Chapter 8
Excess breast cancer risk in first degree relatives of CHEK2*1100delC positive familial breast cancer cases

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Abstract

Aim
The CHEK2*1100delC mutation confers a relative risk of 2 for breast cancer (BC) in the general population. This study aims to explore the excess cancer risk due to the CHEK2*1100delC mutation within a familial non-BRCA1/2 breast cancer setting.

Patients and Methods
Cancer incidences were compared between first degree relatives of 107 familial breast cancer patients positive for the CHEK2*1100delC mutation (CHEK2 positive families) and first degree relatives of 314 familial breast cancer patients without the CHEK2*1100delC mutation (CHEK2 negative families). All families were derived from the same pool of familial non-BRCA1/2 breast cancer families (n=2,554). Medical information of 2,188 first degree relatives of these families was analyzed for cancer risk. CHEK2*1100delC status of relatives was unknown.

Results
Increased breast cancer risk (Hazard ratio (HR) 2.0 (95% confidence interval (CI): 1.4-2.7), p<0.001) was observed in sisters of CHEK2*1100delC positive index cases compared to sisters of CHEK2*1100delC negative index cases. HR was 1.6 (95% CI: 1.0-2.4) for mothers of CHEK2 positive versus negative index cases (p=0.041). For second primary breast cancers HR was increased in CHEK2*1100delC positive index cases (HR 2.1, 95% CI: 1.3-3.3, p=0.003) and their sisters (HR 2.6, 95% CI: 1.1-6.1, p=0.025).

Conclusion
There is an excess breast cancer risk in first degree relatives of CHEK2*1100delC positive non-BRCA1/2 familial breast cancer patients compared to non-CHEK2*1100delC familial breast cancer relatives. Genotyping for the CHEK2*1100delC mutation in a familial breast cancer setting contributes to optimal clinical surveillance in countries in which this mutation is prevalent. Carriers and female relatives are eligible for stringent breast surveillance programs.
Introduction

The breast cancer (BC) risk of a female CHEK2*1100delC carrier is 2-fold increased in the general population. The prevalence of the mutation varies between populations and is highest in North-European populations. In the Netherlands, the prevalence in the general population is 1.1% and increases to 2.5% in unselected breast cancer cases up to 4.9% in familial breast cancer cases.

Lifetime breast cancer risk for unaffected women with a CHEK2*1100delC mutation and a first degree relative with breast cancer has been estimated to be approximately 25%. Fletcher et al. calculated a 37% lifetime risk for carrier daughters of carrier mothers affected with bilaterally breast cancer (n=71) compared to a 18% risk for non-carrier daughters. A CHEK2*1100delC meta-analysis (based upon n=4,546 familial breast cancer cases) concluded that carriers have an estimated cumulative breast cancer risk of 37% (95% confidence interval (CI): 26-56%) up to age 70 when from a familial breast cancer setting.

Recently Cybulski et al. estimated lifetime risk for breast cancer conferred by one of the three known truncated CHEK2 mutations (n=227, CHEK2*1100delC n= 49). The lifetime risk for breast cancer in CHEK2 mutation carriers increased from 20% for a woman with no affected relative up to 44% for a carrier woman with both a first- and second degree relative with breast cancer.

The reported increased risk of heterozygous carriers (or daughters) in a familial breast cancer setting was suggested to be caused by a polygenic model in which other genetic risk factors (common risk alleles) in these families contribute to the individual risk.

So far no consensus has been reached worldwide on the clinical usefulness of diagnostic testing of CHEK2. If a substantial difference in breast cancer risk due to CHEK2 could be confirmed within a familial non-BRCA1/2 setting, the clinical value of genetic testing for the CHEK2*1100delC mutation would become clearer as a more intensive surveillance would be recommendable.

Challenges, such as differences in mutation rates in different populations, incomplete penetrance of the mutation in families, and the relative low lifetime risks in carriers from the general population, fuel the controversy. Our present study was conducted in a country with a high prevalence of CHEK2*1100delC.

The aim of this study was to determine the excess breast cancer risk caused by the CHEK2*1100delC mutation within a familial breast cancer setting in order to assess the clinical usefulness of diagnostic testing for the CHEK2*1100delC mutation in a familial non-BRCA1/2 breast cancer setting in the Dutch population. We compared
cancer incidences in first degree relatives of familial CHEK2*1100delC mutation positive breast cancer patients with the cancer incidences in relatives of familial breast cancer patients without this mutation.

**Patients and Methods**

**Patient selection, study design and data collection**

Female patients with the earliest onset of breast cancer in the family (index case) of a consecutive series of 2,554 independent non-BRCA1/2 breast cancer families from three Dutch Clinical Genetics Centers were genotyped for the CHEK2*1100delC mutation in a previously published familial breast cancer study. The CHEK2*1100delC positive index cases and the CHEK2*1100delC negative index cases were selected from this cohort. All index cases were previously fully screened for BRCA1/2 mutations and found negative. All tested persons had given informed consent to screen for novel breast cancer susceptibility genes. Breast cancer families were predominantly from Caucasian Dutch descent based on last name and birth place ancestors (a GWA study with similar selection showed approximately 2.5% of cases might have a different ethnical background; Dr. Q. Waisfisz, VU University Medical Center).

Heterozygosity for the CHEK2*1100delC mutation was identified in 112/2554 (4.4%) index cases (female breast cancer patients), corresponding with the prevalence in a familial setting.

The remaining families were considered CHEK2*1100delC negative families on the basis of a negative test result of the tested index. For this study breast cancer patients with unconfirmed invasive breast cancer were subsequently excluded, including five CHEK2*1100delC heterozygous breast cancer cases.

Each of the remaining 107 heterozygous CHEK2*1100delC familial breast cancer patients (CHEK2 positive index cases) were matched on birth year (within 1 year) and center with three familial female breast cancer patients without the CHEK2*1100delC mutation from the same non-BRCA1/2 cohort (CHEK2 negative index cases) (Figure 1).

Four heterozygous cases were incompletely matched and therefore 314 CHEK2 negative families (instead of 321) were analyzed.

Both CHEK2*1100delC mutation positive families and CHEK2*1100delC negative families were assumed to share comparable burdens of genetic susceptibility of breast cancer and environmental risk factors, with the only difference CHEK2*1100delC positivity. No actual epidemiological risk factor data were available to test this assumption.
Detailed pedigree and medical information of all first degree relatives, available at the three clinical genetics services were entered in SPSS. All individual birth dates if known were entered, and if applicable, the cancer sites, number of cancers, date or age of cancer diagnosis, if hospital/pathology confirmed, for breast cancer also side and type, and date or age of death. Cancer analysis was performed for the parent and sibling generation of the 421 breast cancer patients (107 \( \text{CHEK2} \) positive and 314 \( \text{CHEK2} \) negative), consisting of a total of 2,188 individuals; 1,057 males and 1,131 females. Half-siblings and persons with unknown gender were excluded from analysis. \( \text{CHEK2}^{*1100\text{delC}} \) mutation status was not known for these relatives. By selection, first degree relatives of the \( \text{CHEK2}^{*1100\text{delC}} \) positive index cases had at least 50% probability of being carrier for the \( \text{CHEK2}^{*1100\text{delC}} \) mutation.

The number of relatives in the parent and sibling generation also matched nicely one to three accordingly to the index cases (\( \text{CHEK2} \) positive versus \( \text{CHEK2} \) negative) (Table 1). The total number of mothers analyzed was 420 (ratio mothers of \( \text{CHEK2} \) positive families : mothers of \( \text{CHEK2} \) negative families was 107 : 313). The total number of sisters analyzed was 711 (ratio sisters of \( \text{CHEK2} \) positive families : sisters of \( \text{CHEK2} \) negative families 176 : 535).

Figure 1 Pedigree example of \( \text{CHEK2} \) positive and negative breast cancer index cases and first degree relatives for analysis
Black circles indicate the non-BRCA1/2 index case with breast cancer, which is either \( \text{CHEK2} \) positive or \( \text{CHEK2} \) negative. \( \text{CHEK2} \) positive index cases were matched 1:3 with \( \text{CHEK2} \) negative index cases only by year of birth and within genetic center. Grey circles and squares represent the first degree relatives that were included for cancer analysis. \( n \) = number of relatives included in analysis depending on the size of families.
Fifty-nine sisters of a total of 711 were missing in the Kaplan-Meier estimates due to missing age (n=8 sisters of CHEK2 positive index cases, n=33 sisters of CHEK2 negative index cases) or death before age 20 (n=3 sisters of CHEK2 positive index cases and n=15 sisters of CHEK2 negative index cases).

Overall, birth cohorts of the CHEK2 positive families and the CHEK2 negative families were comparable. No differences in secular trends for breast cancer were seen between the CHEK2 positive families and CHEK2 negative families.

**Statistical Analysis**

All analyses were performed using SPSS version 15 (SPSS Inc, Chicago, IL). For each individual, follow-up was retrospectively observed from date of birth until date of death or last contact with family.

In this paper the main focus was the breast cancer risk comparison in first degree female relatives (mothers and sisters) of the CHEK2*1100delC positive index cases and CHEK2*1100delC negative index cases. This comparison was performed in two ways. The age-specific cumulative breast cancer incidence was estimated for the sisters and mothers of the CHEK2 positive cases, together and separately, as well as for the sisters and mothers of the CHEK2 negative cases with the Kaplan-Meier estimators. The estimated curves for the sisters of CHEK2 positive index cases and sisters of CHEK2 negative index cases were compared by the log-rank test. p-Values
below 0.05 were considered significant. The same was done for the mothers and the 
combined group of mothers and sisters. Furthermore, with Cox regression analysis 
the uncorrected hazard ratios (HR) (CHEK2 positive versus CHEK2 negative) with 
95% CI were computed for breast cancer in sisters and mothers, as well as for second 
primary breast cancer in index cases.

This latter analysis was also done for other cancer types and overall cancer (i.e. 
except breast cancer), for the parent and sibling generations separately. Male first 
degree relatives were included in these analyses.

Results

The analyzed cohort of first degree relatives of CHEK2 carriers (with at least 50% 
presumed carriers) and non-carrier familial breast cancer patients comprised of 2,188 
individuals.

Figure 2 shows the comparison of the cumulative incidence curves for breast 
cancer until age 75 in the mothers and sisters, combined and separately, of the 
CHEK2*1100delC positive index cases versus the mothers and sisters of the index 
cases without the CHEK2*1100delC mutation.

Cumulative breast cancer incidence at age 75 of first degree female relatives 
(mothers and sisters together) was estimated to be 53% (95% CI: 45 - 62%) in the 
CHEK2 positive families and 34% (95% CI: 29 - 38%) in the CHEK2 negative families. 
For the generations separately, these percentages were 37% (95% CI: 27 - 48%) 
for the mothers of CHEK2 positive index cases, and 27% (95% CI: 21 - 32%) for the 
mothers of CHEK2 negative index cases (p=0.04, log-rank test), and 85% (95% CI: 
71 - 98%) for the sisters of CHEK2 positive index cases and 39% (95% CI: 32 - 46%) 
for the sisters of CHEK2 negative index cases (p<0.001, log-rank test). It is important 
to note that hardly any data were available for the sisters above the age of 65 years as 
reflected by wide confidence intervals above this age. Although sisters and mothers 
of CHEK2 positive index cases had the same prior probability of at least 50% of being 
a CHEK2*1100delC carrier, the sisters showed a higher estimated cumulative breast 
cancer incidence curve than their mothers.

The hazard ratio for breast cancer in CHEK2 positive index cases versus CHEK2 
negative index cases was not significant different from one (HR 0.90, 95% CI: 0.72-
1.1, p=0.35), but it was for their relatives (Table 2). Mean age of first breast cancer 
diagnosis was 46 years for CHEK2 positive index cases and 43 years for CHEK2 
negative index cases.
Figure 2  Kaplan-Meier curves for breast cancer incidence for first degree relatives of CHEK2*1100delC mutation positive (red) and negative (green) breast cancer index cases.

Kaplan-Meier curves for breast cancer incidence in mothers and sisters of CHEK2*1100delC mutation positive index cases (red) and of CHEK2*1100delC negative index cases (green), both from non-BRCA1/2 breast cancer families. (A) Overall (mothers and sisters combined), (B) Mothers, and (C) Sisters of CHEK2 negative and CHEK2 positive index cases.

Number of first degree women at risk for breast cancer are displayed in the table below the x-axis.

Cumulative breast cancer risk (on y-axis) at age 75 was (A) 53% (95% CI: 44-62%) CHEK2 positive and 34% (29-38%) CHEK2 negative, (B) 37% (27%-48%) CHEK2 positive and 27% (21%-32%) CHEK2 negative, and (C) 85% (71%-98%) CHEK2 positive and 39% (32%- 46%) CHEK2 negative.
A significant difference in hazard ratio for breast cancer was seen for the mother and sister generations combined (HR 1.7, 95% CI: 1.3-2.2, \( p < 0.01 \)). Comparing mothers of the CHEK2 positive index cases with mothers of the CHEK2 negative index cases showed a (slightly) significant HR of 1.6 (95% CI: 1.0-2.4, \( p = 0.041 \)).

Furthermore a highly significant HR of 2.0 (95% CI: 1.4-2.7, \( p < 0.001 \)) was found for the sisters of the CHEK2 positive index cases versus the CHEK2 negative index cases (Table 2). Since the number of sisters at risk in the data-set is rapidly decreasing with age, the HR was also estimated when the sisters were censored at the ages 50, 60, 65 and 75. The HR remained significantly different from one; they were 1.5 (95% CI: 0.99-2.4, \( p = 0.053 \)), 1.8 (95% CI: 1.3-2.5, \( p = 0.001 \)), 1.7 (95% CI: 1.2-2.4, \( p = 0.003 \)), and 2.0 (95% CI: 1.4-2.7, \( p < 0.001 \)), respectively.

Cox regression analysis was performed for second primary breast cancer in the index cases’, mothers’ and sisters’ groups, comparing women of the CHEK2 positive families versus the CHEK2 negative families. A HR significantly higher than one was found in the index cases (HR 2.1, 95% CI: 1.3-3.3, \( p = 0.003 \)) and their sisters (HR 2.6, 95% CI: 1.1-6.1, \( p = 0.025 \))(Table 2). Second primary breast cancer in the CHEK2 positive index cases (n=27) were primarily contralateral breast cancers (n=25/27, 93%), which was significantly (\( p = 0.038 \), \( \chi^2 \)-test) different from CHEK2 negative index cases (n=32/46, 70%). Median time between first and second breast cancer in unilateral patients was 8.0 years for CHEK2 positive index cases and 6.7 years for CHEK2 negative index cases.

<table>
<thead>
<tr>
<th>Cancer (site)</th>
<th>Parents</th>
<th>Siblings</th>
<th>Index cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Breast (F)</td>
<td>1.6 (1.0-2.4)</td>
<td>0.041</td>
<td>2.0 (1.4-2.7)</td>
</tr>
<tr>
<td>Second primary breast (F)</td>
<td>1.4 (0.47-4.2)</td>
<td>0.53</td>
<td>2.6 (1.1-6.0)</td>
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<tr>
<td>Colorectal (F)</td>
<td>1.6 (0.23-8.6)</td>
<td>0.60</td>
<td>1.7 (0.32-8.6)</td>
</tr>
<tr>
<td>Colorectal (M)</td>
<td>1.8 (0.52-6.1)</td>
<td>0.35</td>
<td></td>
</tr>
<tr>
<td>Overall (F)</td>
<td>1.0 (0.58-1.7)</td>
<td>0.99</td>
<td>1.2 (0.63-2.4)</td>
</tr>
<tr>
<td>Overall (M)</td>
<td>1.3 (0.81-2.0)</td>
<td>0.30</td>
<td>0.31 (0.07-1.3)</td>
</tr>
</tbody>
</table>

Results from Cox regression analysis with Hazard ratio (HR) of CHEK2 positive versus CHEK2 negative index cases and their parents and siblings with 95% confidence interval (CI) and \( p \)-value for each cancer site. Primary breast cancer was censored at age 75 and calculated for women only. Secondary breast cancer, colorectal cancer and overall cancer were calculated for the whole time-line.
Cox regression analysis was also performed for each cancer site (32 different ones coded) separately. Male first degree relatives were included for analyzing all other cancer types (except breast cancer). A limitation herein was the limited number of certain cancer types for subgroup comparisons. Table 3 shows the total number of above described cancers in the CHEK2 positive and CHEK2 negative index cases and their female and male first degree relatives. The ratio of CHEK2 positive : CHEK2 negative index cases (and relatives) of 1 : 3 should be taken into account in the absolute number of cancers enlisted.

Of note, colorectal cancer incidence in CHEK2 positive families did not differ significantly when compared with CHEK2 negative families. Colorectal cancer was included in Table 2 and 3 because of the previously reported association with the CHEK2*1100delC mutation.14-16

| Table 3 | List and total numbers of described cancers |
|---------------|-----------------|-----------------|
| Cancer (site) | CHEK2 positive | CHEK2 negative |
|               | Parents | Siblings | Index cases | Parents | Siblings | Index cases |
| Breast cancer (trunc. 75) | F 34 | 56 | 106 | 71 | 105 | 313 |
| Second primary breast | F 5 | 11 | 27 | 10 | 11 | 47 |
| Colorectal | F 4 | 2 | 1 | 5 | 5 | 3 |
| | M 6 | 0 | 12 | 3 |
| Overall | F 21 | 14 | 12 | 67 | 52 | 22 |
| | M 36 | 7 | 106 | 42 |

Total numbers of (relevant) cancers in the CHEK2 positive and CHEK2 negative index cases and their female and male first degree relatives. The CHEK2 positive versus CHEK2 negative ratio of 1 : 3 in index cases (and relatives) should be taken into account in the absolute number of cancers enlisted. Two index cases (one CHEK2 positive and one CHEK2 negative) are not listed due to first breast cancer diagnosis above the age of 75.
Discussion

This study strongly confirms an increased breast cancer risk among first degree relatives of CHEK2*1100delC familial non-BRCA1/2 breast cancer patients.

This large familial retrospective cohort is unique to identify the excess breast cancer risk related to the CHEK2*1100delC mutation and its multiplicative effect in a familial non-BRCA1/2 setting. Population heterogeneity and ascertainment bias was minimized by matching CHEK2 positive families and CHEK2 negative families (1:3) randomly and solely by year of birth of the index within the same familial non-BRCA1/2 cohort and center.

It is important to note that the breast cancer risk estimates for the first degree relatives of the CHEK2 negative cohort confirm the previously published increased relative risk (RR) of 2 for first degree relatives of non-BRCA1/2 familial breast cancer cases.\textsuperscript{10,17} Therefore, the difference in breast cancer cumulative incidence curves in Figure 2 implicates a high breast cancer risk due to the CHEK2*1100delC mutation, on top of the currently known increased breast cancer risk in a familial breast cancer setting. Clearly, base-line breast cancer risk is increased in both CHEK2 positive and CHEK2 negative families due to their selection from a strongly enriched cohort of familial breast cancer.

Comparing our study to other prior published studies by Fletcher et al., Weischer et al. and Cybulski et al. is difficult due to their different approaches and different patient ascertainment.\textsuperscript{5-7} In the large meta-analysis of Weischer et al. the cumulative breast cancer risk at age 70 in CHEK2*1100delC carriers was estimated to be 37\% (95\% CI: 26-56\%). Our data suggest a higher breast cancer risk at age 70 years, as we found a cumulative breast cancer risk of 48\% (95\% CI: 40-57\%) in first degree relatives with a likelihood of at least 50\% of being CHEK2*1100delC carrier.

Johnson et al. reported a cumulative breast cancer risk of 59\% (95\% CI: 34-85) in first degree relatives of CHEK2*1100delC positive bilaterally affected breast cancer patients. Their results are well in line with our results.\textsuperscript{18}

In our opinion, the difference in breast cancer risk between the non-BRCA1/2 familial groups in our study warrants CHEK2*1100delC testing in a familial setting and adjusting breast surveillance accordingly. Corresponding with the current guidelines for high risk groups, first degree female relatives of CHEK2*1100delC positive breast cancer cases would be advised intensive breast surveillance in a specialist environment from age 35 onward.

The age-specific cumulative risks as mentioned in the results section should be looked at with cautiousness and are solely indicative for the difference in breast
cancer risk within a familial non-BRCA1/2 cohort. Cumulative risks for the sisters are high in both groups when compared to their mothers. This is likely due to known secular trends in breast cancer incidence, the limited numbers of sisters per family, resulting in wide confidence intervals, their presence in a strongly enriched cohort of familial breast cancer (recruitment influence) and the likelihood of more shared common genetic (oligogenic) risk alleles with their affected sisters (index cases) in comparison to shared genetic factors between mothers and daughters. By the way of recruitment the CHEK2*1100delC carrier ship in the sister and mother group of CHEK2 positive index cases is more likely to be higher than 50%. Due to the selected familial setting, sisters of CHEK2 positive index cases are more likely to be carriers and affected with breast cancer.

Ideally we would like to compare cancer risk in CHEK2*1100delC carrier siblings versus non-carrier siblings of the same CHEK2 positive families; however carrier information was not available. Therefore prospective assessment of the actual cumulative risk for sisters with known genotypes would be an attributable study in the future. This prospective assessment would also be valuable in fine-tuning optimal breast surveillance and determine if it would be reasonable to wait until age 40 to initiate breast surveillance and continue beyond the age of 60 in this specific group.

The current study supports previous studies in which there is a significantly higher risk for secondary breast cancer in CHEK2*1100delC positive index cases ($p=0.003$), as well as the sisters of the CHEK2 positive families.\textsuperscript{5,19-21} Therefore, longer duration of follow-up aiming at early detection of second primary breast tumors seems advisable in CHEK2*1100delC mutation positive breast cancer cases from non-BRCA1/2 settings.

Colorectal cancer incidence was analyzed and no difference between CHEK2 positive and CHEK2 negative index cases and relatives was found. This may be related to the fact that our cohort was selected by the occurrence of familial breast cancer, and not by familial colorectal cancer. The clinical phenotype conferred by CHEK2*1100delC might importantly be influenced by tumor type specific interacting, genetic or non-genetic risk factors.\textsuperscript{14-16,18,21,22} Above findings support that the CHEK2*1100delC allele seems to act in a multiplicative way with other (unknown) additional co-inherited risk alleles in a polygenic model.

Several other founder mutations in CHEK2 are known to confer an increased breast cancer risk. These however occur with a wide variable prevalence in different populations.\textsuperscript{4} It is likely that heterozygosity for other deleterious CHEK2 mutations in women might as well be associated with an excess breast cancer risk in a familial setting. Therefore testing for other deleterious mutations in CHEK2 should be considered in these populations.
Conclusions

A significantly increased breast cancer risk was observed in first degree relatives of familial non-BRCA1/2, CHEK2*1100delC positive breast cancer patients in comparison to first degree relatives of non-BRCA1/2, CHEK2*1100delC negative familial breast cancer patients. This effect was most markedly seen for sisters. In addition, we confirmed that CHEK2*1100delC positive familial breast cancer patients have a higher risk for secondary primary breast cancer risk in comparison to non-CHEK2*1100delC familial breast cancer patients. This study is unique in its ability to quantify the risk for affected and unaffected women with a CHEK2*1100delC positive family history of breast cancer as seen at our genetics departments. Diagnostic testing for the CHEK2*1100delC mutation is in our view important and sensible for both breast cancer patients and their first degree relatives, especially their sisters, in a familial non-BRCA1/2 breast cancer setting to adjust and optimize the necessary preventive strategies.

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References


References


