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ORIGINAL REPORT

# Age- and Tumor Subtype–Specific Breast Cancer Risk Estimates for *CHEK2**1100delC Carriers

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## ABSTRACT

### Purpose

*CHEK2**1100delC is a well-established breast cancer risk variant that is most prevalent in European populations; however, there are limited data on risk of breast cancer by age and tumor subtype, which limits its usefulness in breast cancer risk prediction. We aimed to generate tumor subtype- and age-specific risk estimates by using data from the Breast Cancer Association Consortium, including 44,777 patients with breast cancer and 42,997 controls from 33 studies genotyped for *CHEK2**1100delC.

### Patients and Methods

*CHEK2**1100delC genotyping was mostly done by a custom Taqman assay. Breast cancer odds ratios (ORs) for *CHEK2**1100delC carriers versus noncarriers were estimated by using logistic regression and adjusted for study (categorical) and age. Main analyses included patients with invasive breast cancer from population- and hospital-based studies.

### Results

Proportions of heterozygous *CHEK2**1100delC carriers in controls, in patients with breast cancer from population- and hospital-based studies, and in patients with breast cancer from familial- and clinical genetics center–based studies were 0.5%, 1.3%, and 3.0%, respectively. The estimated OR for invasive breast cancer was 2.26 (95% CI, 1.90 to 2.69; $P = 2.3 \times 10^{-20}$). The OR was higher for estrogen receptor (ER)–positive disease (2.55 [95% CI, 2.10 to 3.10; $P = 4.9 \times 10^{-21}$]) than it was for ER-negative disease (1.32 [95% CI, 0.93 to 1.88; $P = .12$]; $P$ interaction = $9.9 \times 10^{-4}$). The OR significantly declined with attained age for breast cancer overall ($P = .001$) and for ER-positive tumors ($P = .001$). Estimated cumulative risks for development of ER-positive and ER-negative tumors by age 80 in *CHEK2**1100delC carriers were 20% and 3%, respectively, compared with 9% and 2%, respectively, in the general population of the United Kingdom.

### Conclusion

These *CHEK2**1100delC breast cancer risk estimates provide a basis for incorporating *CHEK2**1100delC into breast cancer risk prediction models and into guidelines for intensified screening and follow-up.

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## INTRODUCTION

Susceptibility to breast cancer is known to be conferred by rare mutations in high-risk genes, notably *BRCA1* and *BRCA2*, by mutations in several moderate-risk genes, and by a large number of common genetic variants. Among moderate-risk genes, one of the best established is *CHEK2* (cell-cycle checkpoint kinase 2).[1] The protein encoded by *CHEK2* is a cell-cycle checkpoint regulator and putative tumor suppressor and it plays a critical role in the DNA damage repair pathway.[2-4] The 1100delC germline mutation in *CHEK2*, which is located at 22q12.1 (NM_007194.3(CHEK2):c.1100del: p.(Thr367Metfs*15)), is the most frequently found protein-truncating variant in populations of European descent.[1,5-7] Deletion of a single cytosine at position 1100 in exon 10 introduces a stop codon and results in a kinase-dead CHEK2 protein.

Although the evidence that *CHEK2**1100delC is associated with increased breast cancer risk is unequivocal, the magnitude of the risk is still uncertain, in part because the variant is relatively uncommon and in part because many studies have oversampled cases with a family history of disease, which leads to biased results. Published relative risk estimates for *CHEK2**1100delC carriers vary between 1.5 and 3.[7-10] The largest meta-analysis of breast cancer risk for *CHEK2**1100delC estimated an odds ratio (OR) of 2.7 (95% CI, 2.1 to 3.4) on the basis of unselected breast cancer cases and an almost two times higher OR on the basis of on familial breast cancer cases (OR, 4.8; 95% CI, 3.3 to 7.2).[7] Although *CHEK2**1100delC carriers tend to develop estrogen receptor (ER)–positive tumors, they have a worse breast-cancer specific survival compared with noncarriers.[8,11-14] *CHEK2**1100delC is also associated with a higher risk for contralateral breast cancer.[9,11,12,15] We previously showed that, especially in countries with a high prevalence of *CHEK2**1100delC, this variant occurred relatively frequently in population-based young patients with breast cancer[1,7,11]; however, no unbiased age-specific risk estimates have been reported so far for *CHEK2**1100delC carriers.

In the last few years, clinical genetic testing of women to estimate future risk of breast cancer has progressed beyond *BRCA1* and *BRCA2* testing to the use of gene panel testing, which involves the simultaneous testing of many known or suspected susceptibility genes, including *CHEK2*.[16] Such clinical testing, however, need to be underpinned by reliable risk estimates. Moreover, screening and prevention strategies are age dependent and driven by such factors as family planning,[17] and, hence, require reliable age-specific risks. In addition, knowledge about subtype-specific risks may be relevant for breast cancer prevention strategies.[18] The aim of the current study, therefore, was to provide age- and tumor subtype–specific risk estimates by using data from the Breast Cancer Association Consortium (BCAC), which includes > 85,000 women who have been genotyped for *CHEK2**1100delC.

## PATIENTS AND METHODS

### Patient and Clinical Data Collection

From 36 studies in the BCAC, 96,489 persons were genotyped for *CHEK2**1100delC. After exclusion of non-Europeans and males, 91,147 women from 35 studies remained, including 930 heterozygous and 15 homozygous *CHEK2**1100delC carriers (Appendix Table A1, online only; Appendix Fig A1, online only). Two studies in which fewer than three *CHEK2**1100delC carriers were detected were excluded from further risk analyses, which left 42,977 controls and 44,777 patients with breast cancer from 33 studies (Appendix Fig A1). Genotype data from five studies had been included in a previous meta-analysis,[1] but the majority of data were generated in a new genotyping experiment. Studies were classified according to sampling frame for the cases and controls into population- and hospital-based studies (unselected for family history) or clinical genetics–based and familial studies. Data on patient characteristics—age, family history, and *BRCA1/2* mutation status—and tumor characteristics had also been submitted by individual studies and were centrally harmonized and checked according to a standard data dictionary (Data Supplement). Details of the studies have been published previously (Appendix Table A1),[19,20] and a subset of the data has been previously used for an analysis of *CHEK2**1100delC and disease outcome.[12] All studies were approved by the relevant institutional review boards, and participants provided written informed consent or did not object to the secondary use of their tissue and data following country-specific regulations.[21]

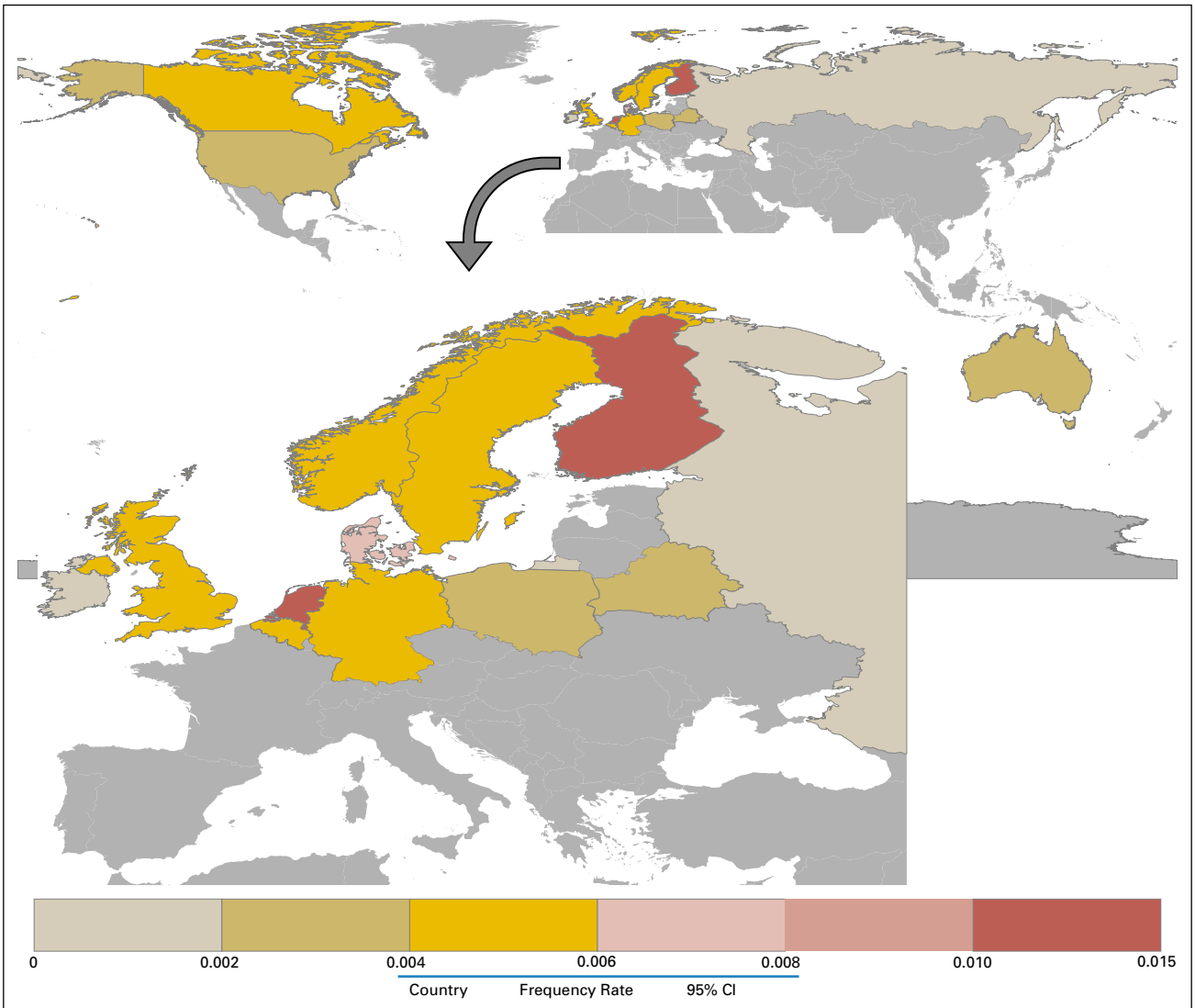
### *CHEK2**1100delC Genotyping

Details of *CHEK2**1100delC genotyping performed in the 35 European studies included are shown in the Data Supplement and in Appendix Table A1. Genotyping of the majority of samples (n = 84,314) was done by using a 5′exonuclease Taqman allelic discrimination assay developed by the Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital. Primers for the custom Taqman assay were specifically designed to be nonbinding to the pseudogenes on chromosomes 15 and 16, which are homologous to exons 10 to 14 of *CHEK2* on chromosome 22. An additional 6,833 samples were genotyped by using a different Taqman, iPlex, or oligohybridization assay.

### Statistical Analyses

Primary analyses were performed by using STATA (version SE11.2; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA), and calculation of cumulative risks, estimates of frequency by country, and graphics in Figures 1 and 2 were performed in R (version 3.2.1; R Foundation for Statitiscal Computing, Vienna, Austria). *P* values reported are two-sided, and *P* values < .05 were considered significant. Differences between proportions were tested by using the Pearson $\chi^2$ test, Fisher's exact test was used for comparisons that included cells with fewer than five observations, and differences and between mean ages were tested by using the *t* test. Breast cancer ORs for *CHEK2**1100delC carriers versus noncarriers were estimated by using logistic regression. All variables were included in analyses as categorical, as indicated in the tables, except for age (continuous in years). All analyses were adjusted for study (categorical). We compared a carrier model—homozygous and heterozygous *CHEK2**1100delC carriers were combined—and a log-additive model, including a linear term of the number of 1100delC alleles, with a saturated model by using likelihood ratio tests. Because no homozygous carriers were observed in controls, the saturated model did not converge, and we determined the likelihood by considering a range of possible values for the homozygote risk—between 5 and 20, in 1-point increments—by using an offset term.

The main analyses focused on the comparison of patients with breast cancer recruited through population- and hospital-based studies. We performed sensitivity analyses that excluded known *BRCA1/2* carriers, in situ and unknown behavior breast cancers, prevalent breast cancers (from patients whose blood was sampled > 1 year after diagnosis), and samples for which *CHEK2**1100delC genotypes were obtained with assays other than the custom Taqman. Subgroup case-control analyses were performed by age, family history, and tumor subtype of patients with breast cancer. To assess statistical significance of differences between subgroups, we compared these subgroups in a case-only analysis with *CHEK2* as the dependent variable. For the forest plot (Appendix Fig A2, online only), the summary estimate was derived from a fixed effect meta-analysis of the log(OR) estimates from individual studies by using the inverse variance method (fixedi in STATA).




| Country | Frequency Rate | 95% CI |
|---|---|---|
| Australia | 0.0030 | 0.0020 to 0.0044 |
| Belarus | 0.0030 | 0.0020 to 0.0047 |
| Belgium | 0.0047 | 0.0030 to 0.0075 |
| Canada | 0.0049 | 0.0025 to 0.0099 |
| Denmark | 0.0066 | 0.0053 to 0.0081 |
| Finland | 0.0124 | 0.0100 to 0.0152 |
| Germany | 0.0054 | 0.0044 to 0.0066 |
| Ireland | 0.0018 | 0.0009 to 0.0038 |
| The Netherlands | 0.0134 | 0.0110 to 0.0162 |
| Norway | 0.0044 | 0.0031 to 0.0063 |
| Poland | 0.0024 | 0.0017 to 0.0036 |
| Russia | 0.0020 | 0.0010 to 0.0038 |
| Sweden | 0.0046 | 0.0032 to 0.0065 |
| UK | 0.0054 | 0.0047 to 0.0062 |
| USA | 0.0037 | 0.0028 to 0.0050 |

**Fig 1.** *CHEK2**1100delC frequency rates per country in legend are shown with 95% confidence intervals and were calculated using a modification of the empirical Bayes approach proposed by Clayton and Kaldor, as described in the methods. Analysis included all controls (44,276 non-carriers and 235 *CHEK2**1100delC carriers) and all population- and hospital-based breast cancer patients (38,783 non-carriers and 502 *CHEK2**1100delC carriers). When the breast cancer patients from the clinical genetics and familial studies were also included, the rates slightly changed, but not the color of the countries in the map (results not shown).

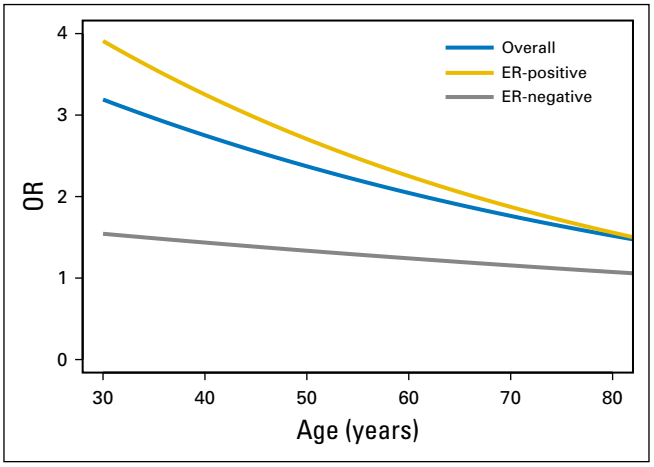



**Fig 2.** Breast cancer relative risk curves for *CHEK2**1100delC carriers by age for invasive breast cancer: overall, estrogen receptor (ER)–positive, and ER-negative disease. OR, odds ratio.

In addition, we modeled the *CHEK2**1100delC breast cancer risk estimates by age by using the more stable interaction estimates for age and *CHEK2**1100delC from the case-only analysis (Data Supplement). Cumulative risks were calculated on the basis of estimated relative breast cancer risks for *CHEK2**1100delC carriers by using United Kingdom breast cancer incidences from 1992 to 2010 and the ratio of ER-positive and ER-negative breast tumors from the BCAC database (Data Supplement). Carrier frequency estimates by country were derived by using a modification of the empirical Bayes approach proposed by Clayton and Kaldor[22] for mapping disease incidence rates (Data Supplement).

## RESULTS

Analyses included 42,977 controls and 44,777 patients with breast cancer from 33 BCAC studies, of which 42,627 patients were recorded as having invasive tumors as well as 1,734 with in situ tumors (Appendix Fig A1). We included in the analysis only European women who had been genotyped for *CHEK2**1100delC because this mutation is rare in other ethnicities[23]; we detected only three carriers of the mutation in non-Europeans. Summaries of patient and tumor characteristics by study are shown in Appendix Tables A2 to A6 (online only), and characteristics of *CHEK2**1100delC carriers and noncarriers are summarized in Appendix Table A7 (online only).

### *CHEK2**1100delC Heterozygous and Homozygous Carriers

Proportions of *CHEK2**1100delC carriers in controls, patients with breast cancer from population- or hospital-based studies, and patients from familial or clinical genetics center–based studies were 0.5%, 1.3%, and 3.0% respectively (Appendix Table A7). Homozygous *CHEK2**1100delC carriers were rare (n = 15; 0.02%) and occurred only in cases. Ten of 15 homozygous carriers were identified in studies from the Netherlands (Appendix Table A1, online only). The frequency of *CHEK2**1100delC in women of European descent displayed wide variation by country, from > 1.2% in the Netherlands and Finland to < 0.3% in Eastern Europe (Fig 1).

Comparison of a carrier model in which both homozygous and heterozygous *CHEK2**1100delC were defined as carriers, with a saturated model (see Patients and Methods) indicated a higher risk estimate for homozygous than heterozygous carriers ($P = .017$ on the basis of population- and hospital-based studies; Appendix Table A8, online only). A log-additive model could not be rejected ($P = .10$ compared with the saturated model); however, the estimated ORs for heterozygotes were similar in the three models. Because homozygous carriers were rare and it would not be possible to obtain reliable estimates for age- and tumor subtype–specific analyses, we excluded the 15 homozygous carriers so that subsequent risk estimates refer to heterozygous carriers.

### *Tumor Characteristics of CHEK2*1100delC Carriers*

*CHEK2**1100delC patients with breast cancer from population- and hospital-based studies were younger and more often developed ER-positive and progesterone receptor (PR)–positive tumors, although carriers and non-carriers were similar with respect to morphology, grade, and human epithelial growth factor receptor 2 (HER2) status (Table 1); results for the clinical genetic and familial studies were similar. *CHEK2**1100delC patients with breast cancer from population- and hospital-based studies more often developed in situ tumors. We suspected that the association between *CHEK2**1100delC and in situ tumors could be a result of differential recruitment related to family history of breast cancer and screening. In support of this hypothesis, there was evidence of an association between *CHEK2**1100delC and first-degree family history of breast cancer for women with in situ cancers ($P = .05$), but not for invasive tumors ($P = .85$; using logistic regression analysis adjusted for study). No such associations were observed for patients with breast cancer in clinical genetic and familial studies. In controls, there was no association between *CHEK2**1100delC carriership and family history (n = 41,529; OR, 1.00; 95% CI, 1.00 to 1.00; $P = .77$) or age (n = 38,358; OR, 1.00; 95% CI, 0.99 to 1.01; $P = .99$).

### *Overall Breast Cancer Risk Estimates and Sensitivity Analyses*

Breast cancer risk estimates for *CHEK2**1100delC carriers, including various sensitivity analyses, are shown in Table 2. ORs for breast cancer of any behavior (in situ or invasive) and invasive breast cancer were 2.32 (95%CI, 1.95 to 2.75; $P = 5.5 \times 10^{-22}$) and 2.26 (95% CI, 1.90 to 2.69; $P = 2.3 \times 10^{-20}$), respectively, using population- and hospital-based studies. There was no evidence of heterogeneity in ORs among the studies (Appendix Fig A2). The OR based on all breast cancers, including those from familial and clinical genetics center-based studies, was higher (OR = 2.44; 95% CI, 2.08 to 2.87; $P = 6.3 \times 10^{-28}$), consistent with overrepresentation of cases with a family history of disease. The OR based on incident breast cancers only was lower (OR = 2.11; 95% CI, 1.69 to 2.65; $P = 6.3 \times 10^{-11}$); in case-only analysis this was significantly different from the OR for prevalent tumors ($P = 1.5 \times 10^{-4}$).

**Table 1.** Associations of Patient and Tumor Characteristics With *CHEK2**1100delC Carriership in Patients With Breast Cancer

| Characteristic | Patients From Population- and Hospital-Based Studies | | | | Patients From Familial or Clinical Genetics Center–Based Studies | | | |
|---|---|---|---|---|---|---|---|---|
| | Total, No. | OR | 95% CI | *P* | Total, No. | OR | 95% CI | *P* |
| Family history* | 37,913 | 1.00 | 1.00 to 1.00 | .44 | 6,849 | 1 | 1.00 to 1.00 | .43 |
| Age, years | 37,566 | 0.99 | 0.98 to 0.99 | $1.0 \times 10^{-3}$ | 6,834 | 0.99 | 0.98 to 1.01 | .37 |
| Tumor behavior | 37,571 | 1.65 | 1.11 to 2.44 | .01 | 6,775 | 0.68 | 0.35 to 1.32 | .25 |
| Morphology | 30,729 | | | | 4,831 | | | |
| Ductal | | Ref | | | | Ref | | |
| Lobular | | 0.91 | 0.68 to 1.22 | .52 | | 0.45 | 0.23 to 0.90 | .02 |
| Medullary | | 0.69 | 0.25 to 1.88 | .46 | | Omitted | | |
| Mixed | | 1.17 | 0.69 to 2.00 | .56 | | 1.37 | 0.59 to 3.21 | .47 |
| Mucinous | | 1.02 | 0.42 to 2.48 | .97 | | Omitted | | |
| Other | | 0.79 | 0.42 to 1.51 | .48 | | 0.69 | 0.39 to 1.22 | .20 |
| Papillary | | 0.83 | 0.11 to 6.02 | .85 | | Omitted | | |
| Tubular | | 0.23 | 0.03 to 1.63 | .14 | | 1.14 | 0.45 to 2.87 | .79 |
| Grade | 25,808 | | | | 3,070 | | | |
| I | | Ref | | | | Ref | | |
| II | | 1.32 | 0.99 to 1.77 | .06 | | 1.35 | 0.77 to 2.36 | .30 |
| III | | 1.13 | 0.82 to 1.55 | .46 | | 1.03 | 0.57 to 1.87 | .91 |
| ER status | 26,103 | | | | 2,532 | | | |
| Negative | | Ref | | | | Ref | | |
| Positive | | 1.92 | 1.42 to 2.61 | $2.7 \times 10^{-5}$ | | 2.36 | 1.24 to 4.48 | .01 |
| PR status | 21,687 | | | | 2,372 | | | |
| Negative | | Ref | | | | Ref | | |
| Positive | | 1.37 | 1.06 to 1.77 | .02 | | 1.58 | 0.95 to 2.63 | .08 |
| HER2 status | 12,687 | | | | 655 | | | |
| Negative | | Ref | | | | Ref | | |
| Positive | | 1.03 | 0.69 to 1.52 | .90 | | 0.69 | 0.24 to 2.01 | .50 |

NOTE. Data given are those included in analyses for each model (Appendix Tables A2 to A5). Homozygous carriers were excluded. Analyses were performed by logistic regression with *CHEK2* as the dependent variable and adjusted for study. For *BRCA1/2* mutation status there was insufficient data for the models to run.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; Ref, reference category.
*Family history: yes, at least one first-degree relative with breast cancer; or no, none.

### *Subgroup Breast Cancer Risk Estimates*

Table 3 gives breast cancer risk estimates for *CHEK2**1100delC carriers by patient subgroup and by tumor subtype. The OR was higher for women without a first-degree relative with breast cancer compared with those with a family history, but not significantly so ($P = .31$). Moreover, this analysis included two studies with outlier results that were caused by the study definitions that were used (Appendix Table A6). Excluding these two studies, ORs for women without and with a first-degree relative with breast cancer were similar: 2.33 (95% CI, 1.76 to 3.08) and 2.26 (95% CI, 1.84 to 2.77), respectively. *CHEK2**1100delC carriers had a significantly higher risk compared with noncarriers of developing an

**Table 2.** Breast Cancer Relative Risk Estimates for *CHEK2**1100delC Carriers Versus Noncarriers; Tumor Behavior Subgroup and Sensitivity Analyses

| Subgroup | Case/Control, No. | OR | 95% CI | *P* |
|---|---|---|---|---|
| All patients with breast cancer | 41,744/39,956 | 2.44 | 2.08 to 2.87 | $6.3 \times 10^{-28}$ |
| Population- and hospital-based patients with breast cancer | 36,029/39,464 | 2.32 | 1.95 to 2.75 | $5.5 \times 10^{-22}$ |
| All invasive tumors | 39,798/39,956 | 2.40 | 2.04 to 2.82 | $2.0 \times 10^{-26}$ |
| Population- and hospital-based patients with breast cancer, invasive tumors | 34,525/36,464 | 2.26 | 1.90 to 2.69 | $2.3 \times 10^{-20}$ |
| Population- and hospital-based patients with breast cancer, invasive tumors, incident breast cancers only* | 16,702/28,772 | 2.11 | 1.69 to 2.65 | $6.3 \times 10^{-11}$ |
| All in situ tumors† | 1,577/34,818 | 3.53 | 2.38 to 5.23 | $3.9 \times 10^{-10}$ |
| Population- and hospital-based patients with breast cancer, in situ tumors† | 1,208/33,379 | 3.36 | 2.15 to 5.25 | $1.0 \times 10^{-7}$ |
| All patients with breast cancer, custom Taqman | 39,440/36,596 | 2.50 | 2.11 to 2.95 | $1.2 \times 10^{-26}$ |
| Population- and hospital-based patients with breast cancer, custom Taqman | 34,485/34,466 | 2.33 | 1.96 to 2.79 | $5.5 \times 10^{-21}$ |
| All patients with breast cancer, non-*BRCA1/2* carriers only | 41,365/39,954 | 2.46 | 2.09 to 2.88 | $2.7 \times 10^{-28}$ |
| Population- and hospital-based patients with breast cancer, non-*BRCA1/2* carriers only | 35,872/36,462 | 2.33 | 1.96 to 2.76 | $4.0 \times 10^{-22}$ |

NOTE. All models were adjusted for age and study.
Abbreviation: OR, odds ratio.
*Incident breast cancer was defined as study entry before and up to 1 year after breast cancer diagnosis.
†Likely biased estimate (see text).

**Table 3.** Breast Cancer Relative Risk Estimates for *CHEK2**1100delC Carriers Versus Noncarriers by Subgroup in Population- and Hospital-Based Patients With Breast Cancer With Invasive Tumors

| Subgroup | Total in Case-Control Analysis, No. | OR | 95% CI | *P* Case-Control Analysis | *P* Case-Only Analysis |
|---|---|---|---|---|---|
| Family history | | | | | |
| Negative | 31,971 | 2.04 | 1.51 to 2.74 | $2.6 \times 10^{-6}$ | .31* |
| Positive | 4,167 | 1.35 | 0.71 to 2.56 | .36 | |
| Age, years | | | | | |
| < 35 | 4,148 | 2.59 | 1.23 to 5.47 | $1.3 \times 10^{-2}$ | Ref† |
| 35-50 | 20,478 | 2.57 | 1.83 to 3.59 | $4.0 \times 10^{-8}$ | .17 |
| 50-65 | 31,736 | 2.36 | 1.80 to 3.10 | $6.5 \times 10^{-10}$ | $5.3 \times 10^{-2}$ |
| > 65 | 14,591 | 1.40 | 0.93 to 2.12 | .11 | $1.8 \times 10^{-2}$ |
| ER status | | | | | |
| Negative | 39,850 | 1.32 | 0.93 to 1.88 | .12 | Ref |
| Positive | 52,939 | 2.55 | 2.10 to 3.10 | $4.9 \times 10^{-21}$ | $9.9 \times 10^{-6}$ |
| PR status | | | | | |
| Negative | 40,041 | 1.72 | 1.29 to 2.30 | $1.9 \times 10^{-4}$ | Ref |
| Positive | 46,648 | 2.51 | 2.02 to 3.12 | $7.6 \times 10^{-17}$ | $1.7 \times 10^{-2}$ |
| HER2 status | | | | | |
| Negative | 37,920 | 2.40 | 1.88 to 3.06 | $1.4 \times 10^{-2}$ | Ref |
| Positive | 29,584 | 2.66 | 1.77 to 4.00 | $2.7 \times 10^{-6}$ | .73 |
| Negative family history by age category, years‡ | | | | | |
| < 35 | 967 | 3.36 | 0.58 to 19.62 | .18 | Ref§ |
| 35-50 | 8,181 | 2.77 | 1.45 to 5.29 | $2.0 \times 10^{-3}$ | .20 |
| 50-65 | 15,544 | 2.06 | 1.33 to 3.19 | $1.0 \times 10^{-3}$ | $9.0 \times 10^{-3}$ |
| > 65 | 7,101 | 1.26 | 0.67 to 2.37 | .47 | $2.1 \times 10^{-2}$ |
| ER-negative by age category, years | | | | | |
| < 35 | 2,855 | 3.02 | 0.93 to 9.86 | $6.7 \times 10^{-2}$ | Ref‖ |
| 35-50 | 11,063 | 1.46 | 0.77 to 2.75 | .25 | .62 |
| 50-65 | 17,739 | 1.48 | 0.85 to 2.57 | .17 | .74 |
| > 65 | 7,826 | 0.96 | 0.36 to 2.53 | .93 | .53 |
| ER-positive by age category, years | | | | | |
| < 35 | 3,262 | 3.26 | 1.05 to 10.18 | $4.2 \times 10^{-2}$ | Ref¶ |
| 35-50 | 14,029 | 3.12 | 2.13 to 4.58 | $5.3 \times 10^{-9}$ | .20 |
| 50-65 | 24,029 | 2.73 | 2.02 to 3.70 | $6.7 \times 10^{-11}$ | $8.2 \times 10^{-2}$ |
| > 65 | 11,597 | 1.58 | 1.01 to 2.49 | $4.6 \times 10^{-2}$ | $3.2 \times 10^{-2}$ |

NOTE. All models were adjusted for study and age, except the models that included age as a categorical variable, which were only adjusted for study.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; Ref, reference category.
**P* value of interaction term of family history and *CHEK2* in case-control analysis.
†Trend test for interaction by including categorical age as a continuous variable in the model $P = .014$.
‡Insufficient data to derive family history–positive estimates.
§Idem $P = .004$.
‖Idem $P = .66$.
¶Idem $P = .026$.

ER-positive versus an ER-negative tumor ($P = 9.9 \times 10^{-6}$), with an OR of 2.55 (95% CI, 2.10 to 3.10; $P = 4.9 \times 10^{-21}$) versus an OR of 1.32 (95% CI, 0.93 to 1.88; $P = .12$;), respectively. Associations with PR status were similar to those for ER, but the OR for PR-negative tumors was higher than that for ER-negative tumors. In the case-only analysis, there was no association with PR status after adjusting for ER status ($P = .84$), whereas *CHEK2**1100delC was still associated with ER status after adjustment for PR ($P = 2.1 \times 10^{-4}$). There was no association with HER2 status ($P = .73$; $P = .32$ after adjustment for ER).

The relative risk of breast cancer for *CHEK2**1100delC carriers significantly decreased with age for overall ($P = .014$ for trend) and for ER-positive disease ($P = .026$ for trend; Table 3; Appendix Fig A3). Smoothed age-specific ORs in years were derived by using a linear *CHEK2* × age interaction from a case-only analysis (Fig 2). There was no evidence for a quadratic (*CHEK2* × age$^2$) term, which indicated that these models were a reasonable fit (data not shown). ORs decreased by age for ER-positive disease (OR, 0.86 per decade; $P = .001$) but not for ER-negative disease (OR, 0.93; $P = .60$). Estimated cumulative risks for ER-positive and ER-negative tumors by age 80 of *CHEK2**1100delC carriers were 20% and 3%, respectively, compared with 9% and 2%, respectively, in the general population of the United Kingdom (Fig 3).

## DISCUSSION

On the basis of analyses of approximately 87,000 controls and patients with breast cancer from population- and hospital-based studies, our best estimate for the relative risk of invasive breast cancer for carriers of the 1100delC mutation in *CHEK2*, compared with noncarriers, was 2.26 (95% CI, 1.90 to 2.69). The relative risk estimates were consistent across studies, which indicates that the above estimate should be broadly applicable to European women.

Consistent with previous reports,[12] the relative risk for ER-negative breast cancer was markedly lower compared with ER-positive breast cancer (OR, 1.32 versus 2.55, respectively; $P = 9.9 \times 10^{-6}$), and the ER-negative risk estimate was not

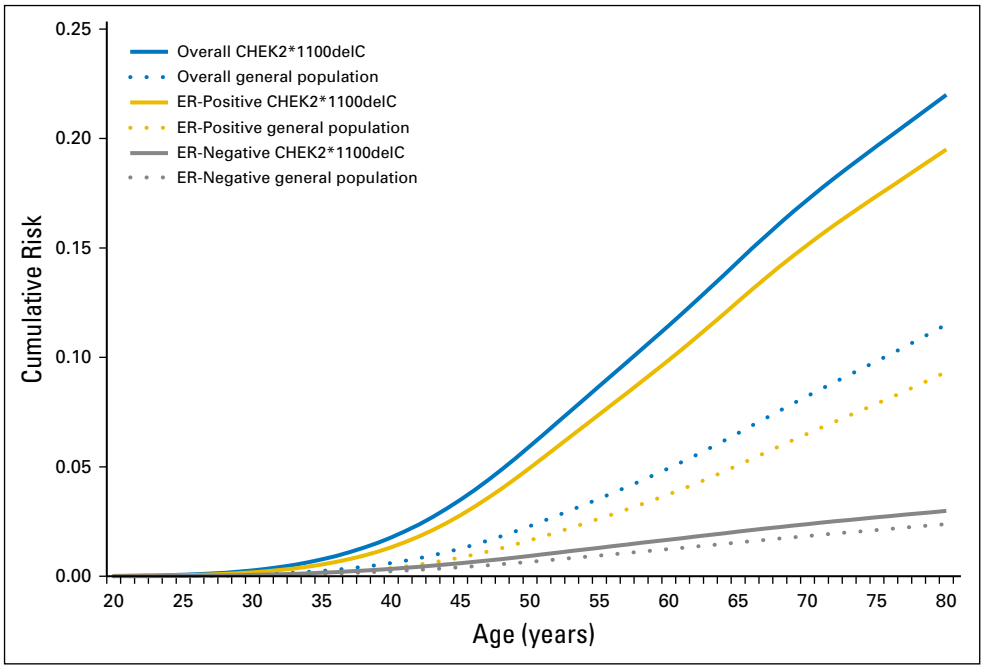



**Fig 3.** Cumulative breast cancer risks for *CHEK2**1100delC carriers and the general female population by attained age. ER, estrogen receptor.

statistically significant. We found neither evidence that risk varied by PR or HER2 status, after adjustment for ER status, nor any evidence for variation in relative risk by grade or morphology.

Previous studies have obtained somewhat higher relative breast cancer risk estimates for *CHEK2**1100delC carriers. In particular, in a previous publication that was based on a subset of BCAC studies (25,571 patients with breast cancers and 30,056 controls) and that focused on survival in *CHEK2**1100delC carriers, higher risk estimates were found compared with our study (overall OR, 3.01 [95% CI, 2.53 to 3.58]; ER-positive OR, 3.47 [95% CI, 2.87 to 4.18]; and ER-negative OR, 1.54 [95% CI, 1.09 to 2.17]).[12] However, these estimates were based on fewer data and were biased as the analyses included clinical genetics–based and familial studies. Our estimate is also somewhat lower than the overall estimate in a previously published meta-analysis (OR, 2.7; 95% CI, 2.1 to 3.4)[7]; however, that meta-analysis also included fewer individuals, and the higher estimate was largely driven by relatively high estimates from only two studies.

The relative risk of breast cancer in our study showed a modest but statistically significant decrease by age for breast cancer overall and for ER-positive disease. Despite the sample size, we had limited power to derive precise, age-specific relative risk estimates at young ages; therefore, to derive more stable, smoothed age-specific relative risks, we applied a method in which we estimated a linear *CHEK2* × age interaction term from case-only analysis (Fig 2). On the basis of this model, a woman age 40 years who carries the *CHEK2**1100delC mutation has a relative risk of 3.25 to develop an ER-positive breast cancer compared with a noncarrier of the same age, whereas relative risk for a *CHEK2**1100delC carrier at age 70 year is 1.87.

Studies on the basis of patients with breast cancer who were recruited through clinical genetic centers can overestimate the relative risk that is attributable to a genetic variant because of an oversampling of patients with a family history of breast cancer. Indeed, we observed a higher relative risk estimate in women from clinical genetic–based and familial studies, which emphasized the fact that population-based studies are required to provide unbiased relative risk estimates. We assumed that the set of studies that we included in the main analyses, which were defined in the BCAC database as hospital- or population-based, provided a sample of patients with breast cancer and controls that was reasonably representative of the general population. The proportion of women with a first-degree family history (16.5%) was consistent with that expected, which suggested that there was little oversampling on the basis of family that could lead to overestimation of relative risk.

Somewhat surprisingly, in the hospital- and population-based studies, the relative risk estimate was higher in women without a first-degree relative with breast cancer compared with the risk of those with family history, but this was not statistically significantly different and disappeared after the exclusion of two studies with outlier results caused by the study definitions that were used. In addition, the risk estimate of 2.04 among women without a family history was also somewhat lower than that of the overall estimate in all studies (2.26), which might indicate some selection of studies for which family history information was available.

We also found that the breast cancer relative risk was lower for incident invasive breast cancers. This finding was somewhat surprising, given that we previously found that *CHEK2**1100delC carriers have a poorer survival compared with noncarriers,[12] which would predict a higher relative risk for incident than prevalent cancers. This did not seem to be the result of differences in subtype, as the proportion of ER-positive tumors in incident versus prevalent tumors was similar (77.8% *v* 77.0%). Larger follow-up studies by genotype and tumor subtype might resolve this discrepancy.

Relative risks in Figure 2 and cumulative risks in Figure 3 provide a basis for counseling. Of note, for all groups, the absolute risks, which take into account death before breast cancer diagnosis

as a competing event, will be somewhat lower than the cumulative risks. Breast cancer risks attributed to *CHEK2**1100delC carriership reported in our results would be sufficient to classify such women in a moderate-risk, but not high-risk, category according to NICE guidelines in the United Kingdom[24]; however, a more appropriate method for use of these data is to incorporate the estimates into a model that includes the combined effects of *CHEK2**1100delC—and other breast cancer susceptibility genes—with a polygenic component that models the effect of other familial factors. This estimation can be accomplished within the framework of the BOADICEA model, in which the effects of susceptibility variants and other familial factors are assumed to combine multiplicatively.[25] Such a model can be used to counsel women with a *CHEK2**1100delC mutation, with or without a family history.

Prompted by high breast cancer risk in homozygous carriers of *CHEK2**1100delC as well as high cumulative risk for female first-degree family members,[9,26,27] testing for this mutation has been already introduced in the Netherlands for female family members who have been referred for *BRCA1/2* counseling and genetic testing.[28] This testing has also been introducted in Germany (R. Schmutzler, personal communication, December 2015) and Poland (A. Jakubowska, personal communication, December 2015), and other countries, such as Australia (G. Chenevix-Trench, personal communication, December 2015), are considering similar steps. Current Dutch guidelines allow *CHEK2**1100delC carriers to be upgraded to more intensive surveillance, without downgrading of noncarriers.[28] Prophylactic measures are generally only discussed with homozygous carriers.

The current study only provides estimates for the *CHEK2**1100delC mutation. No reliable estimates for other protein-truncating variants in *CHEK2* are yet available, but it might be reasonable to assume that the relative risk estimates we present for the 1100delC variant can be applied to carriers of other truncating, though not missense, variants. The results presented here provide a rational basis for deciding whether *CHEK2* testing should be offered more widely, and for counseling women who are from families in which one or more members have received positive test results about the implications for management.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Age- and Tumor Subtype–Specific Breast Cancer Risk Estimates for *CHEK2**1100delC Carriers**

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## *Appendix*

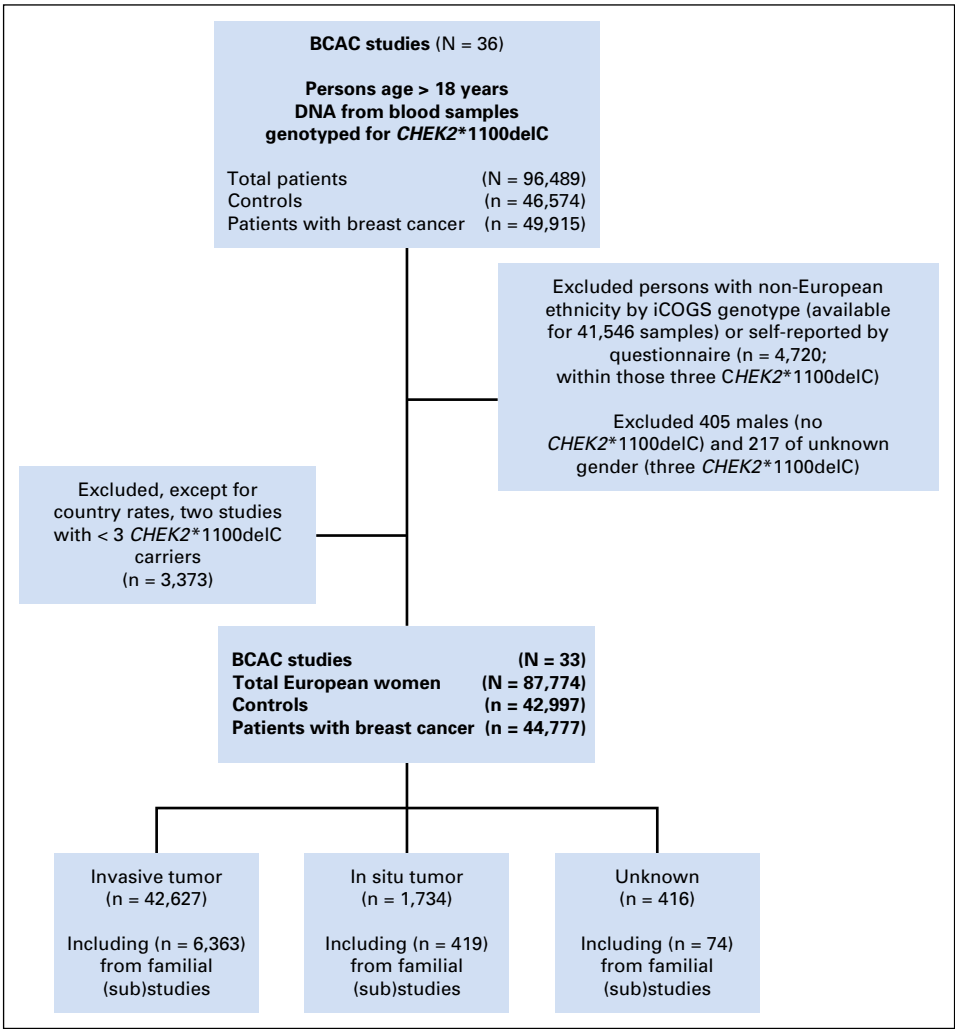


**Fig A1.** Data flowchart of inclusion and exclusion of patients with breast cancer and healthy controls from the Breast Cancer Association Consortium (BCAC) database.

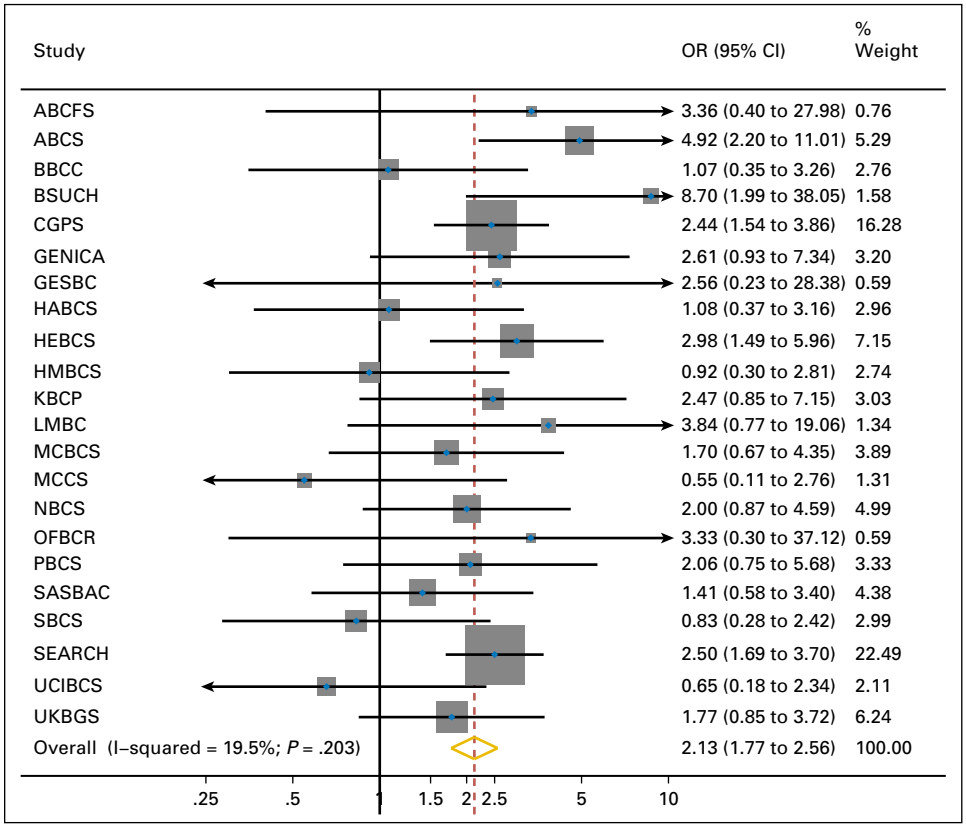


**Fig A2.** Forest plot of odds ratios (ORs) from a fixed meta-analysis of the association between *CHEK2**1100delC and invasive breast cancer by study, using population- and hospital-based studies. ABCFS, Australian Breast Cancer Family Study; ABCS, Amsterdam Breast Cancer Study; BBCC, Bavarian Breast Cancer Cases and Controls; BSUCH, Breast Cancer Study of the University of Heidelberg; CGPS, Copenhagen General Population Study; GENICA, Gene Environment Interaction and Breast Cancer in Germany; GESBC, Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS, Hannover Breast Cancer Study; HEBCS, Helsinki Breast Cancer Study; HMBCS, Hannover-Minsk Breast Cancer Study; KBCP, Kuopio Breast Cancer Project; LMBC, Leuven Multidisciplinary Breast Centre; MCBCS, Mayo Clinic Breast Cancer Study; MCCS, Melbourne Collaborative Cohort Study; NBCS, Norwegian Breast Cancer Study; OFBCR, Ontario Familial Breast Cancer Registry; PBCS, NCI Polish Breast Cancer Study; SASBAC, Singapore and Sweden Breast Cancer Study; SBCS, Sheffield Breast Cancer Study; SEARCH, Study of Epidemiology and Risk factors in Cancer Heredity; UCIBCS, UCI Breast Cancer Study; UKBGS, UK Breakthrough Generations Study.

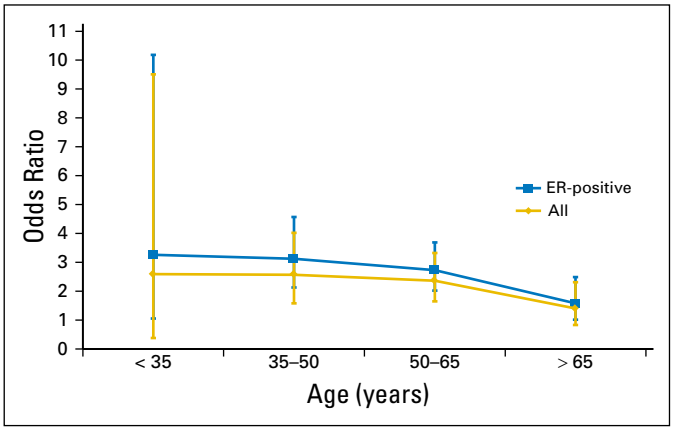


**Fig A3.** *CHEK2**1100delC-associated breast cancer risk per age category: all invasive and invasive estrogen receptor (ER)–positive disease. *P*-value trend for all and ER+ disease: $P = .014$ and $P = .026$, respectively (see Table 3).

**Table A1.** Study Information, Number of *CHEK2**1100delC Genotyped European Women, and Genotyping Assays Used in Each Study

| Study | Study Name | Country | Study Design | *CHEK2**1100delC | | | Total, No. | Type of assay if different from the custom Taqman, No.† |
|---|---|---|---|---|---|---|---|---|
| | | | | Noncarrier, No. | Heterozygous Carrier, No. | Homozygous Carrier, No.* | | |
| ABCFS | Australian Breast Cancer Family Study | Australia | Population-based case-control study | 2,086 | 7 | 0 | 2,093 | Older Taqman assay: 143 |
| ABCS(-F) | Amsterdam Breast Cancer Study | Netherlands | Hospital-based consecutive cases; population-based controls; substudy ABCS-F: patients with breast cancer recruited through the clinical genetic center | 3,317 | 109 | 6 | 3,432 | Sanger sequencing: 20 |
| BBCC | Bavarian Breast Cancer Cases and Controls | Germany | Hospital-based cases; population-based controls | 1,578 | 13 | 0 | 1,591 | |
| BBCS | British Breast Cancer Study | United Kingdom | English and Scottish Cancer Registries: all patients with breast cancer who developed a first primary age < 65 in 1971 or later and who subsequently developed a second primary cancer; patients with unilateral breast cancer diagnosed age < 70 in 1971 or later | 2,562 | 28 | 0 | 2,590 | Older Taqman assay: 568 |
| BIGGS | Breast Cancer in Galway Genetic Study | Ireland | Hospital-based cases; population based-controls | 1,825 | 3 | 0 | 1,828 | |
| BSUCH | Breast Cancer Study of the University of Heidelberg | Germany | Hospital-based cases; healthy blood donator controls | 1,962 | 23 | 0 | 1,985 | |
| CGPS | Copenhagen General Population Study | Denmark | Consecutive, incident cases from one hospital with centralized care for a population of 400,000 women from 2001 to present | 8,670 | 80 | 0 | 8,750 | Older Taqman assay: 12 |
| ESTHER | ESTHER Breast Cancer Study | Germany | Statewide recruitment of breast cancer cases in all hospitals in Saarland/ Germany in 2001-2003 | 991 | 5 | 0 | 996 | |
| GC-HBOC | German Consortium for Hereditary Breast & Ovarian Cancer | Germany | Population-based familial case-control study | 1,936 | 20 | 0 | 1,956 | |
| GENICA | Gene Environment Interaction and Breast Cancer in Germany | Germany | Population-based case-control study | 2,005 | 18 | 0 | 2,023 | |
| GESBC | Genetic Epidemiology Study of Breast Cancer by Age 50 | Germany | Population-based case-control study | 1,194 | 3 | 0 | 1,197 | Older Taqman assay: 1,197 |
| HABCS | Hannover Breast Cancer Study | Germany | Hospital-based case-control study | 2,026 | 27 | 0 | 2,053 | Older Taqman assay: 36 |
| HEBCS | Helsinki Breast Cancer Study | Finland | Hospital-based case-control study and additional familial cases | 3,383 | 100 | 1 | 3,484 | Older Taqman assay: 36 |
| HMBCS | Hannover-Minsk Breast Cancer Study | Belarus | Hospital-based cases; population-based controls | 2,811 | 15 | 0 | 2,826 | Older Taqman assay: 10 |
| HUBCS | Hannover-Ufa Breast Cancer Study | Russia | Hospital-based cases; population-based controls | 2,393 | 5 | 0 | 2,398 | Older Taqman assay: 16 |
| KARBAC | Karolinska Breast Cancer Study | Sweden | Population and hospital-based cases; geographically matched controls | 1,662 | 16 | 0 | 1,678 | |
| KBCP | Kuopio Breast Cancer Project | Finland | Population-based prospective clinical cohort | 888 | 18 | 0 | 906 | Older Taqman assay: 906 |

(continued on following page)

**Table A1.** Study Information, Number of *CHEK2**1100delC Genotyped European Women, and Genotyping Assays Used in Each Study (continued)

| Study | Study Name | Country | Study Design | *CHEK2**1100delC | | | Total, No. | Type of assay if different from the custom Taqman, No.† |
|---|---|---|---|---|---|---|---|---|
| | | | | Noncarrier, No. | Heterozygous Carrier, No. | Homozygous Carrier, No.* | | |
| KConFab/AOCS | Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study | Australia and New Zealand | Clinic-based recruitment of familial patients with breast cancer (cases); population-based case-control study of ovarian cancer (controls only) | 1,539 | 13 | 0 | 1,552 | iPLEX: 1,552 |
| LMBC | Leuven Multidisciplinary Breast Centre | Belgium | Hospital-based case-control study | 1,785 | 14 | 0 | 1,799 | |
| MCBCS | Mayo Clinic Breast Cancer Study | United States | Hospital-based case-control study | 2,371 | 25 | 2 | 2,398 | |
| MCCS | Melbourne Collaborative Cohort Study | Australia | Population-based prospective cohort study | 1,029 | 7 | 0 | 1,036 | |
| MSKCC‡ | Memorial Sloan Kettering Cancer Center Study | United States | Case-control study | 947 | 2 | 0 | 949 | |
| NBCS | Norwegian Breast Cancer Study | Norway | Hospital-based case-control study | 3,483 | 25 | 0 | 3,508 | |
| NC-BCFR | Northern California Breast Cancer Family Registry | United States | Population-based familial case-control study | 531 | 10 | 0 | 541 | |
| OFBCR | Ontario Familial Breast Cancer Registry | Canada | Population-based familial case-control study | 1,535 | 11 | 1 | 1,547 | |
| ORIGO | Leiden University Medical Centre Breast Cancer Study | Netherlands | Hospital-based prospective cohort study | 1,118 | 36 | 0 | 1,154 | Oligohybridization assay: 1,154 |
| PBCS | NCI Polish Breast Cancer Study | Poland | Population-based case-control study | 4,306 | 17 | 0 | 4,323 | |
| RBCS | Rotterdam Breast Cancer Study | Netherlands | Hospital based case-control study, Rotterdam area | 1,519 | 55 | 4 | 1,578 | Oligohybridization assay: 13 |
| SASBAC | Singapore and Sweden Breast Cancer Study | Sweden | Population-based case-control study | 2,518 | 20 | 1 | 2,539 | |
| SBCS | Sheffield Breast Cancer Study | United Kingdom | Hospital-based case-control study | 1,968 | 15 | 0 | 1,983 | |
| SEARCH | Study of Epidemiology and Risk factors in Cancer Heredity | United Kingdom | Population-based case-control study | 14,021 | 131 | 0 | 14,152 | Older Taqman assay: 1,170 |
| SZBCS | IHCC-Szczecin Breast Cancer Study | Poland | Hospital based case-control study | 1,737 | 6 | 0 | 1,743 | |
| UCIBCS | UCI Breast Cancer Study | United States | Population-based case-control study | 1,407 | 13 | 0 | 1,420 | |
| UKBGS | UK Breakthrough Generations Study | United Kingdom | Population-based cohort study | 4,675 | 40 | 0 | 4,715 | |
| US3SS‡ | US Three State Study | United States | Population-based case-control study | 2,424 | 0 | 0 | 2,424 | |
| Total | | | | 90,202 | 930 | 15 | 91,147 | Other assay total: 6,833 |

*Homozygous *CHEK2**1100delC carriers were combined with heterozygous carriers for subsequent Appendix Tables.
†Number of samples genotyped only with the specified assay. See the Data Supplement.
‡Excluded from further analyses, except for estimation of country rates, because of fewer than three *CHEK2**1100delC carriers identified.

**Table A2.** Included Numbers and Proportions of *CHEK2**1100delC Carriers in Controls and Patients With Breast Cancer

| | Controls | | | Patients From Population- and Hospital-Based Studies | | | Patients From Familial or Clinical Genetics Center–Based Studies | | |
|---|---|---|---|---|---|---|---|---|---|
| Study | No. of Non-*CHEK2* | No. of C*HEK2**1110delC | % *CHEK2**1110delC | No. of Non-*CHEK2* | No. of *CHEK2**1110delC | % *CHEK2**1110delC | No. of Non-*CHEK2* | No. of *CHEK2**1110delC | % *CHEK2**1110delC |
| ABCFS | 729 | 1 | 0.1 | 1,357 | 6 | 0.4 | | | |
| ABCS | 966 | 8 | 0.8 | 1,375 | 49 | 3.4 | 976 | 58 | 5.6 |
| BBCC | 743 | 6 | 0.8 | 835 | 7 | 0.8 | | | |
| BBCS | 1,278 | 9 | 0.7 | | | | 1,284 | 19 | 1.5 |
| BIGGS* | 877 | | 0.0 | 948 | 3 | 0.3 | | | |
| BSUCH | 929 | 2 | 0.2 | 1,033 | 21 | 2.0 | | | |
| CGPS | 6,171 | 42 | 0.7 | 2,499 | 38 | 1.5 | | | |
| ESTHER* | 505 | | 0.0 | 486 | 5 | 1.0 | | | |
| GC-HBOC | 1,104 | 6 | 0.5 | | | | 832 | 14 | 1.7 |
| GENICA | 1,004 | 5 | 0.5 | 1,001 | 13 | 1.3 | | | |
| GESBC | 634 | 1 | 0.2 | 560 | 2 | 0.4 | | | |
| HABCS | 986 | 10 | 1.0 | 1,040 | 17 | 1.6 | | | |
| HEBCS | 1,080 | 15 | 1.4 | 1,800 | 53 | 2.9 | 503 | 33 | 6.2 |
| HMBCS | 1,013 | 5 | 0.5 | 1,798 | 10 | 0.6 | | | |
| HUBCS | 1,464 | 1 | 0.1 | 929 | 4 | 0.4 | | | |
| KARBAC | 863 | 1 | 0.1 | 463 | 6 | 1.3 | 336 | 9 | 2.6 |
| KBCP | 441 | 5 | 1.1 | 447 | 13 | 2.8 | | | |
| KConFab | 936 | 5 | 0.5 | | | | 603 | 8 | 1.3 |
| LMBC | 937 | 2 | 0.2 | 848 | 12 | 1.4 | | | |
| MCBCS | 1,114 | 7 | 0.6 | 1,257 | 20 | 1.6 | | | |
| MCCS | 372 | 3 | 0.8 | 657 | 4 | 0.6 | | | |
| NBCS | 1,867 | 9 | 0.5 | 1,616 | 16 | 1.0 | | | |
| NC-BCFR | 153 | 1 | 0.6 | | | | 378 | 9 | 2.3 |
| OFBCR | 343 | 1 | 0.3 | 187 | 3 | 1.6 | 1,005 | 8 | 0.8 |
| ORIGO* | 86 | | 0.0 | 1,032 | 36 | 3.4 | | | |
| PBCS | 2,263 | 6 | 0.3 | 2,043 | 11 | 0.5 | | | |
| RBCS | 788 | 9 | 1.1 | | | | 731 | 50 | 6.4 |
| SASBAC | 1,348 | 9 | 0.7 | 1,170 | 12 | 1.0 | | | |
| SBCS | 986 | 8 | 0.8 | 982 | 7 | 0.7 | | | |
| SEARCH | 7,100 | 38 | 0.5 | 6,921 | 93 | 1.3 | | | |
| SZBCS | 851 | 2 | 0.2 | 886 | 4 | 0.4 | | | |
| UCIBCS | 501 | 5 | 1.0 | 906 | 8 | 0.9 | | | |
| UKBGS | 2,332 | 11 | 0.5 | 2,343 | 29 | 1.2 | | | |
| Total | 42,764 | 233 | 0.5 | 37,419 | 502 | 1.3 | 6,648 | 208 | 3.0 |

Abbreviations: ABCFS, Australian Breast Cancer Family Study; ABCS, Amsterdam Breast Cancer Study; BBCC, Bavarian Breast Cancer Cases and Controls; BBCS, British Breast Cancer Study; BIGGS, Breast Cancer in Galway Genetic Study; BSUCH, Breast Cancer Study of the University of Heidelberg; CGPS, Copenhagen General Population Study; ESTHER, ESTHER Breast Cancer Study; GC-HBOC, German Consortium for Hereditary Breast & Ovarian Cancer; GENICA, Gene Environment Interaction and Breast Cancer in Germany; GESBC, Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS, Hannover Breast Cancer Study; HEBCS, Helsinki Breast Cancer Study; HMBCS, Hannover-Minsk Breast Cancer Study; HUBCS, Hannover-Ufa Breast Cancer Study; KARBAC, Karolinska Breast Cancer Study; KBCP, Kuopio Breast Cancer Project; KConFab, Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer; LMBC, Multidisciplinary Breast Centre; MCBCS, Mayo Clinic Breast Cancer Study; MCCS, Melbourne Collaborative Cohort Study; NBCS, Norwegian Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; OFBCR, Ontario Familial Breast Cancer Registry; ORIGO, Leiden University Medical Centre Breast Cancer Study; PBCS, NCI Polish Breast Cancer Study; RBCS, Rotterdam Breast Cancer Study; SASBAC, Singapore and Sweden Breast Cancer Study; SBCS, Sheffield Breast Cancer Study; SEARCH, Study of Epidemiology and Risk factors in Cancer Heredity; SZBCS, IHCC-Szczecin Breast Cancer Study; UCIBCS, UCI Breast Cancer Study; UKBGS, UK Breakthrough Generations Study.

*Included only in case-only analyses.

**Table A3.** Age of Controls at Interview and of Patients With Breast Cancer at Diagnosis

| | Controls | | | | Patients From Population- and Hospital-Based Studies | | | | Patients From Familial or Clinical Genetics Center–Based Studies | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Study | No. | Mean | SD | No. Missing | No. | Mean | SD | No. Missing | No. | Mean | SD | No. Missing |
| ABCFS | 730 | 41.5 | 9.6 | | 1,363 | 42.3 | 9.2 | | | | | |
| ABCS | 974 | 37.1 | 8.0 | | 1,424 | 42.4 | 5.1 | | 1,032 | 44.6 | 10.3 | 2 |
| BBCC | 749 | 59.6 | 12.5 | | 842 | 54.7 | 11.7 | | | | | |
| BBCS | 1,287 | 51.4 | 9.8 | | | | | | 1,303 | 54.4 | 8.6 | |
| BIGGS | 68 | 63.6 | 14.5 | 809 | 931 | 52.8 | 11.5 | 20 | | | | |
| BSUCH | 931 | 56.7 | 9.8 | | 869 | 54.6 | 12.2 | 185 | | | | |
| CGPS | 6,213 | 55.3 | 12.6 | | 2,537 | 61.3 | 12.6 | | | | | |
| ESTHER | 505 | 62.3 | 7.1 | | 490 | 60.8 | 8.6 | 1 | | | | |
| GC-HBOC | 1,110 | 45.6 | 14.5 | | | | | | 836 | 46.0 | 10.9 | 10 |
| GENICA | 1,009 | 58.2 | 11.1 | | 1,014 | 58.1 | 11.2 | | | | | |
| GESBC | 635 | 42.7 | 5.7 | | 562 | 42.9 | 5.9 | | | | | |
| HABCS | 993 | 33.7 | 12.6 | 3 | 1,057 | 57.4 | 11.8 | | | | | |
| HEBCS | 1,095 | 41.2 | 13.4 | | 1,853 | 57.5 | 12.0 | | 536 | 52.7 | 12.0 | |
| HMBCS | 1,016 | 41.6 | 12.2 | 2 | 1,808 | 48.9 | 12.3 | | | | | |
| HUBCS | 1,025 | 45.7 | 12.9 | 440 | 926 | 52.3 | 10.8 | 7 | | | | |
| KARBAC* | | | | 864 | 469 | 60.6 | 12.0 | | 342 | 54.1 | 12.1 | 3 |
| KBCP | 446 | 53.3 | 10.9 | | 459 | 58.8 | 14.2 | 1 | | | | |
| KConFab | 941 | 58.0 | 11.3 | | | | | | 611 | 44.9 | 9.5 | |
| LMBC | 935 | 43.6 | 9.5 | 4 | 815 | 55.9 | 12.5 | 45 | | | | |
| MCBCS | 1,121 | 58.8 | 12.0 | | 1,277 | 57.3 | 12.3 | | | | | |
| MCCS | 375 | 55.1 | 9.0 | | 661 | 61.5 | 9.0 | | | | | |
| NBCS | 1,842 | 56.2 | 10.2 | 34 | 1,545 | 55.5 | 12.2 | 87 | | | | |
| NC-BCFR | 154 | 56.9 | 4.3 | | | | | | 387 | 54.9 | 7.4 | |
| OFBCR | 344 | 56.9 | 6.3 | | 190 | 55.9 | 6.8 | | 1,013 | 53.0 | 10.4 | |
| ORIGO* | | | | 86 | 1,068 | 53.7 | 10.9 | | | | | |
| PBCS | 2,269 | 55.8 | 10.0 | | 2,054 | 55.8 | 9.9 | | | | | |
| RBCS* | | | | 797 | | | | | 781 | 44.4 | 10.0 | |
| SASBAC | 1,357 | 63.3 | 6.4 | | 1,182 | 63.1 | 6.5 | | | | | |
| SBCS | 994 | 57.6 | 5.7 | | 989 | 59.4 | 12.2 | | | | | |
| SEARCH | 7,136 | 57.9 | 9.1 | 2 | 7,013 | 53.2 | 9.0 | 1 | | | | |
| SZBCS | 853 | 58.4 | 11.0 | | 890 | 55.9 | 11.3 | | | | | |
| UCIBCS | 506 | 54.9 | 12.2 | | 914 | 59.3 | 12.9 | | | | | |
| UKBGS | 2,343 | 58.2 | 9.4 | | 2,372 | 51.2 | 9.4 | | | | | |
| Total | 39,956 | 53.8 | 12.7 | 3,041 | 37,574 | 54.5 | 11.8 | 347 | 6,841 | 49.6 | 11.0 | 15 |

NOTE. This table includes all breast cancers irrespective of tumor behavior.

Abbreviations: ABCFS, Australian Breast Cancer Family Study; ABCS, Amsterdam Breast Cancer Study; BBCC, Bavarian Breast Cancer Cases and Controls; BBCS, British Breast Cancer Study; BIGGS, Breast Cancer in Galway Genetic Study; BSUCH, Breast Cancer Study of the University of Heidelberg; CGPS, Copenhagen General Population Study; ESTHER, ESTHER Breast Cancer Study; GC-HBOC, German Consortium for Hereditary Breast & Ovarian Cancer; GENICA, Gene Environment Interaction and Breast Cancer in Germany; GESBC, Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS, Hannover Breast Cancer Study; HEBCS, Helsinki Breast Cancer Study; HMBCS, Hannover-Minsk Breast Cancer Study; HUBCS, Hannover-Ufa Breast Cancer Study; KARBAC, Karolinska Breast Cancer Study; KBCP, Kuopio Breast Cancer Project; KConFab, Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer; LMBC, Multidisciplinary Breast Centre; MCBCS, Mayo Clinic Breast Cancer Study; MCCS, Melbourne Collaborative Cohort Study; NBCS, Norwegian Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; OFBCR, Ontario Familial Breast Cancer Registry; ORIGO, Leiden University Medical Centre Breast Cancer Study; PBCS, NCI Polish Breast Cancer Study; RBCS, Rotterdam Breast Cancer Study; SASBAC, Singapore and Sweden Breast Cancer Study; SBCS, Sheffield Breast Cancer Study; SEARCH, Study of Epidemiology and Risk factors in Cancer Heredity; SZBCS, IHCC-Szczecin Breast Cancer Study; UCIBCS, UCI Breast Cancer Study; UKBGS, UK Breakthrough Generations Study.

*Included only in case-only analyses.

**Table A4.** Behavior of Breast Tumors

| Study | Patients From Population- and Hospital-Based Studies | | | | Patients From Familial or Clinical Genetics Center–Based Studies | | | |
|---|---|---|---|---|---|---|---|---|
| | No.* | % Invasive | % In Situ | No. Missing | No.* | % Invasive | % In Situ | No. Missing |
| ABCFS | 1,363 | 100.0 | | | | | | |
| ABCS | 1,424 | 99.9 | 0.1 | | 1,034 | 91.7 | 8.3 | |
| BBCC | 842 | 94.4 | 5.6 | | | | | |
| BBCS | | | | | 1,303 | 100.0 | | |
| BIGGS | 951 | 94.5 | 5.5 | | | | | |
| BSUCH | 1,054 | 98.2 | 1.8 | | | | | |
| CGPS | 2,537 | 96.6 | 3.4 | | | | | |
| ESTHER | 489 | 99.0 | 1.0 | 2 | | | | |
| GC-HBOC | | | | | 846 | 100.0 | | |
| GENICA | 1,014 | 100.0 | | | | | | |
| GESBC | 556 | 93.9 | 6.1 | 6 | | | | |
| HABCS | 1,057 | 98.5 | 1.5 | | | | | |
| HEBCS | 1,853 | 93.2 | 6.8 | | 536 | 95.0 | 5.0 | |
| HMBCS† | 1,808 | 99.9 | 0.1 | | | | | |
| HUBCS† | 933 | 99.9 | 0.1 | | | | | |
| KARBAC | 469 | 100.0 | | | 345 | 100.0 | | |
| KBCP | 460 | 92.0 | 8.0 | | | | | |
| KConFab | | | | | 538 | 77.7 | 22.3 | 73 |
| LMBC | 860 | 98.5 | 1.5 | | | | | |
| MCBCS | 1,277 | 84.8 | 15.2 | | | | | |
| MCCS | 661 | 100.0 | | | | | | |
| NBCS† | 1,584 | 99.8 | 0.2 | 48 | | | | |
| NC-BCFR | | | | | 387 | 69.3 | 30.8 | |
| OFBCR | 190 | 100.0 | | | 1,013 | 98.3 | 1.7 | |
| ORIGO | 1,064 | 91.5 | 8.6 | 4 | | | | |
| PBCS | 1,968 | 93.6 | 6.4 | 86 | | | | |
| RBCS | | | | | 780 | 93.6 | 6.4 | 1 |
| SASBAC | 1,182 | 100.0 | | | | | | |
| SBCS | 956 | 92.4 | 7.6 | 33 | | | | |
| SEARCH | 7,014 | 98.0 | 2.0 | | | | | |
| SZBCS | 732 | 95.1 | 4.9 | 158 | | | | |
| UCIBCS | 914 | 85.5 | 14.6 | | | | | |
| UKBGS | 2,367 | 96.6 | 3.4 | 5 | | | | |
| Total | 37,579 | 96.5 | 3.5 | 342 | 6,782 | 93.8 | 6.2 | 74 |

Abbreviations: ABCFS, Australian Breast Cancer Family Study; ABCS, Amsterdam Breast Cancer Study; BBCC, Bavarian Breast Cancer Cases and Controls; BBCS, British Breast Cancer Study; BIGGS, Breast Cancer in Galway Genetic Study; BSUCH, Breast Cancer Study of the University of Heidelberg; CGPS, Copenhagen General Population Study; ESTHER, ESTHER Breast Cancer Study; GC-HBOC, German Consortium for Hereditary Breast & Ovarian Cancer; GENICA, Gene Environment Interaction and Breast Cancer in Germany; GESBC, Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS, Hannover Breast Cancer Study; HEBCS, Helsinki Breast Cancer Study; HMBCS, Hannover-Minsk Breast Cancer Study; HUBCS, Hannover-Ufa Breast Cancer Study; KARBAC, Karolinska Breast Cancer Study; KBCP, Kuopio Breast Cancer Project; KConFab, Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer; LMBC, Multidisciplinary Breast Centre; MCBCS, Mayo Clinic Breast Cancer Study; MCCS, Melbourne Collaborative Cohort Study; NBCS, Norwegian Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; OFBCR, Ontario Familial Breast Cancer Registry; ORIGO, Leiden University Medical Centre Breast Cancer Study; PBCS, NCI Polish Breast Cancer Study; RBCS, Rotterdam Breast Cancer Study; SASBAC, Singapore and Sweden Breast Cancer Study; SBCS, Sheffield Breast Cancer Study; SEARCH, Study of Epidemiology and Risk factors in Cancer Heredity; SZBCS, IHCC-Szczecin Breast Cancer Study; UCIBCS, UCI Breast Cancer Study; UKBGS, UK Breakthrough Generations Study.

*Number with data available.

†This study has fewer than five in situ breast cancers and was excluded from in situ–only analyses.

**Table A5.** Receptor Status of Invasive Breast Tumors From Population- and Hospital-Based Breast Cancer Studies

| | ER | | | PR | | | HER2 | | |
|---|---|---|---|---|---|---|---|---|---|
| Study | No.* | Negative, % | Positive, % | No.* | Negative, % | Positive, % | No.* | Negative, % | Positive, % |
| ABCFS | 1,168 | 34.5 | 65.5 | 1,164 | 30.8 | 69.2 | | | |
| ABCS | 936 | 34.6 | 65.4 | 880 | 48.5 | 51.5 | 898 | 74.8 | 25.2 |
| BBCC | 744 | 29.3 | 70.7 | 741 | 34.7 | 65.3 | 540 | 83.3 | 16.7 |
| BIGGS | 702 | 24.9 | 75.1 | 556 | 24.6 | 75.4 | 447 | 79.2 | 20.8 |
| BSUCH | 700 | 25.1 | 74.9 | 699 | 34.5 | 65.5 | 666 | 82.4 | 17.6 |
| CGPS | 1,758 | 15.1 | 84.9 | 1,267 | 36.2 | 63.8 | 720 | 84.9 | 15.1 |
| ESTHER | 421 | 23.8 | 76.3 | 415 | 33.5 | 66.5 | 192 | 72.4 | 27.6 |
| GENICA | 988 | 22.0 | 78.0 | 985 | 29.8 | 70.3 | 707 | 70.9 | 29.1 |
| GESBC | 443 | 37.0 | 63.0 | 438 | 39.7 | 60.3 | | | |
| HABCS | 812 | 15.6 | 84.4 | 792 | 19.6 | 80.4 | | | |
| HEBCS | 1,694 | 18.2 | 81.8 | 1,694 | 34.8 | 65.2 | 916 | 84.7 | 15.3 |
| HMBCS | 46 | 30.4 | 69.6 | | | | | | |
| HUBCS | 202 | 44.1 | 55.9 | 202 | 43.1 | 56.9 | 191 | 49.7 | 50.3 |
| KARBAC | 440 | 16.8 | 83.2 | 385 | 24.4 | 75.6 | | | |
| KBCP | 389 | 22.6 | 77.4 | 388 | 38.1 | 61.9 | 376 | 87.2 | 12.8 |
| LMBC | 788 | 16.2 | 83.8 | 783 | 23.1 | 76.9 | 705 | 84.4 | 15.6 |
| MCBCS | 1,077 | 16.3 | 83.8 | 1,076 | 25.6 | 74.4 | 808 | 85.0 | 15.0 |
| MCCS | 618 | 23.3 | 76.7 | 621 | 34.8 | 65.2 | 587 | 82.1 | 17.9 |
| NBCS | 1,314 | 27.9 | 72.2 | 1,286 | 41.6 | 58.4 | 631 | 88.0 | 12.0 |
| OFBCR | 176 | 25.0 | 75.0 | 175 | 34.9 | 65.1 | | | |
| ORIGO | 669 | 26.8 | 73.2 | 529 | 42.2 | 57.8 | | | |
| PBCS | 1,676 | 33.8 | 66.2 | 1,670 | 47.0 | 53.0 | 1,203 | 82.5 | 17.5 |
| SASBAC | 821 | 18.0 | 82.0 | 799 | 28.4 | 71.6 | | | |
| SBCS | 540 | 22.6 | 77.4 | 238 | 39.9 | 60.1 | 250 | 92.0 | 8.0 |
| SEARCH | 5,270 | 20.2 | 79.8 | 2,815 | 28.5 | 71.5 | 2,327 | 88.6 | 11.4 |
| SZBCS | 657 | 28.2 | 71.8 | 195 | 60.5 | 39.5 | 532 | 83.8 | 16.2 |
| UCIBCS | 651 | 20.0 | 80.0 | 642 | 30.4 | 69.6 | | | |
| UKBGS† | 4 | 25.0 | 75.0 | 3 | 33.3 | 66.7 | 2 | 50.0 | 50.0 |
| Total | 25,704 | 23.3 | 76.7 | 21,438 | 33.9 | 66.1 | 12,698 | 82.9 | 17.1 |

Abbreviations: ABCFS, Australian Breast Cancer Family Study; ABCS, Amsterdam Breast Cancer Study; BBCC, Bavarian Breast Cancer Cases and Controls; BBCS, British Breast Cancer Study; BIGGS, Breast Cancer in Galway Genetic Study; BSUCH, Breast Cancer Study of the University of Heidelberg; CGPS, Copenhagen General Population Study; ER, estrogen receptor; ESTHER, ESTHER Breast Cancer Study; GC-HBOC, German Consortium for Hereditary Breast & Ovarian Cancer; GENICA, Gene Environment Interaction and Breast Cancer in Germany; GESBC, Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS, Hannover Breast Cancer Study; HEBCS, Helsinki Breast Cancer Study; HER2, human epidermal growth factor receptor 2; HMBCS, Hannover-Minsk Breast Cancer Study; HUBCS, Hannover-Ufa Breast Cancer Study; KARBAC, Karolinska Breast Cancer Study; KBCP, Kuopio Breast Cancer Project; KConFab, Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer; LMBC, Multidisciplinary Breast Centre; MCBCS, Mayo Clinic Breast Cancer Study; MCCS, Melbourne Collaborative Cohort Study; NBCS, Norwegian Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; OFBCR, Ontario Familial Breast Cancer Registry; ORIGO, Leiden University Medical Centre Breast Cancer Study; PBCS, NCI Polish Breast Cancer Study; PR, progesterone receptor; RBCS, Rotterdam Breast Cancer Study; SASBAC, Singapore and Sweden Breast Cancer Study; SBCS, Sheffield Breast Cancer Study; SEARCH, Study of Epidemiology and Risk factors in Cancer Heredity; SZBCS, IHCC-Szczecin Breast Cancer Study; UCIBCS, UCI Breast Cancer Study; UKBGS, UK Breakthrough Generations Study.

*Number with data available.

†Data from this study were excluded from subtype-specific analyses adjusted for study.

**Table A6.** Family History of Controls and Patients With Breast Cancer

| Study | Controls | | | Patients From Population- and Hospital-Based Studies | | | Patients From Familial or Clinical Genetics Center–Based Studies | | |
|---|---|---|---|---|---|---|---|---|---|
| | No.* | No Relative, % | At Least One Relative, % | No.* | No Relative, % | At Least One Relative, % | No.* | No Relative, % | At Least One Relative, % |
| ABCFS | 730 | 93.3 | 6.7 | 1,363 | 82.4 | 17.6 | | | |
| ABCS† | | | | | | | 760 | 50.7 | 49.3 |
| BBCC‡ | 577 | 84.4 | 15.6 | 787 | 85.5 | 14.5 | | | |
| BBCS | 979 | 93.2 | 6.8 | | | | 1,302 | 85.9 | 14.1 |
| BIGGS† | | | | 306 | 62.1 | 37.9 | | | |
| BSUCH† | | | | 287 | 86.4 | 13.6 | | | |
| CGPS† | | | | 2,102 | 80.2 | 19.8 | | | |
| ESTHER | 416 | 89.4 | 10.6 | 438 | 82.9 | 17.1 | | | |
| GENICA | 1,009 | 91.9 | 8.1 | 1,014 | 85.4 | 14.6 | | | |
| GESBC | 635 | 94.0 | 6.0 | 562 | 88.1 | 11.9 | | | |
| HABCS† | | | | 1,024 | 83.8 | 16.2 | | | |
| HEBCS† | | | | 1,849 | 76.8 | 23.2 | 536 | 3.5 | 96.5 |
| HMBCS† | | | | 50 | 94.0 | 6.0 | | | |
| HUBCS | 617 | 98.7 | 1.3 | 907 | 93.8 | 6.2 | | | |
| KARBAC† | | | | 461 | 83.7 | 16.3 | 320 | 22.5 | 77.5 |
| KBCP | 446 | 95.1 | 4.9 | 460 | 88.7 | 11.3 | | | |
| KConFab | 740 | 89.5 | 10.5 | | | | 526 | 14.4 | 85.6 |
| LMBC† | | | | 760 | 81.2 | 18.8 | | | |
| MCBCS | 990 | 81.7 | 18.3 | 1,188 | 78.5 | 21.5 | | | |
| NBCS | 1,021 | 90.8 | 9.2 | 42 | 78.6 | 21.4 | | | |
| NC-BCFR | 154 | 85.1 | 14.9 | | | | 387 | 35.1 | 64.9 |
| OFBCR‡ | 341 | 86.2 | 13.8 | 189 | 93.1 | 6.9 | 1,013 | 53.1 | 46.9 |
| ORIGO† | | | | 891 | 83.7 | 16.3 | | | |
| PBCS | 2,269 | 94.2 | 5.8 | 2,053 | 89.4 | 10.6 | | | |
| RBCS† | | | | | | | 781 | 46.9 | 53.1 |
| SASBAC | 1,233 | 90.3 | 9.7 | 1,152 | 84.6 | 15.4 | | | |
| SBCS | 994 | 89.7 | 10.3 | 989 | 85.8 | 14.2 | | | |
| SEARCH | 4,919 | 93.3 | 6.7 | 6,868 | 83.9 | 16.1 | | | |
| SZBCS† | 853 | 100.0 | | 890 | 89.4 | 10.6 | | | |
| UCIBCS | 461 | 84.2 | 15.8 | 913 | 73.7 | 26.3 | | | |
| UKBGS§ | 4 | 100.0 | | 19 | 94.7 | 5.3 | | | |
| Total | 19,388 | 91.9 | 8.1 | 27,564 | 83.5 | 16.5 | 5,625 | 48.2 | 51.8 |

NOTE. Relatives are first-degree relatives with breast cancer. This table includes all breast cancers irrespective of tumor behavior.

Abbreviations: ABCFS, Australian Breast Cancer Family Study; ABCS, Amsterdam Breast Cancer Study; BBCC, Bavarian Breast Cancer Cases and Controls; BBCS, British Breast Cancer Study; BIGGS, Breast Cancer in Galway Genetic Study; BSUCH, Breast Cancer Study of the University of Heidelberg; CGPS, Copenhagen General Population Study; ESTHER, ESTHER Breast Cancer Study; GC-HBOC, German Consortium for Hereditary Breast & Ovarian Cancer; GENICA, Gene Environment Interaction and Breast Cancer in Germany; GESBC, Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS, Hannover Breast Cancer Study; HEBCS, Helsinki Breast Cancer Study; HMBCS, Hannover-Minsk Breast Cancer Study; HUBCS, Hannover-Ufa Breast Cancer Study; KARBAC, Karolinska Breast Cancer Study; KBCP, Kuopio Breast Cancer Project; KConFab, Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer; LMBC, Multidisciplinary Breast Centre; MCBCS, Mayo Clinic Breast Cancer Study; MCCS, Melbourne Collaborative Cohort Study; NBCS, Norwegian Breast Cancer Study; NC-BCFR, Northern California Breast Cancer Family Registry; OFBCR, Ontario Familial Breast Cancer Registry; ORIGO, Leiden University Medical Centre Breast Cancer Study; PBCS, NCI Polish Breast Cancer Study; RBCS, Rotterdam Breast Cancer Study; SASBAC, Singapore and Sweden Breast Cancer Study; SBCS, Sheffield Breast Cancer Study; SEARCH, Study of Epidemiology and Risk factors in Cancer Heredity; SZBCS, IHCC-Szczecin Breast Cancer Study; UCIBCS, UCI Breast Cancer Study; UKBGS, UK Breakthrough Generations Study.

*Number with data available.

†Included only in case-only analyses.

‡Higher proportion of controls compared with cases, either because of overrepresentation of controls with a family history in the subset genotyped for *CHEK2* (BBCC) or because of the case definition used in the analyses (ie, the subset of nonfamilial cases [OFBCR]).

§Data from this study were excluded from all family history–specific analyses. Of note, there were no data for MCCS and GC-HBOC.

**Table A7.** Characteristics of Controls and Patients With Breast Cancer by *CHEK2**1100delC Carriership

| Characteristic | Controls | | | Patients From Population- and Hospital-Based Studies | | | Patients From Familial or Clinical Genetics Center–Based Studies | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total, No. | Non-*CHEK2**1100delC, % | *CHEK2**1100delC, % | Total, No. | Non-*CHEK2**1100delC, % | *CHEK2**1100delC, % | Total, No. | Non-*CHEK2**1100delC, % | *CHEK2**1100delC, % |
| Genotyped | 42,997 | 95.5 | 0.5 | 37,921 | 98.7 | 1.3 | 6,856 | 97.0 | 3.0 |
| Family history* | | | | | | | | | |
| No | 17,810 | 99.6 | 0.4 | 23,027 | 98.8 | 1.2 | 2,711 | 97.7 | 2.3 |
| Yes | 1,578 | 98.9 | 1.1 | 4,537 | 97.9 | 2.1 | 2,914 | 96.2 | 3.8 |
| *BRCA1/2* germline mutation† | | | | | | | | | |
| No | 42,995 | 99.5 | 0.5 | 32,760 | 98.7 | 1.3 | 6,625 | 96.9 | 3.1 |
| Yes | 2 | 100 | | 161 | 100 | | 231 | 100.0 | |
| Age, years | | | | | | | | | |
| < 35 | 3,267 | 99.3 | 0.7 | 1,399 | 98.4 | 1.6 | 628 | 95.9 | 4.1 |
| 35-50 | 10,418 | 99.4 | 0.6 | 12,004 | 98.5 | 1.5 | 2,797 | 96.9 | 3.1 |
| 50-65 | 18,304 | 99.5 | 0.5 | 16,398 | 98.8 | 1.2 | 2,824 | 97.3 | 2.7 |
| > 65 | 7,967 | 99.4 | 0.6 | 7,765 | 98.9 | 1.1 | 585 | 98.1 | 1.9 |
| All | 39,956 | 99.4 | 0.6 | 37,566 | 98.7 | 1.3 | 6,834 | 97.1 | 2.9 |
| Tumor behavior | | | | | | | | | |
| Invasive | | | | 36,264 | 98.7 | 1.3 | 6,363 | 96.9 | 3.1 |
| In situ | | | | 1,315 | 97.8 | 2.2 | 419 | 97.6 | 2.4 |
| Morphology | | | | | | | | | |
| Ductal | | | | 22,750 | 98.6 | 1.4 | 3,504 | 96.6 | 3.4 |
| Lobular | | | | 4,349 | 98.8 | 1.2 | 522 | 98.3 | 1.7 |
| Medullary | | | | 406 | 99.0 | 1.0 | 53 | 100.0 | 4.8 |
| Mixed | | | | 1,096 | 98.6 | 1.4 | 126 | 95.2 | 2.4 |
| Mucinous | | | | 372 | 98.7 | 1.3 | 56 | 100.0 | 4.7 |
| Other | | | | 1,307 | 99.2 | 0.8 | 572 | 97.6 | |
| Papillary | | | | 77 | 98.7 | 1.3 | 12 | 100.0 | |
| Tubular | | | | 372 | 99.7 | 0.3 | 107 | 95.3 | |
| Grade | | | | | | | | | |
| I | | | | 5,318 | 98.8 | 1.2 | 611 | 97.2 | 2.8 |
| II | | | | 12,440 | 98.6 | 1.4 | 1,293 | 95.9 | 4.1 |
| III | | | | 8,083 | 98.8 | 1.2 | 1,166 | 96.7 | 3.3 |
| ER | | | | | | | | | |
| Negative | | | | 6,170 | 99.2 | 0.8 | 652 | 98.2 | 1.8 |
| Positive | | | | 20,144 | 98.4 | 1.6 | 1,887 | 95.8 | 4.2 |
| PR | | | | | | | | | |
| Negative | | | | 7,450 | 98.8 | 1.1 | 836 | 97.4 | 2.6 |
| Positive | | | | 14,447 | 98.5 | 1.5 | 1,542 | 95.8 | 4.2 |
| HER2 | | | | | | | | | |
| Negative | | | | 10,653 | 98.6 | 1.4 | 560 | 93.9 | 6.1 |
| Positive | | | | 2,231 | 98.6 | 1.4 | 113 | 96.5 | 3.5 |

NOTE. This table shows all available data, without study adjustment, for each of the variables shown, and includes homozygous carriers.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.
*Family history: no, none; or yes, at least one first-degree relative with breast cancer.
†*BRCA1/2* mutation status was only available for a subset of samples, all unknowns are assumed to be noncarriers.

**Table A8.** Breast Cancer Risk Estimates of *CHEK2**1100delC Carriers Using Different Models

| Model | Total, No. | OR | 95% CI | *P* | *P* * |
|---|---|---|---|---|---|
| Carrier model | | | | | |
| All patients with breast cancer | 81,711 | 2.48 | 2.11 to 2.90 | $7.2 \times 10^{-29}$ | .03 |
| Population- and hospital-based patients with breast cancer | 72,501 | 2.36 | 1.99 to 2.80 | $5.6 \times 10^{-23}$ | .02 |
| Log additive model | | | | | |
| All breast patients with cancer | 81,711 | 2.47 | 2.11 to 2.90 | $3.7 \times 10^{-29}$ | .15 |
| Population- and hospital-based patients with breast cancer | 72,501 | 2.36 | 1.99 to 2.80 | $2.1 \times 10^{-23}$ | .10 |
| Saturated model | | | | | |
| All breast patients with cancer | 81,711 | 2.44 | 2.08 to 2.87 | $6.3 \times 10^{-28}$ | |
| Population- and hospital-based patients with breast cancer | 72,501 | 2.32 | 1.95 to 2.75 | $5.5 \times 10^{-22}$ | |
| Carrier model; excluding homozygous *CHEK2* carriers | | | | | |
| All patients with breast cancer | 81,700 | 2.44 | 2.08 to 2.87 | $6.3 \times 10^{-28}$ | |
| Population- and hospital-based patients with breast cancer | 72,493 | 2.32 | 1.95 to 2.75 | $5.5 \times 10^{-22}$ | |

NOTE. Carrier model: *CHEK2* was included as 0 = noncarrier or 1 = carriers; log-additive model, *CHEK2* was included as 0 = noncarriers, 1 = heterozygous *CHEK2*, 2 = homozygous *CHEK2*; saturated model: *CHEK2* was modeled using offset as explained in Patients and Methods.
Abbreviation: OR, odds ratio.
* *P* value of the model concerned versus the saturated model.