Null Results in Brief

No Association between the DNA Repair Gene XRCC3 T241M Polymorphism and Risk of Skin Cancer and Breast Cancer

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Introduction

Skin cancer is the most frequent type of cancer in the Western world, whereas breast cancer is the most common cancer among women. Whereas skin cancer is predominantly induced by UV light, less is known about the pathways leading toward sporadic breast cancer. XRCC3 participates in DNA repair after exposure to UV light, and XRCC3 polymorphisms have previously been associated with risk of breast cancer (1), whereas its association with malignant melanoma has been contradictory (2, 3). Malignant melanoma and basal cell carcinoma share some genetic and environmental risk factors, which make it likely that polymorphisms found to be genetic risk factors for malignant melanoma may also be associated with basal cell carcinoma.

Materials and Methods

We have analyzed DNA samples from one nested case control study regarding basal cell carcinoma development and one nested case control study regarding breast cancer development. Both are based on the Danish prospective cohort “Diet, Cancer and Health” (4). Our basal cell carcinoma study group consisted of 319 incident basal cell carcinoma cases and 321 controls matched on age at inclusion into the cohort (half-year intervals) and sex. The breast cancer study group consisted of 426 breast cancer cases and 424 controls matched on age at inclusion into the cohort (half-year intervals) and sex. The breast cancer study group was selected from the breast cancer study (5). The breast cancer cases matched on half-year intervals were used in the present study. In both studies, the controls were cancer free at the age at diagnosis of the case.

XRCC3 T241M (T/C, position 18067, AF037222) was determined on DNA isolated from lymphocytes using real-time PCR on a SDS ABI-Prism 7700 (Applied Biosystems, Nærum, Denmark). Ten-μl reactions contained 1× MasterMix, 100 nM of each probe, 800 nM primers, and 50 ng of genomic DNA. Cycling conditions were as follows: 50°C for 2 min; 95°C for 10 min; and 45 cycles of 95°C for 1 s and 60°C for 1 min. Primers were as follows: forward, 5′-GTGCTCACTGGTGATGCA-3′; and reverse, 5′-CCAGGGCCAGGTCTCGT-3′. Probes were as follows: T probe (Thr allele), 5′-Vic-TGGGGGCATGT-NFQ-MGB-3′; and C probe (Met allele), 5′-Fam-CTCACGCAGCTGG-NFQ-MGB-3′ (Applied Biosystems, Denmark). Genotyping 100 samples with PCR-RFLP verified the quantitative assay. The PCR fragments were cut using NciI and achieved 100% identical genotyping. Repeated quantitative PCR analysis of 10% of all samples yielded identical results.

Results and Discussion

The T allele frequency varied from 0.34 to 0.39. The frequencies were consistent with previous studies. There was no association between XRCC3 T241M genotypes and risk of basal cell carcinoma or breast cancer (Table 1). Due to the sampling design, the odds ratio for the basal cell carcinoma and the breast cancer study group was estimated using matched logistic regression, thus, only known discordant pairs contribute to this analysis. The procedure PHREG in SAS, release 6.12 (SAS Institute, Inc., Cary, NC) on Unix platform was used for statistical analyses.

The lack of association between risk of nonmelanoma skin cancer and XRCC3 T241M may reflect that gene-environment interactions are required for which the environmental exposures are not present in Denmark, that a putative linkage to the variant homozygotes. There was no effect of age at diagnosis of cancer or sex (data not shown). The design of our study is relatively strong because the study groups were fairly large, and cases and controls were recruited from the same cohort and carefully matched. Given the sample size and the allele frequencies of the controls, we had a 96% and 99% chance of detecting a doubling of the rate between the wild-type homozygote and the variant heterozygote and homozygote combined (α = 0.01, two-sided) for the basal cell carcinoma and the breast cancer group, respectively, if we assume Hardy-Weinberg equilibrium. However, we did not have sufficient power to detect the odds ratio of 1.3 reported for breast cancer by Kuschel et al. (1).

Received 2/7/03; accepted 3/13/03.

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1 Supported by Danish Cancer Society Grant DPh0027 and Grant “Cemik” from the Danish Ministry of Health’s Research Centre for Environmental Health.

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References


Table 1 Basal cell carcinoma and breast cancer risk in relation to XRCC3 codon 241 polymorphisms

The genotype distribution was in Hardy-Weinberg equilibrium for all control groups. The odds ratios for the basal cell carcinoma and the breast cancer groups are based on information from known discordant pairs only, due to matched design.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Basal cell carcinoma</th>
<th>Breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td>CC (Thr/Thr)</td>
<td>129</td>
<td>146</td>
</tr>
<tr>
<td>CT (Thr/Met)</td>
<td>158</td>
<td>129</td>
</tr>
<tr>
<td>TT (Met/Met)</td>
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<td>43</td>
</tr>
<tr>
<td>Missing</td>
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<td>3</td>
</tr>
<tr>
<td>Allele frequency</td>
<td>0.346</td>
<td>0.338</td>
</tr>
</tbody>
</table>

a OR, odds ratio; CI, confidence interval.
b The CC genotype (Thr/Thr) served as reference category.
c Allele frequency of the T allele.
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