size ($P = 0.07$), positive axillary lymph nodes ($P = 0.09$), and high TNM stage ($P = 0.04$).

The tumors of patients with the Leu/Leu genotype were diagnosed outside the screening program more often than those of patients with the Val/Leu or Val/Val genotypes [85% (2 of 13) versus 47% (49 of 104) versus 46% (45 of 100), respectively]. To examine whether any of the above-mentioned relationships could be explained by screening status, we calculated univariate ORs and ORs adjusted for screening status. The univariate OR for a tumor $> 2$ cm for women with the Leu/Leu genotype versus those with the Val/Val or Val/Leu genotype was 3.5 (95% CI, 1.0–11.8), whereas the screening status adjusted OR was 3.2 (95% CI, 0.8–12.3). For positive lymph node status, the univariate OR was 3.0 (95% CI, 0.9–10.3) and the screening status adjusted OR 2.4 (95% CI, 0.7–8.7). For TNM stages more than II, the univariate OR was 5.4 (95% CI, 1.3–22.7) and the screening status adjusted OR 3.8 (95% CI, 0.8–18.9).

The Kaplan-Meier breast cancer survival analysis in Fig. 1 shows a poorer survival for patients with the Leu/Leu genotype relative to those with the Val/Val or Val/Leu genotype ($P = 0.10$). In a univariate Cox proportional hazards model, with the Val/Val genotype included as the reference category, the breast cancer mortality hazard rate ratio for those with the Val/Leu genotype was 1.3 (95% CI, 0.6–3.1) and for those with the Leu/Leu genotype 3.1 (95% CI, 0.8–11.3). After adjusting for screening status the hazard rate ratio was 1.3 (95% CI, 0.5–3.3) for those with the Val/Leu genotype and 2.5 (95% CI, 0.7–9.8) for those with the Leu/Leu genotype. After adjustment for tumor size and/or lymph node status, any relationship between genotype and survival disappeared.

Discussion

We found no evidence for a consistent relationship between the V89L SRD5A2 polymorphism and breast cancer risk. However, the Leu/Leu genotype was associated with larger tumor size, higher frequency of positive lymph nodes, higher TNM stage, and as a result, shorter survival than the Val/Val or Val/Leu genotypes.

The genotype distribution we found in our population-based subcohort is highly comparable with those in other studies examining Caucasian populations (21, 23, 24). Several investigators focused on SRD5A2 polymorphisms and breast cancer risk. Two studies examined the effect of the TA-repeat but could not find evidence for an association (37, 38).

Table 3  Clinical/pathological features of breast cancer in relation to SRD5A2 V89L genotype

<table>
<thead>
<tr>
<th>Features</th>
<th>Val/Val</th>
<th>Val/Leu</th>
<th>Leu/Leu</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 67</td>
<td>47 (47)</td>
<td>49 (47)</td>
<td>7 (54)</td>
<td></td>
</tr>
<tr>
<td>≥ 67</td>
<td>53 (53)</td>
<td>55 (53)</td>
<td>6 (46)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100 (100)</td>
<td>104 (100)</td>
<td>13 (100)</td>
<td>0.89</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 2 cm</td>
<td>72 (74)</td>
<td>72 (74)</td>
<td>5 (45)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2 cm</td>
<td>25 (26)</td>
<td>25 (26)</td>
<td>6 (55)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>97 (100)</td>
<td>97 (100)</td>
<td>11 (100)</td>
<td>0.07b</td>
</tr>
<tr>
<td>Lymph node status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>69 (75)</td>
<td>67 (68)</td>
<td>5 (45)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>23 (25)</td>
<td>31 (32)</td>
<td>6 (55)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>92 (100)</td>
<td>98 (100)</td>
<td>11 (100)</td>
<td>0.09b</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–I–II</td>
<td>89 (96)</td>
<td>88 (93)</td>
<td>9 (75)</td>
<td></td>
</tr>
<tr>
<td>III–IV</td>
<td>4 (4)</td>
<td>7 (7)</td>
<td>3 (25)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>93 (100)</td>
<td>95 (100)</td>
<td>12 (100)</td>
<td>0.04b</td>
</tr>
</tbody>
</table>

* $P$ computed using $\chi^2$ tests.

b Expected numbers in cells were too small to calculate a valid $\chi^2$ value, therefore, Fisher exact test was performed for the categories (Val/Val + Val/Leu) versus (Leu/Leu).
one earlier study, by Yang et al. (25), examined the relationship between V89L genotype and breast cancer risk. In their study of 237 Japanese prevalent breast cancer cases and 185 controls, they found, in contrast with our results, that women with the Leu/Leu genotype had a lower breast cancer risk.

The relationship between the V89L polymorphism and prognostic characteristics of breast cancer patients has been examined in one earlier study (26). Scorilas et al. (26) studied the tumor tissue of 151 Caucasian breast cancer patients and found that the Leu/Leu genotype was associated with unfavorable prognostic tumor characteristics such as lower PSA tumor concentration, younger age at diagnosis, higher tumor grade, and shorter survival, which is in general agreement with our results. The V89L polymorphism has been suggested to exert its effect through an increase in PSA, a protein associated with epiandrosterone (DHEA), DHEA sulfate, and 5-androstene-3,17β-diol to risk of breast cancer in postmenopausal women. J. Natl. Cancer Inst. (Bethesda), 88: 291–296, 1996.

In interpreting our first finding, the lack of an association between the V89L polymorphism and breast cancer risk, several issues have to be taken into account. First, although 5α-reductase enzyme activity has been demonstrated in normal breast tissue (18), no evidence is yet available for V89L expression in normal breast tissue. Furthermore, it is uncertain whether the V89L polymorphism truly affects protein function. In vivo studies did show that the Leu allele is related to lower levels of 5α-androstane-3α,17β-diol-17β-glucuronide, a metabolite commonly used as a measure of 5α-reductase activity (21, 23). These studies were restricted to men, however, and we cannot be certain that these results also pertain to women. On the other hand, our finding of the V89L polymorphism being associated with breast cancer prognosis indicates at least some functional effect of this polymorphism or other variants in linkage disequilibrium with this one.

In interpreting our second finding, the relationship between the V89L polymorphism and prognosis, it should be noted that our sample size was limited and that a larger number of breast cancer patients would be needed to fully evaluate the prognostic data. A disadvantage of using a screening population is that prognostic characteristics and survival are influenced by screening status, i.e., tumor detected in or outside the screening program. Adjusting for screening status in the analyses slightly weakened the relationships but did not alter the conclusion that Leu/Leu genotype appears to be associated with poor prognosis.

To answer the prognosis question it would have been desirable to genotype breast tumor DNA and relate somatic mutations arising during breast cancer progression to stage and survival. Unfortunately, our conclusions are restricted to germ-line mutations because we did not have tumor tissues at our disposal.

In summary, we did not find evidence for a consistent relationship between the V89L polymorphism and breast cancer risk and thus no additional support for a direct effect of androgens in the etiology of breast cancer. However, our data are consistent with the hypothesis that the polymorphism is involved in the prognosis of breast tumors. An important question for future research is whether the polymorphism may affect response to treatment, in particular, adjuvant hormonal therapy. In addition, it would be interesting to study the role of the estrogen receptor status in this relationship. First of all, however, it should be clarified whether it is actually this polymorphism that affects SRD5A2 enzyme activity and breast cancer prognosis or whether other variants, in linkage disequilibrium with this one, explain the relationships. For this purpose, future studies should focus on the effect of the polymorphism on functionality of the protein with respect to mRNA stability and/or protein expression.

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References


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