BRCA1 mutations and prostate cancer in Poland

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Evidence to date that BRCA1 mutation carriers are at an increased risk of prostate cancer is mixed – both positive and negative studies have been published. To establish whether or not inherited variation in BRCA1 influences prostate cancer risk we genotyped 1793 men with prostate cancer in Poland and 4570 controls for three founder mutations (C61G, 4153delA and 5382insC). A BRCA1 mutation was present in 0.45% of the cases and 0.48% of the controls (odds ratio = 0.9; P = 1.0). The odds ratios varied substantially by mutation. The 5382insC mutation is the most common of the three founder mutations. It was detected only in one case (0.06%), whereas it was seen in 0.37% of controls (P = 0.06). In contrast, the 4153delA was more common in prostate cancer cases (0.22%) than in controls (0.04%) (odds ratio = 5.1; 95% confidence interval: 0.9–27.9; P = 0.1). The C61G mutation was also found in excess in cases (0.17%) compared with controls (0.07%) (odds ratio = 2.6; 95% confidence interval: 0.5–12.7; P = 0.5). Eight men with prostate cancer carried a mutation. Only one of these carried the 5382insC mutation, compared with 17 of 22 individuals with mutations in the control population (P = 0.003). These data suggest that the 5382insC mutation is unlikely to be pathogenic for prostate cancer in the Polish population. The presence of one of the other alleles was associated with an increased risk for prostate cancer (odds ratio = 3.6; 95% confidence interval: 1.1–11.3; P = 0.045); in particular for familial prostate cancer (odds ratio = 12; 95% confidence interval: 2.9–51; P = 0.0004). We consider that the risk of prostate cancer in BRCA1 carriers varies with the position of the mutation.

Keywords: BRCA1, hereditary, prostate cancer

Introduction

Identifying risk factors for prostate cancer is potentially important both for screening and prevention. One of the established risk factors for prostate cancer is a positive family history of prostate cancer. Continuing interest exists in identifying DNA variants, which are associated with an increased risk of prostate cancer. Several epidemiological and association studies suggest that there is an increased risk of prostate cancer in men who carry a BRCA1 mutation (Ford et al., 1994; Struweing et al., 1997; Warner et al., 1999; Giusti et al., 2003). A multicenter study of 699 BRCA1 families, however, did not support this association (Thompson and Easton, 2002a) and several negative studies have been published as well (Gayther et al., 2000; Sinclair et al., 2000; Ikonen et al., 2003; Zuhlke et al., 2004).

In Poland, there are three common founder alleles in BRCA1 (C61G, 4153delA and 5382insC), which, in total, account for 90% of all BRCA1 mutations (Gorski et al., 2004). To establish if inherited variation in BRCA1 influences prostate cancer risk in Poland, we genotyped 1793 cases of prostate cancer and 4570 controls. Poland is well suited for this study because of the high frequency of
three BRCA1 founder mutations and the relative genetic homogeneity of the Polish population.

**Methods**

We studied prostate cancer cases diagnosed between 1999 and 2005 in 13 centers situated throughout Poland. This study was initiated in Szczecin in 1999 and was extended to include Białystok and Olsztyn in 2002, and Opole in 2003. Nine other centers began recruiting participants in 2005 (Koszalin, Gdańsk, Lublin, Łódź, Warszawa, Wrocław, Poznań, Rzeszów, Sucha Beskidzka).

Altogether, 1793 unselected prostate cancer cases were collected. Study participants were asked to participate at the time of diagnosis or during an outpatient visit to an oncology clinic. Study participants were unselected for age or family history. The patient participation rate exceeded 75%. The mean age of diagnosis was 67.3 years (range 43–92 years). All patients who agreed to participate and signed informed consent, participated within 6 months from diagnosis. Family histories were obtained from each participant. Two hundred and twenty-nine patients (12.8%) had one or more first- or second-degree relative with prostate cancer (familial cases).

The control group consisted of a mix of 2000 newborn children from 10 hospitals throughout Poland (Szczecin, Białystok, Gorzów, Katowice, Wrocław, Poznan, Opole, Łódź and Rzeszów), 1570 adults selected at random form the rolls of three family doctors practicing in the Szczecin region and 1000 individuals from Szczecin who submitted blood for paternity testing. In total there were 4570 population controls.

Mutation analysis for the common Polish mutations was performed as described previously (Debniak et al., 2003; Gorski et al., 2005). The 4153delA and 5382insC mutations were detected using a multiplex-specific polymerase chain reaction (PCR) assay. The third mutation (C61G) generates a novel restriction enzyme site in exon 5. This mutation is detected after digesting amplified DNA with AvaII. To avoid false results in all reactions positive and negative controls were used. All mutations were confirmed by sequencing. Statistical analysis included the comparison of the proportions of the prevalence of the allele in cases and controls. Odds ratios (ORs) were generated from 2 × 2 tables and statistical significance was assessed using the Fisher exact test. The study was approved by the Ethics Committee of Pomeranian Medical University in Szczecin.

**Results**

A BRCA1 mutation was seen in eight of 1793 (0.45%) cases and in 22 of 4570 (0.48%) controls (OR = 0.9; \( P = 1.0 \)) (Table 1). The risks, however, were different for all mutations. The 5382insC is the most frequent mutation of the three Polish founder mutations. The 5382insC mutation was detected only in 0.06% of cases, compared with 0.37% of controls (OR = 0.15; \( P = 0.06 \)). Only one of eight (12.5%) men with prostate cancer and a BRCA1 mutation carried the 5382insC mutation, compared with 17 of 22 (77.3%) individuals with mutations in the control population (\( P = 0.003 \)). In contrast, the 4153delA was more common in cases than in controls (0.22% versus 0.04%; OR = 5.1; \( P = 0.1 \)). The C61G mutation was also more frequent in cases than in controls (0.17% versus 0.07%; OR = 2.6; \( P = 0.5 \)). A statistical test of homogeneity of the OR rejected the null hypothesis that the ORs associated with the three mutations were similar (\( P = 0.008 \)).

Two hundred and twenty-nine men were present with prostate cancer and a family history of prostate cancer. A BRCA1 mutation was found in three of 229 (1.3%) familial prostate cancer cases, compared with five of 4570 controls [OR = 12; 95% confidence interval (CI) 2.9–51; \( P = 0.0004 \)]. The 4153delA mutation was present in one familial case (OR = 10.0; \( P = 0.3 \)) and the C61G was responsible for two other prostate cancer families (OR = 13.4; \( P = 0.008 \)). The family with the 4153delA mutation contained two men with prostate cancer and the families with the C61G mutation contained four and five men with prostate cancer. We sought to establish if BRCA1 mutation segregated with prostate cancer in these families. We were able to obtain blood samples from additional relatives from families with the C61G (Fig. 1). In the first family the mutation was detected in the proband’s aunt (affected by bilateral breast cancer); this suggests that the deceased father (affected with prostate cancer) also carried the C61G allele. Thus, in this family, two of four men with prostate cancer were likely to be mutation carriers and we were unable to establish the genotype of the other two cases. In the second family, the C61G mutation was detected in the proband’s cousin, suggesting that father and uncle of the proband (both affected by prostate cancer) also carried the C61G mutation. In this family, three of the four men affected

| Table 1 Associations between BRCA1 mutations and prostate cancer risk |
|-----------------------|------------------|--------|---------|--------|
|                       | Unselected cases, \( N=1793 \) | Controls, \( N=4570 \) | OR      | 95% CI  |
| BRCA1 positive        | 8 (0.45%)        | 22 (0.48%) | 0.9     | 0.4–2.1 |
| C61G                  | 3 (0.17%)        | 3 (0.07%)  | 2.6     | 0.5–12.7 |
| 4153delA              | 4 (0.22%)        | 2 (0.04%)  | 5.1     | 0.9–27.9 |
| 5382insC              | 1 (0.06%)        | 17 (0.37%) | 0.15    | 0.02–1.1 |
| C61G or 4153delA      | 7 (0.39%)        | 6 (0.11%)  | 3.6     | 1.1–11.3 |

*OR, Odds ratio; CI, confidence interval. When the 5382insC is excluded as unlikely pathogenic for prostate cancer in the Polish population.
Five of seven men who carried BRCA1 C61G or 4153delA mutation were diagnosed with prostate cancer of Gleason grade 7 or higher, compared with 35% of noncarriers ($P = 0.056$). The mean age at diagnosis in the men who carried BRCA1 mutation was similar to that observed in noncarriers (66.6 versus 67.3 years).

**Discussion**

We observed increased risks for prostate cancer associated with the BRCA1 4153delA and the C61G mutations. One of these two mutations was seen in significant excess in men with unselected prostate cancer (OR = 3.6; $P = 0.05$), but this observation was based on only seven men with prostate cancer and a BRCA1 mutation. The two mutations were seen in excess in men with familial prostate cancer (OR = 12; $P = 0.0004$), but again, the numbers were small. The C61G mutation alone was associated with familial prostate cancer (OR = 13.4; $P = 0.008$). Furthermore, two of the three C61G carriers from a series of unselected cases had strong family histories of prostate cancer (which contained four and five men with prostate cancer). Segregation analysis suggested that five of the nine men with prostate cancer in these families carried the C61G variant and the genotypes of the other four cases could not be determined. In total, these data support the idea that the C61G mutation confers an increased risk of prostate cancer in Poland. A positive association between prostate cancer and the 4153delA variant was also seen, but the evidence is less compelling. Although this alteration was more common in unselected and in familial cases than in controls (OR 5.1 and 10, respectively), these differences were not statistically significant.
In contrast, the 5382insC mutation does not seem to confer an increased risk of prostate cancer in Poland. This mutation was under-represented in cases compared to controls (0.06 versus 0.37%). Only one (12.5%) of the cases with a BRCA1 mutation carried the 5382insC mutation, whereas this mutation constituted 77% of all BRCA1 mutations seen in the control group \( (P = 0.003) \). The 5382insC mutation is also founder allele in the Ashkenazi Jewish population. On the basis of two large epidemiologic studies of breast cancer patients, the risk of prostate cancer among carriers of Ashkenazi founder BRCA1 mutations (185delAG and 5382insC) appears to be twice that of noncarriers (Streuwing et al., 1997; Warner et al., 1999). When the data, however, from seven other studies of Ashkenazi Jews with unselected prostate cancer is combined (Lehrer et al., 1998; Nastiuk et al., 1999; Hubert et al., 1999; Vazina et al., 2000; Giusti et al., 2003; Hamel et al., 2003; Kirchhoff et al., 2004) the evidence is less strong. The 185delAG mutation was seen in 1.4% of 1654 cases versus 0.91% of 9371 population controls \( (OR = 1.5; P = 0.09) \), and the 5283insC mutation was seen in 0.32% of 1544 cases versus 0.27% of 8867 population controls \( (OR = 1.2; P = 0.92) \). Other studies, in non-Jewish populations, have found little or no evidence of an increased risk for prostate cancer in BRCA1 carriers (Gayther et al., 2000; Sinclair et al., 2000; Thompson and Easton, 2002a; Ikonen et al., 2003; Zuhlke et al., 2004).

The risk of prostate cancer, therefore, seems to be dependent on the type and/or location of the BRCA1 mutation. Genotype–phenotype correlations have also been suggested for breast and ovarian cancer risk (Rennert et al., 2005; Gronwald et al., 2006). It has been reported that the breast cancer risk associated with mutations in the central region of BRCA1 (nucleotides 2401–4190) is lower than for mutations located elsewhere (Thompson and Easton, 2002b). It has also been reported that ovarian cancer risk may be lower for mutations, which are localized in 3’ end of BRCA1 gene (Gayther et al., 1995; Holt et al., 1996; Neuhausen et al., 1996). It is also possible that mutations in the 3’ end of BRCA1 (such as the 5382insC) confer a lower risk of prostate cancer than mutations located elsewhere (such as the C61G and 4153delA), but further studies are needed.

BRCA1 acts in the same pathway as BRCA2, NBS1, CHEK2 and ATM proteins. Three of these (BRCA2, NBS1 and CHEK2) are also probable prostate cancer susceptibility genes. The relative risk of developing prostate cancer by age 56 years for men with a deleterious BRCA2 mutation was reported to be 23-fold (Edwards et al., 2003). Germline mutations in CHEK2 and NBS1 have also been reported to predispose to prostate cancer (Dong et al., 2003; Seppala et al., 2003; Cybulski et al., 2004).

We included men and women, of all ages, in the control group. The control group is used to estimate with accuracy the frequency of BRCA1 alleles in the underlying Polish population. The allele frequency should not be dependent on age or sex, but on ethnic group; the frequency of the BRCA1 alleles was similar in the newborn (0.45%) and adult (0.50%) population, in men (0.55%) and women (0.46%) adult controls. Therefore, there is no reason to believe that age or sex are important confounders of the observed association. For a rare disease-like prostate cancer (life-time risk of prostate cancer is 2% in the Polish men) the frequency of the allele (exposure) in the general population is a good estimate of the frequency of the allele in the unaffected population.

It is important that cases and controls have the same ethnic background. Poland is mainly populated by ethnic Poles, and within Poland, geographic mixture has been achieved, largely due to extensive migration after the Second World War. Our cases were recruited from 13 centers throughout Poland. Our control group was drawn both from the adult population of Szczecin and from newborns in 10 cities throughout Poland. No statistical difference exists in the BRCA1 allele frequencies in the newborns recruited from the Szczecin metropolitan region compared with other Polish cities. In addition, a large multicenter study of 122 BRCA1 positive families with hereditary breast and breast–ovarian cancer did not show greater than expected variation in the prevalence or spectrum of mutations in the different regions of Poland. We consider that a problem of population stratification and the composition of our control group are unlikely to explain the observed results. Furthermore, the heterogeneity of our results is due to variation in the allele frequency among cases, not among controls.

In summary, we investigated the role of three Polish BRCA1 founder mutations in the etiology of prostate cancer. It appears that the C61G or the 4153delA mutations are pathogenic for prostate cancer. In contrast, the 5382insC mutation does not seem to increase the risk of prostate cancer in the Polish population. It is important that other studies of genotype/phenotype correlations in BRCA1 mutation carriers in other populations be conducted in order to confirm these results. These observations have important implications for the screening and prevention of cancer in men with BRCA1 mutations.

References


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