Short Report

Age-specific incidence rates for breast cancer in carriers of BRCA1 mutations from Norway


Incidence rates of breast cancer among women with a BRCA1 mutation vary according to their reproductive histories and country of residence. To measure cancer incidence, it is best to follow-up cohort of healthy women prospectively. We followed up a cohort of 675 women with a BRCA1 mutation who did not have breast or ovarian cancer before inclusion and who had a normal clinical examination and mammography at first visit. After a mean of 7.1 years, 98 incident cases of breast cancer were recorded in the cohort. Annual cancer incidence rates were calculated, and based on these, a penetrance curve was constructed. The average annual cancer risk for the Norwegian women from age 25 to 70 was 2.0%. Founder mutations had lower incidence rate (1.7%) than less frequent mutations (2.5%) (p = 0.03). The peak incidence (3.1% annual risk) was observed in women from age 50 to 59. The age-specific annual incidence rates and penetrance estimate were compared with published figures for women from North America and from Poland. The risk of breast cancer to age 70 was estimated to be 61% for women from Norway, compared with 55% for women from Poland and 69% for women from North America.

Conflict of interest
The authors declare no conflict of interest.

For women with a BRCA1 mutation, the risk of breast cancer to age 70 has been estimated to be as high as 84% (1–3). Recently, in a large cohort study, Lubinski et al. (4) compared the risks of breast cancer among BRCA1 mutation carriers from Poland and North America. They found both the annual risks and the lifetime risks to be substantially higher for North American women than for Polish women; the difference was particularly large for women aged 25–39. Among women in this age group, the annual incidence was 3.8% for North American women [95% confidence interval (CI) 2.4 – 4.9%] and was 1.4% (95% CI 0.8 – 2.1%) for Polish women (p < 0.01). The differences in risk could not be explained by differences in reproductive risk factors, by exogenous hormones or by screening practices. Norway is one of a few countries in which there is active surveillance and follow-up for a large cohort of women who are known to carry a BRCA1 mutation (5, 6). The four most frequent BRCA1 founder mutations in Norway (816delGT, 1135insA, 1675delA and 3347delAG) account for more than 50% of BRCA1 mutation carriers (7–9). We estimated the annual age-specific breast cancer risks in Norwegian women and compared these risks with published figures from other countries.

Subjects and methods
Study population and data collection
Eligible study subjects were identified from a cohort of women with a BRCA1 mutation. Subjects were drawn from the Outpatient Cancer Genetics Clinic at the Department of Medical Genetics of Oslo University Hospital, Oslo, Norway (formerly named the Norwegian Radium Hospital and The National Hospital). The cohort study was initiated in 1989 and patients
were followed up until December 2011. All study subjects received genetic counseling and provided written informed consent for study participation. A woman was eligible for the cohort study when molecular analysis established that she was a carrier of a deleterious mutation in BRCA1. Women with a diagnosis of breast or ovarian cancer before, or at the first clinic visit, were excluded. After study entry, each woman had an annual mammography and all mammogram reports were forwarded to the study center. Annual magnetic resonance imaging (MRI) (in addition to mammography) was introduced in 2001. All invasive breast cancers, including screen-detected and interval cancers were included. Patients were followed up from study entry (first visit) until either breast cancer diagnosis, last clinic visit, ovarian cancer, or prophylactic bilateral mastectomy.

Statistical analysis

Data was stored in the medical filing system CGEN which is an Oracle-based relational database (10) and further analyzed with TOAD © and Delphi2007©. Age-specific cancer rates (and their 95% CI) were calculated for four intervals (25–39; 40–49; 50–59 and 60+). For each interval, the number of observed cancers was divided by the total number of person-years at risk contributed by members of the cohort to that interval. Based on the calculated age-specific cancer rates, a smoothed penetrance curve was constructed. The curves were generated by applying the observed cancer rates annually to theoretical cohorts of healthy women from age 25 to 70. Data was analyzed first for all mutations, and then separately for founder and non-founder mutations. The data was compared with the published results of the Polish and North American cohorts. Two-by-two tables were assessed by Fisher’s exact p (two-sided) in StatExact5©.

**Results**

**Risk of breast cancer**

Six hundred seventy-five unaffected women with a BRCA1 mutation were followed up for a total of 4781 years for new cases of breast cancer. After a mean follow-up of 7.1 years, 98 new cases of breast cancer were diagnosed in the cohort, giving an average annual risk of breast cancer of 2.0% (95% CI 1.7–2.5%). The period of maximum risk was observed for women between ages 50 and 59 (3.1% annually) (Table 1, Fig. 1). Using the age-specific cancer rates for breast cancer, we estimated the penetrance to age 70 to be 60.8% (Fig. 2). Scoring carcinoma in situ (CIS) as affected, average annual incidence rate was 2.2% and 1.9%, 2.5%, 3.5% and 1.5% in the age groups 25–39, 40–49, 50–59 and 60+, respectively.

Four hundred twenty-four of the women had a founder mutation and 251 of the women had a less frequent mutation. The estimated annual incidence rate
This annual rate is intermediate of the rate for Poland (1.7%) and Canada or the United States (2.4%). In both Norway and Poland, the rate peaked in the age group 50–59 and declined thereafter. In contrast, in North America, the highest rate was observed for women aged 25–39. The high annual incidence in young ages showed in North America was, however, not found in Norway. By age 50, we estimate the cumulative incidence of breast cancer to be 35% in Poland, 40% in Norway and 58% in North America. By age 70, we estimate the cumulative incidence of breast cancer to be 55% in Poland, 61% in Norway and 69% in North America.

We observed that the incidence rate for the four Norwegian founder mutations to be lower than the rate for the non-founder mutations (1.7% vs 2.5%) and this difference was marginally significant (p = 0.03). Interestingly, the Norwegian and Polish women with founder mutations have similar penetrance estimates (all the mutations in the Polish study were founder mutations). The founder mutations in the two countries were non-overlapping. These may be chance findings or may be because of differences in penetrance associated with different mutations. For example, it is clear that the penetrance of the 6174delT mutation is less than that of other BRCA2 mutations (11). It is also possible that the founder mutations as a class are associated with a relatively low penetrance because high-penetrance mutations might be associated with lower reproductive fitness, and as a result, do not become fixed in a population. Against this hypothesis, however, is our observation that the greatest difference in risk was seen for woman aged 50–59, i.e. after the reproductive period.

In our earlier study, none of the known risk factors for hereditary breast cancer were found to be responsible for the risk differences between North America and Poland. Differences in uptake of prophylactic mastectomies in the different series may not explain the differences, as each woman included was censored at prophylactic mastectomy. The rates were not adjusted for the effects of prophylactic salpingo-oophorectomy, but very few women in any country had an oophorectomy before age 40 and therefore differences in oophorectomy rates should not explain the differences in breast cancer risk in young women. Approximately 70% of mutation carriers over age 40 will have undergone a prophylactic oophorectomy (12).

We compared our results with the Poland, Canada and the United States only, as we found no other corresponding series reported. It is hoped that other countries will develop comparable cohorts to allow for more extensive international comparisons. The results of such larger series will be informative for monitoring the impact of preventive options as well as for studying potential environmental factors.

**References**


