BRCA1 and BRCA2 mutations have no major role in predisposition to prostate cancer in Finland

T Ikonen, M P Matikainen, K Syrjäkoski, N Mononen, P A Koivisto, A Röckman, E H Seppälä, O-P Kallioniemi, T L J Tammela, J Schleutker


After lung cancer, prostate cancer is the second leading cause of death from cancer in men in developed countries. Despite the substantial impact on public health of prostate cancer, the cause of the disease has remained poorly understood, with ethnicity, diet, and family history considered as the major risk factors. A fraction of patients with prostate cancer belong to families with hereditary prostate cancer (HPC). Recently, several loci have been implicated in predisposing to prostate cancer by genetic linkage studies in cancer families, including HPC1 at 1q24-q25, HPC2 at 17p11, PCAP at 1q42.2-q43, HPCX at Xq27-q28, CAPB at 1p36, and HPC20 at 20q13. Only two genes have been identified from these chromosomal regions, ELAC2 (MIM 605367) from the HPC2, locus1 and RNASEL (MIM 180435) from the HPC1, locus2 but none has so far been definitively confirmed. In Finland, neither of these genes alone explains disease segregation in Finnish families with HPC but they seem to have some modifying role in predisposition to cancer.3

Breast cancer predisposing genes BRCA1 (MIM 113705) and BRCA2 (MIM 600185) are involved in repair of DNA damage and transcriptional regulation.3 Clustering of breast, ovarian, and prostate cancer has been reported,3–5 suggesting a role for BRCA1 and BRCA2 in predisposition to prostate cancer. Several epidemiological studies have discovered an increased risk of prostate cancer among BRCA1 and BRCA2 families.6–15 Consistent with this view, loss of heterozygosity at the BRCA1 and BRCA2 loci is commonly encountered in prostate cancer.16–20 Edwards et al interpreted BRCA2 as a high risk gene for early onset prostate cancer. In a recent study in BRCA1 and BRCA2 mutation positive and mutation negative Finnish breast cancer families, the only increased standardised incidence ratio (SIR), besides breast and ovarian cancer, was that for prostate cancer in BRCA2 families (SIR 4.9, 1.8–11).21

To assess the contribution of BRCA2 germline mutations to prostate cancer susceptibility in Finland, we screened seven Finnish BRCA2 founder mutations from 444 unselected, consecutive patients with prostate cancer and from 104 patients with HPC. We also studied the role of BRCA1 in causation of prostate cancer by screening five unique and six founder BRCA1 mutations from 46 Finnish patients with HPC. These BRCA1/2 founder mutations account for the vast majority of all Finnish BRCA1/2 mutations.22–24 All of the BRCA2 founder mutations indicated in the study by Eerola et al,24 showing increased risk of prostate cancer in BRCA2 families, were included in our analysis.

BRCA2 mutations were analysed from 444 unselected patients with prostate cancer. All of these patients, diagnosed between 1996 and 1999, came from the Tampere University Hospital, which serves as the local referral area for treatment of prostate cancer. The average age of diagnosis in these patients was 68.1 years (range 48–94 years). Also, we screened BRCA2 mutations from 104 confirmed families with HPC. Only one affected member from each family was analysed. Collection of Finnish families with HPC has been described elsewhere.27 The mean number of affected members in these families was 2.7 (range 2–6), and the mean age at diagnosis was 67.1 years (range 50–92). Confirmed breast cancer, ovarian cancer, or both cancer types were present in 20, three, and two families, respectively. Six women being first degree relatives to the HPC index, and diagnosed with breast cancer or ovarian cancer, were also analysed for BRCA2 mutations. From 46 Finnish families with HPC, 11 BRCA1 mutations were also screened. This subset of families represented mainly the most extreme HPC families and had a reduced number of smaller families compared to the whole collection of 104 Finnish HPC families. The mean number of affected members in these families was 3.1 (range 2–6), and the mean age at diagnosis was 66.1 years (range 50–82). The patients’ diagnoses and family histories were obtained from questionnaires and subsequently confirmed from the medical records, from the Finnish Cancer Registry, and from parish records. Written informed consent was obtained from all living patients and, in hereditary cases, also from family members. The research protocols were approved by the ethics committee of the Tampere University Hospital (93175, 95062, and 99228). The study of HPC was also approved by the Ministry of Social

Key points

• Familial clustering of breast cancer, ovarian cancer, and prostate cancer has often been reported, suggesting that the breast cancer predisposing genes, BRCA1 and BRCA2, may play a part in causing prostate cancer. Recent studies have implicated BRCA2 as a high risk gene for early onset prostate cancer. Epidemiological analysis in Finnish breast cancer families discovered an excess risk of prostate cancer in BRCA2 families.

• To assess the contribution of BRCA2 germline mutations to causation of prostate cancer in Finland, seven Finnish BRCA2 founder mutations from 444 unselected patients with prostate cancer and 104 hereditary cases of prostate cancer were screened.

• We also studied the role of BRCA1 in causation of prostate cancer by screening 11 BRCA1 mutations from 46 Finnish patients with HPC. We did not find any BRCA1 or BRCA2 mutations, indicating that the recurrent BRCA1 and BRCA2 mutations have no role in predisposition to prostate cancer in Finland.

Abbreviations: ASO, allele specific oligonucleotide hybridisation; BRCA1 and BRCA2, breast cancer predisposing genes; HPC, hereditary prostate cancer; PCR, polymerase chain reaction; SIR, standardised incidence ratio
Oligonucleotides specific to each mutation and its wild type were fixed onto the filter by exposure to UV light for two minutes. Vacuum was applied. 100 minutes) and vacuum was applied. Wells were washed with vacuum apparatus containing a prewetted Gene Screen Plus format. Each sample (50 l of 0.4 mol/l Tris HCl pH 7.5 for 10 minutes) was performed using 5 µl of DNA product from each PCR reaction, which was mixed with 55 µl of denaturation solution (0.4 mol/l NaOH, 25 mmol/l EDTA pH 8.0) in a 96 well plate for one hour. The ASO probe (150 000 cpm/ml) was then added and the mixture incubated at 54°C for three hours. Filters were air dried for five minutes and exposed to x ray film overnight.

We screened 444 unselected patients with prostate cancer and 104 patients with confirmed HPC for seven Finnish BRCA2 founder mutations and 46 patients with HPC for 11 BRCA1 mutations of which six are recurrent in Finland. In the analysis, no mutations were found, suggesting a limited role for BRCA1 and BRCA2 in causing prostate cancer in Finland. However, this conclusion should be treated cautiously as the samples were not screened for new mutations. The negative result was surprising as all the BRCA2 founder mutations indicated by Eerola et al29 in the study showing increased risk of prostate cancer in Finnish BRCA2 families were included in our mutation screening. Our result indicates that if BRCA2 has a role in predisposition to prostate cancer in Finland it is contributed to by other variations than known BRCA2 Finnish founder mutations. Interestingly, Matikainen et al26 showed no association between prostate and breast cancer in a population based cancer registry study in Finland. Besides prostate cancer, gastric cancer was the only cancer type with a significantly increased risk among the relatives of patients with prostate cancer.

The effect of individual risk genes for complex diseases could be identified more readily in isolated and genetically homogeneous populations, such as the Finnish,30–32 the Ashkenazi Jewish, and the Icelandic populations than in more heterogeneous ones. Among the Ashkenazi Jewish population, similar results for a minor role of BRCA1/BRCA2 in causation of prostate cancer have been reported.33–35 In Iceland, however, contradictory results have been presented about the role of BRCA2 founder mutation 999del5 in predisposition to prostate cancer.36–37 Our negative results stand in line with the recent studies in more mixed populations, such as the United Kingdom and the Mayo Clinic in Minnesota, which suggested a minor role for BRCA1 and BRCA2 in HPC.38–40 indicating that the result is not merely a population based phenomenon. Although some studies suggested that BRCA2 may have a role in predisposing to early onset prostate cancer, with or without a family history of cancer,41–44 we found no evidence for that in our study. A significant number of patients with early onset prostate cancer (age at diagnosis <60 years; 18.3% among patients with HPC, and 16.2% among unselected cases of prostate cancer) were analysed but no BRCA2 mutations were found. Further support for our negative result comes from the recently performed genome wide linkage study using Finnish families with HPC, which did not show any linkage to 17q or 13q (J Schleutker, unpublished data), the chromosomal sites of BRCA1 and BRCA2, respectively.45,46

In conclusion, our results indicate that the recurrent BRCA1 and BRCA2 mutations have a limited, if any, role in predisposition to prostate cancer in Finland.

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REFERENCES


Table 1 BRCA1 and BRCA2 mutations screened from patients with unselected PRCA or HPC

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<tr>
<th>Gene and mutation</th>
<th>Type of mutation</th>
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Online mutation report

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