Short Report

The contribution of founder mutations in BRCA1 to breast cancer in Belarus


Mutations in the BRCA1 gene increase susceptibility to both breast and ovarian cancer. In some countries, including several in Eastern Europe, founder mutations in the BRCA1 gene are responsible for a significant proportion of breast cancer cases. To estimate the hereditary proportion of breast cancer in Belarus, we sought the presence of any of three founder mutations in BRCA1 (4153delA, 5382insC and C61G) in 500 unselected cases of breast cancer. These mutations have previously been identified in breast/ovarian cancer families from Belarus and from other Slavic countries, including Poland and Russia. One of the three founder mutations in BRCA1 was present in 38 of 500 unselected cases of breast cancer (7.6%). A mutation was found in 12.6% of women diagnosed before age 50 and 5.6% of women diagnosed after age 50. A mutation was identified in 2 of 251 newborn controls (0.8%). The hereditary proportion of breast cancers in Belarus is among the highest of any countries studied to date.

Belarus is a former Soviet republic of 10 million inhabitants that is bordered by Poland, Russia and Ukraine. It is believed that the inhabitants of Belarus and these three bordering countries have common ethnic origins (Slavic). In previous studies of families from Poland with the hereditary breast–ovarian cancer syndrome, three recurrent mutations in BRCA1 have been identified (4153delA, 5382insC and C61G) (1, 2). Each of these three mutations is a founder mutation in the Polish population, where they account for approximately 80–90% of all detectable BRCA1 and BRCA2 gene mutations (1, 2). Genetic studies of familial breast cancer in Russia have yielded similar results with regards to the same founder mutations (3). There has been one small study from Belarus; in this report, we studied 19 families with the breast–ovarian syndrome, and 11 founder mutations were identified (58%). In this earlier report, individuals were selected for mutation analysis based on their family history; the contribution of these three mutations to the overall burden of breast cancer in Belarus is not known (4). The aim of this study was to estimate the frequency of BRCA1 founder mutations in an unselected series of breast cancer patients from Belarus.
Materials and methods

Cases

Breast cancer cases were identified from patients treated at the Grodno State Medical University in Grodno, between 2006 and 2008. Patients from the western region of Belarus were treated in the hospital. The patients were 500 consecutive, newly diagnosed cases of cancer, unselected for age, sex or family history. The mean age of diagnosis was 58.1 years (range 28–84 years). Each patient provided written informed consent to take part in study. The reference pathologist reviewed a representative slide from each cancer to confirm the diagnosis. A family history of breast and ovarian cancer was obtained through questionnaire, but mutation studies were not conducted on the relatives of the patients. The study was approved by the ethics committee of the Pomeranian Medical University.

Controls

In order to estimate the frequencies of these three mutations in the population of Belarus, we used 251 anonymous blood samples from newborn children (125 girls and 126 boys) collected in the Obstetrics Department of the Grodno State Medical University Hospital between 2008 and 2009.

Laboratory methods

DNA was extracted from peripheral blood lymphocytes for cases and from cord blood for controls using the Puregene kit (Gentra) according to the manufacturer’s instructions. Two BRCA1 mutations (4153delA and 5382insC) were studied using ASA-PCR and one mutation (C61G) was detected with RFLP-PCR, as described elsewhere (5).

Results

A BRCA1 mutation was detected in 38 of 500 (7.6%) unselected breast cancer cases. Two mutations were found among the 251 controls (0.8%). The distribution of mutations is presented in Table 1. The median age of diagnosis of the 38 breast cancer cases with a mutation was 51.2 years (range 32–77 years), compared with a median age of diagnosis of 58.7 years (range 28–84 years) for the 462 cases without mutation. A mutation was found in 11 of 40 women (27.5%) diagnosed with breast cancer at or under the age of 40 (Table 2), compared to 27 of 460 women (5.9%) diagnosed after the age of 40. The odds ratio for breast cancer (any age) associated with a BRCA1 mutation was 9.9 (95%CI: 2.4–42; Fisher exact test).

The family histories of the mutation-positive cases were reviewed. A family history was available for 36 of 38 mutation-positive patients. Among the 36 women with breast cancer and a BRCA1 mutation, 10 reported a first-degree relative with breast cancer and 4 cases reported a first-degree relative with ovarian cancer. In total, 14 of the 36 cases of mutation-positive breast cancer cases had a positive family history (38.9%). Only 1 of the 36 women reported a second-degree relative with breast or ovarian cancer.

Discussion

The current study provides an estimate of the total proportion of breast cancers in Belarus due to BRCA1 founder mutations, and the distribution of the three mutations in patients with breast cancer. We found that 7.6% of unselected cases of breast cancer in Belarus carried one of three founder mutations in the BRCA1 gene. We identified two mutations in our control group of 251 newborns (0.8%). Because of the small number of
mutation-positive controls, it was not possible to estimate the penetrance of these mutations, singly or as a whole. However, based on number of cases and controls studied, we estimate the relative risk to be at approximately 10-fold. The majority of mutation-positive patients did not have a significant family history of breast or ovarian cancer; 61% of the breast cancer patients had no first-degree relative with breast or ovarian cancer (it appears that reporting of cancers in second-degree relatives in Belarus is probably inaccurate – only 1 of 36 carriers reported an affected second-degree relative). Similarly, age of onset was a strong predictor of the presence of a mutation, but the majority of mutations (20 of 37) occurred among women over the age of 50.

This is the first study of BRCA1 mutations in unselected breast cancer patients from Belarus. In a study of early-onset Belorussian breast cancer patients from the region of Minsk, founder mutations in CHEK2 (I157T) and ATM (E1978X) were studied (6, 7). The CHEK2 missense mutation I157T was present in 5.7% of cases and was associated with an odds ratio of 4.5 (95% CI 1.6–13.2) (6). The ATM nonsense mutation, E1978X, was present in 0.5% of cases and was associated with an odds ratio of 5.4 (95% CI 0.7–42) (7).

A high frequency of BRCA1 or BRCA2 founder mutations has been reported in unselected breast cancer patients from countries which border Belarus, including Poland, Russia and Lithuania (3, 5, 8). It is interesting to note that Lithuania, which is not regarded as a Slavic country, has a similar distribution of founder mutations. However, the 4153delA mutation is the most common mutation reported in Lithuania and is relatively rare in Poland, Belarus and Russia. We estimated that almost 1% of the population of Belarus carries a founder mutation, but this estimate is based on a small sample of controls. In Poland, we estimated the mutation prevalence in the general population to be 0.4%. To date, the only countries in which the mutation prevalence is known to be equally as high include Israel (9, 10) and the Bahamas (unpublished data).

The 5382insC mutation alone was found in 5% of the breast cases in Belarus. 5382insC is the most common mutation in breast cancer families in Poland and Russia (3, 5). In Poland, this mutation accounts for 2.1% of early-onset breast cancer cases (<50 years) (11), a much lower prevalence than that observed in Belarus. 5382insC is also a founder mutation in other Slavic countries, such as the Czech Republic (12) Slovenia (13) and northern Greece (14) and is the second most common BRCA1 mutation in the Ashkenazi Jewish population (9, 10).

The majority of our cases were from the region of Grodno within Belarus, which is situated on the eastern border of Poland. For several centuries, this region was a part of the Polish–Lithuanian commonwealth. It is possible that the mutation distribution is different in other regions of the country. It is of interest that the reported breast cancer rate in Belarus is among the lowest in Europe, with an age-standardized incidence rate of 33 per 100,000 per year (which is considerably lower than that of the Mediterranean countries, including Italy and Spain).

There are several limitations to our study. The number of cases is small and the results are based on 38 mutation-positive breast cancer cases. We screened only for the three founder mutations and it is possible that other non-founder mutations were missed. We do not have an estimate of the proportion of founder mutations among all mutations in Belarus, but in Poland, approximately 90% of all BRCA1 mutations are one of these three founder mutations (2). In any case, if we have missed mutations, then our estimate of 7.6% is an underestimate of the total mutation prevalence. The control group was too small (n = 251) to provide a precise estimate of the prevalence of these mutations in the underlying population, and as a result, it was not possible to generate relative risks or lifetime risks of cancer associated with each of the three mutations. It would also be interesting to conduct a similar analysis on unselected cases of ovarian cancer from Belarus.

In populations with a small number of recurrent founder BRCA mutations, such as Belarus, it is reasonable to offer to test all breast cancer patients for the founder mutations. This can be performed cost-effectively and efficiently using a high throughput technique such as ours. A high proportion of carriers of BRCA1 mutations do not have a significant family history of cancer and it is therefore unreliable to rely on family history in order to decide upon whom to test. If the high prevalence of mutations in the general population is confirmed, it is possible to consider testing of the general population. However, it is also important that genetic counseling be in place and there are adequate referral networks and follow-up services so that women found to carry a mutation have opportunities available to them regarding how best to manage their risk.

Conflict of interest
None of the authors declare a conflict of interest.
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References