Null Results in Brief

No Association between a Stop Codon Polymorphism in RAD52 and Breast Cancer Risk

Jiali Han, Susan E. Hankinson, Immaculata De Vivo, Graham A. Colditz, and David J. Hunter

Departments of Nutrition [J. H., D. J. H.] and Epidemiology [S. E. H., I. D., G. A. C., D. J. H.] and Harvard Center for Cancer Prevention [J. H., I. D., G. A. C., D. J. H.], Harvard School of Public Health, and Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School [S. E. H., I. D., G. A. C., D. J. H.], Boston, Massachusetts 02115.

Introduction

The human RAD52 protein plays an important role in DNA homologous recombination and DNA double-strand break repair. BRCA1 and BRCA2 are involved in the DNA damage response pathway shared with RAD51 and RAD52 (1). Bell et al. (2) observed a germ-line Ser346ter truncation polymorphism (TGG to TAG), resulting in removal of 72 COOH-terminal residues, in 3 of 99 cases (<40 years old) with breast cancer and in 5 of 102 controls. We prospectively assessed the association between the RAD52 Ser346ter polymorphism and breast cancer risk in a case-control study nested within the Nurses’ Health Study cohort. In addition, the frequency of the germ-line RAD52 Ser346ter polymorphism was determined among 103 women diagnosed with primary invasive cancer in more than one organ after enrollment in the cohort study.

Materials and Methods

Detailed information about this nested case-control study (cases, n = 727; controls, n = 969) has been reported previously (3). PCR amplification of the polymorphic fragment in RAD52 was generated as described previously (2). A template-directed dye terminator incorporation and fluorescence polarization assay protocol (LJL BioSystems, Sunnyvale, CA) was used for genotyping. Genotyping was performed by laboratory personnel blinded to case-control status, and blinded quality control samples were inserted to validate genotyping procedures; concordance for the blinded samples was 100%. ORs3 and 95% CIs were calculated using conditional logistic regression.

Results

Women with the truncation polymorphism were not at an increased risk of breast cancer; 19 of 956 controls (1.99%) and 12 of 726 cases (1.65%) carried at least one Ser346ter allele (P = 0.61). Compared with the noncarriers, the adjusted OR for the carriers of this polymorphism was 0.97 (95% CI, 0.43–2.21; Table 1). Of the 31 carriers of Ser346ter found in the study population, none had other cancers, except for one carrier who had both breast and uterine cancer; no notable elevation in the prevalence of any other disease was noted. There was only one homozygous variant carrier, who was in the control group and did not have any diagnosed cancer or first-degree family history of cancer. There was no association between the Ser346ter genotype and first-degree family history of cancer. Analysis of 103 multiple-cancer cases revealed four (3.9%) heterozygous RAD52 Ser346ter nonsense polymorphism carriers, which is not significantly higher than the carrier frequency in controls (19 of 956, 1.99%; two-tailed Fisher’s exact test, P = 0.27). Each of the four women had developed breast cancer and an additional cancer (rectal cancer, uterine cancer, ovarian cancer, or melanoma).

Discussion

In this case-control study nested within the Nurses’ Health Study cohort, women with the Ser346ter nonsense polymorphism of RAD52 were not at an increased risk of breast cancer. This study had 80% power to detect an OR of 2.2 between carriers and noncarriers. Bell et al. (2) observed no evidence of an association between Ser346ter and risk of early-onset (before age 40 years) breast cancer. Our results from a prospective study among mainly Caucasian women predominantly over 50 years of age support the finding that the Ser346ter nonsense polymorphism does not confer genetic susceptibility to breast cancer at older age. The prevalence of the Ser346ter allele was similar among 103 women diagnosed with more than one cancer. No significant differences in carrier frequency were noted among women categorized by first-degree family history of cancer, consistent with either no effect or a very low penetrance of the polymorphism. The presence of one woman homozygous for the truncation polymorphism demonstrates that the polymorphism does not confer a lethal embryonic or early life phenotype. None of the diseases reported by the homozygote or seen in the heterozygous group was strikingly suggestive of a DNA repair disorder. The lack of a severe phenotype for the RAD52 Ser346ter truncation polymorphism indicates that the extreme COOH terminus of RAD52 may not contribute to its function. Bell et al. (2) did not observe a significant increase in radiosensitivity in RAD52 Ser346ter/+ cells compared with RAD52+/+ cells, suggesting that this truncation polymorphism may not confer susceptibility to radiation damage. The region of human RAD52 required for the interaction with RAD51 was mapped near the COOH terminus (amino acids 287–333; Ref. 4), which is close to, but proximal to, the position of the Ser346ter nonsense polymorphism. Our data suggest that the Ser346ter truncation polymorphism, present in 2% of Caucasian women in the general population, does not contribute to inherited predisposition to breast cancer.
Acknowledgments

We thank Robert O’Brien, Pamela Lescault, and Lisa Li for technical assistance. We are also indebted to the participants in the Nurses’ Health Study for their dedication and commitment.

References


Table 1 Association between RAD52 genotype and breast cancer risk, Nurses’ Health Study 1989–1996

<table>
<thead>
<tr>
<th></th>
<th>Carriers a</th>
<th>Noncarriers</th>
<th>Simple OR b (95% CI)</th>
<th>Multivariate OR d (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>N (%): 19 (1.99)</td>
<td>937 (98.01)</td>
<td>1.00 (1.00)</td>
<td></td>
</tr>
<tr>
<td>Cases</td>
<td>12 (1.65)</td>
<td>714 (98.35)</td>
<td>0.85 (0.41–1.77)</td>
<td>0.97 (0.43–2.21)</td>
</tr>
</tbody>
</table>

a Five subjects with missing genotype were excluded.

b There was only one homozygous variant carrier, who was in the control group.

Conditional logistic regression adjusted for the matching variables: age, menopausal status, postmenopausal hormone use, date of blood draw, time of blood draw, and fasting status.

d Conditional logistic regression adjusted for the matching variables, and body mass index at age 18 years, weight gain since age 18 years, age at menarche, age at menopause, parity/age of first birth, first-degree family history of breast cancer, history of benign breast disease, and duration of postmenopausal hormone use.

e Nine controls were excluded due to incomplete matching.
No Association between a Stop Codon Polymorphism in RAD52 and Breast Cancer Risk

Jiali Han, Susan E. Hankinson, Immaculata De Vivo, et al.


Updated version
Access the most recent version of this article at:
http://cebp.aacrjournals.org/content/11/10/1138

Cited articles
This article cites 3 articles, 3 of which you can access for free at:
http://cebp.aacrjournals.org/content/11/10/1138.full#ref-list-1

Citing articles
This article has been cited by 1 HighWire-hosted articles. Access the articles at:
http://cebp.aacrjournals.org/content/11/10/1138.full#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.