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Family History, Genetic Testing, and Clinical Risk Prediction: Pooled Analysis of CHEK2*1100delC in 1,828 Bilateral Breast Cancers and 7,030 Controls

Olivia Fletcher¹, Nichola Johnson¹, Isabel dos Santos Silva², Outi Kilpivaara³, Kristiina Aittomäki⁴, Carl Blomqvist⁵, Heli Nevanlinna³, Marijke Wasielewski⁶, Hanne Meijers-Heijerboer⁷, Annegien Broeks⁸, Marjanka K. Schmidt⁸, Laura J. Van't Veer⁸, Michael Bremer⁹, Thilo Dörk¹⁰, Elena V. Chekmariova¹¹, Anna P. Sokolenko¹¹, Evgeny N. Imyanitov¹¹, Ute Hamann¹², Muhammad U. Rashid^{12,13}, Hiltrud Brauch¹⁴, Christina Justenhoven¹⁴, Alan Ashworth¹, and Julian Peto^{2,15}

¹Breakthrough Breast Cancer Research Centre, Institute of Cancer Research London United Kingdom ²Non-communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, London United Kingdom ³Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland ⁴Department of Clinical Genetics, Helsinki University Central Hospital, Helsinki, Finland ⁵Department of Oncology, Helsinki University Central Hospital, Helsinki, Finland ⁶Department of Medical Oncology, Josephine Nefkens Institute, Erasmus Medical Centre, Rotterdam, the Netherlands ⁷Afdeling Klinische Genetica, Amsterdam, the Netherlands ⁸Netherlands Cancer Institute (NKI-AVL), Amsterdam, the Netherlands ⁹Department of Radiation Oncology, Hannover Medical School, Hannover, Germany ¹⁰Department of Gynaecology, Hannover Medical School, Hannover, Germany ¹¹N.N. Petrov Institute of Oncology, St. Petersburg, Russia ¹²Deutsches Krebsforschungszentrum, Heidelberg, Germany ¹³Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan ¹⁴Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart and University of Tübingen, Tübingen, Germany ¹⁵Cancer Research UK Epidemiology and Genetics Unit, Institute of Cancer Research, Sutton, Surrey, United Kingdom

Abstract

If breast cancers arise independently in each breast the odds ratio (OR) for bilateral breast cancer for carriers of *CHEK2*1100delC* should be ~5.5, the square of the reported OR for a first primary (OR, 2.34). In the subset of bilateral cases with one or more affected relatives, the predicted carrier OR should be ~9. We have tested these predictions in a pooled set of 1,828 cases with 2 primaries and 7,030 controls from 8 studies. The second primary OR for *CHEK2*1100delC* carriers was 6.43 (95% confidence interval, 4.33–9.56; $P < 0.0001$), significantly greater than the published estimate for a first primary ($P < 0.001$) but consistent with its square. The predicted increase in carrier OR with increasing numbers of affected relatives was seen using bilateral cases from the UK ($P_{\text{trend}} = 0.0003$) and Finland ($P_{\text{trend}} = 0.37$), although not using those from the Netherlands and Russia ($P = 0.001$ for heterogeneity between countries). Based on a standard genetic model,

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Requests for reprints: Julian Peto, Non-Communicable Disease Epidemiology Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, United Kingdom. Phone: 207-927-2455; Fax: 207-580-6897. E-mail: julian.peto@lshtm.ac.uk.

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we predict lifetime risks for *CHEK2*1100delC* carrier and noncarrier daughters of bilateral breast cancer cases of 37% and 18%, respectively. Our results imply that clinical management of the daughter of a woman with bilateral breast cancer should depend on her *CHEK2*1100delC* carrier status. This and other moderate penetrance breast cancer susceptibility alleles, together with family history data, will thus identify increasing numbers of women at potentially very high risk. Before such predictions are accepted by clinical geneticists, however, further population-based evidence is needed on the effect of *CHEK2*1100delC* and other moderate penetrance alleles in women with a family history of breast cancer.

Introduction

The average lifetime breast cancer risk in a typical Western woman is ~10%. Individual risks probably range from <2% to >50% (1), but apart from carriers of *BRCA1* or *BRCA2* mutations, women at very high risk cannot yet be identified by genetic testing alone. This very wide variation in genetic risk in the general population is predicted by a model in which a large number of “moderate or low penetrance” (2) alleles act in combination to confer high risks in women who carry large numbers of such alleles, and several such alleles have recently been discovered in candidate gene (3-7) and genome-wide (8-11) studies. An important implication of this polygenic model is that a single moderate-penetrance allele such as *CHEK2*1100delC* that doubles the risk in women with no family history is also likely to double the substantially higher risk in women with affected relatives. Predicted personal risks based only on family history rarely reach the threshold at which prophylactic treatment would usually be considered (~10% by age 50 or ~30% lifetime risk),¹⁶ but combining information on carrier status for moderate and low-penetrance alleles and family history may substantially increase the number of women seen in genetics clinics whose predicted risk reaches this level. Women with bilateral breast cancer are themselves at high genetic risk (12) and the lifetime risk among their female first-degree relatives is ~20%. We have analyzed the prevalence of *CHEK2*1100delC* in 1828 bilateral breast cancer cases in relation to family history to compare observed and predicted carrier odds ratios (OR). This comparison also constitutes a test of the polygenic model’s predictions of lifetime risk for carriers of *CHEK2*1100delC* with and without a first degree relative with bilateral breast cancer.

Materials and Methods

Full details of ascertainment of cases and controls for each of the studies have been published previously (3, 4, 13-22). A summary is given in Supplementary Table S1. All of the studies include predominantly, or exclusively, White Northern European subjects. All subjects gave written informed consent, and all studies were approved by the appropriate ethics committee or local institutional review board.

Genotyping methods in each study are described elsewhere (3, 13-16). Study-specific bilateral ORs and exact 95% confidence intervals (95% CI) were calculated using standard methods. Trends in OR for family history and age were calculated among cases, ignoring controls. The pooled OR was estimated by logistic regression with study as a stratifying covariate. Heterogeneity between studies was tested using likelihood ratio tests to compare logistic regression models with and without genotype-stratum interaction terms. Statistical analyses were carried out using Stata statistical software version 9.0 (Stata Corporation).

¹⁶<http://www.nice.org.uk/nicemedia/pdf/CG41NICEguidance.pdf>

Lifetime breast cancer risks in the unaffected daughter of a bilateral case were derived from the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm breast cancer model (23), which incorporates *BRCA1* and *BRCA2* mutations with a polygenic background, and has been calibrated against pooled population-based data on familial risks from several sources (24). We assumed that both cancers in the bilateral mother were diagnosed at age 50 y and that the status of all other female relatives was unknown. The model predictions thus represent the risk to the average 40-year-old daughter of a bilateral breast cancer case over all possible family histories (including both genetic and nongenetic familial factors), but the predictions are not strongly dependent on either the age at diagnosis of the index case or the presence of additional unaffected female relatives (Supplementary Table S2). Lifetime predicted risks in an unaffected 40-year-old daughter were calculated in relation to the daughter's carrier status for *BRCA1*, *BRCA2*, and *CHEK2*1100delC*. The risk in *CHEK2*1100delC* carriers was calculated by multiplying predicted incidence rates at each age by 2.34, the OR estimate derived from pooled data on 10,860 breast cancers and 9,065 controls (15). Ideally, the risk for carriers of *CHEK2*1100delC* should be based on a model in which the polygenic variance is the residual variance after taking into account the effect of *CHEK2*1100delC*. The contribution of *CHEK2*1100delC* to the polygenic variance, however, is predicted to be <1%, and such an adjustment would not, therefore, affect the lifetime predicted risks.

Results

Eight studies from five Northern European countries (UK, Finland, the Netherlands, Germany, and Russia) contributed data to these analyses. The pooled OR estimate from these studies is 6.43 (95% CI, 4.33-9.56; $P < 0.0001$; heterogeneity $\chi^2 = 10.25$ (degrees of freedom, 6); $P = 0.11$; Fig. 1). The OR increases with each additional affected first-degree relative in the British and Finnish studies (OR per relative, 2.39; 95% CI, 1.53-3.73; $P_{\text{trend}} = 0.0003$ for British studies; OR per relative, 1.51; 95% CI, 0.62-3.66; $P_{\text{trend}} = 0.37$ for HEBCS; Table 1). There is, however, no consistent trend with family history for the other studies (Rotterdam, ABCS, and St. Petersburg) for which data on affected relatives were available ($P = 0.001$ for between-study heterogeneity). There is no significant trend with increasing age at first diagnosis in any study or overall, although the pooled OR per decade (1.00; 95% CI 0.75-1.31) is consistent with the modest reduction seen in older unselected cases (15).

The lifetime (to age 80 years) breast cancer risk to a 40-year-old daughter of a woman with bilateral breast cancer and unknown *BRCA* and *CHEK2* carrier status predicted by the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm is 21% (Fig. 2), close to the observed lifetime risk of 24% in mothers and sisters of bilateral breast cancer cases in the BBC study (13). A negative result for a *BRCA* mutation screen reduces this only slightly to 18%. On the assumption that *CHEK2*1100delC* multiplies the risk caused by alleles in genes other than *BRCA1* and *BRCA2*, our analysis suggests that this lifetime risk is doubled to 37% in carriers, more than half the risk to a carrier of *BRCA1* (61%) or *BRCA2* (69%). Her risk between age 40 and 50 years is 4% if she has a negative *BRCA* mutation screen but is increased to 9% if she is found to be a carrier of *CHEK2*1100delC*. If she has not been tested the daughter's relative risk (standardized incidence ratio) compared with the general population is 3.7 at age 40 to 50 years, falling to 1.8 by age 70 to 80 years (Table 2). If she is a carrier of *CHEK2*1100delC*, the corresponding relative risks are 6.8 and 3.8.

Discussion

As predicted, our pooled bilateral OR estimate for *CHEK2*1100delC* carriers (6.43; 95% CI, 4.33-9.56) is significantly higher than the published estimate of 2.34 (95% CI, 1.72-3.20) for unselected cases (difference between ORs: Z , 3.92; $P < 0.001$) but consistent with its square (5.48; ref. 15). Each additional affected first degree relative should increase the carrier OR for bilaterals by a further factor of ~ 1.67 (an excess risk half that in unselected cases, whose reported OR is 2.34). The *CHEK2*1100delC* carrier OR in familial cases is thus expected to be ~ 9 ($2.34 \times 2.34 \times 1.67$). The British and Finnish data are consistent with a trend of this order but cases from the Netherlands and St. Petersburg show no familial trend in OR ($P < 0.001$ for heterogeneity between countries). This heterogeneity is not confined to studies of bilateral breast cancer cases: in studies comparing unselected first primary breast cancers with and without affected relatives, an increased prevalence of *CHEK2*1100delC* has been seen in familial breast cancer cases in some (3, 14) but not all studies (25, 26).

The absence of any familial effect in bilateral cases from the Netherlands and St. Petersburg seems likely to reflect a combination of systematic effects and chance variation. There is epistasis between *CHEK2*1100delC* and inactivating mutations in *BRCA1* and *BRCA2* (3), and epistatic effects with these or other risk alleles that differ in frequency between populations could have contributed to the significant heterogeneity between countries that we observed in relation to family history. Referral of familial cases from population subgroups or other regions may also have affected results in some studies. The reported carrier frequency for *CHEK2*1100delC* varies between 1.3% and 0.5% in Northern European Caucasians (15), and may be even lower locally. There were 6 of 651 carriers in GENICA German population controls and 0 of 600 in KORA German population controls (GENICA versus KORA, $P = 0.03$), and only 1 of 821 in controls from the Russian study, which gave the highest carrier OR (OR, 47.88; 95% CI, 6.30-2,126.8). The high prevalence (10.4%) of the Ashkenazi *BRCA1* 5382insC variant in bilateral cases from the Russian study could reflect nonrandom referral to this specialized research institute (27).

Methods for calculating a woman's personal risk and guidelines for counseling and management in primary, secondary, or tertiary care are still evolving. Under current UK guidelines,¹⁶ a woman should be offered magnetic resonance imaging and mammographic surveillance in secondary care if her predicted breast cancer risk is between 3% and 8% from age 40 to 49 years or her lifetime risk is between 17% and 30%. This "gray area" of concern but limited intervention is shown in Fig. 2. Above this level, she should be offered tertiary care, including risk-reducing surgery.¹⁶ As the carrier OR for *CHEK2*1100delC* measured in unselected cases is a relative measure the implication of being a carrier in terms of absolute risk will depend on the woman's family history of breast cancer. The model on which Fig. 2 is based assumes that *CHEK2*1100delC* interacts multiplicatively with other "polygenes" to increase the familial OR by roughly the same factor as it does in the overall population, and the data from the United Kingdom and Finland support this assumption. The predicted risks shown in Fig. 2 imply that the clinical management of the daughter of a woman with bilateral breast cancer should be different if she were found to carry *CHEK2*1100delC*. Byrnes et al. (28) have reviewed the evidence for an interaction between moderate penetrance alleles in *CHEK2*, *ATM*, *BRIP1*, and *PALB2* and polygenes in the context of familial breast cancer cases, and they too have concluded that detection of these variants in women with a strong family history of breast cancer may be of considerable clinical consequence. Before clinical geneticists accept such predictions for *CHEK2*1100delC* or other moderate penetrance variants, however, they will want more consistent and more extensive population-based evidence on the effect of *CHEK2*1100delC*

and other moderate or low-penetrance alleles in women with a family history of breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

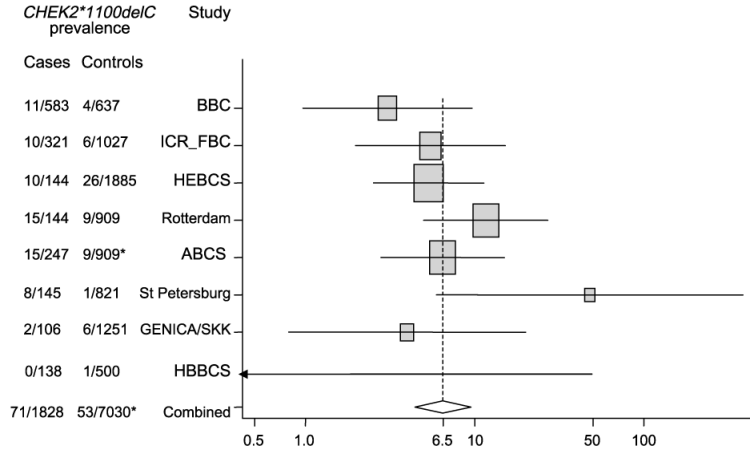
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*The ABCS comprises a series of 247 bilateral cases from the Netherlands with no controls. The ABCS odds ratio was therefore based on the 909 Rotterdam controls, but these two studies were treated as a single study with 391 cases and 909 controls in the combined analysis.

Figure 1. Estimated ORs with 95% CIs for the breast cancer ORs associated with CHEK2*1100delC. The area of each square is proportional to the variance of the log OR. The Hannover Breast Cancer study, where there were no carriers among cases is represented as a line with no square as the log OR and its variance cannot be calculated. An approximate OR and 95% CI were derived for Supplementary Table S1.

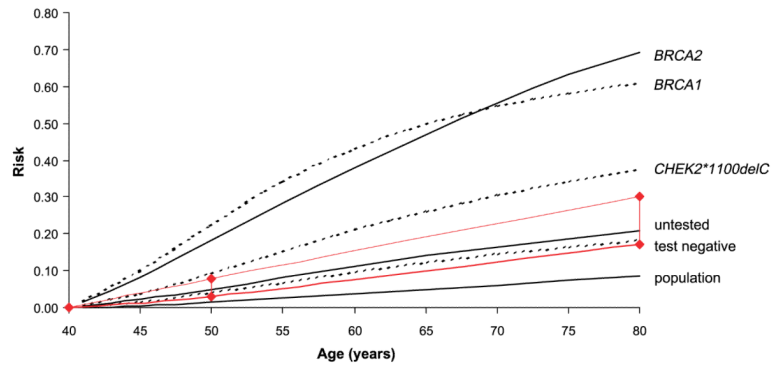


Figure 2.

Lifetime predicted risks in the unaffected 40-year-old daughter of a bilateral breast cancer case in relation to the daughter's carrier status for *BRCA1*, *BRCA2*, and *CHEK2*1100delC*. Risks in the unaffected daughter were derived from the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm breast cancer model and assume that both cancers in the bilateral mother were diagnosed at age 50 y. For the purposes of this analysis, "lifetime risk" is defined as risk by age 80 y in accordance with NICE guidelines for the classification of women at risk of familial breast cancer.

Table 1
Proportion of carriers of CHEK2*1100delC in women with bilateral breast cancer by number of affected first-degree relatives and by age group

	United Kingdom			Finland			the Netherlands			Russia			Germany	
	BBC n/N (%)	ICR_FBC n/N (%)	Pooled OR OR (95% CI)	n/N (%)	HEBCS OR (95% CI)	Rotterdam n/N (%)	ABCS n/N (%)	Pooled OR OR (95% CI)	St. Petersburg n/N (%)	OR (95% CI)	n/N (%)	OR (95% CI)	GENICA/SKK n/N (%)	OR (95% CI)
Controls	4/637 (0.63)	6/1,027 (0.58)	1.00 (Ref)	26/1,885 (1.38)	1.00 (Ref)	9/909 (0.99)	15/247 (6.07)	1.00 (Ref)	1/821 (0.12)	1.00 (Ref)	6/1,251 (0.48)	1.00 (Ref)	2/106 (1.87)	3.99 (0.4-22.6)
All bilaterals	11/583 (1.89)	10/321 (3.12)	3.93 (1.76-9.39)	10/144 (6.94)	5.34 (2.2-11.7)	15/144 (10.42)	15/247 (6.07)	8.31 (3.79-20.1)	8/145 (5.16)	47.88 (6.30-2,126.8)	2/106 (1.87)	3.99 (0.4-22.6)		
Family history														
Bilaterals 0 FDR	4/400 (1.00)	1/96 (1.04)	1.68 (0.45-5.44)	2/55 (3.64)	2.70 (0.30-11.3)	7/59 (11.86)	10/109 (9.17)	11.26 (4.63-29.1)	8/114 (7.02)	47.81 (9.30-464.3)	N/K	—		
Bilaterals 1 FDR	5/158 (3.16)	3/153 (1.96)	4.37 (1.48-12.4)	7/78 (8.97)	7.05 (2.49-17.4)	5/58 (8.62)	1/53 (1.89)	5.71 (1.63-18.3)	0/28 (0)	—	N/K	—		
Bilaterals 2+ FDR	2/25 (8.00)	6/72 (8.33)	10.91 (3.17-33.9)	1/11 (9.09)	7.15 (0.16-53.5)	3/27 (11.11)	0/19 (0)	6.98 (1.17-29.2)	—	—	N/K	—		
Age at first diagnosis														
Bilaterals <40	3/99 (3.03)	3/68 (4.41)	6.28 (1.85-19.3)	0/12 (0)	0	4/40 (10.00)	5/91 (5.49)	9.38 (3.20-27.2)	2/25 (8.00)	55.09 (3.8-774.5)	0/6 (0)	0		
Bilaterals 40-49	4/233 (1.72)	5/124 (4.03)	4.28 (1.52-11.8)	4/37 (10.81)	8.67 (2.1-27.0)	4/59 (6.78)	10/151 (6.62)	7.14 (2.83-18.9)	1/52 (1.92)	12.42 (0.2-240.8)	1/20 (5.00)	10.92 (0.23-96.5)		
Bilaterals 50+	4/250 (1.60)	2/129 (1.55)	2.66 (0.79-8.13)	6/95 (6.32)	4.82 (1.58-12.4)	7/44 (15.91)	0/5 (0)	16.67 (4.97-52.6)	5/63 (7.94)	70.69 (7.63->3,000)	1/80 (1.25)	2.62 (0.06-22.0)		

NOTE: Data from the HBBCS are included in pooled analyses of all studies and tests of heterogeneity between studies but are not included in this table as there were no carriers among 138 cases. There were 113, 21, and 3 cases with 0, 1, and 2 affected first-degree relatives, respectively, with missing information for 1 case. There were 13, 29, 46, and 50 cases age <40, 40-49, 50-59, and 60+, respectively. There was missing information on family history ABCS ($n = 66$), St. Petersburg ($n = 3$), and missing age information on age at diagnosis BBC ($n = 1$), Rotterdam ($n = 1$), St. Petersburg ($n = 5$). Abbreviation: N/K, not known; FDR, first-degree relatives.

Table 2
Age-specific relative risks in daughters of bilateral breast cancer cases compared with the general population

Age (y)	OR						
	Population	Untested	BRCA1/2 negative	CHEK2* 1100delC	BRCA1	BRCA2	
40-49	Ref	3.69	2.91	6.81	18.68	14.85	
50-59	Ref	3.10	2.61	6.12	14.02	12.45	
60-69	Ref	2.46	2.13	4.99	8.95	13.38	
70-79	Ref	1.83	1.63	3.83	6.29	13.00	