

ORIGINAL ARTICLE

Breast Cancer Risk Genes — Association Analysis in More than 113,000 Women

Breast Cancer Association Consortium*

ABSTRACT

BACKGROUND

Genetic testing for breast cancer susceptibility is widely used, but for many genes, evidence of an association with breast cancer is weak, underlying risk estimates are imprecise, and reliable subtype-specific risk estimates are lacking.

METHODS

We used a panel of 34 putative susceptibility genes to perform sequencing on samples from 60,466 women with breast cancer and 53,461 controls. In separate analyses for protein-truncating variants and rare missense variants in these genes, we estimated odds ratios for breast cancer overall and tumor subtypes. We evaluated missense-variant associations according to domain and classification of pathogenicity.

RESULTS

Protein-truncating variants in 5 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) were associated with a risk of breast cancer overall with a P value of less than 0.0001. Protein-truncating variants in 4 other genes (*BARD1*, *RAD51C*, *RAD51D*, and *TP53*) were associated with a risk of breast cancer overall with a P value of less than 0.05 and a Bayesian false-discovery probability of less than 0.05. For protein-truncating variants in 19 of the remaining 25 genes, the upper limit of the 95% confidence interval of the odds ratio for breast cancer overall was less than 2.0. For protein-truncating variants in *ATM* and *CHEK2*, odds ratios were higher for estrogen receptor (ER)-positive disease than for ER-negative disease; for protein-truncating variants in *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*, odds ratios were higher for ER-negative disease than for ER-positive disease. Rare missense variants (in aggregate) in *ATM*, *CHEK2*, and *TP53* were associated with a risk of breast cancer overall with a P value of less than 0.001. For *BRCA1*, *BRCA2*, and *TP53*, missense variants (in aggregate) that would be classified as pathogenic according to standard criteria were associated with a risk of breast cancer overall, with the risk being similar to that of protein-truncating variants.

CONCLUSIONS

The results of this study define the genes that are most clinically useful for inclusion on panels for the prediction of breast cancer risk, as well as provide estimates of the risks associated with protein-truncating variants, to guide genetic counseling. (Funded by European Union Horizon 2020 programs and others.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Easton at the University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge CB1 8RN, United Kingdom, or at dfe20@medschl.cam.ac.uk.

*A complete list of collaborators and investigators is provided in the Supplementary Appendix, available at NEJM.org.

Dr. Dorling, Dr. Carvalho, and Mr. Allen and Drs. Teo, Devilee, and Easton contributed equally to this article.

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GENETIC TESTING FOR CANCER SUSCEPTIBILITY is an established part of medical practice. Until recently, testing was performed mainly in patients with a strong family history of cancer and involved a limited number of genes known to be associated with a high risk of cancer or with specific cancer syndromes. With the advent of affordable sequencing, testing with larger panels of genes has become possible. However, for many genes on such panels, evidence of an association with cancer is often weak and accurate estimates of the cancer risks associated with variants are often not available.¹

To better define the set of genes associated with breast cancer risk, we designed a panel consisting of 34 known or suspected breast cancer susceptibility genes, including genes provided on commercial panels. Using this panel, we sequenced germline DNA from more than 60,000 women with breast cancer and more than 53,000 controls participating in studies of the Breast Cancer Association Consortium (BCAC).² We used these data to estimate the risks of breast cancer overall and tumor subtypes associated with germline protein-truncating variants and rare missense variants in these genes.

METHODS

STUDIES

We included samples from women with breast cancer and unaffected controls participating in 44 BCAC studies (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All the studies were approved by the relevant ethics review boards and used appropriate consent procedures. Overall, 30 studies did not select patients or controls on the basis of family history (population-based studies); the remaining 14 studies oversampled patients with a family history of breast cancer (family-based studies). After all quality-control steps were taken, 53,461 controls and 60,466 women with an invasive tumor (54,624 [90.3%]), in situ tumor (4187 [6.9%]), or tumor of unknown invasiveness (1655 [2.7%]) were included in the analyses. Of these, 48,826 patients and 50,703 controls were from population-based studies.

SEQUENCE ANALYSIS

We analyzed a panel of 34 known or suspected breast cancer susceptibility genes (Tables S3 and

S4), including genes provided on commercial panels. Details regarding library preparation, sequencing, variant calling, quality-control procedures, and variant classification are provided in the Supplementary Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary analyses were burden analyses in which odds ratios and 95% confidence intervals for breast cancer associated with the presence of any variant in a given category were estimated by means of logistic regression. The two main categories were protein-truncating variants and rare missense variants (i.e., variants with a population frequency of <0.001). Missense-variant associations were evaluated according to domain and classification of pathogenicity. Analyses were also conducted according to tumor subtype, age, and ancestry (European vs. Asian).

We conducted separate analyses for the population-based studies and the family-based studies. The inclusion of studies that oversampled patients with a family history of breast cancer improves the power to detect association³ but leads to biased risk estimates. Therefore, we report risk estimates, 95% confidence intervals, and P values from the population-based studies but also report the results of association tests from all studies when appropriate. For protein-truncating variants in each gene, evidence of an association is also expressed in terms of Bayesian false-discovery probabilities, reflecting both evidence from the data in this study and evidence from previous research.⁴ Absolute risks were calculated by combining age-specific estimated odds ratios with population incidences in the United Kingdom in 2016 as a baseline.^{5,6} Details regarding the statistical analysis are provided in Supplementary Methods.

RESULTS

PROTEIN-TRUNCATING VARIANTS

Risk of Breast Cancer Overall

Protein-truncating variants in 5 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) were associated with a significant risk of breast cancer overall ($P < 0.0001$) (Table 1 and Figs. 1 and 2). For these genes, odds ratios ranged from 2.10 to 10.57. In *CHEK2*, the c.1100delC variant accounted for approximately 80% of the protein-truncating vari-

Table 1. Risk of Breast Cancer Overall Associated with Protein-Truncating Variants in 34 Genes in Population-Based Studies and All Studies.*

Gene	Population-Based Studies (48,826 patients and 50,703 controls)†			All Studies (60,466 patients and 53,461 controls)†		Prior Probability‡	BFDP
	No. of Carriers of Protein- Truncating Variants		Odds Ratio (95% CI)	P Value	P Value		
	Women with Breast Cancer	Controls					
ABRAXAS1	17	19	0.98 (0.50–1.94)	0.96	0.93	0.1	0.98
AKT1	3	6	0.47 (0.12–1.93)	0.29	0.14	0.1	0.94
ATM	294	150	2.10 (1.71–2.57)	9.2×10 ^{−13}	5.5×10 ^{−20}	0.8	1.3×10 ^{−18}
BABAM2	7	9	0.62 (0.23–1.71)	0.36	0.34	0.1	0.95
BARD1	62	32	2.09 (1.35–3.23)	0.00098	0.00011	0.2	0.0076
BRCA1	515	58	10.57 (8.02–13.93)	1.1×10 ^{−62}	3.7×10 ^{−65}	0.99	1.5×10 ^{−64}
BRCA2	754	135	5.85 (4.85–7.06)	2.2×10 ^{−75}	8.4×10 ^{−77}	0.99	3.1×10 ^{−76}
BRIP1	86	75	1.11 (0.80–1.53)	0.54	0.54	0.2	0.85
CDH1	11	12	0.86 (0.37–1.98)	0.72	0.58	0.2	0.94
CHEK2	704	315	2.54 (2.21–2.91)	3.1×10 ^{−39}	3.2×10 ^{−61}	0.99	1.3×10 ^{−60}
c.1100delC variant	548	245	2.66 (2.27–3.11)	1.1×10 ^{−33}	5.3×10 ^{−53}		
Other variants	156	70	2.13 (1.60–2.84)	3.0×10 ^{−7}	7.4×10 ^{−10}		
EPCAM	14	19	0.73 (0.36–1.49)	0.39	0.13	0.1	0.95
FANCC	71	65	1.26 (0.89–1.79)	0.20	0.20	0.1	0.87
FANCM	302	300	1.06 (0.90–1.26)	0.48	0.28	0.1	0.96
GEN1	31	43	0.66 (0.41–1.06)	0.088	0.18	0.1	0.95
MEN1	2	5	0.37 (0.07–1.97)	0.24	0.64	0.1	0.95
MLH1	5	9	0.58 (0.19–1.77)	0.34	0.55	0.1	0.95
MRE11	48	55	0.88 (0.59–1.32)	0.54	0.34	0.1	0.98
MSH2	13	13	1.06 (0.47–2.36)	0.89	0.80	0.1	0.92
MSH6	39	23	1.96 (1.15–3.33)	0.013	0.021	0.1	0.55
MUTYH	232	231	1.00 (0.83–1.21)	0.99	0.88	0.1	1.00
NBN	90	103	0.90 (0.67–1.20)	0.48	0.65	0.2	0.95
NF1	31	17	1.76 (0.96–3.21)	0.068	0.011	0.2	0.25
PALB2	274	55	5.02 (3.73–6.76)	1.6×10 ^{−26}	1.1×10 ^{−32}	0.99	2.9×10 ^{−32}
PIK3CA	3	12	0.21 (0.06–0.75)	0.016	0.19	0.1	0.94
PMS2	40	36	1.16 (0.73–1.85)	0.53	0.37	0.1	0.92
PTEN	14	6	2.25 (0.85–6.00)	0.10	0.0040	0.2	0.14
RAD50	120	121	1.08 (0.83–1.40)	0.57	0.45	0.1	0.95
RAD51C	54	26	1.93 (1.20–3.11)	0.0070	0.00026	0.3	0.0090
RAD51D	51	25	1.80 (1.11–2.93)	0.018	0.0018	0.3	0.044
RECQL	103	120	0.84 (0.64–1.10)	0.21	0.89	0.1	0.95
RINT1	32	49	0.72 (0.46–1.14)	0.17	0.31	0.1	0.96
STK11	6	5	1.60 (0.48–5.28)	0.44	0.50	0.2	0.70
TP53	7	2	3.06 (0.63–14.91)	0.17	0.015	0.8	0.033
XRCC2	15	18	0.96 (0.47–1.93)	0.90	0.81	0.1	0.98

* BFD denotes Bayesian false-discovery probability, and CI confidence interval.

† The sample sizes reflect totals after quality control. Analyses for genes other than *BRCA1* and *BRCA2* excluded carriers of protein-truncating variants in *BRCA1* and *BRCA2*; therefore, sample sizes were slightly lower in those analyses (47,522 patients and 50,475 controls in population-based studies, and 58,728 patients and 52,976 controls in all studies).

‡ Details regarding the prior probabilities are provided in the Supplementary Methods section in the Supplementary Appendix.

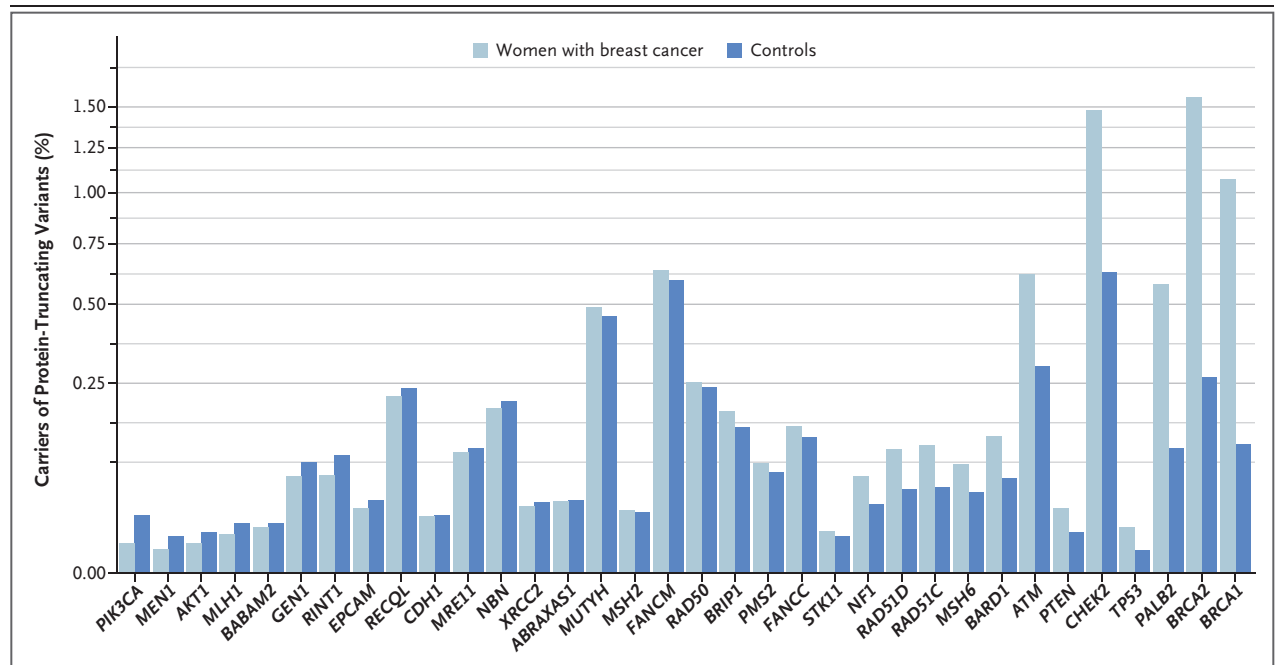


Figure 1. Frequency of Protein-Truncating Variants in 34 Genes in Population-Based Studies.

Shown are percentages of women with breast cancer and controls who were carriers of protein-truncating variants in 34 genes. The genes are listed in order of increasing estimated odds ratios for breast cancer overall.

ants. The effect size for this variant (odds ratio, 2.66; 95% confidence interval [CI], 2.27 to 3.11; $P=1.1\times 10^{-33}$ [$P=5.3\times 10^{-53}$ in all studies]) did not differ significantly from the effect size for all other protein-truncating variants in *CHEK2* (odds ratio, 2.13; 95% CI, 1.60 to 2.84; $P=3.0\times 10^{-7}$ [$P=7.4\times 10^{-10}$ in all studies]), with a P value of 0.19 for the difference in the odds ratios.

There was more modest evidence of an association with breast cancer overall for protein-truncating variants in 7 other genes: *BARD1* (odds ratio, 2.09; 95% CI, 1.35 to 3.23; $P=0.00098$ [$P=0.00011$ in all studies]), *RAD51C* (odds ratio, 1.93; 95% CI, 1.20 to 3.11; $P=0.0070$ [$P=0.00026$ in all studies]), *RAD51D* (odds ratio, 1.80; 95% CI, 1.11 to 2.93; $P=0.018$ [$P=0.0018$ in all studies]), *PTEN* (odds ratio, 2.25; 95% CI, 0.85 to 6.00; $P=0.10$ [$P=0.0040$ in all studies]), *NF1* (odds ratio, 1.76; 95% CI, 0.96 to 3.21; $P=0.068$ [$P=0.011$ in all studies]), *TP53* (odds ratio, 3.06; 95% CI, 0.63 to 14.91; $P=0.17$ [$P=0.015$ in all studies]), and *MSH6* (odds ratio, 1.96; 95% CI, 1.15 to 3.33; $P=0.013$ [$P=0.021$ in all studies]) (Table 1). For 4 of these genes (*BARD1*, *RAD51C*, *RAD51D*, and *TP53*), the Bayesian false-discovery probability was less than 0.05 (Table 1).

For the 12 genes that had evidence of an association with breast cancer overall, the effect size for protein-truncating variants did not differ significantly between European women and Asian women (Table S7). Of the remaining 22 genes, all but 3 (*AKT1*, *MSH2*, and *STK11*) had an upper limit of the 95% confidence interval of the odds ratio of less than 2.0 in the population-based studies.

Risk of Tumor Subtypes

Of the 12 genes that had evidence of an association with breast cancer overall, 2 had a stronger association with estrogen receptor (ER)-positive breast cancer than with ER-negative breast cancer: *ATM* (odds ratio, 2.33 [95% CI, 1.87 to 2.91] for ER-positive disease vs. 1.01 [95% CI, 0.64 to 1.59] for ER-negative disease; $P=0.00055$ for the difference) and *CHEK2* (odds ratio, 2.67 [95% CI, 2.30 to 3.11] for ER-positive disease vs. 1.64 [95% CI, 1.25 to 2.16] for ER-negative disease; $P=3.6\times 10^{-5}$ for the difference) (Fig. 2 and Table S8). *CHEK2* also had evidence of an association with ER-negative, non-triple-negative breast cancer (odds ratio, 2.53; 95% CI, 1.75 to 3.67) but not with triple-negative breast cancer (odds ratio, 1.06; 95% CI, 0.63 to 1.76) (Table S9).

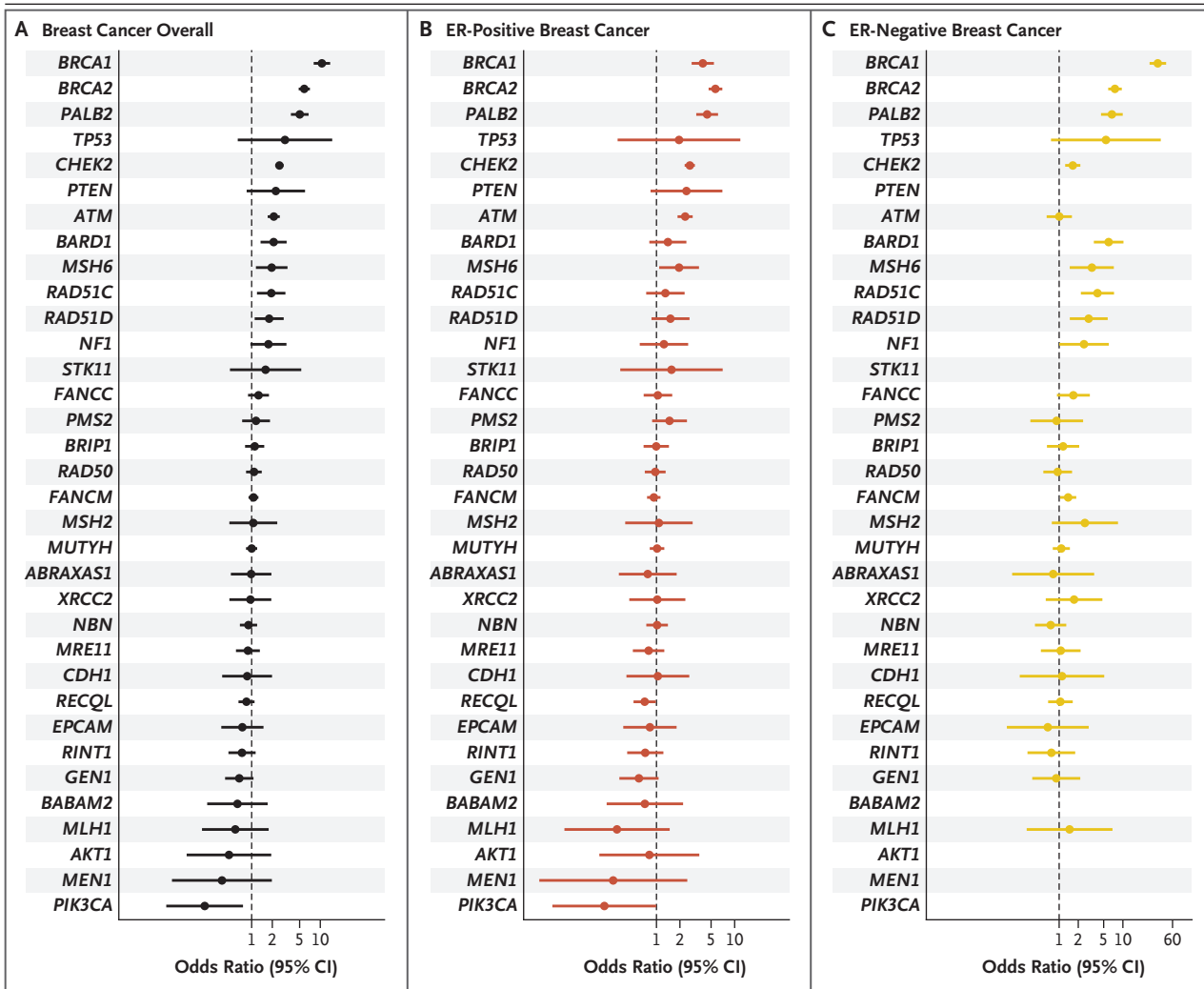


Figure 2. Risk of Breast Cancer Overall and Tumor Subtypes Associated with Protein-Truncating Variants in 34 Genes in Population-Based Studies.

Shown are odds ratios and 95% confidence intervals (CIs) for breast cancer overall (Panel A), estrogen receptor (ER)-positive breast cancer (Panel B), and ER-negative breast cancer (Panel C) associated with protein-truncating variants in 34 genes. The genes are listed in order of decreasing estimated odds ratios for breast cancer overall.

In contrast, for *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D*, odds ratios were higher for ER-negative breast cancer than for ER-positive breast cancer ($P < 0.05$ for all genes). Of these genes, 3 had a stronger association with triple-negative breast cancer than with ER-negative, non-triple-negative breast cancer: *BARD1* ($P = 0.044$), *BRCA1* ($P = 9.6 \times 10^{-17}$), and *BRCA2* ($P = 7.8 \times 10^{-5}$) (Table S8).

Among the genes that had no evidence of an association with breast cancer overall, *FANCM* had some evidence of an association with ER-negative breast cancer ($P = 0.0050$ in all studies) and

FANCC had evidence of an association with triple-negative breast cancer ($P = 0.0021$ in all studies) (Table S9).

For *BRCA1*, *BRCA2*, and *PALB2*, odds ratios were higher for invasive tumors than for in situ tumors. In contrast, for *ATM* and *CHEK2*, odds ratios for invasive tumors and in situ tumors were similar (Table S10).

Age Effects and Absolute Risk

In the population-based studies, odds ratios decreased significantly with increasing age for 6 genes: *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *PTEN*, and

TP53 ($P < 0.01$ for all genes) (Tables S11 and S12). Estimated absolute risks of breast cancer were derived by combining age-specific estimated odds ratios with population incidences in the United Kingdom (Fig. 3). For carriers of protein-truncating variants in *BRCA1*, *BRCA2*, and *PALB2*, the estimated absolute risks by 80 years of age exceeded the 30% threshold for high risk, as defined by National Institute for Health and Care Excellence guidelines.⁷ For carriers of protein-truncating variants in *ATM*, *BARD1*, *CHEK2*, *RAD51C*, and *RAD51D*, the estimated absolute risks by 80 years of age were within the 17 to 30% range for moderate risk.

RARE MISSENSE VARIANTS

There was evidence of an association with breast cancer overall for rare missense variants in 6 genes: *CHEK2* (odds ratio, 1.42; 95% CI, 1.28 to 1.58; $P = 2.5 \times 10^{-11}$ [$P = 2.9 \times 10^{-18}$ in all studies]), *ATM* (odds ratio, 1.06; 95% CI, 1.00 to 1.13; $P = 0.051$ [$P = 0.0010$ in all studies]), *TP53* (odds ratio, 1.10; 95% CI, 0.91 to 1.31; $P = 0.32$ [$P = 0.00080$ in all studies]), *BRCA1* (odds ratio, 1.11; 95% CI, 1.02 to 1.20; $P = 0.010$ [$P = 0.027$ in all studies]), *CDH1* (odds ratio, 1.10; 95% CI, 0.98 to 1.23; $P = 0.096$ [$P = 0.042$ in all studies]), and *RECQL* (odds ratio, 1.12; 95% CI, 1.00 to 1.26; $P = 0.047$ [$P = 0.036$ in all studies]) (Table 2). Of these 6 genes, 2 had a stronger association with ER-positive breast cancer than with ER-negative breast cancer (*CHEK2* [$P = 9.1 \times 10^{-5}$] and *CDH1* [$P = 0.012$]) and 1 had a stronger association with ER-negative breast cancer than with ER-positive breast cancer (*BRCA1* [$P = 0.01$]). Odds ratios decreased with increasing age for *BRCA1* ($P = 0.0026$), *CHEK2* ($P = 0.00022$), and *TP53* ($P = 0.00023$).

For missense variants (in aggregate) in *BRCA1*, the risk of breast cancer overall differed according to domain ($P = 3.0 \times 10^{-6}$); there was an increased risk associated with variants located in the regions encoding the RING domain ($P = 1.0 \times 10^{-6}$) and the BRCT1 domain ($P = 0.00020$) (Tables S13 and S14 and Fig. S1A). For missense variants in *CHEK2*, the odds ratios did not vary according to location ($P = 0.52$), such that the risk associated with variants within domains ($P = 4.2 \times 10^{-9}$) was similar to the risk associated with variants outside domains ($P = 0.001$) (Tables S13 and S15 and Fig. S1B). For *ATM*, there was an increased risk associated with variants in the FRAP-ATM-TRRAP (FAT) domain ($P = 0.00019$ in all studies) and the protein kinase domains ($P = 0.00092$ in all stud-

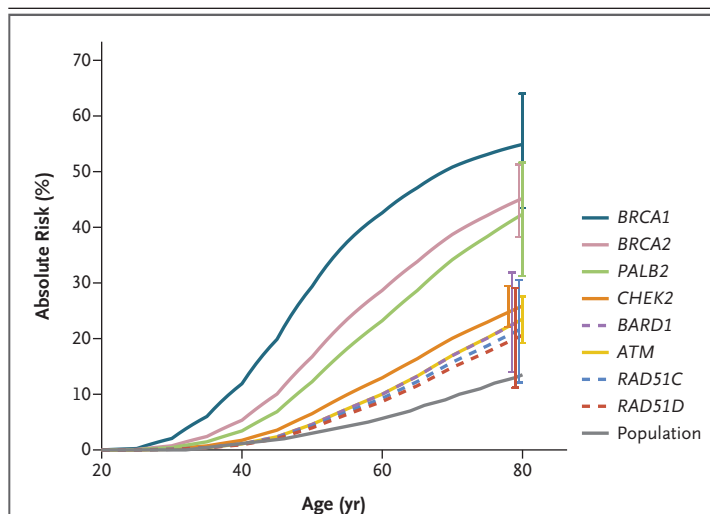


Figure 3. Estimated Absolute Risk of Breast Cancer Associated with Protein-Truncating Variants in 8 Genes.

Shown are absolute risks of breast cancer through 80 years of age associated with protein-truncating variants in 8 genes that had significant evidence of an association with breast cancer overall, on the basis of estimated odds ratios from population-based studies. The absolute risk was not calculated for *TP53* because of the wide 95% confidence interval for the odds ratio and the known association with a substantial risk of childhood cancer. Baseline absolute risks were derived from population incidences in the United Kingdom in 2016.⁶ The I bars indicate 95% confidence intervals.

ies) (Tables S13 and S16 and Fig. S1C). There was no evidence of a risk associated with missense variants in specific domains in *BRCA2* ($P = 0.27$) or *PALB2* ($P = 0.48$) (Tables S13, S17, and S18 and Figs. S1D and S1E).

We specifically examined rare missense variants in *BRCA1*, *BRCA2*, and *TP53* that would be classified as pathogenic according to clinical guidelines. There was clear evidence of an association with breast cancer overall for pathogenic variants (in aggregate) in each gene (odds ratio, 16.11 [95% CI, 5.83 to 44.50] in *BRCA1*, 5.68 [95% CI, 2.62 to 12.29] in *BRCA2*, and 2.91 [95% CI, 1.71 to 4.98] in *TP53*) but not for other missense variants (in aggregate) in each gene (odds ratio, 1.06 [95% CI, 0.98 to 1.15] in *BRCA1*, 0.97 [95% CI, 0.92 to 1.02] in *BRCA2*, and 0.94 [95% CI, 0.77 to 1.14] in *TP53*) (Table S19 and Figs. S2A, S2B, and S2C).

DISCUSSION

This large study, in which we evaluated coding variation in putative breast cancer susceptibility genes, involved more than 60,000 patients and

Table 2. Risk of Breast Cancer Overall Associated with Rare Missense Variants in 34 Genes in Population-Based Studies and All Studies.

Gene	Population-Based Studies (48,826 patients and 50,703 controls)*			All Studies (60,466 patients and 53,461 controls)*	
	No. of Carriers of Rare Missense Variants		Odds Ratio (95% CI)	P Value	P Value
	Women with Breast Cancer	Controls			
<i>ABRAXAS1</i>	233	242	1.04 (0.86–1.25)	0.70	0.40
<i>AKT1</i>	142	156	0.96 (0.76–1.21)	0.72	0.63
<i>ATM</i>	2411	2471	1.06 (1.00–1.13)	0.051	0.0010
<i>BABAM2</i>	167	170	1.01 (0.81–1.26)	0.91	0.63
<i>BARD1</i>	591	616	1.00 (0.89–1.12)	0.94	0.41
<i>BRCA1</i>	1393	1300	1.11 (1.02–1.20)	0.010	0.027
<i>BRCA2</i>	2831	3038	0.98 (0.93–1.04)	0.50	0.58
<i>BRIP1</i>	868	961	0.95 (0.86–1.04)	0.25	0.54
<i>CDH1</i>	682	668	1.10 (0.98–1.23)	0.096	0.042
<i>CHEK2</i>	895	697	1.42 (1.28–1.58)	2.5×10 ⁻¹¹	2.9×10 ⁻¹⁸
<i>EPCAM</i>	290	328	0.97 (0.82–1.14)	0.69	0.43
<i>FANCC</i>	597	620	0.95 (0.85–1.07)	0.42	0.80
<i>FANCM</i>	1434	1566	0.95 (0.88–1.02)	0.17	0.85
<i>GEN1</i>	701	707	1.05 (0.94–1.17)	0.38	0.25
<i>MEN1</i>	109	130	0.86 (0.66–1.12)	0.25	0.81
<i>MLH1</i>	677	711	1.02 (0.91–1.13)	0.78	0.68
<i>MRE11</i>	552	611	0.94 (0.84–1.06)	0.33	0.93
<i>MSH2</i>	908	1024	0.92 (0.84–1.01)	0.093	0.12
<i>MSH6</i>	1088	1155	1.00 (0.92–1.09)	0.98	0.74
<i>MUTYH</i>	659	702	1.00 (0.90–1.12)	1.00	0.58
<i>NBN</i>	665	725	0.95 (0.85–1.06)	0.37	0.71
<i>NF1</i>	816	899	0.94 (0.85–1.03)	0.19	0.53
<i>PALB2</i>	805	892	0.96 (0.87–1.06)	0.39	1.00
<i>PIK3CA</i>	170	205	0.83 (0.67–1.02)	0.080	0.33
<i>PMS2</i>	934	963	0.95 (0.87–1.05)	0.31	0.62
<i>PTEN</i>	68	70	1.08 (0.76–1.53)	0.65	0.48
<i>RAD50</i>	1046	1089	0.99 (0.91–1.08)	0.83	0.44
<i>RAD51C</i>	196	206	0.93 (0.76–1.14)	0.49	0.60
<i>RAD51D</i>	224	212	1.05 (0.86–1.27)	0.64	0.57
<i>RECQL</i>	656	627	1.12 (1.00–1.26)	0.047	0.036
<i>RINT1</i>	732	762	1.01 (0.91–1.12)	0.89	0.18
<i>STK11</i>	114	139	0.83 (0.64–1.07)	0.15	0.16
<i>TP53</i>	257	244	1.10 (0.91–1.31)	0.32	0.00080
<i>XRCC2</i>	207	213	1.03 (0.84–1.25)	0.80	0.53

* The sample sizes reflect totals after quality control. The analysis for each gene excluded carriers of protein-truncating variants in that gene.

53,000 controls, permitting the calculation of risk estimates that are more precise than those obtained previously. We found strong evidence of an association with breast cancer risk (Bayesian false-discovery probability, <0.05) for protein-truncating variants in 9 genes, with a P value of less than 0.0001 for 5 genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, and *PALB2*) and a P value of less than 0.05 for the other 4 genes (*BARD1*, *RAD51C*, *RAD51D*, and *TP53*). We found that, for protein-truncating variants in most of these genes, the odds ratio differed according to breast cancer subtype. Protein-truncating variants in *ATM* and *CHEK2* were more strongly associated with ER-positive disease than with ER-negative disease, a finding consistent with earlier observations,^{5,8} whereas protein-truncating variants in *BARD1*, *BRCA1*, *BRCA2*, *PALB2*, *RAD51C*, and *RAD51D* were more strongly associated with ER-negative disease than with ER-positive disease. None of the other 25 genes in the panel had a Bayesian false-discovery probability of less than 0.10. Of note, 19 genes had an upper limit of the 95% confidence interval of the odds ratio of less than 2.0, with 2.0 representing a proposed threshold for “pathogenic, moderate risk alleles”; we therefore conclude that these genes are not informative for the prediction of breast cancer risk. We confirmed that missense variants in *BRCA1*, *BRCA2*, and *TP53* that would be classified as pathogenic according to clinical guidelines are indeed associated with clinically significant risks. We also found that rare missense variants in *CHEK2* overall, as well as variants in specific domains in *ATM*, are associated with moderate risk.

Our results are broadly consistent with the results of an analysis by Lee et al.,¹⁰ in which the Clinical Genome Resource (ClinGen) clinical validity framework was used (Table S20). Of the 10 genes that were regarded as having definitive evidence of an association with breast cancer risk in that analysis,¹⁰ 7 genes had variants associated with breast cancer risk in our analysis; deleterious variants in the remaining 3 genes (*CDH1*, *PTEN*, and *STK11*) are very rare and confer a predisposition to specific cancer syndromes. Of the 18 genes that were regarded as having moderate, limited, or disputed evidence of an association with breast cancer risk in that analysis, 2 genes (*RAD51C* and *RAD51D*) had protein-truncating variants associated with breast cancer risk in our analysis; 13 of the remaining genes had

an upper limit of the 95% confidence interval of the odds ratio of less than 2.0 (and thus were classified as not conferring moderate or high risk according to our analysis), and the other 3 genes (*MSH2*, *MSH6*, and *NF1*) could not be classified. An association between breast cancer risk and variants in *RAD51C* and *RAD51D* is highly plausible, given that the functions of these genes are related to one another, that both genes had a stronger association with ER-negative breast cancer than with ER-positive breast cancer, and that both genes have evidence of an association with ovarian cancer.¹¹

Association analyses of rare variants are susceptible to bias. Inclusion of studies that oversampled patients with a family history of breast cancer improves the power to detect an association but leads to an upward bias in estimated odds ratios. The expected larger effect size in the family-based studies (as compared with the population-based studies) was seen for protein-truncating variants in all the genes with evidence of an association with breast cancer, except *BRCA1* and *BRCA2*, and was seen for missense variants in *ATM*, *CHEK2*, and *TP53* (Tables S21 and S22). Protein-truncating variants in some of these genes are also associated with other types of cancer. Moreover, testing for cancer susceptibility genes in cancer genetics clinics can lead to a downward bias, because carriers identified through previous testing may be excluded. We observed a depletion of carriers of protein-truncating variants in *BRCA1* and *BRCA2* among women with breast cancer in the family-based studies. Therefore, we regard the estimates from the population-based studies to be the most reliable.

With regard to rare missense variants, the clearest evidence of an association with increased breast cancer risk was for *CHEK2*. For rare missense variants (in aggregate) in *CHEK2*, the odds ratio was approximately 1.4. The association was independent of location, which suggests that a large proportion of missense variants in *CHEK2* confer risk (albeit below the threshold suggested for “pathogenic, moderate risk alleles”). We also found some evidence of an association with risk for rare missense variants (in aggregate) in *ATM*, *BRCA1*, *CDH1*, and *TP53*, with odds ratios of approximately 1.1 ($P<0.05$) for all genes. Furthermore, we found evidence of an association with risk for missense variants in *BRCA1*, *BRCA2*, and *TP53* that would be classified as pathogenic ac-

cording to standard criteria but not for other missense variants in these genes; the odds ratios for the pathogenic variants (in aggregate) were similar to odds ratios for protein-truncating variants in these genes. For *ATM*, evidence of an association with risk appeared to be restricted to variants located in the regions encoding the phosphatidylinositol 3-kinase and 4-kinase and FAT domains, a finding consistent with previous observations.¹²

The absolute risk estimates for protein-truncating variants in previously established risk genes were broadly consistent with previous estimates, except estimates for *BRCA2* and *TP53*, which were lower than risks reported in previous family-based studies.¹³⁻¹⁵ However, the estimate for *TP53* in this study was based on data from only seven carriers and had a wide confidence interval. The low estimate may reflect the significant early mortality among carriers of protein-truncating variants in *TP53*; alternatively, it is possible that the earlier family-based studies had overestimated the risk.¹⁶ The analysis for *TP53* is further complicated by the possibility of unrecognized somatic mutations in the blood due to age-related clonal hematopoiesis.¹⁷⁻²⁰ The fact that the estimate for *BRCA2* was lower than the estimate for *BRCA1* may reflect the older age distribution in this study, as compared with previous studies, and perhaps a disproportionately large effect of genetic modifiers on risk among *BRCA2* carriers, as compared with *BRCA1* carriers.

Among European women, approximately 6.8% of the patients and 2.0% of the controls had protein-truncating variants in any of the 9 genes associated with breast cancer risk; in addition, 2.2% of the patients and 1.4% of the controls had missense variants in *CHEK2*. The frequency of protein-truncating variants among Asian wom-

en (4.4% of the patients and 1.3% of the controls) was lower than the frequency among European women; this finding is attributable to the much lower frequency of the c.1100delC variant in *CHEK2* among Asian women.

The absolute risk estimates place protein-truncating variants in *BRCA1*, *BRCA2*, and *PALB2* in the high-risk category and place protein-truncating variants in *ATM*, *BARD1*, *CHEK2*, *RAD51C*, and *RAD51D* in the moderate-risk category. These results may guide screening, as well as prevention with risk-reducing surgery or medication, in accordance with national guidelines. However, because breast cancer risk is influenced by other genetic and lifestyle factors, in addition to family history, the incorporation of this information into risk models would be required to give appropriate estimates.²¹

Despite the size of this study, the evidence of an association with breast cancer risk for several of the genes we analyzed (e.g., *FANCM*, *MSH6*, and *NFI*) remains equivocal, and even for the genes that had a clear association with risk, the confidence intervals for the risk estimates are wide. Incorporation of pedigree data and combined analyses with other studies may improve the precision of these estimates. In the meantime, these results may help to guide the clinical reporting of results generated by multigene-panel testing and the counseling of women who are undergoing genetic testing for breast cancer susceptibility.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Requests for individual-level data used in these analyses should be made through the BCAC Data Access Co-ordinating Committee (bcac@medschl.cam.ac.uk).

APPENDIX

The authors' full names and academic degrees are as follows: Leila Dorling, Ph.D., Sara Carvalho, Ph.D., Jamie Allen, M.Res., Anna González-Neira, Ph.D., Craig Luccarini, Cecilia Wahlström, B.Sc., Karen A. Pooley, Ph.D., Michael T. Parsons, Cristina Fortuno, M.Sc., Qin Wang, M.Sc., Manjeet K. Bolla, M.Sc., Joe Dennis, M.Sc., Renske Keeman, M.Sc., M. Rosario Alonso, Nuria Álvarez, Belen Herraiz, Victoria Fernandez, Rocio Núñez-Torres, Ph.D., Ana Osorio, Ph.D., Jeanette Valcich, B.Sc., Minerva Li, M.Sc., Therese Törngren, M.Sc., Patricia A. Harrington, Caroline Baynes, Don M. Conroy, Brennan Decker, M.D., Ph.D., Laura Fachal, Ph.D., Nasim Mavaddat, Ph.D., Thomas Ahearn, Ph.D., Kristiina Aittomäki, M.D., Ph.D., Natalia N. Antonenkova, M.D., D.Sc., Norbert Arnold, Ph.D., Patrick Arveux, Margaret G.E.M. Ausems, M.D., Ph.D., Päivi Auvinen, M.D., Heiko Becher, Matthias W. Beckmann, M.D., Sabine Behrens, Marina Bermisheva, Ph.D., Katarzyna Bialkowska, Ph.D., Carl Blomqvist, M.D., Ph.D., Natalia V. Bogdanova, Ph.D., Nadja Bogdanova-Markov, M.D., Ph.D., Stig E. Bojesen, Dr.Med.Sci., Bernardo Bonanni, M.D., Anne-Lise Børresen-Dale, Ph.D., Hiltrud Brauch, Ph.D., Michael Bremer, M.D., Ignacio Briceno, M.D., Ph.D., Thomas Brüning, M.D., Barbara Burwinkel, David A. Cameron, M.D., Nicola J. Camp, Ph.D., Archie Campbell, M.A., Angel Carracedo, M.D., Jose E. Castelao, M.D., Melissa H. Cessna, M.D., Stephen J. Chanock, M.D., Hans Christiansen, M.D., J. Margriet Collée, M.D., Emilie Cordina-Duverger, Ph.D., Sten Cornelissen, B.Sc., Kamila Czene, Ph.D., Thilo Dörk, Ph.D., Arif B. Ekici, Ph.D., Christoph Engel, M.D., Mikael Eriksson, M.Sc., Peter A. Fasching, M.D., Jonine Figueroa, Ph.D., Henrik Flyger, Ph.D., Asta Försti, Ph.D., Marike Gabrielson, Ph.D., Manuela Gago-Dominguez, Vassilios Georgoulas, M.D.,

Fabian Gil, M.D., Graham G. Giles, Ph.D., Gord Glendon, M.Sc., Encarna B. Gómez García, M.D., Ph.D., Grethe I. Grenaker Alnæs, M.Sc., Pascal Guénel, Ph.D., Andreas Hadjisavvas, Ph.D., Lothar Haeblerle, Ph.D., Eric Hahnen, Ph.D., Per Hall, M.D., Ph.D., Ute Hamann, Ph.D., Elaine F. Harkness, Ph.D., Jaana M. Hartikainen, Ph.D., Mikael Hartman, M.D., Ph.D., Wei He, Ph.D., Bernadette A.M. Heemskerk-Gerritsen, Ph.D., Peter Hillemanns, M.D., Frans B.L. Hogervorst, Antoinette Hollestelle, Ph.D., Weang Kee Ho, Ph.D., Maartje J. Hoening, Ph.D., Anthony Howell, M.B., B.S., Keith Humphreys, Ph.D., Faiza Idris, Anna Jakubowska, Ph.D., Audrey Jung, Ph.D., Pooja Middha Kapoor, Ph.D., Michael J. Kerin, M.Ch., Elza Khushnutdinova, M.D., Sung-Won Kim, M.D., Ph.D., Yon-Dschun Ko, M.D., Veli-Matti Kosma, M.D., Vessela N. Kristensen, Ph.D., Kyriacos Kyriacou, Ph.D., Inge M.M. Lakeman, Jong Won Lee, Ph.D., Min Hyuk Lee, M.D., Ph.D., Jingmei Li, Ph.D., Annika Lindblom, M.D., Ph.D., Wing-Yee Lo, Ph.D., Maria A. Loizidou, Ph.D., Artitaya Lophatananon, Ph.D., Jan Lubiński, M.D., Ph.D., Robert J. MacInnis, Ph.D., Michael J. Madsen, M.Stat., Arto Mannerman, Ph.D., Mehdi Manoochehri, Ph.D., Siranoush Manoukian, M.D., Sara Margolin, M.D., Ph.D., Maria Elena Martinez, Ph.D., Tabea Maurer, Dipl. Psych., Dimitrios Mavroudis, M.D., Catriona McLean, M.D., Alfons Meindl, Ph.D., Arjen R. Mensenkamp, Ph.D., Kyriaki Michailidou, Ph.D., Nicola Miller, Ph.D., Nur Aishah Mohd Taib, Kenneth Muir, Ph.D., Anna Marie Mulligan, M.B., B.Ch., Heli Nevanlinna, Ph.D., William G. Newman, M.D., Ph.D., Børge K. Nordestgaard, M.D., Pei-Sze Ng, Jan C. Oosterwijk, M.D., Ph.D., Sue K. Park, M.D., Ph.D., Tjong-Won Park-Simon, M.D., Jose I.A. Perez, Ph.D., Paolo Peterlongo, Ph.D., David J. Porteous, Ph.D., Karolina Prajzandanc, Ph.D., Darya Prokofyeva, Ph.D., Paolo Radice, Ph.D., Muhammad U. Rashid, M.D., Ph.D., Valerie Rhenius, B.Sc., Matti A. Rookus, Ph.D., Thomas Rüdiger, Emmanouil Saloustros, M.D., D.Sc., Elinor J. Sawyer, Ph.D., Rita K. Schmutzler, M.D., Andreas Schneeweiss, Peter Schürmann, B.T.A., Mitul Shah, M.Sc., Christof Sohn, Melissa C. Southey, Ph.D., Harald Surowy, Ph.D., Maija Suvalo, Ph.D., Somchai Thanasitthichai, M.D., Ian Tomlinson, Ph.D., Diana Torres, Ph.D., Thérèse Truong, Ph.D., Maria Tzardi, M.D., Ph.D., Yana Valova, M.Sc., Christi J. van Asperen, Rob M. Van Dam, Ans M.W. van den Ouweland, Ph.D., Lizet E. van der Kolk, M.D., Ph.D., Elke M. van Veen, Ph.D., Camilla Wendt, M.D., Ph.D., Justin A. Williams, M.P.H., Xiaohong R. Yang, Ph.D., Sook-Yee Yoon, M. Pilar Zamora, D. Gareth Evans, M.D., Miguel de la Hoya, Ph.D., Jacques Simard, Ph.D., Antonis C. Antoniou, Ph.D., Åke Borg, Ph.D., Irene L. Andruelis, Ph.D., Jenny Chang-Claude, Ph.D., Montserrat García-Closas, M.D., Dr.P.H., Georgia Chenevix-Trench, Ph.D., Roger L. Milne, Ph.D., Paul D.P. Pharoah, Ph.D., Marjanka K. Schmidt, Ph.D., Amanda B. Spurdle, Ph.D., Maaïke P.G. Vreeswijk, Javier Benitez, Ph.D., Alison M. Dunning, Ph.D., Anders Kvist, Ph.D., Soo H. Teo, Ph.D., Peter Devilee, Ph.D., and Douglas F. Easton, Ph.D.

The authors' affiliations are as follows: the Centre for Cancer Genetic Epidemiology, Departments of Public Health and Primary Care (L.D., S. Carvalho, J.A., K.A.P., Q.W., M.K.B., J.D., B.D., N. Mavaddat, K. Michailidou, A.C.A., P.D.P.P., D.F.E.) and Oncology (C.L., P.A.H., C. Baynes, D.M.C., L.F., V.R., M. Shah, P.D.P.P., A.M.D., D.F.E.), University of Cambridge, Cambridge, the Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine (A. Campbell, D.J.P.), and the Centre for Cognitive Ageing and Cognitive Epidemiology, Department of Psychology (D.J.P.), University of Edinburgh, the Cancer Research UK Edinburgh Centre (D.A.C., J.F.), and the Usher Institute of Population Health Sciences and Informatics, University of Edinburgh Medical School (A. Campbell, J.F.), Edinburgh, the Divisions of Informatics, Imaging, and Data Sciences (E.F.H.), Cancer Sciences (A. Howell), Population Health, Health Services Research, and Primary Care (A. Lophatananon, K. Muir), and Evolution and Genomic Sciences, School of Biological Sciences (W.G.N., E.M.V., D.G.E.), University of Manchester, the NIHR Manchester Biomedical Research Unit (E.F.H.) and the Nightingale Breast Screening Centre, Wythenshawe Hospital (E.F.H., H.I.), Academic Health Science Centre and North West Genomics Laboratory Hub, and the Manchester Centre for Genomic Medicine, St. Mary's Hospital, Manchester University NHS Foundation Trust (W.G.N., E.M.V., D.G.E.), Manchester, the School of Cancer and Pharmaceutical Sciences, Comprehensive Cancer Centre, Guy's Campus, King's College London, London (E.J.S.), the Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham (I.T.), and the Wellcome Trust Centre for Human Genetics and Oxford NIHR Biomedical Research Centre, University of Oxford, Oxford (I.T.) — all in the United Kingdom; the Human Genotyping-CEGEN Unit, Human Cancer Genetic Program (A.G.-N., M.R.A., N.A., B.H., R.N.-T.), and the Human Genetics Group (V.F., A.O., J.B.), Spanish National Cancer Research Center, Centro de Investigación en Red de Enfermedades Raras (A.O., J.B.), Servicio de Oncología Médica, Hospital Universitario La Paz (M.P.Z.), and Molecular Oncology Laboratory, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (M. de la Hoya), Madrid, the Genomic Medicine Group, Galician Foundation of Genomic Medicine, Instituto de Investigación Sanitaria de Santiago de Compostela, Complejo Hospitalario Universitario de Santiago (A. Carracedo, M.G.-D.), and Centro de Investigación en Red de Enfermedades Raras y Centro Nacional de Genotipado, Universidad de Santiago de Compostela (A. Carracedo), Santiago de Compostela, the Oncology and Genetics Unit, Instituto de Investigación Sanitaria Galicia Sur, Xerencia de Xestión Integrada de Vigo—Servizo Galeo de Saúde, Vigo (J.E.C.), and Servicio de Cirugía General y Especialidades, Hospital Monte Naranco, Oviedo (J.I.A.P.) — all in Spain; the Division of Oncology and Pathology, Department of Clinical Sciences Lund, Lund University, Lund (C. Wahlström, J.V., M.L., T. Törngren, Å.B., A.K.), the Department of Oncology, Örebro University Hospital, Örebro (C. Blomqvist), and the Departments of Medical Epidemiology and Biostatistics (K.C., M.E., M.G., P. Hall, W.H., K.H.), Oncology, Södersjukhuset (P. Hall, S. Margolin), Molecular Medicine and Surgery (A. Lindblom), and Clinical Science and Education, Södersjukhuset (S. Margolin, C. Wendt), Karolinska Institutet, and the Department of Clinical Genetics, Karolinska University Hospital (A. Lindblom), Stockholm — all in Sweden; the Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD (M.T.P., C.F., G.C.-T., A.B.S.), the Cancer Epidemiology Division, Cancer Council Victoria (G.G.G., R.J.M., R.L.M.), the Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health (G.G.G., R.J.M., R.L.M.), and the Department of Clinical Pathology (M.C.S.), University of Melbourne, Anatomical Pathology, Alfred Hospital (C.M.), and the Cancer Epidemiology Division, Cancer Council Victoria (M.C.S.), Melbourne, VIC, and Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC (G.G.G., M.C.S., R.L.M.) — all in Australia; the Division of Molecular Pathology (R.K., S. Cornelissen, M.K.S.), Family Cancer Clinic (F.B.L.H., L.E.K.), Department of Epidemiology (M.A.R.), and Division of Psychosocial Research and Epidemiology (M.K.S.), the Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, Division Laboratories, Pharmacy and Biomedical Genetics, Department of Genetics, University Medical Center, Utrecht (M.G.E.M.A.), the Department of Clinical Genetics, Erasmus University Medical Center (J.M.C., A.M.W.O.), and the Department of Medical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute (B.A.M.H.-G., A. Hollestelle, M.J.H.), Rotterdam, the Department of Clinical Genetics, Maastricht University Medical Center, Maastricht (E.B.G.G.), the Departments of Human Genetics (I.M.M.L., M.P.G.V., P.D.), Clinical Genetics (C.J.A.), and Pathology (P.D.), Leiden University Medical Center, Leiden, the Department of Human Genetics, Radboud University Medical Center, Nijmegen (A.R.M.), and the Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen (J.C.O.) — all in the Netherlands; the Cancer Genetics and Comparative Genomics Branch, National Human Genome Research Institute (B.D.), and the Division of Cancer Epidemiology and Genetics, National Cancer Institute (T.A., S.J.C., X.R.Y., M.G.-C.), National Institutes of Health, Bethesda, MD; the Department of Pathology, Brigham and Women's Hospital, Harvard Medical School (B.D.), and the Depart-

ment of Nutrition, Harvard T.H. Chan School of Public Health (R.M.V.D.), Boston; the Departments of Clinical Genetics (K.A.), Oncology (C. Blomqvist), and Obstetrics and Gynecology (H.N., M. Suvanto), Helsinki University Hospital, University of Helsinki, Helsinki, and the Unit of Clinical Oncology, Kuopio University Hospital (P. Auvinen), the Institute of Clinical Medicine, Oncology (P. Auvinen), the Translational Cancer Research Area (J.M.H., V.-M.K., A. Mannermaa), and the Institute of Clinical Medicine, Pathology, and Forensic Medicine (J.M.H., V.-M.K., A. Mannermaa), University of Eastern Finland, and the Biobank of Eastern Finland, Kuopio University Hospital (V.-M.K., A. Mannermaa), Kuopio — both in Finland; the N.N. Alexandrov Research Institute of Oncology and Medical Radiology, Minsk, Belarus (N.N.A., N.V.B.); the Department of Gynecology and Obstetrics and Institute of Clinical Molecular Biology, University Hospital of Schleswig-Holstein, Campus Kiel, Christian-Albrechts University Kiel, Kiel (N.A.), the Institute of Medical Biometry and Epidemiology (H. Becher) and Cancer Epidemiology Group (T.M., J.C.-C.), University Cancer Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, the Department of Gynecology and Obstetrics (M.W.B., P.A.F., L.H.) and Institute of Human Genetics (A.B.E.), University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nuremberg, Comprehensive Cancer Center Erlangen–European Metropolitan Region of Nuremberg, Erlangen, the Division of Cancer Epidemiology (S.B., A. Jung, P.M.K., J.C.-C.), Molecular Epidemiology Group, C080 (B. Burwinkel, H.S.), Division of Pediatric Neurooncology (A.F.), and Molecular Genetics of Breast Cancer (U.H., M.M., M.U.R., D.T.), German Cancer Research Center, Molecular Biology of Breast Cancer, University Women's Clinic Heidelberg, University of Heidelberg (B. Burwinkel, A.S., H.S.), Hopp Children's Cancer Center (A.F.), Faculty of Medicine, University of Heidelberg (P.M.K.), and National Center for Tumor Diseases, University Hospital and German Cancer Research Center (A.S., C.S.), Heidelberg, the Department of Radiation Oncology (N.V.B., M. Bremer, H.C.) and the Gynecology Research Unit (N.V.B., T.D., P. Hillemanns, T.-W.P.-S., P.S.), Hannover Medical School, Hannover, the Institute of Human Genetics, University of Münster, Münster (N.B.-M.), Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart (H. Brauch, W.-Y.L.), iFIT-Cluster of Excellence, University of Tübingen, and the German Cancer Consortium, German Cancer Research Center, Partner Site Tübingen (H. Brauch), and the University of Tübingen (W.-Y.L.), Tübingen, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum, Bochum (T.B.), Institute for Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Leipzig (C.E.), Center for Hereditary Breast and Ovarian Cancer (E.H., R.K.S.) and Center for Integrated Oncology (E.H., R.K.S.), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, the Department of Internal Medicine, Evangelische Kliniken Bonn, Johanniter Krankenhaus, Bonn (Y.-D.K.), the Department of Gynecology and Obstetrics, University of Munich, Campus Großhadern, Munich (A. Meindl), and the Institute of Pathology, Städtisches Klinikum Karlsruhe, Karlsruhe (T.R.) — all in Germany; the Gynecological Cancer Registry, Centre Georges-François Leclerc, Dijon (P. Arveux), and the Center for Research in Epidemiology and Population Health, Team Exposome and Heredity, INSERM, University Paris-Saclay, Villejuif (E.C.-D., P.G., T. Truong) — both in France; the Institute of Biochemistry and Genetics, Ufa Federal Research Center of the Russian Academy of Sciences (M. Bermisheva, E.K.), the Department of Genetics and Fundamental Medicine, Bashkir State University (E.K., D.P., Y.V.), and the Ufa Research Institute of Occupational Health and Human Ecology (Y.V.), Ufa, Russia; the Department of Genetics and Pathology (K.B., A. Jakubowska, J. Lubiński, K.P.) and the Independent Laboratory of Molecular Biology and Genetic Diagnostics (A. Jakubowska), Pomeranian Medical University, Szczecin, Poland; the Copenhagen General Population Study, the Department of Clinical Biochemistry (S.E.B., B.G.N.), and the Department of Breast Surgery (H.F.), Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, and the Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen (S.E.B., B.G.N.) — both in Denmark; the Division of Cancer Prevention and Genetics, European Institute of Oncology Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) (B. Bonanni), the Unit of Medical Genetics, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano (S. Manoukian), the Genome Diagnostics Program, FIRG Institute of Molecular Oncology (P.P.), and the Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori (P.R.), Milan; the Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital-Radiumhospitalet (A.-L.B.-D., G.I.G.A., V.N.K.), and the Institute of Clinical Medicine, Faculty of Medicine, University of Oslo (A.-L.B.-D., V.N.K.), Oslo, Medical Faculty, Universidad de La Sabana (I.B.), and the Clinical Epidemiology and Biostatistics Department (F.G.) and Institute of Human Genetics (D.T.), Pontificia Universidad Javeriana, Bogota, Colombia; the Department of Internal Medicine and Huntsman Cancer Institute, University of Utah (N.J.C., M.J.M., J.A.W.), and the Intermountain Healthcare Biorepository and Department of Pathology, Intermountain Healthcare (M.H.C.), Salt Lake City; the David Geffen School of Medicine, Department of Medicine Division of Hematology and Oncology, University of California, Los Angeles (P.A.F.), and Moores Cancer Center (M.G.-D., M.E.M.) and the Department of Family Medicine and Public Health (M.E.M.), University of California San Diego, La Jolla; the Departments of Medical Oncology (V.G., D.M.) and Pathology (M.T.), University Hospital of Heraklion, Heraklion, and the Department of Oncology, University Hospital of Larissa, Larissa (E.S.) — both in Greece; the Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital (G.G., I.L.A.), the Departments of Laboratory Medicine and Pathobiology (A.M.M.) and Molecular Genetics (I.L.A.), University of Toronto, and the Laboratory Medicine Program, University Health Network (A.M.M.), Toronto, and the Genomics Center, Centre Hospitalier Universitaire de Québec–Université Laval Research Center, Québec City, QC (J.S.) — both in Canada; the Department of Electron Microscopy and Molecular Pathology (A. Hadjisavvas, K.K., M.A.L.), the Cyprus School of Molecular Medicine (A. Hadjisavvas, K.K., M.A.L., K. Michailidou), and the Biostatistics Unit (K. Michailidou), Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus; the Saw Swee Hock School of Public Health (M. Hartman, R.M.V.D.) and the Department of Medicine, Yong Loo Lin School of Medicine (R.M.V.D.), National University of Singapore, the Department of Surgery, National University Health System (M. Hartman, J. Li), and the Human Genetics Division, Genome Institute of Singapore (J. Li), Singapore; the Department of Mathematical Sciences, Faculty of Science and Engineering, University of Nottingham Malaysia (W.K.H.), and the Breast Cancer Research Programme, Cancer Research Malaysia (W.K.H., P.S.N., S.-Y.Y., S.H.T.), Selangor, and the Breast Cancer Research Unit, Cancer Research Institute (N.A.M.T.), and the Department of Surgery, Faculty of Medicine (N.A.M.T., P.S.N., S.H.T.), University Malaya, Kuala Lumpur — both in Malaysia; Surgery, School of Medicine, National University of Ireland, Galway (M.J.K., N. Miller); the Department of Surgery, Daerim Saint Mary's Hospital (S.-W.K.), the Department of Surgery, Ulsan University College of Medicine and Asan Medical Center (J.W.L.), the Department of Surgery, Soonchunhyang University College of Medicine and Soonchunhyang University Hospital (M.H.L.), Integrated Major in Innovative Medical Science, Seoul National University College of Medicine (S.K.P.), and the Cancer Research Institute, Seoul National University (S.K.P.), Seoul, South Korea; the Department of Basic Sciences, Shaikat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan (M.U.R.); and the National Cancer Institute, Ministry of Public Health, Nonthaburi, Thailand (S.T.).

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