Progesterone Receptor Gene Polymorphism Is Associated with Decreased Risk for Breast Cancer by Age 50

Shan Wang-Gohrke, Jenny Chang-Claude, Heiko Becher, Dirk G. Kieback, and Ingo B. Runnebaum

Abstract
In a population-based case-control study for breast cancer before the age of 51 years, 554 cases and 559 age-matched controls were genotyped for the polymorphic progesterone receptor allele PROGINS. Breast cancer risk was decreased in women carrying the PROGINS allele. The odds ratio adjusted for age and study region was 0.76 (95% confidence interval [CI], 0.58–1.00). Compared with wild-type A1/A1 homozygotes, the odds ratio for A1/A2 heterozygotes and A2/A2 homozygotes was 0.82 (95% CI, 0.62–1.08) and 0.27 (95% CI, 0.10–0.74), respectively, suggesting a gene dosage effect of the A2 allele. There was suggestive evidence for a differential effect by menopausal status (P = 0.07) and by family history of breast cancer (P = 0.15).

Introduction
The HPR gene is located on chromosome 11q22–23 and belongs to the steroid-thyroid-retinoic acid receptor superfamily of transcription factors (1). HPR exists in two isoforms, HPR-A and HPR-B, transcribed from the HPR gene by alternative initiation. HPR-A represses estrogen receptor gene activation and gene activation by HPR-B. Rowe et al. (2) identified a 306-bp insertion of the PV/HS-1 Alu subfamily in intron 7 of the HPR gene. Kieback et al. (3) demonstrated that the Alu insertion identifies an allele, named PROGINS, which is in linkage disequilibrium with a silent mutation in exon 5 and a mutation in exon 4, causing an amino acid change in the hinge region of the receptor. Four hospital-based case-control studies have been published that analyzed the association between this polymorphism and breast or ovarian cancer risk in patient populations with different ethnic backgrounds without analyses regarding age and menopausal status (4–7). It is unclear whether the mutant allele alters the risk for breast or ovarian cancer. We used a population-based case-control study to determine whether PROGINS was associated with breast cancer in a German Caucasian population under the age of 51 years.

Study Population.
We assessed the relationship between PROGINS and breast cancer risk in a population-based genetic epidemiological case-control study in Germany designed to quantify the effect of relevant reproductive and life-style risk factors as well as genetic factors (8). The study was carried out in two geographical areas, covering a population of about 1.3 million in the Rhein-Neckar-Odenwald study region and a population of about 0.9 million in the Freiburg study region. Cases and controls were restricted to women who could speak and read German and who were residents of the study region. Patients had to be <51 years of age when first diagnosed with either in situ or invasive primary breast cancer between January 1, 1992 and December 31, 1995 in the Rhein-Neckar-Odenwald region and between January 1, 1993 and December 31, 1995 in the Freiburg region. Complete ascertainment of incident breast cancer patients was carried out at all of the hospitals in the study region (40 hospitals in total), with periodic checks with the pathology institutes serving these hospitals. Patients were either approached in the hospital before first discharge or invited to participate in the study by a letter signed by the attending physician after discharge. Clinical and pathological characteristics of the diagnosed breast cancers were abstracted from hospital records, and pathology reports were requested if possible. After approval for the study was given by all of the communities involved, the population registries of the two study regions provided a sample of 11,000 female residents between 20 and 75 years of age that was generated by systematic sampling. From this list, two controls matched by age and study region were randomly selected for each case and invited by letter to participate in the study. Controls up to 52 years of age at interview were eligible for inclusion. Reasons for nonparticipation were refusal of physicians to allow contact, health problems, nonresponse, and refusal of participation. Overall, 70% of eligible cases and 61% of eligible population controls participated by completing the study questionnaire.

Using a self-administered risk factor questionnaire, detailed information was collected from cases and controls on demographic factors; anthropometric measures; menstrual, reproductive, and breastfeeding histories; family history of cancer; selected occupational exposures; smoking history; and alcohol consumption. In addition, subjects were asked to give a blood sample of 20 ml. All information on case and control exposures was truncated at the date of diagnosis for cases and at the date of completion of the risk factor questionnaire for controls.

For this analysis, we included only cases and controls who were Germans (defined as having at least one parent of German nationality; 91% of cases and 96% of controls) and from whom both questionnaire data and DNA from a blood sample were available by mid-1997. Overall, 3% of the participants refused to provide a blood sample. One control per case (usually the first recruited control, unless a blood sample was not available) was chosen. A total of 577 cases and 579 controls were included in the molecular genetic analysis. Due to the failure of genotyping in 18 cases and 25 controls, the following analysis is based on 559 cases and 554 controls. The mean ages of cases and controls were 42.9 and 42.8 years, respectively.

Genotyping PROGINS. Genomic DNA was extracted from the EDTA blood samples using Blood & Cell Culture DNA kits as described by manufacturer (Qiagen GmbH, Hilden, Germany). The analysis of PROGINS was based on the PCR amplification of a fragment encompassing the 306-bp insertion polymorphism in intron 7 using the following primers: (a) sense primer OL-334, 5’-GCCTCTAAAAATGAAAGGCAGAAACGC-3’; and (b) an-
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Interaction between PROGINS and Other Risk Factors for Breast Cancer. Because it has been suggested that PROGINS may affect ligand and hormone binding properties and hence hormonal regulation (3), we explored the effects of interaction between the PROGINS genotype and reproductive risk factors for breast cancer. The distribution of controls and cases for the different categories of risk factors considered was as follows: (a) age at menarche (12 or less years, 214 cases and 199 controls; 13 or more years, 345 cases and 355 controls); and (b) parity (two or less births, 501 cases and 464 controls; three or more births, 58 cases and 89 controls). For the categories such as age at menarche, parity, and duration of breastfeeding (in months), there was a decrease in risk with increasing copies of the A2 allele. There was no interaction between the PROGINS genotype and age at menarche (P = 0.32), parity (P = 0.57), and duration of breastfeeding (P = 0.35) on disease risk.

For the analysis of effect modification by menopausal status, women who were under the age of 51 years and who had undergone hysterectomy but not bilateral ovariectomy were considered to be of unknown menopausal status (89 cases and 74 controls). We were left with a small group of 35 cases and 39 controls who were postmenopausal, and 435 cases and 441 controls who were premenopausal. PROGINS A2 allele was associated with a reduced risk for premenopausal breast cancer but was not associated with postmenopausal breast cancer, thus giving weak evidence for differential effects of the PROGINS genotype on disease risk by menopausal status (Table 3). A statistical test of interaction, however, did not yield a significant result (P = 0.07 for interaction).

We also examined the data for effect modification by family history of breast cancer. Seventy cases and 27 controls had a first-degree family member with breast cancer, whereas 489 cases and 527 controls had no family history. The protective effect of the PROGINS A2 allele was evident among women without a first-degree family history of breast cancer, but not among women with such a first-degree family history. However, the association with the A2 allele was not significantly modified by a positive family history (P = 0.15 for interaction).

Table 3 Analysis of interaction between the PROGINS allele and established risk factors for breast cancer

<table>
<thead>
<tr>
<th>OR</th>
<th>Age at menarche (yrs)</th>
<th>Parity</th>
<th>Menopausal status</th>
<th>Family history of breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤12</td>
<td>≥2</td>
<td>Premenopausal/unknown</td>
<td>(first-degree relative)</td>
</tr>
<tr>
<td></td>
<td>≤13</td>
<td>≥3</td>
<td>Postmenopausal</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>A1/A1</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>A1/A2</td>
<td>0.85</td>
<td>0.71</td>
<td>0.69</td>
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<td>A2/A2</td>
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<td>0.50</td>
<td>0.47</td>
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<td>0.35</td>
<td>0.35</td>
<td>0.35</td>
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</tbody>
</table>

Interaction between PROGINS allele and parity (P = 0.07 for interaction).

Discussion

This is the first population-based age-matched case-control study to our knowledge to examine the possible role of PROGINS in the development of breast cancer. We found a reduced risk of breast cancer in women by the age of 50 years who carry at least one A2 allele and a statistically significant trend of decrease in risk with an increase in the number of A2 alleles.
PROGINS has been suggested to show an association with ovarian and breast cancer. An increased frequency of the A2 allele was first reported in a group of 67 patients with ovarian cancer that was pooled from 26 German and 41 Irish patients (6). The observed difference between cases and controls, however, was predominantly due to a low frequency of the PROGINS allele among the 101 German control subjects. This association has not been confirmed in other studies (4, 5). Clearly, larger studies with well-characterized study populations are needed to clarify the effect of PROGINS on ovarian cancer risk. An association of PROGINS with breast cancer was suggested in a study reporting a significant ($P > 0.05$) deviation from Hardy-Weinberg equilibrium in the genotype distribution of 187 Irish breast cancer patients (7). There was a deficit of breast cancer patients homozygous for the A2 allele, which is compatible with our observation of a decreased risk of breast cancer associated with the A2 allele. The association of PROGINS with breast cancer was further examined in two studies in North America (68 patients and 101 hospital controls) and in the south of England (292 patients and 220 healthy volunteers; Refs. 4 and 5). The allele frequency of PROGINS was slightly lower in the North American Caucasian breast cancer patients compared with the hospital controls, but the difference was not statistically significant (4). No difference between cases and controls was observed in the English study (5).

The previous studies have not used a well-defined patient population and appropriately selected controls. Population controls with similar genetic background are generally preferable when one wishes to detect a possible (statistically significant) deviation of the distribution of allele frequencies among the cases compared to the “expected” distribution and thus provide evidence for an association of the respective genetic variants with the disease of interest. Therefore, it may not be surprising that the previously reported results are inconsistent. Furthermore, no information on cases and controls was given by any of the above studies with respect to age at diagnosis, menopause status, family history, and other variables that could have made an impact on the results. The design of our study reduces many possible biases and issues of comparability of the case and control groups that may arise in other study designs. Our finding of a reduced risk of breast cancer in women with the A2 allele is strengthened by the observation of an allelic dosage effect of the A2 allele. Our data provide suggestive evidence that the protective effect of the polymorphic progesterone receptor allele is confined to premenopausal women.

The HPR-A form of the progesterone receptor has been shown to repress estrogen receptor activation and the transcriptional activity of the HPR-B form. The polymorphic HPR-A PROGINS allele has been shown to have increased transcriptional activity and increased stability (3). HPR-A PROGINS could thereby repress estrogen receptor activation more efficiently and contribute to estrogen-related tumor promotion in the mammary gland of premenopausal women. Ongoing functional studies on PROGINS should provide more information on how the polymorphic progesterone receptor modifies the risk for breast cancer on the molecular level.

Acknowledgments

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