

Susceptibility genes in hereditary breast cancer

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Breast cancer is the most common malignancy among women worldwide. Most cases are sporadic, but an estimated 5-10% are due to hereditary predisposition. Two major susceptibility genes, *BRCA1* and *BRCA2*, have thus far been identified. Germline mutations in *BRCA1* and *BRCA2* explain the majority of families with both early-onset breast cancer and ovarian cancer, but a considerably lower fraction of families with site-specific breast cancer. This suggests the presence of other predisposing genes. The contribution of *BRCA1* and *BRCA2* to breast cancer incidence remains also unresolved, presumably because most studies have focused on high-risk families with multiple affected relatives, on highly recurrent founder mutations in isolated populations, or on patients diagnosed at early age. The aim of this study was to examine the frequency of the known Finnish *BRCA1* and *BRCA2* mutations in breast cancer patients unselected for family history and age at diagnosis, and to identify clinical risk factors that could be used in predicting the probability of finding a *BRCA1* or *BRCA2* mutation in a family. We also wanted to evaluate the role of *p53*, *CHEK1*, and a newly proposed tumor suppressor gene *CHEK2* in multicancer Li-Fraumeni syndrome of which breast carcinomas are the major component tumors, and to further assess the significance of the identified *CHEK2* variant 1100delC in familial breast cancer.

To estimate the contribution of *BRCA1* and *BRCA2* germline mutations to breast cancer incidence, we analyzed the frequency of the known Finnish mutations in a consecutive series of 1035 unselected breast cancer patients. Mutations were observed in 1.8% of the patients. The strongest predictors of a mutation were the positive family history of ovarian cancer and an early age at breast cancer diagnosis. In contrast, the family history of site-specific breast cancer was not strongly suggestive of a mutation. The low frequency of *BRCA1* and *BRCA2* mutations in unselected breast cancer patients illustrates that mutation screening is not warranted in the general breast cancer population, and confirms that strict criteria needs to be applied when considering genetic testing.

Identification of predisposing genes has enabled presymptomatic diagnostics of breast cancer susceptibility. The mutation screening of *BRCA1* and *BRCA2* is, however, very laborious and expensive, and it may be difficult to distinguish *BRCA* families from other familial breast cancer families or clusters of sporadic cases. In order to be able to better direct the mutation screening to potential mutation carrier families, we aimed at identifying the clinical risk factors that associate

with a positive mutation status. We analyzed 148 families with at least three affected family members, and found that the only independent predictors of a mutation were the number of ovarian cancer cases in a family and the age at diagnosis of the youngest breast cancer patient. We utilized this data to devise a probability model that can be used to assess the likelihood of carrying a predisposing *BRCA1* or *BRCA2* mutation in each family.

CHEK2 is a checkpoint kinase that has a central role in mediating cellular responses after DNA damage. It was first suggested as a susceptibility gene for Li-Fraumeni syndrome (LFS) when germline mutations were observed in families with LFS and Li-Fraumeni-like (LFL) syndrome. Our analysis of 44 families with LFS, LFL, or breast cancer families with phenotypical features of LFS revealed two mutation positive breast cancer patients with family history only suggestive of LFS. We further analyzed the frequency of the observed mutation, 1100delC, in a series 1035 newly diagnosed breast cancer patients, 507 breast cancer families, and 1885 healthy controls. The mutation frequency was slightly elevated among unselected breast cancer patients as compared to population controls, and a significantly higher frequency was observed among breast cancer families. The 1.4% frequency of the variant among healthy controls, the presence of healthy carriers in the families, and high frequency in families with only a few affected family members suggest that the variant acts as a low-penetrance breast cancer susceptibility allele. Despite the low penetrance, high frequency of the mutation in families with only a few affected relatives, the most common type of breast cancer families, suggests that the allele is likely to make a significant contribution to familial clustering of breast cancer. This data also indicates that *CHEK2* is unlikely a susceptibility gene for LFS, and still other unknown genes lie behind this cancer predisposition syndrome.

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