Contribution of the Defective \textit{BRCA1}, \textit{BRCA2} and \textit{CHEK2} Genes to the Familial Aggregation of Breast Cancer: a Simulation Study Based on the Swedish Family-Cancer Database

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Abstract

The known breast cancer susceptibility genes only account for 20% to 25% of the excess familial risk of the disease [1]. The present study assessed the contribution of \textit{BRCA1}/\textit{2} mutations and \textit{CHEK2} variants to the relative risk of breast cancer for women with affected mothers or sisters. The familial relative risks were estimated by Poisson regression based on the Swedish Family-Cancer Database. The Database was also used to calculate the distribution of life expectancy, the number of daughters per family and the age specific cumulative risk of female breast cancer. This information, together with the penetrances of \textit{BRCA1}, \textit{BRCA2} and \textit{CHEK2} from the literature, was used to simulate the familial clustering of breast cancer under different scenarios. The excess risk explained by \textit{BRCA1}, \textit{BRCA2} and \textit{CHEK2} decreased steeply with the age at diagnosis of the cancers. Around 40% of the familial risk for cases diagnosed before the age of 50 years was associated with \textit{BRCA1}/\textit{2} mutations. In contrast, roughly 85% of the familial risk of breast cancer diagnosed before the age of 69 years remained unexplained. The contribution of \textit{CHEK2} to familial breast cancer was small.

Introduction

Breast cancer aggregates in families, the disease being about twice as common in mothers and sisters of cases as it is in the general population [2]. The higher risks of breast cancer for monozygotic than for dizygotic twins of cases suggest that the familial aggregation of breast cancer is mainly due to genetic effects, rather than to shared environmental factors [3]. Germline mutations in \textit{BRCA1} and \textit{BRCA2} are frequently found in families containing multiple individuals affected by breast cancer [4]. However, \textit{BRCA1} and \textit{BRCA2} mutations are only identified in about 15-20% of multiple-case families affected by breast cancer alone [5]. \textit{CHEK2}*1100delC, a truncating variant that abrogates the kinase activity of \textit{CHEK2} [6], has been also found to contribute significantly to the familial clustering of breast cancer [7]. The variant has shown a frequency of 1.1% in healthy individuals and it has been associated with a breast cancer risk ratio of 1.7 in families without \textit{BRCA1}/\textit{2} mutations. By contrast, the variant conferred no increased cancer risk in carriers of \textit{BRCA1}/\textit{2} mutations. The low proportion of familial breast
cancers attributable to known genes, from 20% to 25% [1], reflects major gaps in our knowledge of the genetic background of familial breast cancer.

In addition to the age, sex and genotype specific penetrance, the family history of breast cancer is influenced by demographic factors such as family size and mortality [8]. The aim of the present study was to assess the contribution of the BRCA1/2 mutations and CHEK2 variants to the relative risk of breast cancer for women with affected mothers or sisters. We used the Swedish Family-Cancer (SFC) Database to estimate the distribution of life expectancy, the number of daughters per family and the age specific cumulative risk of female breast cancer in Sweden. The penetrances associated with BRCA1/2 and CHEK2 were taken from the literature. This information was used to simulate the familial clustering of breast cancer under different scenarios.

Patients and methods

The Swedish Family-Cancer Database was created in mid 1990s by linking census information, death notifications and the administrative family registry at Statistics Sweden to the Swedish Cancer Registry. The Database was updated at the end of 2002 to include more than 10.34 million individuals born in Sweden after 1931 as well as more than 810,000 invasive cancers diagnosed after 1958. The Swedish Cancer Registry is based on separate compulsory notifications of cases from clinicians/pathologists or cytologists and is considered to have completeness close to 100% [9]. The incidence of cancer in the Database is similar to the incidence in the Cancer Registry [10, 11]. Data on parity were complete, information on the socioeconomic index and the region was based on population censuses from 1960, 1970, 1980 and 1990. The age of the women in the first generation (mothers) was unrestricted, but the maximum age of women in the second generation (daughters) was 68 years. The present study included 20,742 cases of invasive breast cancer among 3.25 million daughters and 67,575 cases of invasive breast cancer among 2.23 million mothers.

Poisson regression

The relative risk of breast cancer for daughters (RR\textsubscript{mother}) and sisters (RR\textsubscript{sister}) of Swedish women affected by breast cancer was estimated by Poisson regression. The women in the SFC Database were followed from birth, immigration date or 1961, whichever came latest, until diagnosis of breast cancer, death, emigration date or 31 December 2000. The incidence of breast cancer was explained by the variables: age (5-year bands), period (10-year bands), parity (six groups from ‘any parturition’ to ‘more than five parturitions’), socioeconomic status (six groups), age at first birth (five groups, 5-year bands between ‘before age of 20’ and ‘after age of 35’) and residential area (four groups). The analyses were carried out for different restrictions of the age at diagnosis of breast cancer, which varied from 50 to 69 years. Computations were performed with the SAS software using the procedure GENMOD.

Simulation

The SFC Database was used to estimate the cumulative risks of female breast cancer before specific ages. The incidences in BRCA1/2 mutation carriers reported by Antoniou et al [12] were transformed into cumulative risks by the formula: cumulative risk (%) = 100 × (1 - exp [0.05 × Σxi]), where Σxi was the sum of the five-year incidences before the age under consideration. The cumulative risks before the age of 69 years were calculated by linear interpolation. The cumulative risks from the SFC Database, the cumulative risks for BRCA1/2 mutation carriers from the literature and the prevalences of BRCA1/2 mutations found by Loman et al among affected Swedish women [13] were used to estimate the frequency of BRCA1/2 mutations in Sweden. For example, the cumulative risk of female breast cancer before the age of 40 years of 0.31%, the cumulative risk of breast cancer by the age of 40 years in BRCA1 mutation carriers of 11.57% and the prevalence of BRCA1 mutation carriers in women affected by breast cancer before the age of 40 years of 7.26%, would result in a frequency of BRCA1 mutations in Sweden of 0.098%. The prevalence and penetrance of CHEK2 variants were based on the study of the CHEK2 Breast Cancer Consortium [7]. The distribution of the number of daughters per family and the distribution of life expectancy were calculated using the SFC Database.

The distribution of family size was used to generate one hundred million nuclear families. The genotypes of the parents were created by using the calculated prevalences of BRCA1/2 mutations and the frequency of CHEK2 variants from the literature. One allele was taken at random from each parent in order to simulate the genotypes of the daughters, under the assumption that women carrying two copies of one mutated genes were nonviable. The individual’s age at death was generated by using the distribution of life expectancy.
Contribution of the Defective BRCA1, BRCA2 and CHEK2 Genes to the Familial Aggregation of Breast Cancer: a Simulation Study Based on the Swedish Family-Cancer Database

from the SFC Database. The phenotype of each woman (affected or unaffected) was conditional on her genotype and her age at death. The familial aggregation of breast cancer was explored under different scenarios. The simplest scenario included only one gene; the most elaborated model considered simultaneously BRCA1, BRCA2 and CHEK2. The simulated disease phenotypes were used to calculate the relative risks for daughters and sisters of affected women.

The proportion of familial relative risk attributable to BRCA1, BRCA2 and CHEK2 was assessed by comparing the results from the Poisson regression with the data from the simulation. The formula: \( \frac{100 \cdot (\text{RR}_{\text{BRCA1,2,CHEK2}} - 1)}{\text{RR}_{\text{mother}} - 1} \) was used to calculate the percentage of maternal excess risk attributable to the three genes, where \( \text{RR}_{\text{BRCA1,2,CHEK2}} \) was the estimated relative risk for daughters of affected women when the simulation included the BRCA1, BRCA2 and CHEK2 genes, and \( \text{RR}_{\text{mother}} \) was the relative risk for daughters of affected women estimated by the Poisson regression based on the SFC Database. Similar calculations were carried out to assess the contribution of BRCA1, BRCA2 and CHEK2 to the relative risk for sisters of affected women.

**Results**

The cumulative risks of breast cancer used in the simulation are presented in Table 1. Based on the SFC Database, 0.003% of the women had breast cancer by the age of 25 years and 6.48% of them were affected before the age of 69 years. The penetrances of BRCA1/2 mutations estimated by Antoniou et al [12] are also shown in Table 1. These were 63% for women who carried BRCA1 mutations and 42% for BRCA2 mutations carriers by the age of 69 years. The distribution of the number of daughters in the SFC Database was as follows: 68% of the families had one daughter, 26% had two daughters, 5% had three daughters and 1% of the families had four or more daughters. The calculated distribution of life expectancy is shown in Table 1; 77.3% of the women reached the age of 69 years. The cumulative risks of breast cancer from the SFC Database and previous data from the literature resulted in an estimated prevalence of BRCA1 mutations in Sweden of 0.098%, whereas the estimated prevalence of BRCA2 mutations was 0.052%. Following the study of the CHEK2 Breast Cancer Consortium, 1.1% of the simulated individuals were CHEK2 mutation carriers [7]. These data were taken into account to generate the phenotype distribution of a large population, which was utilized to compute the familial risk of breast cancer under different scenarios.

The relative risks of breast cancer for women with affected mothers based on the SFC Database are shown in Fig. 1. The \( \text{RR}_{\text{mother}} \) was 2.11 (95%CI: 1.85-2.41) for breast cancers diagnosed before the age of 50 years, and it decreased to 1.56 (95%CI: 1.46-1.66)

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**Table 1. Cumulative risk of breast cancer in Sweden, penetrance of BRCA1 and BRCA2 mutations based on the literature and life expectancy of Swedish women**

| by age | all women | BRCA1 mutation carriers | BRCA2 mutation carriers | % alive |
|--------|-----------|-------------------------|-------------------------|---------|
| 25     | 0.003     | 0.10                    | 0.10                    | 99.1    |
| 30     | 0.02      | 0.65                    | 0.70                    | 98.8    |
| 35     | 0.09      | 4.26                    | 2.47                    | 98.4    |
| 40     | 0.31      | 11.57                   | 6.20                    | 97.7    |
| 45     | 0.85      | 23.59                   | 10.37                   | 96.5    |
| 50     | 1.74      | 38.31                   | 16.18                   | 94.3    |
| 55     | 2.95      | 45.96                   | 23.05                   | 90.5    |
| 60     | 4.26      | 53.51                   | 30.55                   | 85.9    |
| 65     | 5.59      | 59.38                   | 38.61                   | 80.5    |
| 69     | 6.48      | 62.73                   | 42.25                   | 77.3    |

*(12); see Patients and methods for details*
for cancers under the age of 65 years. The scenario ‘cancer occurs due to CHEK2 mutations’ led to estimates of the RRmother practically identical to unity. When only BRCA2 mutations were considered, the estimated RRmother decreased from 1.04 (breast cancers before the age of 50 years) to 1.01 (cancers before the age of 69 years). The scenario ‘cancer is attributable BRCA1 mutations’ showed the RRmother of 1.43 (cancers diagnosed before the age of 50 years) and the RRmother of 1.07 (cancers before the age of 69 years). The maternal risks under the scenario ‘BRCA1 and BRCA2 mutations’ were similar to those after the simultaneous consideration of BRCA1, BRCA2 and CHEK2 mutations; the RRmother was 1.47 for breast cancer before the age of 50 years and 1.09 for breast cancer before the age of 69 years.

The RR_sister from the Poisson regression decreased from 2.19 (95%CI: 1.98-2.43), for breast cancers diagnosed before the age of 50 years, to 1.97 (95%CI: 1.86-2.09), for cancers diagnosed before the age of 60 years (Fig. 2). The scenario ‘only BRCA2 mutations’ resulted in the RR_sister of 1.02 (breast cancers diagnosed before the age of 50 years) and the RR_sister of 1.01 (cancers before the age of 69 years). BRCA1 mutations showed the RR_sister of 1.41 for breast cancers diagnosed before the age of 50 years, and the RR_sister of 1.06 for cancers before the age of 69 years. The results for BRCA1 and BRCA2 mutations were similar to the results for BRCA1, BRCA2 and CHEK2; the RR_sister was 1.46 for breast cancer diagnosed before the age of 50 years and it was 1.08 for cancers before the age of 69 years.

The excess risk explained by BRCA1, BRCA2 and CHEK2 decreased with increasing ages at diagnosis and it was higher for daughters than for sisters of affected women. For example, 14% of the relative risk for daughters of women affected by the age of 69 years was related to BRCA1, BRCA2 and CHEK2 mutations, but the corresponding proportion for sisters of affected women was only around 8%.

**Discussion**

The most direct way to address the question concerning the existence of other breast cancer susceptibility genes is to ask whether the known genes can explain the observed familial aggregation of breast cancer [1]. Germline mutations in the p53,
PTEN, STK11/LKB1 and ATM genes are rare in familial breast cancer [14]. The present study assessed the contribution of BRCA1, BRCA2 and CHEK2 to the relative risk of breast cancer. The estimated familial risks for Swedish women relied entirely on registered data of complete coverage. Other important features of this study were the large number of cases analyzed, the standardization for parity and age of first birth, and the inclusion of information on family size and life expectancy in the simulation. The age of the individuals from the first generation in the SFC Database was unrestricted, but the maximum age of the individuals in the second generation (68 years) was a limitation on the present study.

Mutations in BRCA1 and BRCA2 show considerable ethnic and geographic variation [15]. Specific BRCA1 or BRCA2 mutations have become common as a result of founder effects in Ashkenazi Jewish populations [15-17], Poland [18], Iceland [19] and the European part of Russia [20]. The contribution of BRCA1 and BRCA2 to familial breast cancer in those populations is likely to be more important than in Sweden. The mutation prevalences assumed in this study, 0.098% for BRCA1 and 0.052% for BRCA2, were calculated using the SFC Database and the Swedish results of Lohman et al [13]. These prevalences are in agreement with the literature, e.g. Easton proposed frequencies between 0.05% and 0.20% for both BRCA1 and BRCA2 [1] and Domchek et al estimated a prevalence of BRCA1 mutations of 0.125% [21]. The prevalence and penetrance assumed for CHEK2 variants may be more inaccurate. This study concentrated on the 1100delC frameshift mutation and was based on the results from the CHEK2-Breast Cancer Consortium, but the same conclusions were reached by using German [22] or Finish [23] data (results not shown).

The estimated risks were higher for sisters than for daughters of affected women, and the difference between the two familial relative risks increased with the age at diagnosis of breast cancer. Several studies have suggested that this difference is mostly attributable to the unequal number of parturitions and the different calendar year of diagnosis of mothers and sisters [2, 24]. Since 97% of the analyzed daughters were parous, the contribution of parity to the difference of relative risks, if any, should be small. In contrast, the median calendar year of diagnosis of mothers was 1971 and that of sisters - 1996. The establishment of screening services in Sweden has resulted in the earlier detection
of breast cancers [25] and may also affected the detection of familial cancers.

In contrast to the familial relative risks estimated by the Poisson regression, the relative risks associated with BRCA1 and BRCA2 mutations in the simulation were slightly lower for sisters than for mothers of affected women, especially when the cancers were diagnosed before the age of 50 years. The separate analysis of each gene showed that BRCA1 mutations would explain 34% to 39% of the familial relative risk by the age of 50 years, the corresponding figure would be 2% to 4% for BRCA2 mutations, and less than 1% of the familial risk was attributable to CHEK2 variants.

In conclusion, the proportion of excess familial risk due to BRCA1/2 mutations cited in the literature of about 15% [26], varies considerably with the population and the age at diagnosis of the cancers. In Sweden roughly 40% of the familial relative risk for breast cancers diagnosed before the age of 50 years is likely to be associated with BRCA1/2 mutations, but around 85% of the excess risk remains unexplained when all cancers diagnosed before the age of 69 years are considered. The proportion of familial excess attributable to CHEK2 variants, or other low susceptibility genes, is small.

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Contribution of the Defective BRCA1, BRCA2 and CHEK2 Genes to the Familial Aggregation of Breast Cancer: a Simulation Study Based on the Swedish Family-Cancer Database

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