Article:
Schmidt, M.J., Cox, A., Hogervorst, F. et al. (2016) Age- and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2*1100delC Carriers. Journal of Clinical Oncology, 34 (23). pp. 2750-2760. ISSN: 0732-183X

https://doi.org/10.1200/JCO.2016.66.5844

Published Ahead of Print on June 6, 2016 as 10.1200/JCO.2016.66.5844
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2016.66.5844

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

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

Marjanka K. Schmidt, Frans Hogervorst, Richard van Hien, Sten Cornelissen, Annegien Broeks, Muriel A. Adank, Hanne Meijers, Quinten Waisfisz, Antoinette Hollestelle, Mieke Schutte, Ans van den Ouweland, Maartje Hooning, Irene L. Andrulis, Hoda Anton-Culver, Natalia N. Antonenkova, Antonis C. Antoniou, Volker Arndt, Marina Bermisheva, Natalia V. Bogdanova, Manjeet K. Bolla, Hiltrud Brauch, Hermann Brenner, Thomas Brüning, Barbara Burwinkel, Jenny Chang-Claude, Georgia Chenevix-Trench, Fergus J. Couch, Angela Cox, Simon S. Cross, Kamila Czene, Alison M. Dunning, Peter A. Fasching, Jonine Figueroa, Olivia Fletcher, Henrik Flyger, Eva Galle, Montserrat García-Closas, Graham G. Giles, Lothar Haeberle, Per Hall, Peter Hillemanns, John L. Hopper, Anna Jakubowska, Esther M. John, Michael Jones, Elza Khusnutdinova, Julia A. Knight, Veli-Matti Kosma, Vessela Kristensen, Andrew Lee, Annika Lindblom, Jan Lubinski, Arto Mannermaa, Sara Margolin, Alfons Meindl, Roger L. Milne, Taru A. Muranen, Polly A. Newcomb, Kenneth Offit, Tjoung-Won Park-Simon, Julian Peto, Paul D.P. Pharoah, Mark Robson, Anja Rudolph, Elinor J. Sawyer, Rita K. Schmutzler, Caroline Seynaeve, Julie Soens, Melissa C. Southey, Amanda B. Spurdle, Harald Surowy, Anthony Swerdlow, Rob A.E.M. Tollenaar, Ian Tomlinson, Amy Trentham-Dietz, Celine Vachon, Qin Wang, Alice S. Whittemore, Argyrios Ziogas, Lizet van der Kolk, Heli Nevanlinna, Thilo Dörk, Stig Bojesen, and Douglas F. Easton

Author affiliations appear at the end of this article.

Published online ahead of print at www.jco.org on June 6, 2016.

Written on behalf of Norwegian Breast Cancer Study Investigators.

Support information appears at the end of this article.

Authors' disclosures of potential conflicts of interest are found in the article online at www.jco.org. Author contributions are found at the end of this article.

Corresponding author: Marjanka K. Schmidt, MD, Division of Molecular Pathology, and Division of Psychosocial Research and Epidemiology, Netherlands Cancer Institute, Antoni van Leeuwenhoek hospital, Plesmanlaan 121, 1066CX Amsterdam, the Netherlands; e-mail: mk.schmidt@nki.nl.

0732-183X/16/3499-1/$20.00

DOI: 10.1200/JCO.2016.66.5844

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 = 9.9×10^{-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.

J Clin Oncol 34. © 2016 by American Society of Clinical Oncology

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]

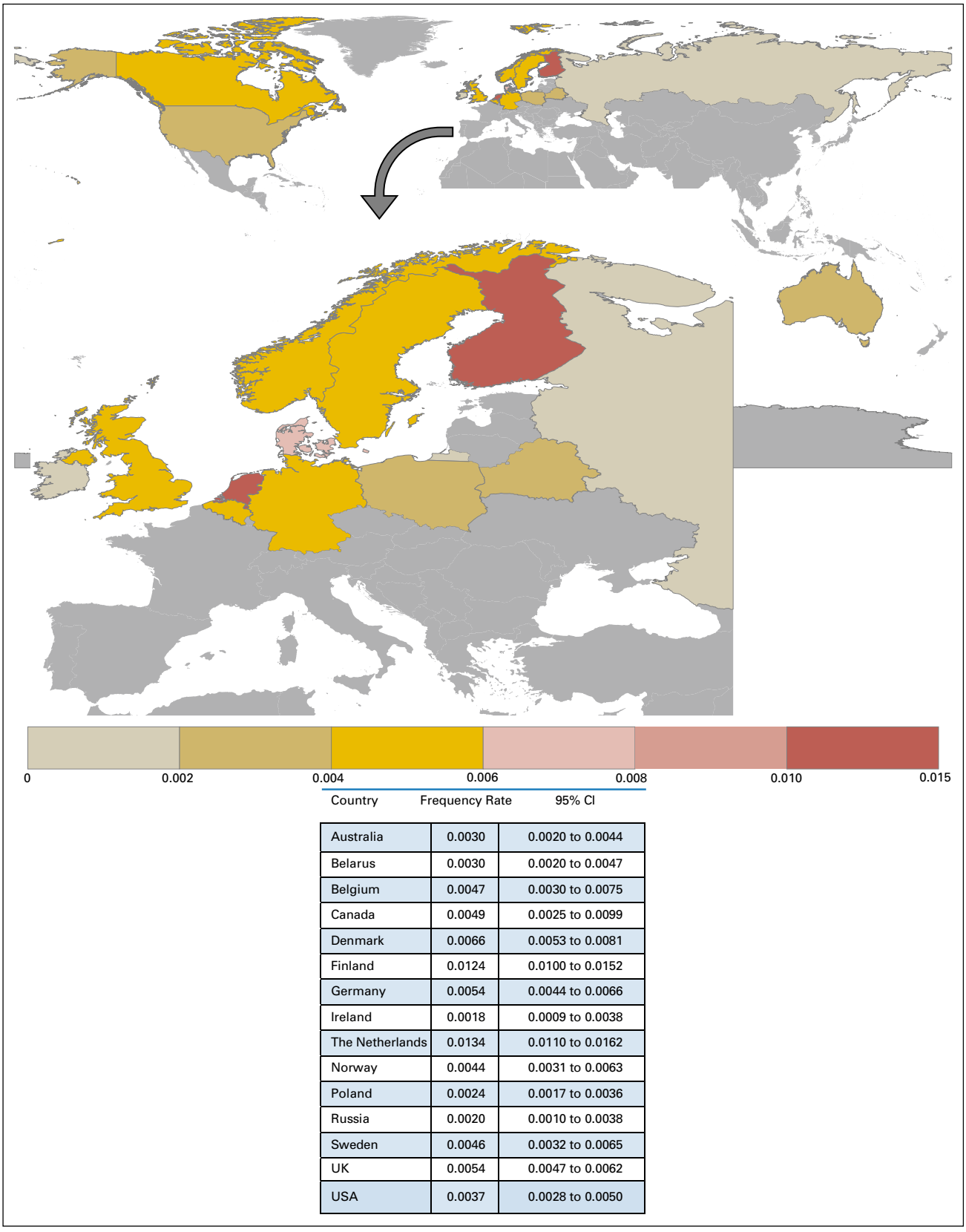
CHEK2*1100delC Genotyping

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 χ^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).

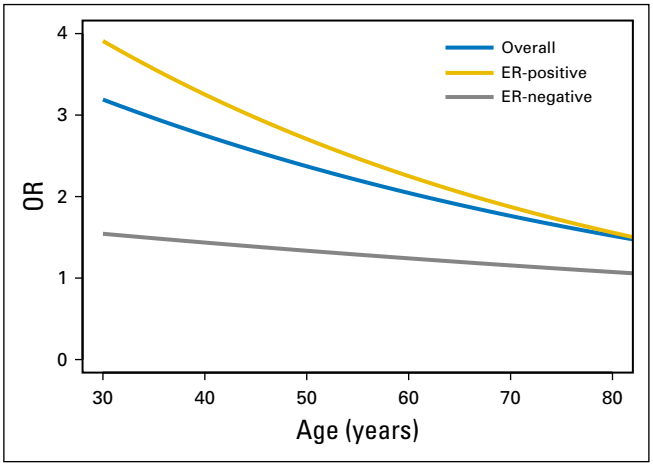


Fig 2. Breast cancer relative risk curves for *CHEK2**1100delC carriers by age for invasive breast cancer: overall, estrogen receptor (ER)–positive, and ER-negative disease. OR, odds ratio.

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	1.0×10^{-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	2.7×10^{-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	6.3×10^{-28}
Population- and hospital-based patients with breast cancer	36,029/39,464	2.32	1.95 to 2.75	5.5×10^{-22}
All invasive tumors	39,798/39,956	2.40	2.04 to 2.82	2.0×10^{-26}
Population- and hospital-based patients with breast cancer, invasive tumors	34,525/36,464	2.26	1.90 to 2.69	2.3×10^{-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	6.3×10^{-11}
All in situ tumors†	1,577/34,818	3.53	2.38 to 5.23	3.9×10^{-10}
Population- and hospital-based patients with breast cancer, in situ tumors†	1,208/33,379	3.36	2.15 to 5.25	1.0×10^{-7}
All patients with breast cancer, custom Taqman	39,440/36,596	2.50	2.11 to 2.95	1.2×10^{-26}
Population- and hospital-based patients with breast cancer, custom Taqman	34,485/34,466	2.33	1.96 to 2.79	5.5×10^{-21}
All patients with breast cancer, non-*BRCA1/2* carriers only	41,365/39,954	2.46	2.09 to 2.88	2.7×10^{-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	4.0×10^{-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	2.6×10^{-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	1.3×10^{-2}	Ref†
35-50	20,478	2.57	1.83 to 3.59	4.0×10^{-8}	.17
50-65	31,736	2.36	1.80 to 3.10	6.5×10^{-10}	5.3×10^{-2}
> 65	14,591	1.40	0.93 to 2.12	.11	1.8×10^{-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	4.9×10^{-21}	9.9×10^{-6}
PR status					
Negative	40,041	1.72	1.29 to 2.30	1.9×10^{-4}	Ref
Positive	46,648	2.51	2.02 to 3.12	7.6×10^{-17}	1.7×10^{-2}
HER2 status					
Negative	37,920	2.40	1.88 to 3.06	1.4×10^{-2}	Ref
Positive	29,584	2.66	1.77 to 4.00	2.7×10^{-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	2.0×10^{-3}	.20
50-65	15,544	2.06	1.33 to 3.19	1.0×10^{-3}	9.0×10^{-3}
> 65	7,101	1.26	0.67 to 2.37	.47	2.1×10^{-2}
ER-negative by age category, years					
< 35	2,855	3.02	0.93 to 9.86	6.7×10^{-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	4.2×10^{-2}	Ref¶
35-50	14,029	3.12	2.13 to 4.58	5.3×10^{-9}	.20
50-65	24,029	2.73	2.02 to 3.70	6.7×10^{-11}	8.2×10^{-2}
> 65	11,597	1.58	1.01 to 2.49	4.6×10^{-2}	3.2×10^{-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

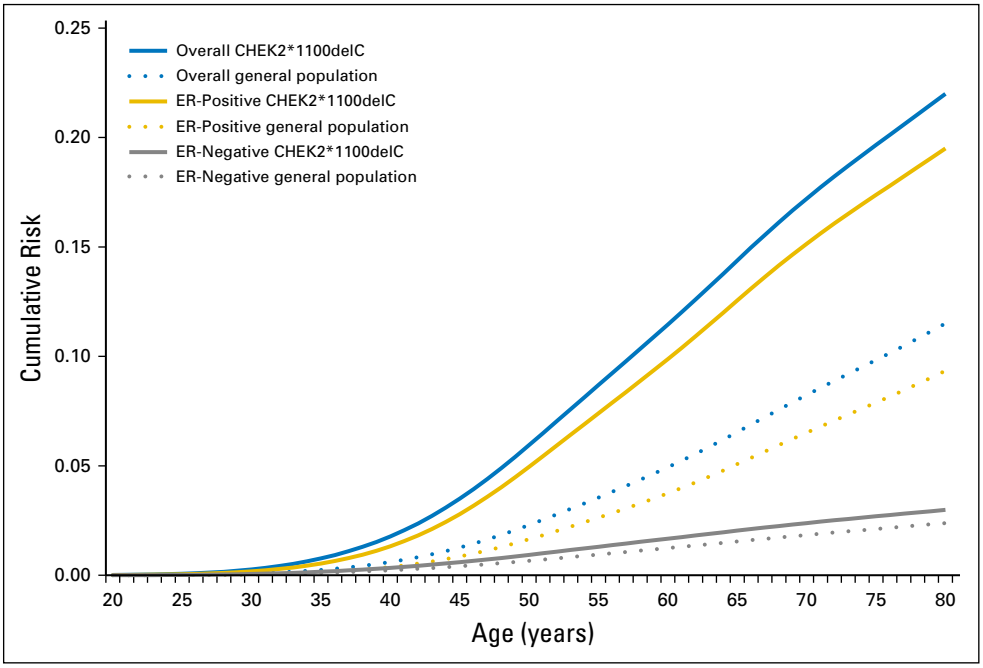


Fig 3. Cumulative breast cancer risks for *CHEK2**1100delC carriers and the general female population by attained age. ER, estrogen receptor.

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

Disclosures provided by the authors are available with this article at www.jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: Marjanka K. Schmidt, Douglas F. Easton
Financial support: Marjanka K. Schmidt, Frans Hogervorst
Administrative support: Marjanka K. Schmidt, Manjeet K. Bolla, Qin Wang
Provision of study materials or patients: Marjanka K. Schmidt, Frans Hogervorst, Muriel A. Adank, Hanne Meijers, Quinten Waisfisz, Antoinette Hollestelle, Mieke Schutte, Ans van den Ouweland, Irene L. Andrulis, Hoda Anton-Culver, Natalia N. Antonenkova, Volker Arndt, Marina Bermisheva, Natalia V. Bogdanova, Hiltrud Brauch, Hermann Brenner, Thomas Brüning, Barbara Burwinkel, Jenny Chang-Claude, Georgia Chenevix-Trench, Fergus J. Couch, Angela Cox, Simon S. Cross, Kamila Czene, Alison M. Dunning, Peter A. Fasching, Jonine Figueroa, Olivia Fletcher, Henrik Flyger, Eva Galle, Montserrat García-Closas, Graham G. Giles, Lothar Haeberle, Per Hall, Peter Hillemanns, John L. Hopper, Anna Jakubowska, Esther M. John, Michael Jones, Elza Khusnutdinov, Julia A. Knight, Veli-Matti Kosma, Vessela Kristensen, Annika Lindblom, Jan Lubinski, Arto Mannermaa, Sara Margolin, Alfons Meindl, Roger L. Milne, Taru A. Muranen, Polly A. Newcomb, Kenneth Offit, Tjoung-Won Park-Simon, Julian Peto, Paul D.P. Pharoah, Mark Robson, Anja Rudolph, Elinor J. Sawyer, Rita K. Schmutzler, Caroline Seynaeve, Julie Soens, Melissa C. Southey, Rob A.E.M. Tollenaar, Ian Tomlinson, Amy Trentham-Dietz, Celine Vachon, Alice S. Whittemore, Argyrios Ziogas, Lizet van der Kolk, Heli Nevanlinna, Thilo Dörk, Stig Bojesen
Collection and assembly of data: Marjanka K. Schmidt, Frans Hogervorst, Richard van Hien, Sten Cornelissen, Annegien Broeks, Muriel A. Adank, Hanne Meijers, Quinten Waisfisz, Antoinette Hollestelle, Mieke Schutte, Ans van den Ouweland, Maartje Hooning, Irene L. Andrulis, Hoda Anton-Culver, Natalia N. Antonenkova, Volker Arndt, Marina Bermisheva, Natalia V. Bogdanova, Manjeet K. Bolla, Hiltrud Brauch, Hermann Brenner, Thomas Brüning, Barbara Burwinkel, Jenny Chang-Claude, Georgia Chenevix-Trench, Fergus J. Couch, Angela Cox, Simon S. Cross, Kamila Czene, Alison M. Dunning, Peter A. Fasching, Jonine Figueroa, Olivia Fletcher, Henrik Flyger, Eva Galle, Montserrat García-Closas, Graham G. Giles, Lothar Haeberle, Per Hall, Peter Hillemanns, John L. Hopper, Anna Jakubowska, Esther M. John, Michael Jones, Elza Khusnutdinov, Julia A. Knight, Veli-Matti Kosma, Vessela Kristensen, Andrew Lee, Annika Lindblom, Jan Lubinski, Arto Mannermaa, Sara Margolin, Alfons Meindl, Roger L. Milne, Taru A. Muranen, Polly A. Newcomb, Kenneth Offit, Tjoung-Won Park-Simon, Julian Peto, Paul D.P. Pharoah, Mark Robson, Anja Rudolph, Elinor J. Sawyer, Rita K. Schmutzler, Caroline Seynaeve, Julie Soens, Melissa C. Southey, Amanda B. Spurdle, Harald Surowy, Anthony Swerdlow, Rob A.E.M. Tollenaar, Ian Tomlinson, Amy Trentham-Dietz, Celine Vachon, Qin Wang, Alice S. Whittemore, Argyrios Ziogas, Lizet van der Kolk, Heli Nevanlinna, Thilo Dörk, Stig Bojesen, Douglas F. Easton
Data analysis and interpretation: Marjanka K. Schmidt, Antonis C. Antoniou, Stig Bojesen, Douglas F. Easton
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. CHEK2 Breast Cancer Case-Control Consortium: CHEK2*1100delC and susceptibility to breast cancer: A collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. Am J Hum Genet 74:1175-1182, 2004
2. Bartek J, Lukas J: Chk1 and Chk2 kinases in checkpoint control and cancer. Cancer Cell 3:421-429, 2003
3. Shieh SY, Ahn J, Tamai K, et al: The human homologs of checkpoint kinases Chk1 and Cds1 (Chk2) phosphorylate p53 at multiple DNA damage-inducible sites. Genes Dev 14:289-300, 2000
4. Craig AL, Hupp TR: The regulation of CHK2 in human cancer. Oncogene 23:8411-8418, 2004
5. Schutte M, Seal S, Barfoot R, et al: Variants in CHEK2 other than 1100delC do not make a major contribution to breast cancer susceptibility. Am J Hum Genet 72:1023-1028, 2003
6. Cybulski C, Górski B, Huzarski T, et al: CHEK2-positive breast cancers in young Polish women. Clin Cancer Res 12:4832-4835, 2006
7. Weischer M, Bojesen SE, Ellervik C, et al: CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: Meta-analyses of 26,000 patient cases and 27,000 controls. J Clin Oncol 26:542-548, 2008
8. Zhang S, Phelan CM, Zhang P, et al: Frequency of the CHEK2 1100delC mutation among women with breast cancer: An international study. Cancer Res 68:2154-2157, 2008
9. Fletcher O, Johnson N, Dos Santos Silva I, et al: Family history, genetic testing, and clinical risk prediction: Pooled analysis of CHEK2 1100delC in 1,828 bilateral breast cancers and 7,030 controls. Cancer Epidemiol Biomarkers Prev 18:230-234, 2009

10. Meijers-Heijboer H, van den Ouweland A, Klijn J, et al: Low-penetrance susceptibility to breast cancer due to CHEK2(*)1100delC in noncarriers of BRCA1 or BRCA2 mutations. Nat Genet 31:55-59, 2002

11. Schmidt MK, Tollenaar RAEM, de Kemp SR, et al: Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2*1100delC germline mutation. J Clin Oncol 25:64-69, 2007

12. Weischer M, Nordestgaard BG, Pharoah P, et al: CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. J Clin Oncol 30:4308-4316, 2012

13. de Bock GH, Schutte M, Krol-Warmerdam EM, et al: Tumour characteristics and prognosis of breast cancer patients carrying the germline CHEK2*1100-delC variant. J Med Genet 41:731-735, 2004

14. Nagel JH, Peeters JK, Smid M, et al: Gene expression profiling assigns CHEK2 1100delC breast cancers to the luminal intrinsic subtypes. Breast Cancer Res Treat 132:439-448, 2012

15. Meyer A, Dörk T, Sohn C, et al: Breast cancer in patients carrying a germ-line CHEK2 mutation: Outcome after breast conserving surgery and adjuvant radiotherapy. Radiother Oncol 82:349-353, 2007

16. Easton DF, Pharoah PD, Antoniou AC, et al: Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 372:2243-2257, 2015

17. Meijers-Heijboer EJ, Verhoog LC, Brekelmans CT, et al: Presymptomatic DNA testing and prophylactic surgery in families with a BRCA1 or BRCA2 mutation. Lancet 355:2015-2020, 2000

18. Howell A, Anderson AS, Clarke RB, et al: Risk determination and prevention of breast cancer. Breast Cancer Res 16:446, 2014

19. Michailidou K, Hall P, Gonzalez-Neira A, et al: Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 45:353-361, 361e1-361e2, 2013

20. Mavaddat N, Pharoah PD, Michailidou K, et al: Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 107:djv036, 2015

21. Coebergh JW, van Veen EB, Vandenbroucke JP, et al: One-time general consent for research on biological samples: Opt out system for patients is optimal and endorsed in many countries. BMJ 332: 665, 2006

22. Clayton D, Kaldor J: Empirical Bayes estimates of age-standardized relative risks for use in disease mapping. Biometrics 43:671-681, 1987

23. Lee AS, Ang P: CHEK2*1100delC screening of Asian women with a family history of breast cancer is unwarranted. J Clin Oncol 26:2419, author reply 2419-2420, 2008

24. National Institute for Health and Care Excellence: Familial breast cancer: Classification, care and managing breast cacer and related risks in people with a family history of breast cancer. https://www.nice.org.uk/guidance/cg164

25. Lee AJ, Cunningham AP, Kuchenbaecker KB, et al: BOADICEA breast cancer risk prediction model: Updates to cancer incidences, tumour pathology and web interface. Br J Cancer 110:535-545, 2014

26. Adank MA, Jonker MA, Kluijt I, et al: CHEK2*1100delC homozygosity is associated with a high breast cancer risk in women. J Med Genet 48:860-863, 2011

27. Adank MA, Verhoef S, Oldenburg RA, et al: Excess breast cancer risk in first degree relatives of CHEK2∗1100delC positive familial breast cancer cases. Eur J Cancer 49:1993-1999, 2013

28. Adank M, Hes FJ, van Zelst-Stams WA, et al: CHEK2-mutatie diagnostiek in Nederlandse borstkankerfamilies. Uitbreiding van het genetisch diagnostisch pakket [in Dutch]. Ned Tijdschr Geneeskd 159:A8910, 2015.

Affiliations

Marjanka K. Schmidt, Frans Hogervorst, Richard van Hien, Sten Cornelissen, Annegien Broeks, and Lizet van der Kolk, Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital; Muriel A. Adank, Hanne Meijers, and Quinten Waisfisz, VU University Medical Center, Amsterdam; Antoinette Hollestelle, Mieke Schutte, Maartje Hooning, and Caroline Seynaeve, Erasmus MC Cancer Institute; Ans van den Ouweland, Erasmus University Medical Center, Rotterdam; Rob A.E.M. Tollenaar, Leiden University Medical Center, Leiden, the Netherlands; Irene L. Andrulis and Julia A. Knight, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital; Irene L. Andrulis and Julia A. Knight, University of Toronto, Toronto, Ontario, Canada; Hoda Anton-Culver and Argyrios Ziogas, University of California, Irvine; Peter A. Fasching, David Geffen School of Medicine, University of California, Los Angeles; Esther M. John, Cancer Prevention Institute of California, Fremont; Esther M. John, Alice S. Whittemore, Stanford University School of Medicine, Stanford, CA; Natalia N. Antonenkova, N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus; Antonis C. Antoniou, Manjeet K. Bolla, Andrew Lee, Alison M. Dunning, Paul D.P. Pharoah, Qin Wang, and Douglas F. Easton, University of Cambridge, Cambridge; Angela Cox and Simon S. Cross, University of Sheffield, Sheffield; Olivia Fletcher, Michael Jones, and Anthony Swerdlow, The Institute of Cancer Research; Julian Peto, London School of Hygiene and Tropical Medicine; Elinor J. Sawyer, King's College London, London; Jonine Figueroa, University of Edinburgh Medical School, Edinburgh; Ian Tomlinson, University of Oxford, Oxford, United Kingdom; Volker Arndt, Hiltrud Brauch, Hermann Brenner, Barbara Burwinkel, Jenny Chang-Claude, Anja Rudolph, Harold Surowy, German Cancer Research Center; Barbara Burwinkel and Harald Surowy, University of Heidelberg, Heidelberg; Natalia V. Bogdanova, Peter Hillemanns, Tjoung-Won Park-Simon, and Thilo Dörk, Hannover Medical School, Hannover; Hiltrud Brauch, Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart; Hiltrud Brauch, University of Tübingen, Tübingen; Thomas Brüning, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum, Bochum; Jenny Chang-Claude, University Medical Center Hamburg-Eppendorf, Hamburg; Peter A. Fasching and Lothar Haeberle, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen-EMN, Erlangen; Alfons Meindl, Technische Universität München, Munich; Rita K. Schmutzler, University Hospital of Cologne; Rita K. Schmutzler, University of Cologne, Cologne, Germany; Marina Bermisheva, Ufa Scientific Center of Russian Academy of Sciences; Elza Khusnutdinova, Bashkir State University, Ufa, Russia; Georgia Chenevix-Trench and Amanda B. Spurdle, QIMR Berghofer Medical Research Institute, Brisbane; Graham G. Giles and Roger L. Milne, Cancer Council Victoria; Graham G. Giles, John L. Hopper, Roger L. Milne, and Melissa C. Southey, The University of Melbourne, Melbourne, Australia; Fergus J. Couch and Celine Vachon, Mayo Clinic, Rochester, MN; Kamila Czene, Per Hall, Annika Lindblom, and Sara Margolin, Karolinska Institutet, Stockholm, Sweden; Jonine Figueroa, Montserrat García-Closas, National Cancer Institute, Rockville, MD; Henrik Flyger and Stig Bojesen, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev; Stig Bojesen, University of Copenhagen, Copenhagen, Denmark; Eva Galle, University of Leuven; Eva Galle, Vesalius Research Center; Julie Soens, University Hospital Gasthuisberg, Leuven, Belgium; Anna Jakubowska and Jan Lubinski, Pomeranian Medical University, Szczecin, Poland; Veli-Matti Kosma and Arto Mannermaa, University of Eastern Finland; Veli-Matti Kosma and Arto Mannermaa, Kuopio University Hospital, Kuopio; Taru A. Muranen and Heli Nevanlinna, University of Helsinki, Helsinki, Finland; Vessela Kristensen, Oslo University Hospital Radiumhospitalet; Vessela Kristensen, University of Oslo, Oslo, Norway; Polly A. Newcomb and Amy Trentham-Dietz, University of Wisconsin, Madison, WI; Polly A. Newcomb, Fred Hutchinson Cancer Research Center, Seattle, WA; and Kenneth Offit, Mark Robson, Memorial Sloan Kettering Cancer Center, New York, NY.

Support

Supported by NIHR Comprehensive Biomedical Research Centre, Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London, United Kingdom (to E.J.S.). G.C.-T. is supported by the NHMRC. Supported by (for Breast Cancer Association Consortium) Cancer Research UK [C1287/A10118, C1287/A12014] and by the European Community's Seventh Framework Programme under grant agreement number 223175 (Grant No. HEALTH-F2-2009-223175; COGS); The Australian Breast Cancer Family Study (ABCFS) was supported by Grant No. UM1 CA164920 from the National Cancer Institute, the National Health and Medical Research Council of Australia, the New South Wales Cancer Council, the Victorian Health Promotion Foundation (Australia), and the Victorian Breast Cancer Research Consortium; the Amsterdam Breast Cancer Study was supported by the Dutch Cancer Society (Grants No. NKI 2007-3839; 2009 4363), BBMRI-NL, which is a Research Infrastructure financed by the Dutch government (NWO 184.021.007), and the Dutch National Genomics Initiative; the Bavarian Breast Cancer Cases and Controls was partly funded by ELAN-Fond of the University Hospital of Erlangen; the British Breast Cancer Study is funded by Cancer Research UK and Breast Cancer Now and acknowledges NHS funding to the NIHR Biomedical Research Centre and the National Cancer Research Network; the Breast Cancer Study of the University of Heidelberg was supported by the Dietmar-Hopp Foundation, the Helmholtz Society, and the German Cancer Research Center (DKFZ); the Copenhagen General Population Study was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council, and Herlev Hospital; the ESTHER Breast Cancer Study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts; the German Consortium for Hereditary Breast & Ovarian Cancer is supported by the German Cancer Aid (Grant No. 110837); the Gene Environment Interaction and Breast Cancer in Germany study was funded by the Federal Ministry of Education and Research Germany Grants No. 01KW9975/5, 01KW9976/8, 01KW9977/0, and 01KW0114, the Robert Bosch Foundation, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, the Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany; the Genetic Epidemiology Study of Breast Cancer by Age 50 was supported by the Deutsche Krebshilfe e. V. [70492] and the German Cancer Research Center (DKFZ); the Hannover Breast Cancer Study was supported by an intramural grant from Hannover Medical School; the Helsinki Breast Cancer Study was financially supported by the Helsinki University Central Hospital Research Fund, Academy of Finland (266528), the Finnish Cancer Society, The Nordic Cancer Union, and the Sigrid Juselius Foundation; the Hannover-Minsk Breast Cancer Study was supported by a grant from the Friends of Hannover Medical School and by the Rudolf Bartling Foundation; the Hannover-Ufa Breast Cancer Study was supported by a grant from the German Federal Ministry of Research and Education (RUS08/017); the Karolinska Breast Cancer Study was supported by the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet, the Swedish Cancer Society, The Gustav V Jubilee Foundation, and and Bert von Kantzows Foundation; the Kuopio Breast Cancer Project was supported by the special Government Funding (EVO) of Kuopio University Hospital grants, Cancer Fund of North Savo, the Finnish Cancer Organizations, and by the strategic funding of the University of Eastern Finland; the Kathleen Cuningham Foundation Consortium for Research Into Familial Breast Cancer is supported by a grant from the National Breast Cancer Foundation, and previously by the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania, and South Australia, and the Cancer Foundation of Western Australia; the Australian Ovarian Cancer Study was supported by the United States Army Medical Research and Materiel Command [DAMD17-01-1-0729], Cancer Council Victoria, Queensland Cancer Fund, Cancer Council New South Wales, Cancer Council South Australia, The Cancer Foundation of Western Australia, Cancer Council Tasmania, and the National Health and Medical Research Council of Australia (NHMRC; 400413, 400281, 199600); the Mayo Clinic Breast Cancer Study was supported by NIH Grants No. CA192393, CA116167, CA176785, an NIH Specialized Program of Research Excellence (SPORE) in Breast Cancer [CA116201], the Breast Cancer Research Foundation, and a generous gift from the David F. and Margaret T. Grohne Family Foundation; the Melbourne Collaborative Cohort Study was funded by VicHealth and Cancer Council Victoria and was further supported by Australian NHMRC Grants No. 209057, 251553, and 504711 and by infrastructure provided by Cancer Council Victoria; the Memorial Sloan Kettering Cancer Center Study is supported by grants from the Breast Cancer Research Foundation and Robert and Kate Niehaus Clinical Cancer Genetics Initiative; the Norwegian Breast Cancer Study has received funding from the K.G. Jebsen Centre for Breast Cancer Research, the Research Council of Norway grant 193387/V50 (to V.K.) and Grant No. 193387/H10 (to V.K.), South Eastern Norway Health Authority (Grant No. 39346), and the Norwegian Cancer Society (to V.K.); the Northern California Breast Cancer Family Registry was supported by Grant No. UM1 CA164920 from the National Cancer Institute; the Ontario Familial Breast Cancer Registry was supported by Grant No. UM1 CA164920 from the National Cancer Institute; the Leiden University Medical Centre Breast Cancer Study study was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16); the NCI Polish Breast Cancer Study was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services; the Rotterdam Breast Cancer Study was funded by the Dutch Cancer Society (Grants No. DDHK 2004-3124, DDHK 2009-4318); the Singapore and Sweden Breast Cancer Study study was supported the Agency for Science, Technology and Research of Singapore (A*STAR), the National Institutes of Health, and the Susan G. Komen Breast Cancer Foundation; the Sheffield Breast Cancer Study was supported by Yorkshire Cancer Research S295, S299, S305PA, and Sheffield Experimental Cancer Medicine Centre; the Study of Epidemiology and Risk factors in Cancer Heredity is funded by a programme grant from Cancer Research UK (C490/A10124) and supported by the UK National Institute for Health Research

Biomedical Research Centre at the University of Cambridge; the IHCC-Szczecin Breast Cancer Study was supported by Grant No. PBZ_KBN_122/P05/2004; the UCI Breast Cancer Study component of this research was supported by the NIH (Grants No. CA58860, CA92044) and the Lon V Smith Foundation (LVS39420); the UK Breakthrough Generations Study is funded by Breast Cancer Now and the Institute of Cancer Research, London; the US Three State Study was supported by Massachusetts (Grant No. R01CA47305), Wisconsin (Grant No. R01 CA47147), and New Hampshire (Grant No. R01CA69664) centers, and Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services; and the Leuven Multidisciplinary Breast Centre is supported by the 'Stichting tegen Kanker' (232-2008 and 196-2010) and core funding to the Wellcome Trust Centre for Human Genetics from the Wellcome Trust (090532/Z/09/Z).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Age- and Tumor Subtype–Specific Breast Cancer Risk Estimates for *CHEK21100delC Carriers**

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Marjanka K. Schmidt
No relationship to disclose

Frans Hogervorst
No relationship to disclose

Richard van Hien
No relationship to disclose

Sten Cornelissen
No relationship to disclose

Annegien Broeks
No relationship to disclose

Muriel A. Adank
No relationship to disclose

Hanne Meijers
No relationship to disclose

Quinten Waisfisz
No relationship to disclose

Antoinette Hollestelle
No relationship to disclose

Mieke Schutte
No relationship to disclose

Ans van den Ouweland
No relationship to disclose

Maartje Hooning
No relationship to disclose

Irene L. Andrulis
No relationship to disclose

Hoda Anton-Culver
No relationship to disclose

Natalia N. Antonenkova
No relationship to disclose

Antonis C. Antoniou
No relationship to disclose

Volker Arndt
No relationship to disclose

Marina Bermisheva
No relationship to disclose

Natalia V. Bogdanova
No relationship to disclose

Manjeet K. Bolla
No relationship to disclose

Hiltrud Brauch
No relationship to disclose

Hermann Brenner
No relationship to disclose

Thomas Brüning
No relationship to disclose

Barbara Burwinkel
No relationship to disclose

Jenny Chang-Claude
No relationship to disclose

Georgia Chenevix-Trench
No relationship to disclose

Fergus J. Couch
No relationship to disclose

Angela Cox
No relationship to disclose

Simon S. Cross
No relationship to disclose

Kamila Czene
No relationship to disclose

Alison M. Dunning
No relationship to disclose

Peter A. Fasching
Honoraria: Novartis, Amgen, Pfizer, Celgene, Roche, Genomic Health, NanoString Technologies
Consulting or Advisory Role: Roche, Novartis, Pfizer, Celgene
Speakers' Bureau: Novartis, Celgene, Pfizer, Roche, Amgen
Research Funding: Novartis (Inst), Amgen (Inst), Celgene (Inst), Pfizer (Inst), Siemens (Inst)

Jonine Figueroa
No relationship to disclose

Olivia Fletcher
No relationship to disclose

Henrik Flyger
No relationship to disclose

Eva Galle
No relationship to disclose

Montserrat García-Closas
No relationship to disclose

Graham G. Giles
No relationship to disclose

Lothar Haeberle
No relationship to disclose

Per Hall
No relationship to disclose

Peter Hillemanns
Honoraria: Roche, SPMSD, Hologic, Abbott Laboratories
Research Funding: GlaxoSmithKline (Inst), Vaccibody (Inst)

John L. Hopper
No relationship to disclose

Anna Jakubowska
No relationship to disclose

Esther M. John
No relationship to disclose

Michael Jones
No relationship to disclose

Elza Khusnutdinov
No relationship to disclose

Julia A. Knight
No relationship to disclose

Veli-Matti Kosma
No relationship to disclose

Vessela Kristensen
No relationship to disclose

Andrew Lee
No relationship to disclose

Annika Lindblom
No relationship to disclose

Jan Lubinski
No relationship to disclose

Arto Mannermaa
No relationship to disclose

Sara Margolin
No relationship to disclose

Alfons Meindl
No relationship to disclose

Roger L. Milne
No relationship to disclose

Taru A. Muranen
No relationship to disclose

Polly A. Newcomb
No relationship to disclose

Kenneth Offit
No relationship to disclose

Tjoung-Won Park-Simon
No relationship to disclose

Julian Peto
No relationship to disclose

Paul D.P. Pharoah
Consulting or Advisory Role: Check4Cancer (I)
Patents, Royalties, Other Intellectual Property: Patent on seven SNP breast cancer risk test

Mark Robson
Honoraria: AstraZeneca
Consulting or Advisory Role: Bayer, Pfizer, McKesson
Research Funding: AstraZeneca (Inst), AbbVie (Inst), Myriad Genetics (Inst), Medivation (Inst)
Travel, Accommodations, Expenses: AstraZeneca, Biomarin

Anja Rudolph
No relationship to disclose

Elinor J. Sawyer
No relationship to disclose

Rita K. Schmutzler
No relationship to disclose

Caroline Seynaeve
No relationship to disclose

Julie Soens
No relationship to disclose

Melissa C. Southey
No relationship to disclose

Amanda B. Spurdle
No relationship to disclose

Harald Surowy
No relationship to disclose

Anthony Swerdlow
Stock or Other Ownership: GlaxoSmithKline (I)

Rob A.E.M. Tollenaar
No relationship to disclose

Ian Tomlinson
No relationship to disclose

Amy Trentham-Dietz
No relationship to disclose

Celine Vachon
No relationship to disclose

Qin Wang
No relationship to disclose

Alice S. Whittemore
No relationship to disclose

Argyrios Ziogas
No relationship to disclose

Lizet van der Kolk
No relationship to disclose

Heli Nevanlinna
No relationship to disclose

Thilo Dörk
No relationship to disclose

Stig Bojesen
No relationship to disclose

Douglas F. Easton
No relationship to disclose

Acknowledgment

We thank all the individuals who took part in these studies and all the researchers, clinicians, technicians, and administrative staff who have enabled this work to be carried out. Furthermore, several studies wish to acknowledge specific persons or institutions: Australian Breast Cancer Family Study: Maggie Angelakos, Judi Maskiell, Gillian Dite; Amsterdam Breast Cancer Study: the NKI-AVL Medical Registry and the Family Cancer Clinic, Tony van der Velde, Daoud Ait Moha, Roelof Pruntel, Carla van Tiggelen, and Laura van 't Veer; British Breast Cancer Study: Eileen Williams, Elaine Ryder-Mills, Kara Sargus; Breast Cancer in Galway Genetic Study: Niall McInerney, Gabrielle Colleran, Andrew Rowan, Angela Jones, Nicola Miller, Michael Kerin; Breast Cancer Study of the University of Heidelberg: Peter Bugert, Medical Faculty Mannheim; Copenhagen General Population Study: staff and participants of the Copenhagen General Population Study, Dorthe Uldall Andersen, Maria Birna Arnadottir, Anne Bank, Dorthe Kjeldgård Hansen; ESTHER Breast Cancer Study: Hartwig Ziegler, Sonja Wolf, Volker Hermann, Christa Stegmaier, Katja Butterbach; German Consortium for Hereditary Breast & Ovarian Cancer: Stefanie Engert, Heide Hellebrand, Sandra Kröber; Gene Environment Interaction and Breast Cancer in Germany (GENICA): the GENICA Network: Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany [HB, Wing-Yee Lo, Christina Justenhoven], German Cancer Consortium (DKTK) and German Cancer Research Center (DKFZ) [HB], Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany [Yon-Dschun Ko, Christian Baisch], Institute of Pathology, University of Bonn, Germany [Hans-Peter Fischer], Molecular Genetics of Breast Cancer, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany [Ute Hamann], Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum (IPA), Bochum, Germany [TB, Beate Pesch, Sylvia Rabstein, Anne Lotz], and Institute of Occupational Medicine and Maritime Medicine, University Medical Center Hamburg-Eppendorf, Germany [Volker Harth]; Genetic Epidemiology Study of Breast Cancer by Age 50: Ursula Eilber; Hannover Breast Cancer Study: Michael Bremer; Helsinki Breast Cancer Study: Carl Blomqvist, Kristiina Aittomäki, Sofia Khan and Irja Erkkilä; Hannover-Minsk Breast Cancer Study: Peter Hillemanns, Hans Christiansen, and Johann H. Karstens; Kuopio Breast Cancer Project: Eija Myöhänen, Helena Kemiläinen; Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer (KConFab)/Australian Ovarian Cancer Study: all kCOnFab authors, and Heather Thorne, Eveline Niedermayr, all the KConFab research nurses and staff, the heads and staff of the Family Cancer Clinics, and the Clinical Follow Up Study; Leuven Multidisciplinary Breast Centre: Gilian Peuteman, Dominiek Smeets, Thomas Van Brussel, Kathleen Corthouts; Memorial Sloan Kettering Cancer Center Study: Marina Corines, Lauren Jacobs; Ontario Familial Breast Cancer Registry: Teresa Selander, Nayana Weerasooriya; Leiden University Medical Centre Breast Cancer Study: E. Krol-Warmerdam, J. Blom, J. Molenaar, MD; NCI Polish Breast Cancer Study: Louise Brinton, Mark Sherman, Neonila Szeszenia-Dabrowska, Beata Peplonska, Witold Zatonski, Pei Chao, Michael Stagner; Rotterdam Breast Cancer Study: Petra Bos, Jannet Blom, Ellen Crepin, Elisabeth Huijskens, Annette Heemskerk, the Erasmus MC Family Cancer Clinic; Singapore and Sweden Breast Cancer Study: the Swedish Medical Research Counsel; Sheffield Breast Cancer Study: Sue Higham, Helen Cramp, Ian Brock, Sabapathy Balasubramanian, Malcolm Reed, Dan Connley; Study of Epidemiology and Risk factors in Cancer Heredity (SEARCH): the SEARCH and EPIC teams; and UCI Breast Cancer Study: Irene Masunaka.

Appendix

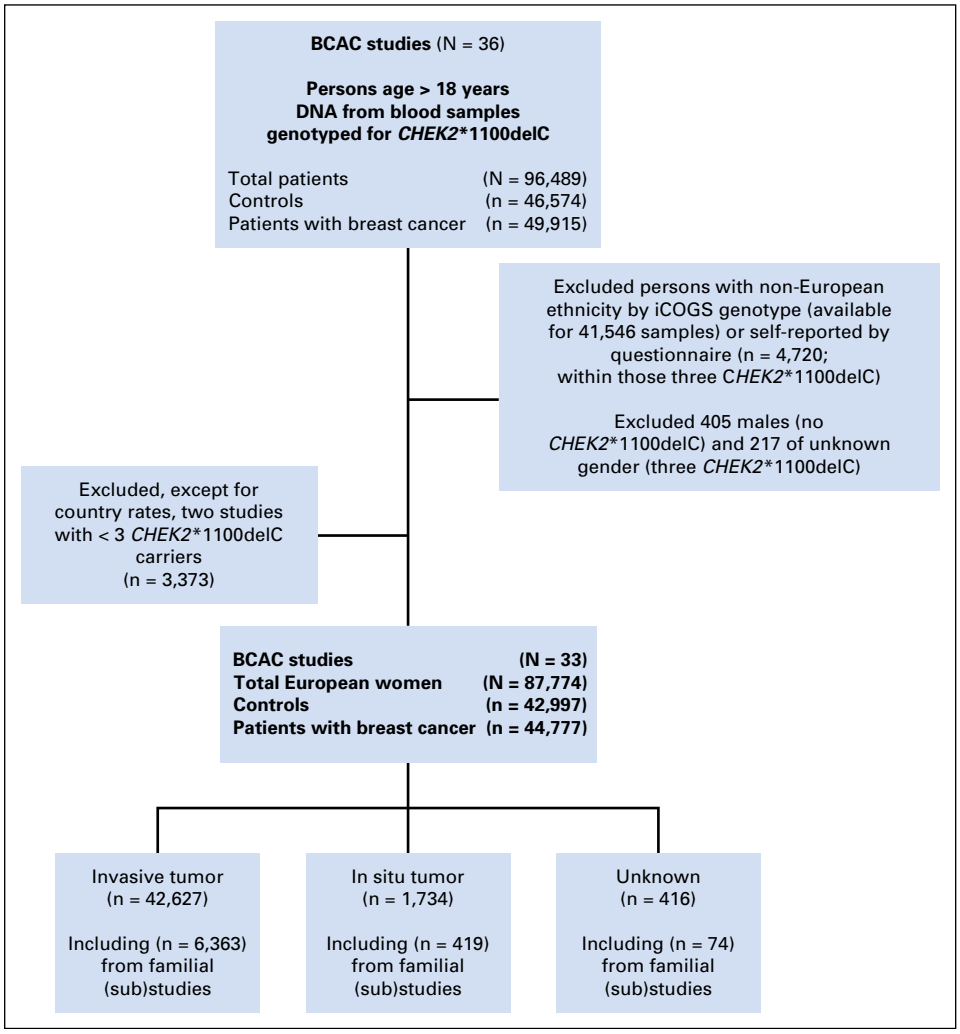


Fig A1. Data flowchart of inclusion and exclusion of patients with breast cancer and healthy controls from the Breast Cancer Association Consortium (BCAC) database.

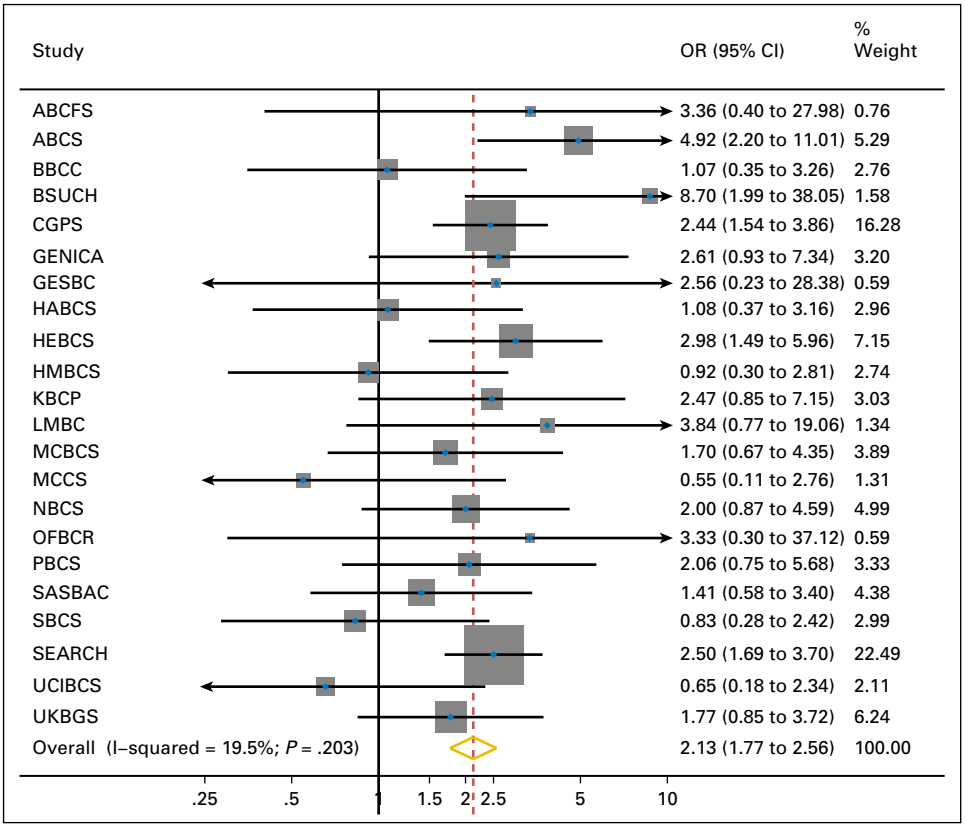


Fig A2. Forest plot of odds ratios (ORs) from a fixed meta-analysis of the association between *CHEK2**1100delC and invasive breast cancer by study, using population- and hospital-based studies. ABCFS, Australian Breast Cancer Family Study; ABCS, Amsterdam Breast Cancer Study; BBCC, Bavarian Breast Cancer 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.

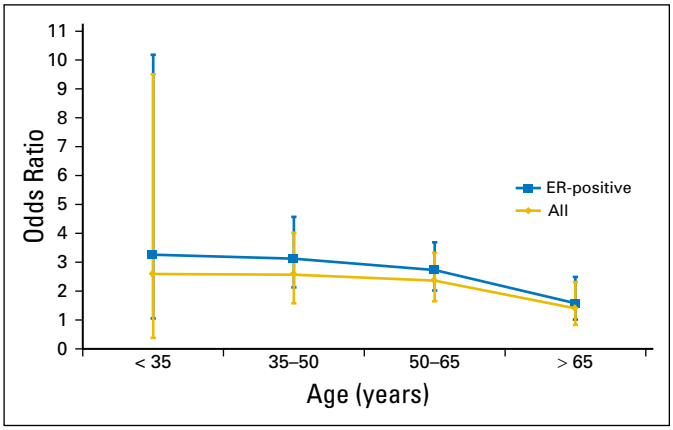


Fig A3. *CHEK2**1100delC-associated breast cancer risk per age category: all invasive and invasive estrogen receptor (ER)–positive disease. *P*-value trend for all and ER+ disease: $P = .014$ and $P = .026$, respectively (see Table 3).

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

	Patients From Population- and Hospital-Based Studies				Patients From Familial or Clinical Genetics Center–Based Studies			
Study	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	7.2×10^{-29}	.03
Population- and hospital-based patients with breast cancer	72,501	2.36	1.99 to 2.80	5.6×10^{-23}	.02
Log additive model					
All breast patients with cancer	81,711	2.47	2.11 to 2.90	3.7×10^{-29}	.15
Population- and hospital-based patients with breast cancer	72,501	2.36	1.99 to 2.80	2.1×10^{-23}	.10
Saturated model					
All breast patients with cancer	81,711	2.44	2.08 to 2.87	6.3×10^{-28}	
Population- and hospital-based patients with breast cancer	72,501	2.32	1.95 to 2.75	5.5×10^{-22}	
Carrier model; excluding homozygous *CHEK2* carriers					
All patients with breast cancer	81,700	2.44	2.08 to 2.87	6.3×10^{-28}	
Population- and hospital-based patients with breast cancer	72,493	2.32	1.95 to 2.75	5.5×10^{-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.