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

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**Running head:** Polygenic Risk Score and Breast Cancer Outcome

This study has been presented in part at the following conference:

* ASCO Annual Meeting: Breast Cancer – Local/Regional/Adjuvant Poster Session, June 2022, Chicago, IL, USA

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**ABSTRACT**

**PURPOSE:** A polygenic risk score (PRS) consisting of 313 common genetic variants (PRS313) is associated with risk of breast cancer and contralateral breast cancer. This study aimed to evaluate the association of the PRS313 with clinical-pathological characteristics of, and survival following, breast cancer.

**PATIENTS AND 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 PRS313 and clinical-pathological characteristics, including the 70-gene signature for MINDACT, were evaluated using logistic regression analyses. Associations of PRS313 (continuous, per SD) with overall survival (OS) and breast cancer-specific survival (BCSS) were evaluated with Cox regression, adjusted for clinical-pathological characteristics and treatment.

**RESULTS:** The PRS313 was associated with more favorable tumor characteristics. In BCAC, increasing PRS313 was associated with lower grade, hormone receptor-positive status, and smaller tumor size. In MINDACT, PRS313 was associated with a low risk 70-gene signature. In European women from BCAC, higher PRS313 was associated with better OS and BCSS: hazard ratio (HR) 0.96 (95% confidence interval (CI):0.94-0.97) and 0.96 (95%CI:0.94-0.98), but the association disappeared after adjustment for clinical-pathological characteristics (and treatment): OS HR:1.01 (95%CI:0.98-1.05) and BCSS HR:1.02 (95%CI:0.98-1.07). Results in MINDACT and Asian women from BCAC were consistent.

**CONCLUSION:** An increased PRS313 is associated with favorable tumor characteristics, but is not independently associated with prognosis. Thus, PRS313 has no role in the clinical management of primary breast cancer at time of diagnosis. Nevertheless, breast cancer mortality rates will be higher for women with higher PRS313 as increasing PRS313 is associated with an increased risk of disease. This information is crucial for modelling effective stratified screening programs.

**CONTEXT SUMMARY**

**Key objective**

An optimized and extensively validated polygenic risk score (PRS) consisting of 313 common genetic variants (PRS313) 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 PRS313 affects breast cancer prognosis has not yet been addressed, and is important for incorporating PRS into clinical practice.

**Knowledge generated**

PRS313 was associated with more favorable tumor characteristics. PRS313 was not independently associated with prognosis. Nevertheless, breast cancer mortality rates will be higher for women with higher PRS313 as increasing PRS313 is associated with an increased risk of disease.

**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 (PRS313) and the risk of breast cancer using data from the Breast Cancer Association Consortium (BCAC).6,12 PRS313 is predictive of overall breast cancer risk, with an odds ratio (OR) per standard deviation (SD) of 1.61 (95% confidence interval (95%CI): 1.57–1.65).12 PRS313 is also associated with a higher risk of contralateral breast cancer with a hazard ratio (HR) per SD of 1.25 (95%CI: 1.18-1.33).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 in order 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 effectiveness of incorporating risk-based screening based on 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 PRS313 and clinical-pathological characteristics of breast cancer and disease outcome. In a subgroup of patients from the MINDACT study, we also explored associations of PRS313 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**

***BCAC***
We selected women diagnosed with a first invasive breast cancer from the BCAC database version 13. All women of European and Asian ancestry, based on genotyping, who were 18 years and older were included, including 98,397 European women (74 studies) and 12,920 Asian women (10 studies) (Figure S1A). SNP genotyping was performed using the iCOGS array21,22 or the OncoArray10,11. 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 PRS313 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 EORTC 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 (Figure S1B). MINDACT included women aged 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, 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 PRS313 results to the MINDACT study database.

**Polygenic risk scores (PRSs)**The PRS313 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 standard deviation of PRS313 of the control subjects (PRS313 SD=0.61; ER-positive PRS313 SD=0.65; ER-negative PRS313 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 PRS313 and clinical-pathological characteristics including the 70-gene signature. In BCAC, models were adjusted for country.

The primary outcome was to evaluate the association between PRS313 (per SD) and outcome after breast cancer. This was assessed for three different endpoints; 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 PRS313 and survival endpoints in univariable models and in multivariable models adjusted for clinical-pathological characteristics and treatment (chemotherapy and endocrine therapy). Additionally, in a univariable Cox model, the association between the PRS313 and BCSS was evaluated in subgroups based on clinical-pathological 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 to 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 to 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 PRS313 and clinical-pathological characteristics and survival endpoints, because of the smaller size of the dataset with shorter follow-up time than for the European BCAC studies, and because 26 variants of the PRS313 were imputed with a low (<.9) imputation score.27 Similarly, analysis in MINDACT were also limited to the main analyses, because of the smaller dataset.

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.

**RESULTS**

**Association between PRS313 and clinical-pathological characteristics**

The association between the PRS313 and individual clinical-pathological 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 were similar for BCAC and MINDACT; although there was substantial missing information in BCAC for some variables. Table 2 and Figure 1 show the association between specific tumor characteristics and PRS313. Generally, an increase in PRS313 was associated with a decreased probability of unfavorable tumor characteristics. Patients with a higher PRS313 were less likely to have ER-negative or progesterone receptor (PR)-negative tumors, higher grade tumors or larger tumors. However, a higher PRS313 was associated with a higher probability of lymph node positive tumors, and with a younger age at diagnosis. In the MINDACT study, a higher PRS313 was associated with a lower probability of a high-risk 70-gene signature, and the association was attenuated after adjusting for other clinical-pathological characteristics (adjusted OR 0.97 (95%CI: 0.78-1.21)). 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 non-significant.

**Association between PRS313 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 overall survival was 7.7 years in BCAC and 8.3 years in MINDACT. In BCAC, an increase in PRS313 was associated with a slightly better OS, HR per unit SD of PRS313 0.96 (95%CI: 0.94-0.97); BCSS, 0.96 (95%CI: 0.94-0.98); and DMFI, 0.98 (95%CI: 0.96-1.00) (Table 3 and Figure 2). For all endpoints, the associations disappeared after adjusting for clinical-pathological characteristics and treatment. The adjusted HR per unit SD of PRS313 was 1.01 (95%CI: 0.98-1.05) for OS, 1.02 (95%CI: 0.98-1.07) for BCSS and 1.03 (95%CI: 0.99-1.07) for DMFI (Table 3 and Figure 2). Of note, the association with PRS313 that was seen in the unadjusted analysis disappeared after adjusting for ER status and grade only (BCSS, 1.01 [95%CI: 0.98-1.04]). The estimates for individual clinical-pathological characteristics from the complete case analyses are provided in the Supplementary Appendix (Supplementary Table S1-3). The HR estimates in MINDACT were close to 1, and consistent with the estimates in BCAC, but with very wide 95%CIs.

Furthermore, 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 overall survival of 4.2 years, were consistent with those of women of European ancestry in BCAC and MINDACT (Table 3 and Figure 2). The adjusted HR per unit SD of PRS313 was 0.96 (95%CI: 0.87-1.07) for OS; BCSS, 0.93 (95%CI: 0.75-1.17), and DMFI 0.98 (95%CI: 0.87-1.10).

We also evaluated the associations between subtype-specific PRS and breast cancer-specific survival in women of European ancestry (Supplementary Table S4). For BCSS the HR estimates for ER-positive PRS313 were similar to the PRS313 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 PRS313 and BCSS, either in all patients nor in ER-negative patients. The association between PRS313 and BCSS was also evaluated in subgroups based on clinical-pathological characteristics (Supplementary Table S5). There were no subgroups of patients with a higher probability of breast cancer related death per unit SD increase in PRS313.

**DISCUSSION**

The observed association between the PRS313 and the lower probability of distant metastasis or (breast cancer related) death in the unadjusted analysis disappeared after adjustment for clinical-pathological characteristics. In line with this observation, an increase in PRS313 was associated both with more favorable clinical-pathological characteristics and with a low risk 70-gene signature. The simplest interpretation of these results is that clinical-pathological characteristics, particularly ER-status and grade, act as intermediates on the causal pathway from germline PRS313 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 clinical-pathological 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 with more favorable clinical-pathological characteristics.28,30,31 Screen-detection itself has been shown to be a prognostic factor for good prognosis, independent of clinical-pathological characteristics.32,33

The 313 SNP PRS is currently the most comprehensively validated PRS of breast cancer risk prediction. In the largest cohort to date, in accordance with previous studies, we observed that higher PRS313 was associated with favorable tumor characteristics. Every SD increase in PRS was associated with lower grade, ER- and PR-positive tumors. We also found associations with smaller size and HER2-negative tumors, but these associations were weaker. In our study, we observed no association between the PRS313 and overall survival (HR per unit SD increase in PRS; 1.01 (95%CI: 0.98-1.05)), breast cancer-specific survival (HR; 1.02 (95%CI: 0.98-1.07)) or distant metastasis free interval (HR; 1.03 (95%CI: 0.99-1.07)) 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 amongst those women that develop breast cancer. The PRS313 does not have independent prognostic value in addition to clinical-pathological characteristics, and has no role in the clinical management of primary breast cancer at 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 breast cancer-specific survival (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 PRS313 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 cancer risk with PRS313 is better for ER-positive disease than for ER-negative disease, despite using subtype specific PRSs (ER-positive and ER-negative), likely due to 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 PRS313 and the three survival endpoints 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 PRS313 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 PRS313 with favorable clinical-pathological 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 PRS313 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 modelling 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 down-staging at time of diagnosis, are necessary to demonstrate the (cost-)effectiveness of risk-stratified screening.16,34,35

Wordcount: 2823/3000

**ACKNOWLEDGEMENTS**

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 Surveillance Epidemiology and End Results 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 (USA)) 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).

**SUPPORT/FUNDING:**BCAC:
**BCAC** is funded by the European Union's Horizon 2020 Research and Innovation Programme (grant numbers 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, 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 U19 CA148065, and Cancer Research UK Grant C1287/A16563 and the PERSPECTIVE project supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research (grant 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 n° 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 Defence (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 (USA). 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 USA Government or the BCFR. 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 [grants 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 number Z01-CP010119), and the National Institute of Environmental Health Sciences (grant number 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 UM1 CA164920 from the National Cancer Institute. 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 **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. IT 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 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 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 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 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 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 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 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 grants 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 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 (№АААА-А16-116020350032-1). The **HERPACC** was supported by MEXT Kakenhi (No. 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, Labour and Welfare of Japan, by Health and Labour Sciences Research Grants for Research on Applying Health Technology from Ministry Health, Labour 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. RB 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'. DL 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 grants 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 grants 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/HlR/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 193387/V50 (to A-L Børresen-Dale and V.N. Kristensen) and grant 193387/H10 (to A-L Børresen-Dale and V.N. Kristensen), South Eastern Norway Health Authority (grant 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 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 USA National Cancer Institute of the National Institutes of Health. 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 USA Government or the BCFR. 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 grants P01 CA87969, UM1 CA186107, and U19 CA148065. The **NHS2** was supported by NIH grants UM1 CA176726 and U19 CA148065. The **OBCS** was supported by research grants from the Finnish Cancer Foundation, the Academy of Finland (grant number 250083, 122715 and Center of Excellence grant number 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 towards 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, USA. 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 (grants 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 grants 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 [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 12 000 000 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 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 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.

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.

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**Final approval of manuscript:** All authors
**Accountable for all aspects of the work:** All authors

**CONFLICT OF INTERESTS DISCLOSURES**

Peter A. Fasching conducts research funded by Amgen, Novartis and Pfizer. He received Honoraria from Roche, Novartis and Pfizer. Emiel J.T. Rutgers has received personal fees from Guerbet. Laura J. van 't Veer reports being shareholder and part-time employee of Agendia. Matthias W. Beckmann conducts research funded by Amgen, Novartis and Pfizer. F. Cardoso has received personal fees from Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Debiopharm, Eisai, GE Oncology, Genentech, Gilead, GlaxoSmithKline, Iqvia, Macrogenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre-Fabre, prIME Oncology, Roche, Sanofi, Samsung Bioepis, Seagen, Teva, Touchime. Vijai Joseph reports being an inventor of diagnosis and treatment of ERCC3-mutant cancer; inventors: Vijai Joseph, Sabine Topka, Kenneth Offit; WIPO WO2018170230A1. Allison W. Kurian reports research funding to her institution from Myriad Genetics for an unrelated project (funding dates 2017-2019). All other authors report no conflict of interests.

**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 clinical-pathological and/or full-transcriptome data for translational research.

**ETHICS APPROVAL:**

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

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**Figure 1** Association between PRS313 and clinical-pathological characteristics in BCAC and MINDACT

See Table 2 for exact numeric estimates.
Univariable (multinomial/binary) logistic regression models with clinical-pathological characteristics as the dependent variable and PRS313 as the independent variable and for BCAC with country as co-variable.
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation

**Figure 2** Association between PRS313 and overall survival, 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.
\*Additionally adjusted for age (continuous), tumor size, lymph node status, grade, ER, PR and HER2 status.
\*\*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.
BCSS, breast cancer-specific survival; DMFI, distant metastasis-free interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OS, overall survival; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation.

**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 (mean, SD)** | 57.1 ± 12.1 | 54.4 ±9.2 | 50.9 ± 11.1 |
| **Age** |  |  |  |
|  | <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** |  |  |  |
|  | T1 (≤2cm) | 46,123 (47)[64] | 484 (71) | 4,132 (32)[51] |
|  | T2 (2-5 cm) | 22,522 (23)[31] | 194 (28) | 3,328 (26)[41] |
|  | T3 (>5 cm) | 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] |
|  | 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] |
| **PRS313 (mean, range)** | -0.15 (-4.56 – 4.08) | -0.15 (-3.54 – 2.94) | 0.65 (-3.86 – 4.27) |

ER, Estrogen receptor; HER2, Human epidermal growth factor receptor 2; PR, Progesterone receptor; PRS, polygenic risk score; SD, standard deviation.

**Table 2** Association between PRS313 and clinical-pathological characteristics in BCAC and MINDACT

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | BCAC - European (N=98,397) | MINDACT (N=683) | BCAC - Asian (N=12,920) |
|  |  | **Unadjusted OR per Unit SD of PRS313a** | **95% CI** | ***P*** | **Unadjusted OR per Unit SD of PRS313a** | **95% CI** | ***P*** | **Unadjusted OR per Unit SD of PRS313a** | **95% CI** | ***P*** |
| Age at diagnosis |  |  |  |  |  |  |  |  |  |
|  | <40 | 1.11 | 1.08-1.14 | <.0001 | 0.90 | 0.65-1.25 | .52 | 1.04 | 0.97-1.11 | .28 |
|  | ≥40-50  | 1.12 | 1.10-1.14 | <.0001 | 1.05 | 0.86-1.27 | .65 | 1.05 | 1.00-1.11 | .06 |
|  | ≥50-60  | 1.07 | 1.05-1.09 | <.0001 | 1.12 | 0.93-1.35 | .24 | 0.99 | 0.94-1.04 | .69 |
|  | ≥60  | Reference |  |  | Reference |  |  | Reference |  |  |
| Tumor stage |  |  |  |  |  |  |  |  |  |  |
|  | Stage I-III | Reference |  |  | - |  |  | Reference |  |  |
|  | Stage IV | 1.01 | 0.96-1.08 | .63 | - |  |  | 1.04 | 0.92-1.19 | .52 |
| Tumor size, cm |  |  |  |  |  |  |  |  |  |  |
|  | ≤2 | Reference |  |  | Reference |  |  | Reference |  |  |
|  | 2-5 | 0.97 | 0.96-0.99 | .002 | 1.01 | 0.86-1.19 | .91 | 0.98 | 0.93-1.03 | .41 |
|  | >5 | 1.02 | 0.98-1.06 | .28 | 1.37 | 0.58-3.27 | .47 | 1.00 | 0.91-1.10 | .96 |
| Lymph node status |  |  |  |  |  |  |  |  |  |
|  | Negative | Reference |  |  | Reference |  |  | Reference |  |  |
|  | Positive | 1.02 | 1.01-1.04 | .003 | 1.07 | 0.89-1.27 | .48 | 1.01 | 0.96-1.05 | .77 |
| Tumor histology |  |  |  |  |  |  |  |  |  |
|  | Ductal | Reference |  |  | Reference |  |  | Reference |  |  |
|  | Lobular  | 1.06 | 1.04-1.08 | <.0001 | 1.34 | 1.06-1.68 | .013 | 1.05 | 0.94-1.19 | .39 |
|  | Other | 0.97 | 0.95-0.99 | .015 | 1.07 | 0.55-2.07 | .85 | 0.98 | 0.88-1.07 | .62 |
|  | Mixed | 1.08 | 1.05-1.12 | <.0001 | 0.83 | 0.57-1.21 | .33 | 0.99 | 0.78-1.25 | .91 |
|  | Unknown | 1.03 | 1.00-1.05 | .017 |  |  |  | 1.00 | 0.94-1.06 | .89 |
| Grade |  |  |  |  |  |  |  |  |  |  |
|  | 1 | Reference |  |  | Reference |  |  | Reference |  |  |
|  | 2 | 0.98 | 0.96-1.00 | .054 | 1.10 | 0.90-1.33 | .37 | 1.01 | 0.94-1.08 | .84 |
|  | 3 | 0.85 | 0.83-0.86 | <.0001 | 0.80 | 0.65-0.99 | .041 | 0.94 | 0.87-1.01 | .08 |
| ER status |  |  |  |  |  |  |  |  |  |  |
|  | Negative | 0.80 | 0.79-0.82 | <.0001 | 0.80 | 0.65-0.99 | .038 | 0.86 | 0.82-0.89 | <.0001 |
|  | Positive  | Reference |  |  | Reference |  |  | Reference |  |  |
| PR status |  |  |  |  |  |  |  |  |  |  |
|  | Negative | 0.85 | 0.83-0.86 | <.0001 | 0.84 | 0.71-1.00 | .047 | 0.89 | 0.86-0.94 | <.0001 |
|  | Positive  | Reference |  |  | Reference |  |  | Reference |  |  |
| HER2 status |  |  |  |  |  |  |  |  |  |  |
|  | Negative | Reference |  |  | Reference |  |  | Reference |  |  |
|  | Positive  | 0.97 | 0.94-0.99 | .003 | 1.02 | 0.80-1.31 | .87 | 0.99 | 0.95-1.04 | .75 |
| 70-gene signature |  |  |  |  |  |  |  |  |  |
|  | Low risk | **-** |  |  | Reference |  |  | - |  |  |
|  | High risk | **-** |  |  | 0.86 | 0.74-1.01 | .064 | - |  |  |

aUnivariable (multinomial/binary) logistic regression models with clinical-pathological characteristics as the dependent variable and PRS313 as the independent variable and for BCAC with country as co-variable.
CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio; PR, progesterone receptor; PRS, polygenic risk score; SD, standard deviation

**Table 3** Association between PRS313 and overall survival, breast cancer-specific survival and distant metastasis-free interval in BCAC and MINDACT

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Endpoint | No. of patientsa | No. of eventsa | Unadjusted HR per Unit SD of PRS313b | 95% CI | *P* | Adjusted HR per Unit SD of PRS313c | 95% CI | *P* | Adjusted HR per Unit SD of PRS313d | 95% CI | *P* |
| OS |  |  |  |  |  |  |  |  |  |  |  |
| BCAC - European | 95,955 | 16,582 | 0.96 | 0.94-0.97 | <.0001 | 1.00 | 0.97-1.02 | .88 | 1.01 | 0.98-1.05 | .46 |
| MINDACT | 683 | 61 | 0.91 | 0.71-1.17 | .45 | 0.90 | 0.69-1.17 | .42 | 0.91 | 0.69-1.18 | .91 |
| BCAC - Asian | 12,528 | 1,323 | 0.97 | 0.91-1.02 | .24 | 0.97 | 0.88-1.07 | .53 | 0.96 | 0.87-1.07 | .48 |
| BCSS |  |  |  |  |  |  |  |  |  |  |  |
| BCAC - European | 95,955 | 7,635 | 0.96 | 0.94-0.98 | .001 | 1.00 | 0.96-1.03 | .83 | 1.02 | 0.98-1.07 | .39 |
| MINDACT | 683 | 31 | 1.10 | 0.77-1.56 | .60 | 1.02 | 0.70-1.49 | .93 | 1.01 | 0.69-1.49 | .95 |
| BCAC - Asian | 12,528 | 316 | 1.05 | 0.93-1.19 | .40 | 0.93 | 0.74-1.16 | .50 | 0.93 | 0.75-1.17 | .55 |
| DMFI |  |  |  |  |  |  |  |  |  |  |  |
| BCAC - European | 95,587 | 8,931 | 0.98 | 0.96-1.00 | .050 | 1.00 | 0.97-1.04 | .79 | 1.03 | 0.99-1.07 | .12 |
| MINDACT | 683 | 60 | 1.03 | 0.80-1.33 | .82 | 0.95 | 0.72-1.25 | .72 | 0.94 | 0.72-1.24 | .68 |
| BCAC - Asian | 12,361 | 775 | 1.02 | 0.94-1.10 | .64 | 0.96 | 0.86-1.07 | .44 | 0.98 | 0.87-1.10 | .74 |

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, 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 clinical-pathological characteristics from the complete case analyses are provided in the Supplementary Appendix (Supplementary Table S1-3).
BCSS, breast cancer-specific survival; CI, confidence interval; 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.