CORRESPONDENCE

Re: Integrin β₃ Leu33Pro Homozygosity and Risk of Cancer

Altered expression of the β₃ integrin gene has been implicated in the metastasis of breast cancer (1). A single-nucleotide polymorphism at codon 33 of the β₃ integrin gene that exchanges a leucine (Leu) for a proline (Pro) seems to modify the function of cells expressing β₃ integrins ([2] and references therein). Recently, Bojesen et al. (2) carried out a cohort study on the Leu33Pro polymorphism and showed an increased risk of breast cancer among individuals who were homozygous Pro/Pro carriers of the polymorphism. At almost the same time, Ayala et al. (3) showed an increased risk of breast cancer among individuals who were homozygous Leu/Leu carriers. These observations raise the question of which allele, if any, reflects a true association with an increased risk of breast cancer.

The number of breast cancers in each study (2,3) was small (195 and 101, respectively). We performed a case–control study of 886 women with breast cancer, including 221 postmenopausal women with breast cancer from Finland unselected for family history of breast cancer and 665 women with familial breast cancer from Poland, Germany, and Sweden (4,5). All case subjects were ethnically and geographically matched with control subjects as described (4,5). The German women with breast cancer did not carry mutations in their BRCA1 or BRCA2 genes. Among the women with familial breast cancer, 25% were diagnosed as having bilateral breast cancer. The use of familial cases can substantially increase the power of association studies (6). The study was approved by the ethics committee of the Karolinska Institute Syd. DNA samples were genotyped for the Leu33Pro polymorphism by the polymerase chain reaction and restriction fragment length analysis, as described (7).

The genotype and allele distribution among the breast cancer case and control subjects is shown in Table 1. There was no deviation from the expected Hardy–Weinberg distribution in any group. The frequency of the Pro allele among the control groups was approximately 14%, which is in agreement with the reports regarding the frequency of the allele among Caucasian populations (2,3). We observed no differences in the allele or genotype frequencies between the unselected breast cancer group and the familial breast cancer group. We determined the odds ratios for genotype distribution between the case subjects with breast cancer and control subjects and found no differences in either population. The lack of association remained when the data for the case subjects with familial breast cancer were stratified into two groups by bilateral breast cancer status (data not shown). With our sample size, we had a more than 90% power to detect a 1.6-fold increased risk of breast cancer. Because our study was 4.5 times larger than the largest of the published studies (2,3), and because we used mainly familial case subjects, our study provides strong evidence that the β₃ integrin Leu33Pro polymorphism does not appreciably modify breast cancer risk.

QIANREN JIN
KARI HIMMINKI
EWA GRZYBOWSKA
RUDIGER KLAES
MAGNUS SODERBERG
ASTA FORSTI

REFERENCES


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Affiliations of authors: Department of Bio sciences at Novum, Karolinska Institute, Huddinge, Sweden (QJ, KH, AF); Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany.
larger series of 1.4 (95% confidence interval [CI] = 1.1 to 1.9) (1). When the 1660 primary cancers were separated into 27 different subtypes, relative risks in homozygotes versus noncarriers were 4.7 (95% CI = 1.6 to 14), 1.9 (95% CI = 1.0 to 3.7), and 3.5 (95% CI = 1.1 to 12) for ovarian cancer, breast cancer, and melanoma, respectively. Because P is equal to .06 for breast cancer, this finding could be due to chance alone, particularly because we did not correct for multiple comparisons.

In accordance with this possibility, Jin et al. did not find a statistically significant association between 33Pro/Pro homozygosity and breast cancer risk. However, like our study, their study has limitations. First, they included heterogeneous groups of breast cancer case and control subjects, with case subjects who were ascertained by four different methods from three different countries and who were not matched with control subjects for age and sex (2,3). Second, their study had limited statistical power to exclude an odds ratio of 1.9 for breast cancer in homozygotes versus noncarriers, equivalent to the hazard ratio of 1.9 observed in our study (1).

We used NCSS 2001 and PASS 2000 power calculation software (4) and a logistic regression power analysis to show that the power in the case-control study by Jin et al. to detect an odds ratio of 1.9 was 35% (Fig. 1). This suggests that an odds ratio of 1.9 could have been overlooked in their study. Jin et al. had “more than 90% power to detect a 1.6-fold increased risk of breast cancer” in heterozygotes and homozygotes combined versus noncarriers, and for the 33Pro allele versus the 33Leu allele; however, our study showed that risk in heterozygotes and noncarriers did not differ (1).

For comparison, with respect to total cancer and breast cancer risk using a log-rank survival power analysis (4), the power of our prospective study to detect a hazard ratio for breast cancer of 1.9 was 52% (Fig. 1). The case-control study by Ayala et al. (5) had only 7% power to detect an odds ratio of 1.9 for breast cancer in homozygotes versus noncarriers.

In conclusion, although our study suggests that 33Pro/Pro homozygosity of the β3 subunit of integrins is associated with an increased risk of all cancer (1), the finding that this risk is, in part, due to breast cancer is based on limited statistical power. Because the study by Jin et al. does not have more statistical power than our own study, we do not agree that their study “provides strong evidence that the β3 integrin Leu33Pro polymorphism does not appreciably modify breast cancer risk.” We rather prefer to conclude that this issue is unresolved, and that other large, preferably prospective population-based studies are needed.

STIG E. BOJENSEN
ANNE TYBJÆRGM-HANSEN
BØRGE G. NORDESTGAARD

REFERENCES


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Affiliations of authors: Department of Clinical Biochemistry, Herlev University Hospital, Herlev, Denmark (SEB, BGN); The Copenhagen City Heart Study, Bispebjerg University Hospital, Copenhagen, Denmark (ATH, BGN); Department of Clinical Biochemistry, Rigshospitalet, Copenhagen University Hospital, Copenhagen (ATH).

Correspondence to: Børge G. Nordestgaard, MD, DMSc, Department of Clinical Biochemistry, Herlev University Hospital, Herlev Ringvej 75, DK-2730 Herlev, Denmark (e-mail: brno@herlevhosp.kbhamt.dk).

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RESPONSE

We thank Jin et al. for their comments and for providing more data on the importance of integrin β3 Leu33Pro homozygosity for risk of cancer. In 9242 individuals, aged 20–95 years, sampled from the Danish general population and followed prospectively for 24 years, we observed a relative risk of all cancers in 33Pro/Pro homozygotes versus noncarriers of 1.4 (95% confidence interval [CI] = 1.1 to 1.9) (1). When the 1660 primary cancers were separated into 27 different subtypes, relative risks in homozygotes versus noncarriers were 4.7 (95% CI = 1.6 to 14), 1.9 (95% CI = 1.0 to 3.7), and 3.5 (95% CI = 1.1 to 12) for ovarian cancer, breast cancer, and melanoma, respectively. Because P is equal to .06 for breast cancer, this finding could be due to chance alone, particularly because we did not correct for multiple comparisons.

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