Associations of a Breast Cancer Polygenic Risk Score With Tumor Characteristics and Survival

Published in:
Journal of clinical oncology : official journal of the American Society of Clinical Oncology

Publication status and date:
Published: 01/04/2023

DOI (link to publisher):
10.1200/jco.22.01978

Document Version
Publisher's PDF, also known as Version of record

original reports

Associations of a Breast Cancer Polygenic Risk Score With Tumor Characteristics and Survival

Josephine M.N. Lopes Cardozo, MD, PhD[1,2]; Irene L. Andrulis, PhD[3,4]; Stig E. Bojesen, MD, PhD[5,6,7]; Thilo Dörk, PhD[8]; Diana M. Eccles, MD, PhD[9]; Peter A. Fasching, MD, PhD[10]; Maartje J. Hooning, PhD[11]; Renske Keeman, MSc[12]; Heli Nevanlinna, MD, PhD[13]; Emiel J.T. Rutgers, MD, PhD[1]; Douglas F. Easton, PhD[14,15]; Per Hall, MD, PhD[16,17]; Paul D.P. Pharoah, PhD[14,15]; Laura J. van 't Veer, PhD[18]; and Marjanka K. Schmidt, PhD[12,19,20]; on behalf of the Breast Cancer Association Consortium and MINDACT Collaborators

abstract

PURPOSE A polygenic risk score (PRS) consisting of 313 common genetic variants (PRS_{313}) is associated with risk of breast cancer and contralateral breast cancer. This study aimed to evaluate the association of the PRS_{313} with clinicopathologic characteristics of, and survival following, breast cancer.

METHODS Women with invasive breast cancer were included, 98,397 of European ancestry and 12,920 of Asian ancestry, from the Breast Cancer Association Consortium (BCAC), and 683 women from the European MINDACT trial. Associations between PRS_{313} and clinicopathologic characteristics, including the 70-gene signature for MINDACT, were evaluated using logistic regression analyses. Associations of PRS_{313} (continuous, per standard deviation) with overall survival (OS) and breast cancer–specific survival (BCSS) were evaluated with Cox regression, adjusted for clinicopathologic characteristics and treatment.

RESULTS The PRS_{313} was associated with more favorable tumor characteristics. In BCAC, increasing PRS_{313} was associated with lower grade, hormone receptor–positive status, and smaller tumor size. In MINDACT, PRS_{313} was associated with a low risk 70-gene signature. In European women from BCAC, higher PRS_{313} was associated with better OS and BCSS: hazard ratio (HR) 0.96 (95% CI, 0.94 to 0.97) and 0.96 (95% CI, 0.94 to 0.98), but the association disappeared after adjustment for clinicopathologic characteristics (and treatment): OS HR, 1.01 (95% CI, 0.98 to 1.05) and BCSS HR, 1.02 (95% CI, 0.98 to 1.07). The results in MINDACT and Asian women from BCAC were consistent.

CONCLUSION An increased PRS_{313} is associated with favorable tumor characteristics, but is not independently associated with prognosis. Thus, PRS_{313} has no role in the clinical management of primary breast cancer at the time of diagnosis. Nevertheless, breast cancer mortality rates will be higher for women with higher PRS_{313} as increasing PRS_{313} is associated with an increased risk of disease. This information is crucial for modeling effective stratified screening programs.

J Clin Oncol 41:1849-1863. © 2023 by American Society of Clinical Oncology

INTRODUCTION

Over recent years, there has been an increased understanding of genetic factors that contribute to risk of breast cancer.[1-6] Large-scale genome-wide association studies (GWAS) have identified hundreds of common genetic variants (mostly single nucleotide-polymorphisms [SNPs]) that are associated with breast cancer risk.[5-12] Together, these common genetic variants explain approximately 20% of the hereditary component of breast cancer risk.[11]

Individual SNPs have a small effect on risk, but their joint effects can be substantial, and can be efficiently summarized in terms of polygenic risk scores (PRS), which are the weighted sum of risk alleles.[6,7,12] We previously reported the association between an optimized and validated PRS consisting of 313 SNPs (PRS_{313}) and the risk of breast cancer using data from the Breast Cancer Association Consortium (BCAC).[6,12] PRS_{313} is predictive of overall breast cancer risk, with an odds ratio (OR) per standard deviation (SD) of 1.61 (95% CI, 1.57 to 1.65).[12] PRS_{313} is also associated with a higher risk of contralateral breast cancer with a HR per SD of 1.25 (95% CI, 1.18 to 1.33).[13] PRS for subtype-specific disease (estrogen receptor [ER]–positive and ER-negative disease) have also been established, although currently the risk prediction for ER-positive disease is better than for ER-negative disease.[7,12]

One of the most promising clinical applications for PRS is to provide a personalized risk assessment to individualize breast cancer screening. For women with a higher risk of developing breast cancer, this could involve starting screening at a younger age and offering more frequent screening, while women at lower risk could be offered less frequent screening.[7,14] Currently, several large studies are investigating the feasibility and

ASSOCIATED CONTENT

Appendix

Data Supplement

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 16, 2022 and published at ascopubs.org/journal/jco on January 23, 2023: DOI https://doi.org/10.1200/JCO.22.01978

CONTEXT

Key Objective

An optimized and extensively validated polygenic risk score (PRS) consisting of 313 common genetic variants (PRS_{313}) has been associated with risk of first breast cancer and contralateral breast cancer, and has a promising role for risk stratification in screening and prevention programs. Whether PRS_{313} affects breast cancer prognosis has not yet been addressed, and is important for incorporating PRS into clinical practice.

Knowledge Generated

PRS_{313} was associated with more favorable tumor characteristics. PRS_{313} was not independently associated with prognosis. Nevertheless, breast cancer mortality rates will be higher for women with higher PRS_{313} as increasing PRS_{313} is associated with an increased risk of disease.

Relevance *(K.D. Miller)*

PRS_{313} identifies women predominantly at risk for developing estrogen receptor–positive breast cancers. Use of PRS_{313} could target hormonal prevention strategies to women most likely to benefit.*

*Relevance section written by *JCO* Senior Deputy Editor Kathy D. Miller, MD.

effectiveness of incorporating risk-based screening on the basis of PRS and other risk factors into breast cancer screening programs.[15-19] Since the ultimate goal of screening programs is to reduce mortality, an important question is whether PRS are associated with survival of women with breast cancer. The aim of this study was to investigate the association between PRS_{313} and clinicopathologic characteristics of breast cancer and disease outcome. In a subgroup of patients from the MINDACT study, we also explored associations of PRS_{313} with the 70-gene signature (MammaPrint), which has been shown to predict distant metastasis within 5 years of breast cancer diagnosis.[20]

METHODS

Study Subjects and SNP Genotyping

Breast Cancer Association Consortium. We selected women diagnosed with a first invasive breast cancer from the BCAC database version 13. All women of European and Asian ancestry, on the basis of genotyping, who were age 18 years and older were included, including 98,397 European women (74 studies) and 12,920 Asian women (10 studies; Data Supplement, online only). SNP genotyping was performed using the iCOGS array[21,22] or the OncoArray.[10,11] Genotypes for variants that were not on the arrays were estimated by imputation.[11,22] For samples that were genotyped with both arrays, OncoArray data were used. As previously described, adjustment for type of array was not needed because of the high correlation of PRS_{313} between the two platforms.[12,13] All participants provided written informed consent, and all studies were approved by the relevant institutional review boards. BCAC data were centrally harmonized and cleaned in consultation with the study data managers and principal investigators.

MINDACT. A selection of 1,139 women who were screened for participation in the European Organisation for Research and Treatment of Cancer 10041/BIG 3-04 MINDACT study also participated in the iCOGS project. In this project, genotyping was performed using the iCOGS array.[21,22] Of these, 683 women were eventually enrolled in the MINDACT trial, for whom clinical and outcome data were available (Data Supplement). MINDACT included women age 18-70 years with operable invasive breast cancer (T1-3), 0-3 positive lymph nodes (N0-1), and no distant metastasis (M0).[23,24] Further details on the MINDACT study design and the trial results have been previously described.[23,24] For all patients enrolled in the MINDACT trial, a tumor sample was shipped to Agendia (Amsterdam, the Netherlands) for 70-gene signature testing.[23,24] The 70-gene signature classifies tumors as high or low risk of developing distant metastasis within 5 years after breast cancer diagnosis.[20] All patients provided written informed consent for participation in the iCOGS project as part of the informed consent for the MINDACT study, which allowed linkage of the PRS_{313} results to the MINDACT study database.

Polygenic Risk Scores

The PRS_{313} and the ER-specific PRSs (hybrid method) were calculated and validated as described by Mavaddat et al[12]; MINDACT and the Asian BCAC set were not included in that study, but the BCAC European data were. For consistency with other PRS analyses, we standardized the PRS by dividing it by the SD of PRS_{313} of the control subjects (PRS_{313} SD, 0.61; ER-positive PRS_{313} SD, 0.65; ER-negative PRS_{313} SD, 0.59).[12,13]

Statistical Analysis

All analyses were performed separately in the BCAC and MINDACT databases. Univariable logistic regression models were used to test the association between the PRS_{313} and clinicopathologic characteristics including the 70-gene signature. In BCAC, models were adjusted for country.

The primary outcome was to evaluate the association between PRS_{313} (per SD) and outcome after breast cancer. This was assessed for three different end points: overall survival (OS),

breast cancer-specific survival (BCSS) and distant metastasis-free interval (DMFI). OS was defined as the time from breast cancer diagnosis until death from any cause. BCSS was defined as the time from breast cancer diagnosis until death due to breast cancer. DMFI was defined as the time from breast cancer diagnosis until first distant metastasis or death due to breast cancer. Patients who developed a contralateral breast cancer during follow-up were not censored. For MINDACT, death from unknown cause was included as an event for DMFI. For BCAC, death from unknown cause was not included as an event for DMFI, because of the high number of patients with unknown causes of death.

Cox proportional hazards models were used to test the association between PRS_{313} and survival end points in univariable models and in multivariable models adjusted for clinicopathologic characteristics and treatment (chemotherapy and endocrine therapy). Additionally, in a univariable Cox model, the association between the PRS_{313} and BCSS was evaluated in subgroups on the basis of clinicopathologic characteristics.

In BCAC, all analyses were stratified by country, and for the survival analyses, patients with stage IV breast cancer (n = 1,379) were excluded to allow for comparison with MINDACT. The entire follow-up duration was considered for the analyses in MINDACT. For BCAC, follow-up was right-censored at 15 years, accounting for the large variation in follow-up durations for different studies; this did not lead to different conclusions compared with the analyses when all follow-up was considered. Analyses in BCAC allowed for delayed study entry (after breast cancer diagnosis) using left truncation. Cases with missing data for a given variable were excluded for any analysis using that variable. A sensitivity analysis was performed in BCAC including only cases with complete data for all variables. Details on the different studies included in BCAC, including information on number of patients and collection of follow-up per study, have been described previously.[25,26] Women of Asian ancestry were analyzed separately, and this analysis was limited to the main analyses of the association between PRS_{313} and clinicopathologic characteristics and survival end points, because of the smaller size of the data set with shorter follow-up time than for the European BCAC studies, and because 26 variants of the PRS_{313} were imputed with a low (< 0.9) imputation score.[27] Similarly, analyses in MINDACT were also limited to the main analyses, because of the smaller data set.

All analyses in MINDACT were performed using SPSS (version 27.0) or R (version 3.6.3). All analyses in BCAC were performed using STATA/SE (version 15.1). All plots were made using R (version 3.6.3). All tests of statistical significance were two-sided, with the level of significance defined as a P value of < .05.

Each study included in this analysis was approved by its institutional ethics review board, and all participants provided written informed consent.

RESULTS

Association Between PRS_{313} and Clinicopathologic Characteristics

The association between the PRS_{313} and individual clinicopathologic characteristics was evaluated for 98,397 women of European ancestry and 12,920 women of Asian ancestry with invasive breast cancer included in BCAC and 683 women included in MINDACT. Patient, tumor, and treatment characteristics are shown in Table 1. BCAC included more patients with tumors of larger size and positive lymph nodes than MINDACT. The distribution of other tumor and treatment characteristics was similar for BCAC and MINDACT; however, there was substantial missing information in BCAC for some variables. Table 2 and Figure 1 show the association between specific tumor characteristics and PRS_{313}. Generally, an increase in PRS_{313} was associated with a decreased probability of unfavorable tumor characteristics. Patients with a higher PRS_{313} were less likely to have ER-negative or progesterone receptor–negative tumors, higher-grade tumors, or larger tumors. However, a higher PRS_{313} was associated with a higher probability of lymph node–positive tumors, and with a younger age at diagnosis. In the MINDACT study, a higher PRS_{313} was associated with a lower probability of a high-risk 70-gene signature, and the association was attenuated after adjusting for other clinicopathologic characteristics (adjusted OR, 0.97 [95% CI, 0.78 to 1.21]). This is not unexpected, as we know from previous studies that 70-gene signature low-risk tumors are mostly hormone receptor–positive, with favorable tumor characteristics. The estimates in BCAC and MINDACT were in the same direction for most factors, although results in the smaller MINDACT study and the subset of women of Asian ancestry in BCAC were statistically nonsignificant.

Association Between PRS_{313} and Breast Cancer Outcome

Data from 95,955 women of European ancestry with primary invasive breast cancer with 16,582 deaths (7,635 known breast cancer deaths) within 15 years from BCAC and 683 women with 61 deaths (31 breast cancer deaths) from MINDACT were included for the primary survival analysis. Median follow-up for OS was 7.7 years in BCAC and 8.3 years in MINDACT. In BCAC, an increase in PRS_{313} was associated with a slightly better OS, HR per unit SD of PRS_{313} 0.96 (95% CI, 0.94 to 0.97); BCSS, 0.96 (95% CI, 0.94 to 0.98); and DMFI, 0.98 (95% CI, 0.96 to 1.00; Table 3 and Fig 2). For all end points, the associations disappeared after adjusting for clinicopathologic characteristics and treatment. The adjusted HR per unit SD of PRS_{313} was 1.01 (95% CI, 0.98 to 1.05) for OS, 1.02 (95% CI, 0.98 to 1.07) for BCSS, and 1.03 (95% CI, 0.99 to 1.07) for DMFI (Table 3 and Fig 2). Of note, the association with PRS_{313} that was seen in the unadjusted analysis disappeared after adjusting for ER status and grade only (BCSS, 1.01 [95% CI, 0.98 to 1.04]). The

TABLE 1. Patient, Tumor, and Treatment Characteristics of Women Diagnosed With Invasive Breast Cancer Included in BCAC and MINDACT

Characteristic	BCAC—European (N = 98,397), No. (% including missing) [% excluding missing]	MINDACT (N = 683), No. (%)	BCAC—Asian (N = 12,920), No. (% including missing) [% excluding missing]
Years of diagnosis (median)	1947-2018 (2004)	2007-2011	1967-2016 (2006)
Age, years, mean ± SD	57.1 ± 12.1	54.4 ± 9.2	50.9 ± 11.1
Age, years			
< 40	8,182 (8)	43 (6)	1,937 (15)
≥ 40-50	19,180 (20)	190 (28)	4,290 (33)
≥ 50-60	27,485 (28)	225 (33)	3,876 (30)
≥ 60	43,550 (44)	225 (33)	2,817 (22)
Tumor stage			
Stage I	26,302 (27) [45]		3,707 (29) [36]
Stage II	25,494 (26) [44]		4,683 (36) [46]
Stage III	5,504 (6) [9]		1,578 (12) [15]
Stage IV	1,101 (1) [2]		283 (2) [3]
Missing/unknown	39,669 (41) [0]	683 (100)	2,669 (21) [0]
Tumor size, cm			
T1 (≤ 2)	46,123 (47) [64]	484 (71)	4,132 (32) [51]
T2 (2-5)	22,522 (23) [31]	194 (28)	3,328 (26) [41]
T3 (> 5)	3,261 (3) [5]	5 (1)	654 (5) [8]
Missing/unknown	26,491 (27) [0]		4,806 (37) [0]
Lymph node status			
Negative	49,348 (50) [63]	521 (76)	5,751 (44) [60]
Positive	29,335 (30) [37]	162 (24)	3,827 (30) [40]
Missing/unknown	19,714 (20) [0]		3,342 (26) [0]
Grade			
1	15,778 (16) [20]	151 (22)	1,165 (9) [13]
2	37,654 (38) [48]	300 (44)	3,890 (30) [43]
3	24,666 (25) [32]	215 (32)	3,960 (31) [44]
Missing/unknown	20,299 (21) [0]	17 (2)	3,905 (30) [0]
Tumor histology			
Ductal	62,644 (64) [73]	559 (82)	8,514 (66) [90]
Lobular	12,451 (13) [14]	85 (12)	338 (3) [3]
Mixed (ductolobular)	4,386 (4) [5]	30 (4)	82 (1) [1]
Other	6,731 (7) [8]	9 (1)	568 (4) [6]
Unknown	12,185 (12) [0]		3,418 (26) [0]
ER status			
Positive	67,248 (68) [81]	579 (85)	8,326 (65) [69]
Negative	15,502 (16) [19]	104 (15)	3,792 (29) [31]
Missing/unknown	15,647 (16) [0]		802 (6) [0]
PR status			
Positive	49,634 (50) [69]	462 (71)	7,244 (56) [63]
Negative	22,637 (23) [31]	187 (29)	4,169 (32) [37]
Missing/unknown	26,126 (27) [0]		1,507 (12) [0]
HER2 status			
Positive	8,723 (9) [16]	68 (10)	3,310 (26) [38]

(continued on following page)

TABLE 1. Patient, Tumor, and Treatment Characteristics of Women Diagnosed With Invasive Breast Cancer Included in BCAC and MINDACT (continued)

Characteristic	BCAC—European (N = 98,397), No. (% including missing) [% excluding missing]	MINDACT (N = 683), No. (%)	BCAC—Asian (N = 12,920), No. (% including missing) [% excluding missing]
Negative	45,072 (46) [84]	614 (90)	5,454 (42) [62]
Missing/unknown	44,602 (45) [0]		4,156 (32) [0]
70-gene signature			
Low risk		403 (59)	
High risk		280 (41)	
Missing/unknown	98,397 (100)		12,920 (100)
Chemotherapy			
No	29,148 (30) [52]	367 (54)	2,673 (21) [25]
Yes	26,914 (27) [48]	315 (46)	8,089 (63) [75]
Missing/unknown	42,335 (43) [0]	1 (0.1)	2,158 (17) [0]
Endocrine therapy			
No	14,186 (14) [28]	199 (29)	2,622 (20) [30]
Yes	36,416 (37) [72]	480 (71)	6,214 (48) [70]
Missing/unknown	47,795 (49) [0]		4,085 (32) [0]
Trastuzumab			
No	24,635 (25) [93]	632 (92)	3,526 (27) [88]
Yes	1,919 (2) [7]	47 (7)	503 (4) [12]
Missing/unknown	71,843 (73) [0]	4 (1)	8,891 (69) [0]
PRS_{313}, mean (range)	–0.15 (–4.56 to 4.08)	–0.15 (–3.54 to 2.94)	0.65 (–3.86 to 4.27)

Abbreviations: BCAC, Breast Cancer Association Consortium; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, Progesterone receptor; PRS, polygenic risk score; PRS_{313}, PRS consisting of 313 common genetic variants; SD, standard deviation.

estimates for individual clinicopathologic characteristics from the complete case analyses are provided in the Data Supplement. The HR estimates in MINDACT were close to 1, and consistent with the estimates in BCAC, but with very wide 95% CIs.

Furthermore, the results of the analyses in 12,528 women of Asian ancestry with 1,323 deaths (316 known breast cancers deaths) included in BCAC, with a median follow-up for OS of 4.2 years, were consistent with those of women of European ancestry in BCAC and MINDACT (Table 3 and Fig 2). The adjusted HR per unit SD of PRS_{313} was 0.96 (95% CI, 0.87 to 1.07) for OS; BCSS, 0.93 (95% CI, 0.75 to 1.17), and DMFI, 0.98 (95% CI, 0.87 to 1.10).

We also evaluated the associations between subtype-specific PRS and BCSS in women of European ancestry (Data Supplement). For BCSS, the HR estimates for ER-positive PRS_{313} were similar to the PRS_{313} for overall breast cancer, but the association disappeared when analyses were restricted to ER-positive patients. There was no evidence of association between the ER-negative PRS_{313} and BCSS, neither in all patients nor in ER-negative patients. The association between PRS_{313} and BCSS was also evaluated in subgroups on the basis of clinicopathologic characteristics (Data Supplement). There were no subgroups of patients with a higher probability of breast cancer–related death per unit SD increase in PRS_{313}.

DISCUSSION

The observed association between the PRS_{313} and the lower probability of distant metastasis or (breast cancer–related) death in the unadjusted analysis disappeared after adjustment for clinicopathologic characteristics. In line with this observation, an increase in PRS_{313} was associated both with more favorable clinicopathologic characteristics and with a low-risk 70-gene signature. The simplest interpretation of these results is that clinicopathologic characteristics, particularly ER status and grade, act as intermediates on the causal pathway from germline PRS_{313} to outcomes of breast cancer.

Three studies, each including between 5,000 and 9,000 patients, have previously investigated the association of PRSs consisting of smaller SNP sets (ranging from 77 to 162 SNPs) with clinicopathologic characteristics and clinical outcomes after breast cancer, all in women of European descent.[28-30] These PRSs were found to be associated with favorable tumor characteristics: smaller, lower grade, and hormone receptor–positive tumors. No associations with survival outcomes were observed for any of these PRSs, with HRs per unit SD ranging from 0.91 to 1.02, and all 95% CI including 1.00.[28-30] Furthermore, Li et al have shown that patients with a higher PRS are more likely to be found as a screen-detected cancer, which is in line with the findings that an increase in PRS is associated

TABLE 2. Association Between PRS_{313} and Clinicopathologic Characteristics in BCAC and MINDACT

	BCAC—European (N = 98,397)			MINDACT (N = 683)			BCAC—Asian (N = 12,920)		
Characteristic	**Unadjusted OR Per Unit SD of PRS_{313}[a]**	**95% CI**	***P***	**Unadjusted OR Per Unit SD of PRS_{313}[a]**	**95% CI**	***P***	**Unadjusted OR Per Unit SD of PRS_{313}[a]**	**95% CI**	***P***
Age at diagnosis, years									
< 40	1.11	1.08 to 1.14	< .0001	0.90	0.65 to 1.25	.520	1.04	0.97 to 1.11	.280
≥ 40-50	1.12	1.10 to 1.14	< .0001	1.05	0.86 to 1.27	.650	1.05	1.00 to 1.11	.060
≥ 50-60	1.07	1.05 to 1.09	< .0001	1.12	0.93 to 1.35	.240	0.99	0.94 to 1.04	.690
≥ 60	Reference			Reference			Reference		
Tumor stage									
Stage I-III	Reference			—			Reference		
Stage IV	1.01	0.96 to 1.08	.630	—			1.04	0.92 to 1.19	.520
Tumor size, cm									
≤ 2	Reference			Reference			Reference		
2-5	0.97	0.96 to 0.99	.002	1.01	0.86 to 1.19	.910	0.98	0.93 to 1.03	.410
> 5	1.02	0.98 to 1.06	.280	1.37	0.58 to 3.27	.470	1.00	0.91 to 1.10	.960
Lymph node status									
Negative	Reference			Reference			Reference		
Positive	1.02	1.01 to 1.04	.003	1.07	0.89 to 1.27	.480	1.01	0.96 to 1.05	.770
Tumor histology									
Ductal	Reference			Reference			Reference		
Lobular	1.06	1.04 to 1.08	< .0001	1.34	1.06 to 1.68	.013	1.05	0.94 to 1.19	.390
Other	0.97	0.95 to 0.99	.015	1.07	0.55 to 2.07	.850	0.98	0.88 to 1.07	.620
Mixed	1.08	1.05 to 1.12	< .0001	0.83	0.57 to 1.21	.330	0.99	0.78 to 1.25	.910
Unknown	1.03	1.00 to 1.05	.017				1.00	0.94 to 1.06	.890
Grade									
1	Reference			Reference			Reference		
2	0.98	0.96 to 1.00	.054	1.10	0.90 to 1.33	.370	1.01	0.94 to 1.08	.840
3	0.85	0.83 to 0.86	< .0001	0.80	0.65 to 0.99	.041	0.94	0.87 to 1.01	.080
ER status									
Negative	0.80	0.79 to 0.82	< .0001	0.80	0.65 to 0.99	.038	0.86	0.82 to 0.89	< .0001
Positive	Reference			Reference			Reference		
PR status									
Negative	0.85	0.83 to 0.86	< .0001	0.84	0.71 to 1.00	.047	0.89	0.86 to 0.94	< .0001
Positive	Reference			Reference			Reference		
HER2 status									
Negative	Reference			Reference			Reference		
Positive	0.97	0.94 to 0.99	.003	1.02	0.80 to 1.31	.870	0.99	0.95 to 1.04	.750
70-gene signature									
Low risk	—			Reference			—		
High risk	—			0.86	0.74 to 1.01	.064	—		

Abbreviations: BCAC, Breast Cancer Association Consortium; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; PRS, polygenic risk score; PRS_{313}, PRS consisting of 313 common genetic variants; SD, standard deviation.

[a]Univariable (multinomial/binary) logistic regression models with clinicopathologic characteristics as the dependent variable and PRS_{313} as the independent variable and for BCAC, with country as covariable.

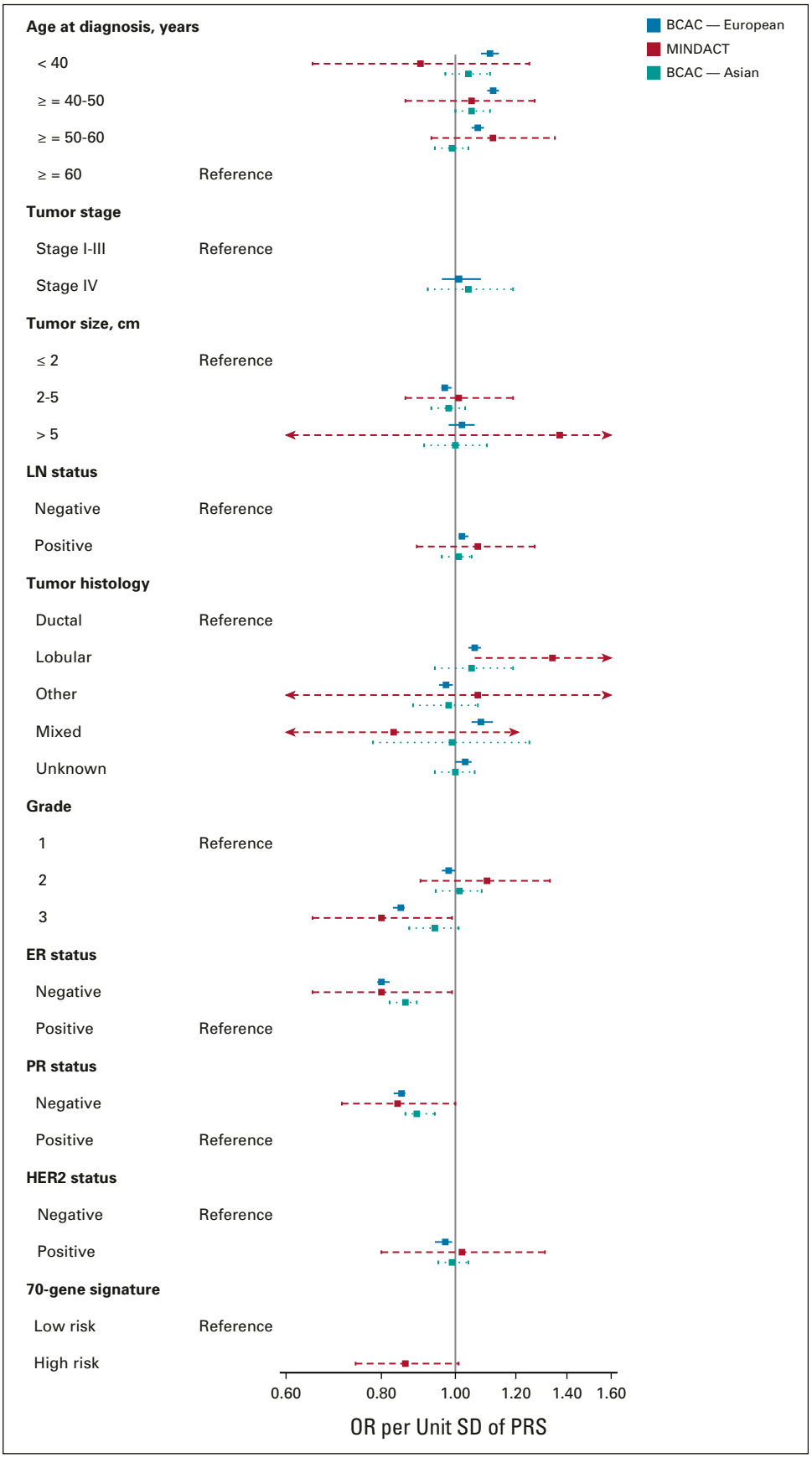

FIG 1. Association between PRS_{313} and clinicopathologic characteristics in BCAC and MINDACT. See Table 2 for exact numeric estimates. Univariable (multinomial/binary) logistic regression (continued on following page)

FIG 1. (Continued). models with clinicopathologic characteristics as the dependent variable and PRS_{313} as the independent variable and for BCAC with country as covariable. BCAC, Breast Cancer Association Consortium; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN, lymph node; OR, odds ratio; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation.

with more favorable clinicopathologic characteristics.[28,30,31] Screen detection itself has been shown to be a prognostic factor for good prognosis, independent of clinicopathologic characteristics.[32,33]

To our knowledge, the 313 SNP PRS is currently the most comprehensively validated PRS of breast cancer risk prediction. In the largest cohort to date to our knowledge, in accordance with previous studies, we observed that higher PRS_{313} was associated with favorable tumor characteristics. Every SD increase in PRS was associated with lower grade, and ER- and progesterone receptor–positive tumors. We also found associations with smaller size and human epidermal growth factor receptor 2–negative tumors, but these associations were weaker. In our study, we observed no association between the PRS_{313} and OS (HR per unit SD increase in PRS, 1.01 [95% CI, 0.98 to 1.05]), BCSS (HR, 1.02 [95% CI, 0.98 to 1.07]), or distant metastasis-free interval (HR, 1.03 [95% CI, 0.99 to 1.07]) in the adjusted models. Of note, the favorable association that was seen in the unadjusted analysis already disappeared after only adjusting for ER status and grade. Our results, together with those previously reported, demonstrate that a higher PRS, and thus higher breast cancer risk, does not imply a poorer outcome among those women who develop breast cancer. The PRS_{313} does not have independent prognostic value in addition to clinicopathologic characteristics, and has no role in the clinical management of primary breast cancer at the time of diagnosis. It is important to emphasize, however, that the absolute mortality from breast cancer will still be higher among women with a higher PRS, because more of them will develop breast cancer and die from the disease. To illustrate this, multiplying the OR per unit SD increase in PRS for breast cancer risk (OR, 1.61) with the HR per unit SD increase in PRS for BCSS (HR, 0.96) gives an approximate estimate for the relative risk of breast cancer mortality per unit SD of the PRS of 1.55. This is an important message to convey when counseling women about the PRS, and as PRS_{313} mostly predicts the development of ER-positive breast cancer, it could be used to identify women eligible for endocrine risk reduction.

A limitation of this study is that the analyses were mostly limited to patients of European ancestry, and similar analyses in patients of non-European ancestry are therefore needed. However, an analysis in a subgroup of women of Asian ancestry showed HR estimates that were consistent with those of women of European ancestry.[27] Prediction of breast

TABLE 3. Association Between PRS_{313} and OS, BCSS, and DMFI in BCAC and MINDACT

End Point	Patients, No.[a]	Events, No.[a]	Unadjusted HR Per Unit SD of PRS_{313}[b]	95% CI	*P*	Adjusted HR Per Unit SD of PRS_{313}[c]	95% CI	*P*	Adjusted HR Per Unit SD of PRS_{313}[d]	95% CI	*P*
OS											
BCAC—European	95,955	16,582	0.96	0.94 to 0.97	< .0001	1.00	0.97 to 1.02	.88	1.01	0.98 to 1.05	.46
MINDACT	683	61	0.91	0.71 to 1.17	.450	0.90	0.69 to 1.17	.42	0.91	0.69 to 1.18	.91
BCAC—Asian	12,528	1,323	0.97	0.91 to 1.02	.240	0.97	0.88 to 1.07	.53	0.96	0.87 to 1.07	.48
BCSS											
BCAC—European	95,955	7,635	0.96	0.94 to 0.98	.001	1.00	0.96 to 1.03	.83	1.02	0.98 to 1.07	.39
MINDACT	683	31	1.10	0.77 to 1.56	.600	1.02	0.70 to 1.49	.93	1.01	0.69 to 1.49	.95
BCAC—Asian	12,528	316	1.05	0.93 to 1.19	.400	0.93	0.74 to 1.16	.50	0.93	0.75 to 1.17	.55
DMFI											
BCAC—European	95,587	8,931	0.98	0.96 to 1.00	.050	1.00	0.97 to 1.04	.79	1.03	0.99 to 1.07	.12
MINDACT	683	60	1.03	0.80 to 1.33	.820	0.95	0.72 to 1.25	.72	0.94	0.72 to 1.24	.68
BCAC—Asian	12,361	775	1.02	0.94 to 1.10	.640	0.96	0.86 to 1.07	.44	0.98	0.87 to 1.10	.74

Abbreviations: BCAC, Breast Cancer Association Consortium; BCSS, breast cancer–specific survival; DMFI, distant metastasis-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PR, progesterone receptor; PRS, polygenic risk score; PRS_{313}, PRS consisting of 313 common genetic variants; SD, standard deviation.

[a]Number of patients (and events) included in the univariable analysis. Cases with missing values were not included in the multivariable analyses.

[b]Cox regression models: unadjusted analysis was stratified for country in BCAC.

[c]Additionally adjusted for age (continuous), tumor size, lymph node status, grade, and ER, PR, and HER2 status.

[d]Additionally adjusted for age (continuous), tumor size, lymph node status, grade, ER, PR, HER2 status, chemotherapy, and endocrine therapy. For analysis using BCAC data, follow-up was right-censored at 15 years and patients with stage 4 disease were excluded from the analysis. For BCAC—European, the estimates for individual clinicopathologic characteristics from the complete case analyses are provided in the Data Supplement.

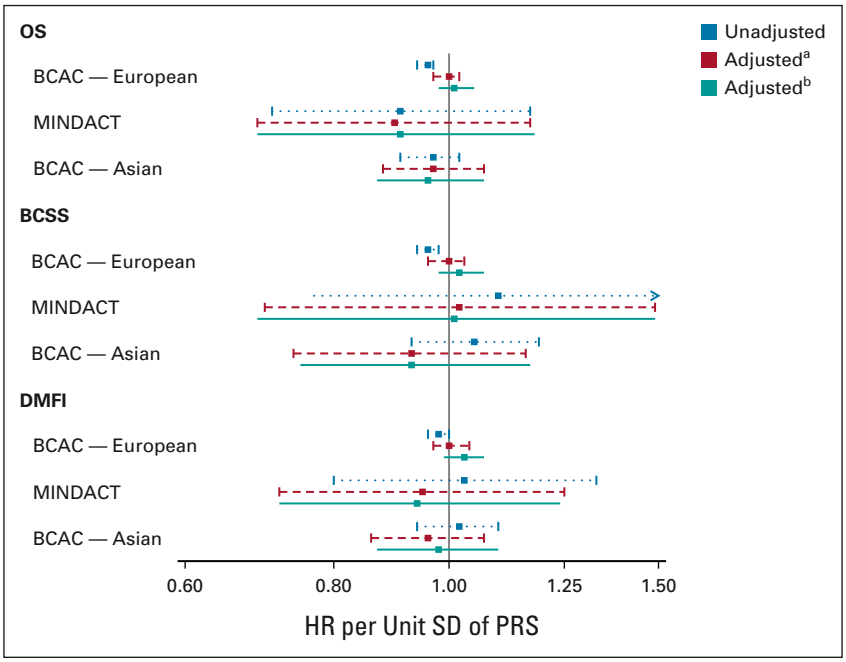

FIG 2. Association between PRS_{313} and OS, breast cancer–specific survival, and distant metastasis-free interval in BCAC and MINDACT. See Table 3 for exact numeric estimates. Cox regression models: unadjusted analysis was stratified for country in BCAC. [a]Additionally adjusted for age (continuous), tumor size, lymph node status, grade, and ER, PR, and HER2 status. [b]Additionally adjusted for age (continuous), tumor size, lymph node status, grade, ER, PR, and HER2 status, chemotherapy, and endocrine therapy. For analysis using BCAC data, follow-up was right-censored at 15 years and patients with stage 4 disease were excluded from the analysis. BCAC, Breast Cancer Association Consortium; BCSS, breast cancer–specific survival; DMFI, distant metastasis-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation.

cancer risk with PRS_{313} is better for ER-positive disease than for ER-negative disease, despite using subtype-specific PRSs (ER-positive and ER-negative), likely because of the inclusion of more ER-positive cases in most GWAS and consequently a higher identification of loci that are specifically associated with ER-positive breast cancer than with ER-negative breast cancer.[7,12] There was substantial missing information in BCAC for some variables; however, similar results were seen in a complete case sensitivity analysis. Furthermore, data on cause of death were missing or incomplete in some studies in BCAC, possibly underestimating the number of breast cancer deaths in BCAC; however, the outcomes of the association between PRS_{313} and the three survival end points were consistent. The average duration of follow-up of approximately 8 years precludes strong conclusions on late recurrences and long-term outcomes of breast cancer. The association between PRS_{313} and the 70-gene signature could only be evaluated in a relatively small subgroup of 683 patients from the MINDACT study, leading to uncertain HR estimates with wide 95% CI. Nevertheless, the estimates were in the expected direction, given the association of PRS_{313} with favorable clinicopathologic characteristics.

Several ongoing studies are evaluating the effectiveness of using comprehensive risk prediction models, including the PRS and other breast cancer risk factors, to adapt the age at initiation and frequency of breast cancer screening according to risk.[15-19] However, our findings that the PRS_{313} is associated with favorable tumor characteristics imply that improvements in cancer detection may not translate straightforwardly into improvements in breast cancer mortality. The results from these analyses will be important for modeling the effectiveness of different stratified screening approaches, especially since there is also an association between higher PRS and screen-detected cancers. Randomized trials (such as MyPeBS and WISDOM) powered to measure overall downstaging at time of diagnosis are necessary to demonstrate the (cost-)effectiveness of risk-stratified screening.[16,34,35]

AFFILIATIONS

[1]Department of Surgery, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
[2]European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium
[3]Fred A. Litwin Center for Cancer Genetics, Lunenfeld-Tanenbaum Research Institute of Mount Sinai Hospital, Toronto, Ontario, Canada
[4]Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada
[5]Copenhagen General Population Study, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark
[6]Department of Clinical Biochemistry, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark
[7]Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[8]Gynaecology Research Unit, Hannover Medical School, Hannover, Germany
[9]Faculty of Medicine, University of Southampton, Southampton, United Kingdom
[10]Department of Gynecology and Obstetricss, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, University Hospital Erlangen, Erlangen, Germany
[11]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
[12]Division of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, the Netherlands
[13]Department of Obstetrics and Gynecology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[14]Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, United Kingdom
[15]Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
[16]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[17]Department of Oncology, Södersjukhuset, Stockholm, Sweden
[18]UCSF Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA
[19]Division of Psychosocial Research and Epidemiology, The Netherlands Cancer Institute—Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands
[20]Department of Clinical Genetics, Leiden University Medical Center, Leiden, the Netherlands

CORRESPONDING AUTHOR

Marjanka K. Schmidt, PhD, Division of Molecular Pathology, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands; e-mail:: mk.schmidt@nki.nl.

DISCLAIMER

The content of this manuscript does not necessarily reflect the views or policies of the National Cancer Institute or any of the collaborating centers in the Breast Cancer Family Registry (BCFR), nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCFR. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. The opinions, findings, and conclusions expressed herein are those of the author(s) and do not necessarily reflect the official views of the State of California, Department of Public Health, the National Cancer Institute, the National Institutes of Health, the Centers for Disease Control and Prevention or their contractors and subcontractors, or the Regents of the University of California, or any of its programs. The funding sources had no role in the study design, data collection, data analysis, data interpretation, in writing the report, or in the decision to submit for publication.

PRIOR PRESENTATION

Presented in part at the ASCO Annual Meeting: Breast Cancer—Local/Regional/Adjuvant Poster Session, Chicago, IL, June 3–7, 2022.

SUPPORT

BCAC: BCAC is funded by the European Union's Horizon 2020 Research and Innovation Programme (Grant Nos. 634935 and 633784 for BRIDGES and B-CAST respectively), and the PERSPECTIVE I&I project, funded by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the Ministère de l'Économie et de l'Innovation du Québec through Genome Québec, and the Quebec Breast Cancer Foundation. The EU Horizon 2020 Research and Innovation Programme funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. Additional funding for BCAC is provided via the Confluence project, which is funded with intramural funds from the National Cancer Institute Intramural Research Program, National Institutes of Health. Genotyping of the OncoArray was funded by the NIH Grant No. U19 CA148065, and Cancer Research UK Grant No. C1287/A16563 and the PERSPECTIVE project supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research (Grant No. GPH-129344), and the Ministère de l'Économie, Science et Innovation du Québec through Genome Québec and the PSRSIIRI-701 grant, and the Quebec Breast Cancer Foundation. Funding for iCOGS came from the European Community's Seventh Framework Programme under Grant Agreement No. 223175 (HEALTH-F2-2009-223175; COGS), Cancer Research UK (C1287/A10118, C1287/A10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565), the National Institutes of Health (CA128978) and Post-Cancer GWAS initiative (1U19 CA148537, 1U19 CA148065 and 1U19 CA148112—the GAME-ON initiative), the Department of Defense (W81XWH-10-1-0341), the Canadian Institutes of Health Research (CIHR) for the CIHR Team in Familial Risks of Breast Cancer, and Komen Foundation for the Cure, the Breast Cancer Research Foundation, and the Ovarian Cancer Research Fund. The Australian Breast Cancer Family Study (ABCFS) was supported by grant UM1 CA164920 from the National Cancer Institute (United States). The ABCFS was also supported by 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. J.L.H. is a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellow. M.C.S. is a NHMRC Senior Research Fellow. The ABCS study was supported by the Dutch Cancer Society (Grant Nos. NKI 2007-3839; 2009 4363). The Australian Breast Cancer Tissue Bank (ABCTB) was supported by the National Health and Medical Research Council of Australia, The Cancer Institute NSW, and the National Breast Cancer Foundation. The AHS study is supported by the intramural research program of the National Institutes of Health, the National Cancer Institute (Grant No. Z01-CP010119), and the National Institute of Environmental Health Sciences (Grant No. Z01-ES049030). The work of the BBCC was partly funded by ELAN-Fond of the University Hospital of Erlangen. The BBCS 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 (NCRN). The BCEES was funded by the National Health and Medical Research Council, Australia, and the Cancer Council Western Australia, and acknowledges funding from the National Breast Cancer Foundation (JS). For the BCFR-NY, BCFR-PA, BCFR-UT, this work was supported by Grant No. UM1 CA164920 from the National Cancer Institute. The BCINIS study is supported in part by the Breast Cancer Research Foundation (BCRF). For BIGGS, ES is supported by NIHR Comprehensive Biomedical Research Centre, Guy's & St Thomas' NHS Foundation Trust in partnership with King's College London, United Kingdom. I.T. is supported by the Oxford Biomedical Research Centre. BOCS is supported by funds from Cancer Research UK (C8620/A8372/A15106) and the Institute of Cancer Research (UK). The BREast Oncology GAlician

Network (BREOGAN) is funded by Acción Estratégica de Salud del Instituto de Salud Carlos III FIS PI12/02125/Cofinanciado and FEDER PI17/00918/Cofinanciado FEDER; Acción Estratégica de Salud del Instituto de Salud Carlos III FIS Intrasalud (PI13/01136); Programa Grupos Emergentes, Cancer Genetics Unit, Instituto de Investigacion Biomedica Galicia Sur. Xerencia de Xestion Integrada de Vigo-SERGAS, Instituto de Salud Carlos III, Spain; Grant No. 10CSA012E, Consellería de Industria Programa Sectorial de Investigación Aplicada, PEME I + D e I + D Suma del Plan Gallego de Investigación, Desarrollo e Innovación Tecnológica de la Consellería de Industria de la Xunta de Galicia, Spain; Grant No. EC11-192. Fomento de la Investigación Clínica Independiente, Ministerio de Sanidad, Servicios Sociales e Igualdad, Spain; and Grant FEDER-Innterconecta. Ministerio de Economia y Competitividad, Xunta de Galicia, Spain. The BSUCH study was supported by the Dietmar-Hopp Foundation, the Helmholtz Society and the German Cancer Research Center (DKFZ). The CAMA study was funded by Consejo Nacional de Ciencia y Tecnología (CONACyT; SALUD-2002-C01-7462). Sample collection and processing was funded in part by grants from the National Cancer Institute (NCI R01CA120120 and K24CA169004). CCGP is supported by funding from the University of Crete. The CECILE study was supported by Fondation de France, Institut National du Cancer (INCa), Ligue Nationale contre le Cancer, Agence Nationale de Sécurité Sanitaire, de l'Alimentation, de l'Environnement et du Travail (ANSES), Agence Nationale de la Recherche (ANR). The CGPS was supported by the Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council, and Herlev and Gentofte Hospital. The CNIO-BCS was supported by the Instituto de Salud Carlos III, the Red Temática de Investigación Cooperativa en Cáncer and grants from the Asociación Española Contra el Cáncer and the Fondo de Investigación Sanitario (PI11/00923 and PI12/00070). The American Cancer Society funds the creation, maintenance, and updating of the CPS-II cohort. The California Teachers Study (CTS) and the research reported in this publication were supported by the National Cancer Institute of the National Institutes of Health under award number U01-CA199277; P30-CA033572; P30-CA023100; UM1-CA164917; and R01-CA077398. The collection of cancer incidence data used in the California Teachers Study was supported by the California Department of Public Health pursuant to California Health and Safety Code Section 103885; Centers for Disease Control and Prevention's National Program of Cancer Registries, under cooperative agreement 5NU58DP006344; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201800032I awarded to the University of California, San Francisco, contract HHSN261201800015I awarded to the University of Southern California, and contract HHSN261201800009I awarded to the Public Health Institute. The University of Westminster curates the DietCompLyf database funded by Against Breast Cancer Registered Charity No. 1121258 and the NCRN. The coordination of EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM; France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF; Germany); the Hellenic Health Foundation, the Stavros Niarchos Foundation (Greece); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (the Netherlands); Health Research Fund (FIS), PI13/00061 to Granada, PI13/01162 to EPIC-Murcia, Regional Governments of Andalucía, Asturias, Basque Country, Murcia and Navarra, ISCIII RETIC (RD06/0020; Spain); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford, United Kingdom). The ESTHER study was supported by a grant from the Baden Württemberg Ministry of Science, Research and Arts. Additional cases were recruited in the context of the VERDI study, which was supported by a grant from the German Cancer Aid (Deutsche Krebshilfe). FHRISK and PROCAS are funded from NIHR Grant No. PGfAR 0707-10031. DGE, AH and WGN are supported by the NIHR Manchester Biomedical Research Centre (IS-BRC-1215-20007). The GC-HBOC (German Consortium of Hereditary Breast and Ovarian Cancer) is supported by the German Cancer Aid (Grant No. 110837 and 70114178, coordinator: Rita K. Schmutzler, Cologne) and the Federal Ministry of Education and Research, Germany (Grant No. 01GY1901). This work was also funded by the European Regional Development Fund and Free State of Saxony, Germany (LIFE—Leipzig Research Centre for Civilization Diseases, project numbers 713-241202, 713-241202, 14505/2470, 14575/2470). The GENICA was funded by the Federal Ministry of Education and Research (BMBF) Germany Grant Nos. 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, Johanniter GmbH Bonn, Johanniter Krankenhaus, Bonn, Germany. The GESBC was supported by the Deutsche Krebshilfe e. V. [70492] and the German Cancer Research Center (DKFZ). The HABCS study was supported by the Claudia von Schilling Foundation for Breast Cancer Research, by the Lower Saxonian Cancer Society, and by the Rudolf Bartling Foundation. The HEBCS was financially supported by the Helsinki University Hospital Research Fund, the Sigrid Juselius Foundation, and the Cancer Foundation, Finland. The HUBCS was supported by a grant from the German Federal Ministry of Research and Education (RUS08/017), B.M. was supported by Grant Nos. 17-44-020498, 17-29-06014 of the Russian Foundation for Basic Research, D.P. was supported by grant 18-29-09129 of the Russian Foundation for Basic Research, E.K. was supported by the mega grant from the Government of Russian Federation (2020-220-08-2197), and the study was performed as part of the assignment of the Ministry of Science and Higher Education of the Russian Federation (No. AAAA-A16-116020350032-1). The HERPACC was supported by MEXT Kakenhi (Nos. 170150181 and 26253041) from the Ministry of Education, Science, Sports, Culture, and Technology of Japan, by a Grant-in-Aid for the Third Term Comprehensive 10-Year Strategy for Cancer Control from Ministry Health, Labor, and Welfare of Japan, by Health and Labor Sciences Research Grants for Research on Applying Health Technology from Ministry Health, Labor and Welfare of Japan, by National Cancer Center Research and Development Fund, and Practical Research for Innovative Cancer Control (15ck0106177h0001 and 20ck0106553) from Japan Agency for Medical Research and development, AMED, and Cancer Bio Bank Aichi. Financial support for KARBAC was provided through 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 Bert von Kantzows foundation. The KARMA study was supported by Märit and Hans Rausings Initiative Against Breast Cancer. The KBCP was financially supported by the special Government Funding (VTR) 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. kConFab 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. Financial support for the AOCS was provided 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). G.C.T. and P.W. are supported

by the NHMRC. R.B. was a Cancer Institute NSW Clinical Research Fellow. The KOHBRA study was partially supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), and the National R&D Program for Cancer Control, Ministry of Health & Welfare, Republic of Korea (HI16C1127; 0720450; 1020350; 1420190). LAABC is supported by grants (1RB-0287, 3PB-0102, 5PB-0018, 10PB-0098) from the California Breast Cancer Research Program. Incident breast cancer cases were collected by the USC Cancer Surveillance Program (CSP), which is supported under subcontract by the California Department of Health. The CSP is also part of the National Cancer Institute's Division of Cancer Prevention and Control Surveillance, Epidemiology, and End Results Program, under contract number N01CN25403. LMBC is supported by the Stichting tegen Kanker. D.L. is supported by the FWO. The MABCS study is funded by the Research Centre for Genetic Engineering and Biotechnology Georgi D. Efremov, MASA. The MARIE study was supported by the Deutsche Krebshilfe e.V. (70-2892-BR I, 106332, 108253, 108419, 110826, 110828), the Hamburg Cancer Society, the German Cancer Research Center (DKFZ), and the Federal Ministry of Education and Research (BMBF) Germany (01KH0402). MBCSG is supported by grants from the Italian Association for Cancer Research (AIRC). The MCBCS was supported by the NIH Grant Nos. R35CA253187, R01CA192393, R01CA116167, R01CA176785, a NIH Specialized Program of Research Excellence (SPORE) in Breast Cancer (P50CA116201), the Breast Cancer Research Foundation, and the Paul Calabresi Program in Clinical/Translational Research at Mayo Clinic (2K12CA090628-21). The Melbourne Collaborative Cohort Study (MCCS) cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and 1074383 and by infrastructure provided by Cancer Council Victoria. Cases and their vital status were ascertained through the Victorian Cancer Registry and the Australian Institute of Health and Welfare, including the National Death Index and the Australian Cancer Database. The MEC was supported by NIH Grant Nos. CA63464, CA54281, CA098758, CA132839 and CA164973. The MISS study was supported by funding from ERC-2011-294576 Advanced grant, Swedish Cancer Society CAN 2018/675, Swedish Research Council, Local hospital funds, Berta Kamprad Foundation FBKS 2021-19, Gunnar Nilsson. The MMHS study was supported by NIH grants CA97396, CA128931, CA116201, CA140286 and CA177150. MSKCC is supported by grants from the Breast Cancer Research Foundation and Robert and Kate Niehaus Clinical Cancer Genetics Initiative. MYBRCA is funded by research grants from the Wellcome Trust (v203477/Z/16/Z), the Malaysian Ministry of Higher Education (UM.C/HIR/MOHE/06) and Cancer Research Malaysia. The NBCS has received funding from the K.G. Jebsen Centre for Breast Cancer Research; the Research Council of Norway Grant No. 193387/V50 (to A.-L. Børresen-Dale and V.N. Kristensen) and Grant No. 193387/H10 (to A.-L. Børresen-Dale and V.N. Kristensen), South Eastern Norway Health Authority (Grant No. 39346 to A.-L. Børresen-Dale) and the Norwegian Cancer Society (to A.-L. Børresen-Dale and V.N. Kristensen). The NBHS was supported by NIH Grant No. R01CA100374. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. The Northern California Breast Cancer Family Registry (NC-BCFR) and Ontario Familial Breast Cancer Registry (OFBCR) were supported by grant U01CA164920 from the US National Cancer Institute of the National Institutes of Health. The Carolina Breast Cancer Study (NCBCS) was funded by Komen Foundation, the National Cancer Institute (P50 CA058223, U54 CA156733, U01 CA179715), and the North Carolina University Cancer Research Fund. The NHS was supported by NIH Grant Nos. P01 CA87969, UM1 CA186107, and U19 CA148065. The NHS2 was supported by NIH Grant Nos. UM1 CA176726 and U19 CA148065. The OBCS was supported by research grants from the Finnish Cancer Foundation, the Academy of Finland (Grant No. 250083, 122715 and Center of Excellence Grant No. 251314), the Sigrid Juselius Foundation, the University of Oulu general as well as strategic funding, the University of Oulu Support Foundation and the special Governmental VTR funds toward Oulu University Hospital-based research activities. The ORIGO study was supported by the Dutch Cancer Society (RUL 1997-1505) and the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL CP16). The PBCS was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services. Genotyping for PLCO was supported by the Intramural Research Program of the National Institutes of Health, NCI, Division of Cancer Epidemiology and Genetics. The PLCO is supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics and supported by contracts from the Division of Cancer Prevention, National Cancer Institute, National Institutes of Health. The POSH study is funded by Cancer Research UK (Grant Nos. C1275/A11699, C1275/C22524, C1275/A19187, C1275/A15956) and Breast Cancer Campaign 2010PR62, 2013PR044. The RBCS was funded by the Dutch Cancer Society (DDHK 2004-3124, DDHK 2009-4318). The SASBAC study was supported by funding from the Agency for Science, Technology and Research of Singapore (A*STAR), the US National Institute of Health (NIH) and the Susan G. Komen Breast Cancer Foundation. The SBCGS was supported primarily by NIH Grant Nos. R01CA64277, R01CA148667, UMCA182910, and R37CA70867. Biological sample preparation was conducted the Survey and Biospecimen Shared Resource, which is supported by P30 CA68485. The scientific development and funding of this project were, in part, supported by the Genetic Associations and Mechanisms in Oncology (GAME-ON) Network U19 CA148065. The SBCS was supported by Sheffield Experimental Cancer Medicine Centre and Breast Cancer Now Tissue Bank. The SCCS is supported by a grant from the National Institutes of Health (R01 CA092447). SEARCH is funded by Cancer Research UK (C490/A10124, C490/A16561) and supported by the UK National Institute for Health Research Biomedical Research Centre at the University of Cambridge. The University of Cambridge has received salary support for PDPP from the NHS in the East of England through the Clinical Academic Reserve. SEBCS was supported by the BRL (Basic Research Laboratory) program through the National Research Foundation of Korea funded by the Ministry of Education, Science, and Technology (2012-0000347). SGBCC was supported by the Agency for Science, Technology, and Research (A*STAR), National Research Foundation Singapore (NRF-NRFF2017-02, awarded to J Li), NUS start-up Grant, National University Cancer Institute Singapore (NCIS) Centre Grant Nos. NMRC/CG/NCIS/2010, NMRC/CG/012/2013, CGAug16M005, Breast Cancer Prevention Programme (BCPP), Asian Breast Cancer Research Fund, and the NMRC Clinician Scientist Award (SI Category; NMRC/CSA-SI/0015/2017). SKKDKFZS is supported by the DKFZ. The SMC is funded by the Swedish Cancer Foundation and the Swedish Research Council (VR 2017-00644) grant for the Swedish Infrastructure for Medical Population-based Life-course Environmental Research (SIMPLER). The SZBCS was supported by Grant PBZ_KBN_122/P05/2004 and the program of the Minister of Science and Higher Education under the name Regional Initiative of Excellence in 2019-2022 project number 002/RID/2018/19, amount of financing 12000 000 PLN. The TWBCS is supported by the Taiwan Biobank project of the Institute of Biomedical Sciences, Academia Sinica, Taiwan. UBCS was supported by funding from National Cancer Institute (NCI) grant R01 CA163353 (to N.J. Camp) and the Women's Cancer Center at the Huntsman Cancer Institute (HCI). Data collection for UBCS was supported by the Utah Population Database (UPDB) and Utah Cancer Registry (UCR). The UPDB is supported by HCI (including Huntsman Cancer Foundation, HCF), the University of Utah, and NCI Grant No. P30 CA2014. The UCR is funded by the NCI's SEER Program, Contract No. HHSN261201800016I, the US Center for Disease Control and Prevention's National Program of Cancer Registries (Cooperative Agreement No. NU58DP006320), the University of Utah, and HCF. The UCIBCS component of this research was supported by the NIH [CA58860, CA92044] and the Lon V Smith Foundation [LVS39420]. The UKBGS is funded by Breast Cancer

Now and the Institute of Cancer Research (ICR), London. ICR acknowledges NHS funding to the NIHR Biomedical Research Centre. The USRT Study was funded by Intramural Research Funds of the National Cancer Institute, Department of Health and Human Services, USA. The WHI program is funded by the National Heart, Lung, and Blood Institute, the US National Institutes of Health, and the US Department of Health and Human Services (HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C and HHSN271201100004C). This work was also funded by NCI U19 CA148065-01. MINDACT: Josephine Lopes Cardozo's work as Fellow at EORTC Headquarters was supported by a grant from the EORTC Breast Cancer Group and from the Netherlands Cancer Institute. The MINDACT study was supported by grants from the European Commission Sixth Framework Program (FP6-LSHC-CT-2004-503426, to the TRANSBIG Network of Excellence), the Breast Cancer Research Foundation, Novartis, F. Hoffmann–La Roche, Sanofi-Aventis, Eli Lilly, Veridex, the European Breast Cancer Council–Breast Cancer Working Group (BCWG grant for the MINDACT biobank), the Jacqueline Seroussi Memorial Foundation for Cancer Research (JSMF; 2006 JSMF Award), Prix Mois du Cancer du Sein (2004 award), Susan G. Komen for the Cure (SG05-0922-02), Fondation Belge contre le Cancer (SCIE 2005-27), Dutch Cancer Society (KWF), the Netherlands Genomics Initiative–Cancer Genomics Center (2008-2012), Association le Cancer du Sein, Parlons-en!, the Brussels Breast Cancer Walk-Run and the American Women's Club of Brussels, NIF Trust, German Cancer Aid, the Grant Simpson Trust and Cancer Research UK, Ligue Nationale contre le Cancer, and the EORTC Cancer Research Fund. Whole-genome analysis was provided by Agendia without cost.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.01978.

DATA SHARING STATEMENT

BCAC: Data of the Breast Cancer Association Consortium may be requested for non-profit research through an application procedure with the Breast Cancer Association Consortium. MINDACT: The MINDACT dataset with patient characteristics and clinical outcomes was made available by the EORTC (https://www.eortc.org/data-sharing/). Following a successful data request procedure, the EORTC can share all or a selection of the clinicopathologic and/or full-transcriptome data for translational research.

AUTHOR CONTRIBUTIONS

Conception and design: Josephine M.N. Lopes Cardozo, Douglas F. Easton, Per Hall, Paul D.P. Pharoah, Laura J. van 't Veer, Marjanka K. Schmidt

Financial support: Stig E. Bojesen, Douglas F. Easton, Marjanka K. Schmidt

Administrative support: Stig E. Bojesen, Maartje J. Hooning, Renske Keeman, Emiel J.T. Rutgers, Marjanka K. Schmidt

Provision of study materials or patients: All authors

Collection and assembly of data: Irene L. Andrulis, Stig E. Bojesen, Thilo Dörk, Diana M. Eccles, Peter A. Fasching, Maartje J. Hooning, Renske Keeman, Heli Nevanlinna, Emiel J.T. Rutgers, Per Hall, Paul D.P. Pharoah, Laura J. van 't Veer, Marjanka K. Schmidt

Data analysis and interpretation: Josephine M.N. Lopes Cardozo, Irene L. Andrulis, Stig E. Bojesen, Emiel J.T. Rutgers, Douglas F. Easton, Paul D.P. Pharoah, Marjanka K. Schmidt

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

BCAC: 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. ABCFS thank Maggie Angelakos, Judi Maskiell, Gillian Dite. ABCS thanks the Blood bank Sanquin, The Netherlands. ABCTB Investigators: Christine Clarke, Deborah Marsh, Rodney Scott, Robert Baxter, Desmond Yip, Jane Carpenter, Alison Davis, Nirmala Pathmanathan, Peter Simpson, J. Dinny Graham, Mythily Sachchithananthan. Samples are made available to researchers on a non-exclusive basis. BBCS thanks Eileen Williams, Elaine Ryder-Mills, Kara Sargus. BCEES thanks Allyson Thomson, Christobel Saunders, Terry Slevin, BreastScreen Western Australia, Elizabeth Wylie, Rachel Lloyd. The BCINIS study would not have been possible without the contributions of Dr K. Landsman, Dr N. Gronich, Dr A. Flugelman, Dr W. Saliba, Dr F. Lejbkowicz, Dr E. Liani, Dr I. Cohen, Dr S. Kalet, Dr V. Friedman, Dr O. Barnet of the NICCC in Haifa, and all the contributing family medicine, surgery, pathology and oncology teams in all medical institutes in Northern Israel. BIGGS thanks Niall McInerney, Gabrielle Colleran, Andrew Rowan, Angela Jones. The BREOGAN study would not have been possible without the contributions of the following: Angel Carracedo, Victor Muñoz Garzón, Alejandro Novo Domínguez, Maria Elena Martinez, Sara Miranda Ponte, Carmen Redondo Marey, Maite Peña Fernández, Manuel Enguix Castelo, Maria Torres, Manuel Calaza (BREOGAN), José Antúnez, Máximo Fraga and the staff of the Department of Pathology and Biobank of the University Hospital Complex of Santiago-CHUS, Instituto de Investigación Sanitaria de Santiago, IDIS, Xerencia de Xestion Integrada de Santiago-SERGAS; Joaquín González-Carreró and the staff of the Department of Pathology and Biobank of University Hospital Complex of Vigo, Instituto de Investigacion Biomedica Galicia Sur, SERGAS, Vigo, Spain. The BSUCH study thanks Peter Bugert, Medical Faculty Mannheim. CCGP thanks Styliani Apostolaki, Anna Margiolaki, Georgios Nintos, Maria Perraki, Georgia Saloustrou, Georgia Sevastaki, Konstantinos Pompodakis. CGPS thanks staff and participants of the Copenhagen General Population Study. For the excellent technical assistance: Dorthe Uldall Andersen, Maria Birna Arnadottir, Anne Bank, Dorthe Kjeldgård Hansen. The Danish Cancer Biobank is acknowledged for providing infrastructure for the collection of blood samples for the cases. CNIO-BCS thanks Guillermo Pita, Charo Alonso, Nuria Álvarez, Pilar Zamora, Primitiva Menendez, the Human Genotyping-CEGEN Unit (CNIO). Investigators from the CPS-II cohort thank the participants and Study Management Group for their invaluable contributions to this research. They also acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, as well as cancer registries supported by the National Cancer Institute SEER program. The authors would like to thank the California Teachers Study Steering Committee that is responsible for the formation and maintenance of the Study within which this research was conducted. A full list of California Teachers Study (CTS) team members is available at https://www.calteachersstudy.org/team. DIETCOMPLYF thanks the patients, nurses and clinical staff involved in the study. The DietCompLyf study was funded by the charity Against Breast Cancer (Registered Charity Number 1121258) and the NCRN. We thank the participants and the investigators of EPIC (European Prospective Investigation into Cancer and Nutrition). ESTHER thanks Hartwig Ziegler, Sonja Wolf, Volker Hermann, Christa Stegmaier, Katja Butterbach. FHRISK and PROCAS thank NIHR for funding. The GENICA Network: Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, and University of Tübingen, Germany [RH, Hiltrud Brauch, Wing-Yee Lo], Department of Internal Medicine, Johanniter GmbH Bonn, 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]. HABCS thanks Peter Schürmann, Peter Hillemanns, Natalia Bogdanova, Michael Bremer, Johann Karstens, Hans Christiansen and the Breast Cancer Network in Lower Saxony for continuous support. HEBCS thanks Johanna Kiiski, Taru A. Muranen, Kristiina Aittomäki, Kirsimari Aaltonen, Karl von Smitten, Irja Erkkilä. HKBCS thanks Hong Kong Sanatorium and Hospital, Dr Ellen Li Charitable Foundation, The Kerry Group Kuok Foundation, National Institute of Health 1R03CA130065 and the North California Cancer Center for support. HUBCS thanks Darya Prokofyeva and Shamil Gantsev. KARMA and SASBAC thank the Swedish Medical Research Counsel. KBCP thanks Eija Myöhänen. kConFab/AOCS wish to thank 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 (which has received funding from the NHMRC, the National Breast Cancer Foundation, Cancer Australia, and the National Institute of Health, United States) for their contributions to this resource, and the many families who contribute to kConFab. We thank all investigators of the KOHBRA (Korean Hereditary Breast Cancer) Study. LAABC thanks all the study participants and the entire data collection team, especially Annie Fung and June Yashiki. LMBC thanks Gilian Peuteman, Thomas Van Brussel, EvyVanderheyden and Kathleen Corthouts. MABCS thanks Snezhana Smichkoska, Emilija Lazarova, Marina Iljoska (University Clinic of Radiotherapy and Oncology), Dzengis Jasar, Mitko Karadjozov (Adzibadem-Sistina Hospital), Andrej Arsovski and Liljana Stojanovska (Re-Medika Hospital) for their contributions and commitment to this study. MARIE thanks Petra Seibold, Ursula Eilber and Muhabbet Celik. MBCSG (Milan Breast Cancer Study Group): Paolo Peterlongo, Siranoush Manoukian, Bernard Peissel, Jacopo Azzollini, Erica Rosina, Daniela Zaffaroni, Irene Feroce, Mariarosaria Calvello, Aliana Guerrieri Gonzaga, Monica Marabelli, Davide Bondavalli and the personnel of the Cogentech Cancer Genetic Test Laboratory. The MCCS was made possible by the contribution of many people, including the original investigators, the teams that recruited the participants and continue working on follow-up, and the many thousands of Melbourne residents who continue to participate in the study. The MISS study group acknowledges the former Principal Investigator, professor Håkan Olsson. We thank the coordinators, the research staff and especially the MMHS participants for their continued collaboration on research studies in breast cancer. MSKCC thanks Marina Corines, Lauren Jacobs. MYBRCA thanks study participants and research staff (particularly Patsy Ng, Nurhidayu Hassan, Joanna Lim, Tiara Hassan, Yoon Sook-Yee, Daphne Lee and Lee Yong Quan) for their contributions and commitment to this study. The following are NBCS Collaborators: Kristine K. Sahlberg, PhD, Anne-Lise Børresen-Dale, Prof Em, Lars Ottestad, MD, Rolf Kåresen, Prof Em Dr Ellen Schlichting, MD, Marit Muri Holmen, MD, Toril Sauer, MD, Vilde Haakensen, MD, Olav Engebråten, MD, Bjørn Naume, MD, Alexander Fosså, MD, Cecile E. Kiserud, MD, Kristin V. Reinertsen, MD, Åslaug Helland, MD, Margit Riis, MD, Jürgen Geisler, MD, OSBREAC and Grethe I. Grenaker Alnæs, MSc. For NHS and NHS2 the study protocol was approved by the institutional review boards of the Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, and those of participating registries as required. We would like to thank the participants and staff of the NHS and NHS2 for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data. OBCS thanks Arja Jukkola, Mervi Grip, Saila Kauppila, Meeri Otsukka, Leena Keskitalo and Kari Mononen for their contributions to this study. The OFBCR thanks Teresa Selander, Nayana Weerasooriya and Steve Gallinger. ORIGO thanks E. Krol-Warmerdam, and J. Blom for patient accrual, administering questionnaires, and managing clinical information. The LUMC survival data were retrieved from the Leiden hospital-based cancer registry system (ONCDOC) with the help of Dr J. Molenaar. PBCS thanks Louise Brinton, Mark Sherman, Neonila Szeszenia-Dabrowska, Beata Peplonska, Witold Zatonski, Pei Chao, Michael Stagner. The ethical approval for the POSH study is MREC/00/6/69, UKCRN ID: 1137. We thank staff in the Experimental Cancer Medicine Centre (ECMC) supported Faculty of Medicine Tissue Bank and the Faculty of Medicine DNA Banking resource. The authors wish to acknowledge the roles of the Breast Cancer Now Tissue Bank in collecting and making available the samples and/or data, and the patients who have generously donated their tissues and shared their data to be used in the generation of this publication. PREFACE thanks Sonja Oeser and Silke Landrith. The RBCS thanks Jannet Blom, Saskia Pelders, Wendy J.C. Prager—van der Smissen, and the Erasmus MC Family Cancer Clinic. SBCGS thanks study participants and research staff for their contributions and commitment to the studies. SBCS thanks Sue Higham, Helen Cramp, Dan Connley, Ian Brock, Sabapathy Balasubramanian and Malcolm W.R. Reed. We thank the SEARCH and EPIC teams. SGBCC thanks the participants and all research coordinators for their excellent help with recruitment, data and sample collection. SKKDKFZS thanks all study participants, clinicians, family doctors, researchers and technicians for their contributions and commitment to this study. We thank the SUCCESS Study teams in Munich, Duessldorf, Erlangen and Ulm. UBCS thanks all study participants as well as the ascertainment, laboratory, analytics and informatics teams at Huntsman Cancer Institute and Intermountain Healthcare. We thank Justin Williams, Brandt Jones, Myke Madsen, Stacey Knight and Kerry Rowe for their important contributions to this study. UCIBCS thanks Irene Masunaka. UKBGS thanks Breast Cancer Now and the Institute of Cancer Research for support and funding of the Generations Study, and the study participants, study staff, and the doctors, nurses and other health care providers and health information sources who have contributed to the study. We acknowledge NHS funding to the Royal Marsden/ICR NIHR Biomedical Research Centre. The authors thank the WHI investigators and staff for their dedication and the study participants for making the program possible. MINDACT: The authors are indebted to all the women who participated in the MINDACT trial. They acknowledge the contribution of the European Organisation for Research and Treatment of Cancer (EORTC) and the Breast International Group (BIG). They are grateful to all patients and families and all the investigators, surgeons, pathologists, and research nurses who participated in the MINDACT study. They are grateful to the European Commission Sixth Framework Programme (FP6-LSHC-CT-2004-503426), the European Community Seventh Framework Programme (HEALTH-F2-2009-223175 to the Collaborative Oncological Gene-environment Study), the Breast International Group (BIG) AISBL, F. Hoffmann-La Roche, Novartis, Sanofi-Aventis, for supporting this independent EORTC Study. They also acknowledge all national coordinating centers and BIG Groups participating in MINDACT (BOOG, EORTC-BCG, GOIRC, NCRI-BCSG, SOLTI, UNICANCER-UCBG, WSG).

REFERENCES

1. Easton DF, Pharoah PDP, Antoniou AC, et al: Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 372:2243-2257, 2015
2. Hu C, Hart SN, Gnanaolivu R, et al: A population-based study of genes previously implicated in breast cancer. N Engl J Med 384:440-451, 2021
3. Melchor L, Benítez J: The complex genetic landscape of familial breast cancer. Hum Genet 132:845-863, 2013

4. Dorling L, Carvalho S, Allen J, et al: Breast cancer risk genes—Association analysis in more than 113, 000 women. N Engl J Med 384:428-439, 2021
5. Bahcall OG: Common variation and heritability estimates for breast, ovarian and prostate cancers. Nat Genet 45:343, 2013
6. Mavaddat N, Pharoah PDP, Michailidou K, et al: Prediction of breast cancer risk based on profiling with common genetic variants. J Natl Cancer Inst 107: djv036, 2015
7. Yanes T, Young MA, Meiser B, et al: Clinical applications of polygenic breast cancer risk: A critical review and perspectives of an emerging field. Breast Cancer Res 22:21, 2020
8. The Breast Cancer Association Consortium, Georgia CT, Spurdle AB, et al: Commonly studied single-nucleotide polymorphisms and breast cancer: Results from the Breast Cancer Association Consortium. J Natl Cancer Inst 98:1382-1396, 2006
9. Bahcall OG: COGS project and design of the iCOGS array. Nat Genet 45:343, 2013
10. Amos CI, Dennis J, Wang Z, et al: The OncoArray consortium: A Network for understanding the genetic architecture of common cancers. Cancer Epidemiol Biomarkers Prev 26:126-135, 2017
11. Michailidou K, Lindström S, Dennis J, et al: Association analysis identifies 65 new breast cancer risk loci. Nature 551:92-94, 2017
12. Mavaddat N, Michailidou K, Dennis J, et al: Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. Am J Hum Genet 104:21-34, 2019
13. Kramer I, Hooning MJ, Mavaddat N, et al: Breast cancer polygenic risk score and contralateral breast cancer risk. Am J Hum Genet 107:837-848, 2020
14. Van Den Broek JJ, Schechter CB, Van Ravesteyn NT, et al: Personalizing breast cancer screening based on polygenic risk and family history. J Natl Cancer Inst 113:434-442, 2021
15. Shieh Y, Eklund M, Madlensky L, et al: Breast cancer screening in the precision medicine era: Risk-based screening in a population-based trial. J Natl Cancer Inst 109:djw290, 2017
16. Esserman LJ, the WISDOM Study and Athena Investigators: The WISDOM study: Breaking the deadlock in the breast cancer screening debate. NPJ Breast Cancer 3:34, 2017
17. Giordano L, the Andromeda working group, Gallo F, et al: The ANDROMEDA prospective cohort study: Predictive value of combined criteria to tailor breast cancer screening and new opportunities from circulating markers: Study protocol. BMC Cancer 17:785-787, 2017
18. French DP, Brentnall AR, Astley S, et al: What are the benefits and harms of risk stratified screening as part of the NHS breast screening Programme? Study protocol for a multi-site non-randomised comparison of BC-predict versus usual screening (NCT04359420). BMC Cancer 20:570, 2020
19. Clift AK, Dodwell D, Lord S, et al: The current status of risk-stratified breast screening. Br J Cancer 126:533-550, 2021
20. van 't Veer LJ, Dai H, van de Vijver MJ, et al: Gene expression profiling predicts clinical outcome of breast cancer. Nature 415:530-536, 2002
21. Michailidou K, Beesley J, Lindstrom S, et al: Genome-wide association analysis of more than 120, 000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet 47:373-380, 2015
22. Michailidou K, The Breast and Ovarian Cancer Susceptibility Collaboration, Hall P, et al: Large-scale genotyping identifies 41 new loci associated with breast cancer risk. Nat Genet 45:353-361, 2013
23. Cardoso F, van 't Veer LJ, Bogaerts J, et al: 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med 375:717-729, 2016
24. Piccart M, van 't Veer LJ, Poncet C, et al: 70-Gene signature as an aid for treatment decisions in early breast cancer: Updated results of the phase 3 randomised MINDACT trial with an exploratory analysis by age. Lancet Oncol 22:476-488, 2021
25. Escala-Garcia M, NBCS Collaborators, Guo Q, et al: Genome-wide association study of germline variants and breast cancer-specific mortality. Br J Cancer 120: 647-657, 2019
26. Morra A, Jung AY, Behrens S, et al: Breast cancer risk factors and survival by tumor subtype: Pooled analyses from the breast cancer association consortium. Cancer Epidemiol Biomarkers Prev 30:623-642, 2021
27. Ho WK, Tan MM, Mavaddat N, et al: European polygenic risk score for prediction of breast cancer shows similar performance in Asian women. Nat Commun 11: 3833, 2020
28. Holm J, Li J, Darabi H, et al: Associations of breast cancer risk prediction tools with tumor characteristics and metastasis. J Clin Oncol 34:251-258, 2016
29. Curtit E, Pivot X, Henriques J, et al: Assessment of the prognostic role of a 94-single nucleotide polymorphisms risk score in early breast cancer in the SIGNAL/ PHARE prospective cohort: No correlation with clinico-pathological characteristics and outcomes. Breast Cancer Res 19:98-99, 2017
30. Li J, Ugalde-Morales E, Wen WX, et al: Differential burden of rare and common variants on tumor characteristics, survival, and mode of detection in breast cancer. Cancer Res 78:6329-6338, 2018
31. Li J, Holm J, Bergh J, et al: Breast cancer genetic risk profile is differentially associated with interval and screen-detected breast cancers. Ann Oncol 26: 517-522, 2015
32. Mook S, van 't Veer LJ, Rutgers EJ, et al: Independent prognostic value of screen detection in invasive breast cancer. J Natl Cancer Inst 103:585-597, 2011
33. Lopes Cardozo JMN, Schmidt MK, van 't Veer LJ, et al: Combining method of detection and 70-gene signature for enhanced prognostication of breast cancer. Breast Cancer Res Treat 189:399-410, 2021
34. Pashayan N, Antoniou AC, Ivanus U, et al: Personalized early detection and prevention of breast cancer: ENVISION consensus statement. Nat Rev Clin Oncol 17:687-705, 2020
35. UNICANCER: My Personalized Breast Screening—ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03672331

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Associations of a Breast Cancer Polygenic Risk Score With Tumor Characteristics and Survival

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. 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 ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Diana M. Eccles
Honoraria: AstraZeneca, Pierre Fabre
Consulting or Advisory Role: AstraZeneca, AstraZeneca
Research Funding: AstraZeneca
Travel, Accommodations, Expenses: Pierre Fabre

Peter A. Fasching
Honoraria: Roche, Novartis, Pfizer, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, AstraZeneca, Hexal, Lilly, Cepheid (Inst), BionTech (Inst), Pierre Fabre, Seattle Genetics, Agendia, Gilead Sciences
Consulting or Advisory Role: Roche, Novartis, Pfizer, Daiichi Sankyo, Eisai, Merck Sharp & Dohme, AstraZeneca, Hexal, Pierre Fabre, Seattle Genetics, Agendia, Lilly, Gilead Sciences
Research Funding: Novartis (Inst), BioNTech (Inst), Cepheid (Inst), Roche

Emiel J.T. Rutgers
Honoraria: Guerbet

Douglas F. Easton
Patents, Royalties, Other Intellectual Property: Royalties from Canrisk/BOADICEA risk prediction tool (Inst)

Per Hall
Stock and Other Ownership Interests: ICAD
Consulting or Advisory Role: Atossa Therapeutics
Research Funding: Atossa Therapeutics (Inst)
Patents, Royalties, Other Intellectual Property: Licensed the algorithm for risk prediction on the basis of analyses of mammographic features to iCAD, Pending patent on compositions and methods for prevention of breast cancer with an option to license to Atossa Therapeutics

Paul D.P. Pharoah
Patents, Royalties, Other Intellectual Property: The PREDICT breast cancer prognostic model is licensed to OncoAssist by the University of Cambridge. I receive a share of the fees, I receive a share of the fees for a patent held by the University of Cambridge of a seven-SNP polygenic risk assay

Laura J. van 't Veer
Employment: Agendia
Stock and Other Ownership Interests: Agendia

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators

Name	Affiliations
Thomas U. Ahearn	Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD
Hoda Anton-Culver	Department of Medicine, Genetic Epidemiology Research Institute, University of California Irvine, Irvine, CA
Volker Arndt	Division of clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany
Paul L. Auer	Division of Biostatistics, Institute for Health and Equity, and Cancer Center, Medical College of Wisconsin, Milwaukee, WI
Annelie Augustinsson	Oncology, Department of Clinical Sciences in Lund, Lund University, Lund, Sweden
Laura E. Beane Freeman	Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, National Institutes of Health, Bethesda, MD
Heiko Becher	Institute for Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Matthias W. Beckmann	Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, University Hospital Erlangen, Erlangen, Germany
Sabine Behrens	Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Javier Benitez	Human Genetics Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain Center for Biomedical Network Research on Rare Diseases (CIBERER), Instituto de Salud Carlos III, Madrid, Spain
Marina Bermisheva	Institute of Biochemistry and Genetics of the Ufa Federal Research Center of the Russian Academy of Sciences, Ufa, Russia
Carl Blomqvist	Department of Oncology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
Manjeet K. Bolla	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Bernardo Bonanni	Division of Cancer Prevention and Genetics, IEOO, European Institute of Oncology IRCCS, Milan, Italy
Terry Boyle	Australian Centre for Precision Health, University of South Australia, Adelaide, SA, Australia
Hermann Brenner	Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
Sara Y. Brucker	Department of Women's Health, Tuebingen University Hospital, Tuebingen, Germany
Thomas Brüning	Institute for Prevention and Occupational Medicine of the German Social Accident Insurance, Institute of the Ruhr University Bochum, Bochum, Germany
Barbara Burwinkel	Molecular Epidemiology Group, C080, German Cancer Research Center (DKFZ), Heidelberg, Germany Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg, University of Heidelberg, Heidelberg, Germany
Saundra S. Buys	Department of Internal Medicine and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
Nicola J. Camp	Department of Internal Medicine and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT
Federico Canzian	Genomic Epidemiology Group, German Cancer Research Center (DKFZ), Heidelberg, Germany
Fatima Cardoso	Breast Unit, Champalimaud Clinical Center, Champalimaud Foundation, Lisbon, Portugal
Jose E. Castelao	Oncology and Genetics Unit, Instituto de Investigación Sanitaria Galicia Sur (IISGS), Xerencia de Xestion Integrada de Vigo-SERGAS, Vigo, Spain
Melissa H. Cessna	Intermountain Healthcare, Salt Lake City, UT
Tsun L. Chan	Hong Kong Hereditary Breast Cancer Family Registry, Hong Kong Department of Molecular Pathology, Hong Kong Sanatorium and Hospital, Hong Kong

(continued on following page)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Jenny Chang-Claude	Division of cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany Cancer Epidemiology Group, University Cancer Center Hamburg (UCCH), University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Georgia Chenevix-Trench	Cancer Division, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia
Ji-Yeob Choi	Department of Biomedical Sciences, Seoul National University Graduate School, Seoul, Korea Cancer Research Institute, Seoul National University, Seoul, Korea Institute of Health Policy and Management, Seoul National University Medical Research Center, Seoul, Korea
NBCS Collaborators	Department of Cancer Genetics, Institute for Cancer Research, Oslo University Hospital-Radiumhospitalet, Oslo, Norway Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway Department of Research, Vestre Viken Hospital, Drammen, Norway Section for Breast- and Endocrine Surgery, Department of Cancer, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Ullevål, Oslo, Norway Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway Department of Pathology, Akershus University Hospital, Lørenskog, Norway Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway Department of Oncology, Division of Surgery, Cancer and Transplantation Medicine, Oslo University Hospital-Radiumhospitalet, Oslo, Norway National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital, Oslo, Norway Department of Oncology, Akershus University Hospital, Lørenskog, Norway Oslo Breast Cancer Research Consortium, Oslo University Hospital, Oslo, Norway Department of Medical Genetics, Oslo University Hospital and University of Oslo, Oslo, Norway
Sarah V. Colonna	Department of Internal Medicine and Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
CTS Consortium	Department of Computational and Quantitative Medicine, City of Hope, Duarte, CA City of Hope Comprehensive Cancer Center, City of Hope, Duarte, CA
Ellen Copson	Department of Medical Oncology, University of Southampton, Southampton, United Kingdom
Fergus J. Couch	Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN
Angela Cox	Sheffield Institute for Nucleic Acids (SInFoNiA), Department of Oncology and Metabolism, University of Sheffield, Sheffield, United Kingdom
Simon S. Cross	Academic Unit of Pathology, Department of Neuroscience, University of Sheffield, Sheffield, United Kingdom
Kamila Czene	Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
Mary B. Daly	Department of Clinical Genetics, Fox Chase Cancer Center, Philadelphia, PA
Joe Dennis	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
Peter Devilee	Department of Pathology, Leiden University Medical Center, Leiden, the Netherlands Department of Human Genetics, Leiden University Medical Center, Leiden, the Netherlands
Caroline A. Drukker	Department of Surgery, The Netherlands Cancer Institute——Antoni van Leeuwenhoek hospital, Amsterdam, the Netherlands
Alison M. Dunning	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, United Kingdom
Miriam Dwek	School of Life Sciences, University of Westminster, London, United Kingdom
A. Heather Eliassen	Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA

(continued on following page)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Christoph Engel	Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany LIFE—Leipzig Research Centre for Civilization Diseases, University of Leipzig, Leipzig, Germany
D. Gareth Evans	Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom North West Genomics Laboratory Hub, Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom
Jonine D. Figueroa	Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD Usher Institute of Population Health Sciences and Informatics, The University of Edinburgh, Edinburgh, United Kingdom Cancer Research UK Edinburgh Centre, The University of Edinburgh, Edinburgh, United Kingdom
Olivia Fletcher	The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, United Kingdom
Henrik Flyger	Department of Breast Surgery, Herlev and Gentofte Hospital, Copenhagen University Hospital, Herlev, Denmark
Manuela Gago-Dominguez	Genomic Medicine Group, International Cancer Genetics and Epidemiology Group, Fundación Pública Galega de Medicina Xenómica, Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS), Complejo Hospitalario Universitario de Santiago, SERGAS, Santiago de Compostela, Spain
Montserrat García-Closas	Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD
José A. García-Sáenz	Medical Oncology Department, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria San Carlos (IdISSC), Centro Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Jeanine Genkinger	Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY Herbert Irving Comprehensive Cancer Center, New York, NY
Graham G. Giles	Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia
Anna González-Neira	Human Genotyping Unit-CeGen, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
Pascal Guénel	Team Exposome and Heredity, CESP, Gustave Roussy, INSERM, University Paris-Saclay, UVSQ, Villejuif, France
Melanie Gündert	Molecular Epidemiology Group, C080, German Cancer Research Center (DKFZ), Heidelberg, Germany Molecular Biology of Breast Cancer, University Womens Clinic Heidelberg, University of Heidelberg, Heidelberg, Germany Institute of Diabetes Research, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany
Eric Hahnen	Center for Familial Breast and Ovarian Cancer, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany Center for Integrated Oncology (CIO), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
Christopher A. Haiman	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA
Niclas Håkansson	Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
Ute Hamann	Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

(continued on following page)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Mikael Hartman	Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore Department of Surgery, National University Health System, Singapore, Singapore Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore
Bernadette A.M. Heemskerk-Gerritsen	Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
Alexander Hein	Department of Gynecology and Obstetrics, Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, University Hospital Erlangen, Erlangen, Germany
Weang-Kee Ho	Department of Mathematical Sciences, Faculty of Science and Engineering, University of Nottingham Malaysia Campus, Semenyih, Selangor, Malaysia Breast Cancer Research Programme, Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia
Reiner Hoppe	Dr Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany University of Tübingen, Tübingen, Germany
John L. Hopper	Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia
Richard S. Houlston	Division of Genetics and Epidemiology, The Institute of Cancer Research, London, United Kingdom
Anthony Howell	Division of Cancer Sciences, University of Manchester, Manchester, United Kingdom
David J. Hunter	Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
kConFab Investigators	Research Department, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria, Australia
ABCTB Investigators	Australian Breast Cancer Tissue Bank, Westmead Institute for Medical Research, University of Sydney, Sydney, New South Wales, Australia

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
SGBCC Investigators	Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore Department of Surgery, National University Health System, Singapore, Singapore Human Genetics Division, Genome Institute of Singapore, Singapore, Singapore Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore and National University Health System, Singapore, Singapore Cancer Genetics Service, National Cancer Centre, Singapore, Singapore Breast Department, KK Women's and Children's Hospital, Singapore, Singapore SingHealth Duke-NUS Breast Centre, Singapore, Singapore Department of General Surgery, Tan Tock Seng Hospital, Singapore, Singapore Division of Surgical Oncology, National Cancer Centre, Singapore, Singapore Department of General Surgery, Singapore General Hospital, Singapore, Singapore Division of Breast Surgery, Department of General Surgery, Changi General Hospital, Singapore, Singapore Division of Radiation Oncology, National Cancer Centre, Singapore, Singapore Division of Medical Oncology, National Cancer Centre, Singapore, Singapore
Hidemi Ito	Division of Cancer Information and Control, Aichi Cancer Center Research Institute, Nagoya, Japan Division of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
Anna Jakubowska	Department of Genetics and Pathology, Pomeranian Medical University, Unii Lubelskiej, Szczecin, Poland Independent Laboratory of Molecular Biology and Genetic Diagnostics, Pomeranian Medical University, Unii Lubelskiej, Szczecin, Poland
Helena Jernström	Oncology, Department of Clinical Sciences in Lund, Lund University, Lund, Sweden
Esther M. John	Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA

(continued on following page)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Nichola Johnson	The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, United Kingdom
Michael E. Jones	Division of Genetics and Epidemiology, The Institute of Cancer Research, London, United Kingdom
Vijai Joseph	Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, Memorial Sloan Kettering Cancer Center, New York, NY Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
Rudolf Kaaks	Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany
Daehee Kang	Cancer Research Institute, Seoul National University, Seoul, Korea Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea
Sung-Won Kim	Department of Surgery, Daerim Saint Mary's Hospital, Seoul, Korea
Cari M. Kitahara	Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD
Linetta B. Koppert	Department of Surgical Oncology, Family Cancer Clinic, Erasmus MC Cancer Institute, Rotterdam, the Netherlands
Veli-Matti Kosma	Translational Cancer Research Area, University of Eastern Finland, Kuopio, Finland Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland Biobank of Eastern Finland, Kuopio University Hospital, Kuopio, Finland
Peter Kraft	Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA Program in Genetic Epidemiology and Statistical Genetics, Harvard TH Chan School of Public Health, Boston, MA
Vessela N. Kristensen	Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway Department of Medical Genetics, Oslo University Hospital and University of Oslo, Oslo, Norway
Katerina Kubelka-Sabit	Department of Histopathology and Cytology, Clinical Hospital Acibadem Sistina, Skopje, Republic of North Macedonia

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Stella Koutros	Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD
Allison W. Kurian	Department of Epidemiology and Population Health, Stanford University School of Medicine, Stanford, CA Department of Medicine, Division of Oncology, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA
Ava Kwong	Hong Kong Hereditary Breast Cancer Family Registry, Hong Kong Department of Surgery, The University of Hong Kong, Hong Kong Department of Surgery and Cancer Genetics Center, Hong Kong Sanatorium and Hospital, Hong Kong
James V. Lacey	Department of Computational and Quantitative Medicine, City of Hope, Duarte, CA City of Hope Comprehensive Cancer Center, City of Hope, Duarte, CA
Diether Lambrechts	Laboratory for Translational Genetics, Department of Human Genetics, KU Leuven, Leuven, Belgium VIB Center for Cancer Biology, VIB, Leuven, Belgium
Loic Le Marchand	Epidemiology Program, University of Hawaii Cancer Center, Honolulu, HI
Jingmei Li	Human Genetics Division, Genome Institute of Singapore, Singapore, Singapore
Jan Lubiński	Department of Genetics and Pathology, Pomeranian Medical University, Unii Lubelskiej, Szczecin, Poland
Michael Lush	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
Arto Mannermaa	Translational Cancer Research Area, University of Eastern Finland, Kuopio, Finland Institute of Clinical Medicine, Pathology and Forensic Medicine, University of Eastern Finland, Kuopio, Finland Biobank of Eastern Finland, Kuopio University Hospital, Kuopio, Finland
Mehdi Manoochehri	Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

(continued on following page)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Sara Margolin	Department of Oncology, Södersjukhuset, Stockholm, Sweden Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
Keitaro Matsuo	Division of Cancer Epidemiology, Nagoya University Graduate School of Medicine, Nagoya, Japan Division of Cancer Epidemiology and Prevention, Aichi Cancer Center Research Institute, Nagoya, Japan
Dimitrios Mavroudis	Department of Medical Oncology, University Hospital of Heraklion, Heraklion, Greece
Kyriaki Michailidou	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom Biostatistics Unit, The Cyprus Institute of Neurology & Genetics, Nicosia, Cyprus
Roger L. Milne	Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia
Nur Aishah Mohd Taib	Department of Surgery, Faculty of Medicine, University of Malaya, UM Cancer Research Institute, Kuala Lumpur, Malaysia
Anna Marie Mulligan	Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario, Canada Laboratory Medicine Program, University Health Network, Toronto, Ontario, Canada
Patrick Neven	Leuven Multidisciplinary Breast Center, Department of Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium
William G. Newman	Division of Evolution and Genomic Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, United Kingdom North West Genomics Laboratory Hub, Manchester Centre for Genomic Medicine, St Mary's Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Nadia Obi	Institute for Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
Kenneth Offit	Clinical Genetics Research Lab, Department of Cancer Biology and Genetics, Memorial Sloan Kettering Cancer Center, New York, NY Clinical Genetics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY
Andrew F. Olshan	Department of Epidemiology, Gillings School of Global Public Health and UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC
Sue K. Park	Cancer Research Institute, Seoul National University, Seoul, Korea Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Korea Integrated Major in Innovative Medical Science, Seoul National University College of Medicine, Seoul, South Korea
Tjoung-Won Park-Simon	Gynaecology Research Unit, Hannover Medical School, Hannover, Germany
Alpa V. Patel	Department of Population Science, American Cancer Society, Atlanta, GA
Dijana Plaseska-Karanfilska	Research Centre for Genetic Engineering and Biotechnology Georgi D, Efremov, MASA, Skopje, Republic of North Macedonia
Coralie Poncet	European Organisation for Research and Treatment of Cancer Headquarters, Brussels, Belgium
Ross L. Prentice	Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, WA
Nadege Presneau	School of Life Sciences, University of Westminster, London, United Kingdom
Renate Prevos	Leuven Multidisciplinary Breast Center, Department of Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium
Katri Pylkäs	Laboratory of Cancer Genetics and Tumor Biology, Translational Medicine Research Unit, Biocenter Oulu, University of Oulu, Oulu, Finland Laboratory of Cancer Genetics and Tumor Biology, Northern Finland Laboratory Centre Oulu, Oulu, Finland
Paolo Radice	Unit of Molecular Bases of Genetic Risk and Genetic Testing, Department of Research, Fondazione IRCCS Istituto Nazionale dei Tumori (INT), Milan, Italy

(continued on following page)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Gad Rennert	Clalit National Cancer Control Center, Carmel Medical Center and Technion Faculty of Medicine, Haifa, Israel
Hedy S. Rennert	Clalit National Cancer Control Center, Carmel Medical Center and Technion Faculty of Medicine, Haifa, Israel
Atocha Romero	Medical Oncology Department, Hospital Universitario Puerta de Hierro, Madrid, Spain
Emmanouil Saloustros	Department of Oncology, University Hospital of Larissa, Larissa, Greece
Elinor J. Sawyer	School of Cancer and Pharmaceutical Sciences, Comprehensive Cancer Centre, Guy's Campus, King's College London, London, United Kingdom
Rita K. Schmutzler	Center for Familial Breast and Ovarian Cancer, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany Center for Integrated Oncology (CIO), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
Lukas Schwentner	Department of Gynaecology and Obstetrics, University Hospital Ulm, Ulm, Germany
Christopher Scott	Department of Health Sciences Research, Mayo Clinic, Rochester, MN
Mitul Shah	Centre for Cancer Genetic Epidemiology, Department of Oncology, University of Cambridge, Cambridge, United Kingdom
Chen-Yang Shen	Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan School of Public Health, China Medical University, Taichung, Taiwan
Xiao-Ou Shu	Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN
Xueling Sim	Saw Swee Hock School of Public Health, National University of Singapore and National University Health System, Singapore, Singapore

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Melissa C. Southey	Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Victoria, Australia Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia Department of Clinical Pathology, The University of Melbourne, Melbourne, Victoria, Australia
Jennifer Stone	Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia Genetic Epidemiology Group, School of Population and Global Health, University of Western Australia, Perth, Western Australia, Australia
Daniel O. Stram	Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA
Rulla M. Tamimi	Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA Department of Population Health Sciences, Weill Cornell Medicine, New York, NY
Soo Hwang Teo	Department of Surgery, Faculty of Medicine, University of Malaya, UM Cancer Research Institute, Kuala Lumpur, Malaysia Breast Cancer Research Programme, Cancer Research Malaysia, Subang Jaya, Selangor, Malaysia
Lauren R. Teras	Department of Population Science, American Cancer Society, Atlanta, GA
Mary Beth Terry	Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY
Katarzyna Tomczyk	The Breast Cancer Now Toby Robins Research Centre, The Institute of Cancer Research, London, United Kingdom
Ian Tomlinson	Cancer Research Centre, The University of Edinburgh, Edinburgh, United Kingdom
Melissa A. Troester	Department of Epidemiology, Gillings School of Global Public Health and UNC Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC
Thérèse Truong	Team Exposome and Heredity, CESP, Gustave Roussy, INSERM, University Paris-Saclay, UVSQ, Villejuif, France

(continued on following page)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Celine M. Vachon	Division of Epidemiology, Department of Quantitative Health Sciences, Mayo Clinic, Rochester, MN
Chantal van Ongeval	Leuven Multidisciplinary Breast Center, Department of Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium
Qin Wang	Centre for Cancer Genetic Epidemiology, Department of Public Health and Primary Care, University of Cambridge, Cambridge, United Kingdom
Barbara Wappenschmidt	Center for Familial Breast and Ovarian Cancer, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany Center for Integrated Oncology (CIO), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany
Camilla Wendt	Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
Robert Winqvist	Laboratory of Cancer Genetics and Tumor Biology, Translational Medicine Research Unit, Biocenter Oulu, University of Oulu, Oulu, Finland Laboratory of Cancer Genetics and Tumor Biology, Northern Finland Laboratory Centre Oulu, Oulu, Finland
Alicja Wolk	Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

(continued in next column)

TABLE A1. Breast Cancer Association Consortium and Mindact Collaborators (continued)

Name	Affiliations
Anna H. Wu	Department of Population Health and Public Health Sciences, Keck School of Medicine, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA
Siddhartha Yadav	Department of Medical Oncology, Mayo Clinic, Rochester, MN
Cheng Har Yip	Department of Surgery, Faculty of Medicine, University of Malaya, UM Cancer Research Institute, Kuala Lumpur, Malaysia Subang Jaya Medical Centre, Subang Jaya, Selangor, Malaysia
Wei Zheng	Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University School of Medicine, Nashville, TN
Argyrios Ziogas	Department of Medicine, Genetic Epidemiology Research Institute, University of California Irvine, Irvine, CA