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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

Justo Lorenzo Bermejo[1], Alfonso García Pérez[2], Kari Hemminki[1,3]

[1]Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), Heidelberg, Germany; [2]Department of Statistics, Spanish Open University (UNED), Madrid, Spain; [3]Department of Biosciences at Novum, Karolinska Institute, Huddinge, Sweden

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Corresponding author: Justo Lorenzo Bermejo, Division of Molecular Genetic Epidemiology, German Cancer Research Centre (DKFZ), Im Neuenheimer Feld 580, D-69120, Heidelberg, Germany, e-mail: J.Lorenzo@dkfz.de

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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 *BRCA1/2* mutations and *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 *BRCA1, BRCA2* and *CHEK2* from the literature, was used to simulate the familial clustering of breast cancer under different scenarios. The excess risk explained by *BRCA1, BRCA2* and *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 *BRCA1/2* mutations. In contrast, roughly 85% of the familial risk of breast cancer diagnosed before the age of 69 years remained unexplained. The contribution of *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 *BRCA1* and *BRCA2* are frequently found in families containing multiple individuals affected by breast cancer [4]. However, *BRCA1* and *BRCA2* mutations are only identified in about 15-20% of multiple-case families affected by breast cancer alone [5]. *CHEK2**1100delC, a truncating variant that abrogates the kinase activity of *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 *BRCA1/2* mutations. By contrast, the variant conferred no increased cancer risk in carriers of *BRCA1/2* 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_{mother}) and sisters (RR_{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 (%) = $100 \bullet (1\text{-}\exp [0.05 \bullet \Sigma x_i])$, where Σx_i 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

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: $100 \bullet (RR_{BRCA1/2,CHEK2} - 1)/(RR_{mother} - 1)$ was used to calculate the percentage of maternal excess risk attributable to the three genes, where $RR_{BRCA1/2,CHEK2}$ was the estimated relative risk for daughters of affected women when the simulation included the *BRCA1, BRCA2* and *CHEK2* genes, and RR_{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 RR_{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)

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*

	Cumulative risk of breast cancer (%)			% alive
by age	all women	*BRCA1* mutation carriers	*BRCA2* mutation carriers	
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 RR_{mother} practically identical to unity. When only *BRCA2* mutations were considered, the estimated RR_{mother} 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 RR_{mother} of 1.43 (cancers diagnosed before the age of 50 years) and the RR_{mother} 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 RR_{mother} 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,*

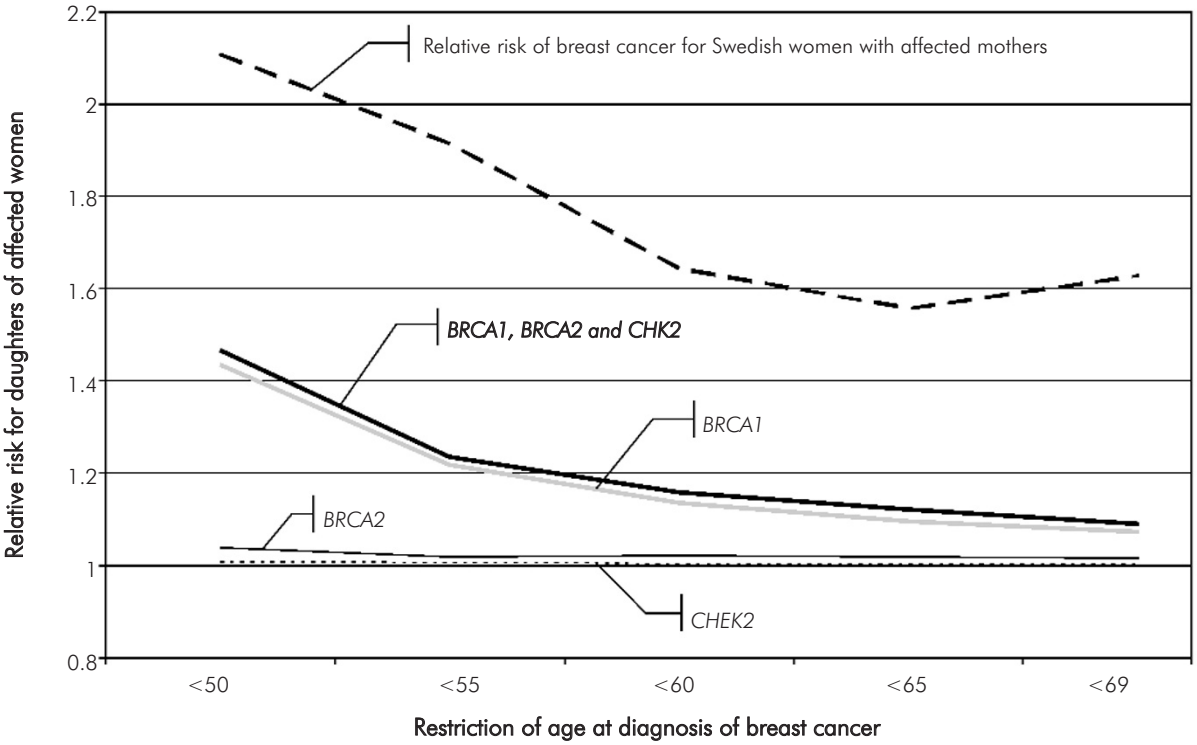

Fig. 1. Relative risk of breast cancer for daughters of women with breast cancer in Sweden and effect of *BRCA1*, *BRCA2* and *CHEK2* mutations on the relative risk of breast cancer for daughters of affected women. Both the cases and the probands are restricted to the indicated age

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

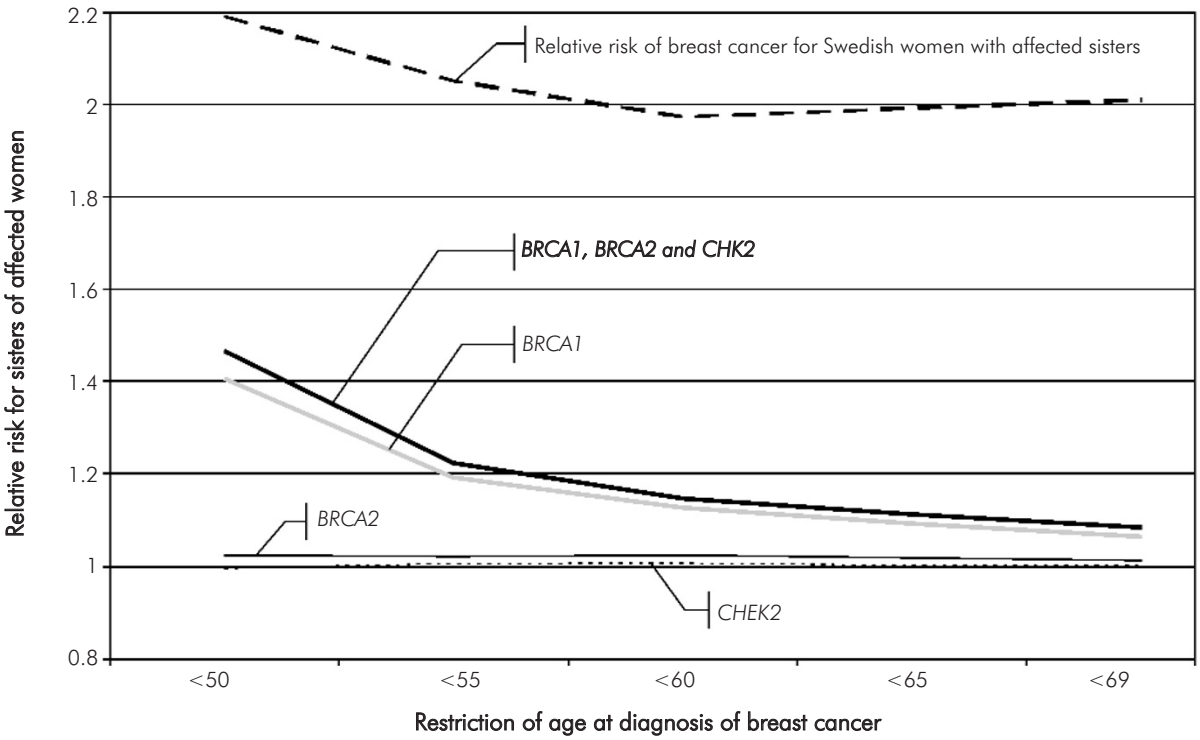

Fig. 2. Relative risk of breast cancer for sisters of women with breast cancer in Sweden and effect of *BRCA1, BRCA2* and *CHEK2* mutations on the relative risk of breast cancer for sisters of affected women. Both the cases and the probands are restricted to the indicated age

of breast cancers [25] and may have 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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