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Interaction of BRCA1 and AR genes in breast cancer risk

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Keywords

BRCA1 carriers, androgen receptor gene, polymorphism, interaction

Introduction

Germline mutations in BRCA1 confer Mendelian inheritance of breast cancer in carrier families, but there remain large differences in age-at-onset of the cancer, which might be explained by modifier genes. Genes in the steroid hormone pathways are strong candidates for being such modifiers. Among these, androgen receptor (AR) gene expression is known to affect breast tumor growth and progression. The AR gene has an expressed CAG repeat polymorphism which alters the length of a glutamine tract in the protein and is inversely related to the transactivation efficiency of the AR signalling system.

Aims

This study investigates whether the AR CAG trinucleotide repeat polymorphism affects breast cancer age at onset in genetically high-risk individuals.

Comments

This is one of the first reports suggesting that the interaction of different genes may alter breast cancer risk or penetrance. Although this study was carried out in women who were already at very high genetic risk of developing cancer, similar factors may also play a role in common or sporadic breast cancer susceptibility.

Methods

AR CAG repeats were genotyped in 304 female BRCA1 mutation carriers. At the time of the study 54% were already affected by breast cancer, while the rest were still unaffected. Of the BRCA1

mutations 65% were deletions and the remaining mutations were insertions, nonsense and mis-sense mutations. Analysis by class of mutation was not possible due to the large number of different BRCA1 mutations present in the women studied. Differences in breast cancer penetrance by repeat length were evaluated by Cox proportional hazards models.

Results

The distribution of CAG repeat lengths is similar in affected and cancer-free women and other published control populations. The median is 22 repeats (range = 8-32). There is no association between breast cancer penetrance and the mean CAG repeat length of a subject's two alleles. However, women who carried an allele encoding 28 repeats or more, had a significantly earlier age at onset of cancer. Those with more than 29 repeats, developed breast cancer on average 6.3 years earlier than women with only short alleles, and all of these women were already affected at the time of the study. There was no apparent difference in survival due to differences in repeat length.

Discussion

Longer AR CAG repeats, which are known to correlate with decreased AR transactivation efficiency, also appear to be associated with earlier onset of breast cancer in high-risk women. The authors hypothesise that this may be a result of increased breast cell proliferation due, in some way, to the presence of the long repeat.

Additional information

This study is primarily a hypothesis-generating exercise and needs confirmation.The authors are also aware of the problem of needing to treat the many different BRCA1 mutations as having the same effect on risk, particularly when there is a well documented genotype-phenotype correlation across the BRCA1 gene.

References

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