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

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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.

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## 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.
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## 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.

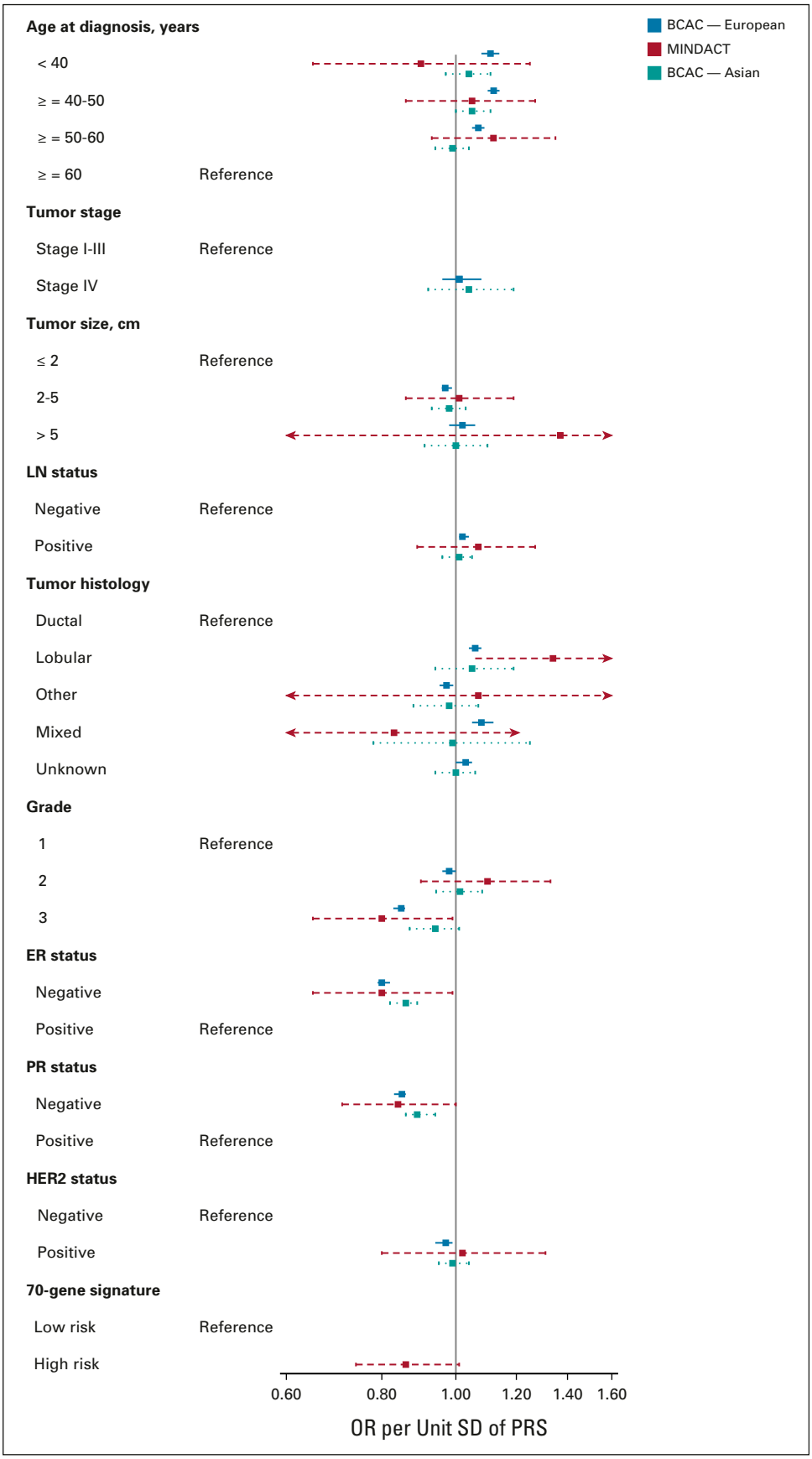


**FIG 1.** Association between $PRS_{313}$ and clinicopathologic characteristics in BCAC and MINDACT. See Table 2 for exact numeric estimates. Univariable (multinomial/binary) logistic regression (continued on following page)

**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.

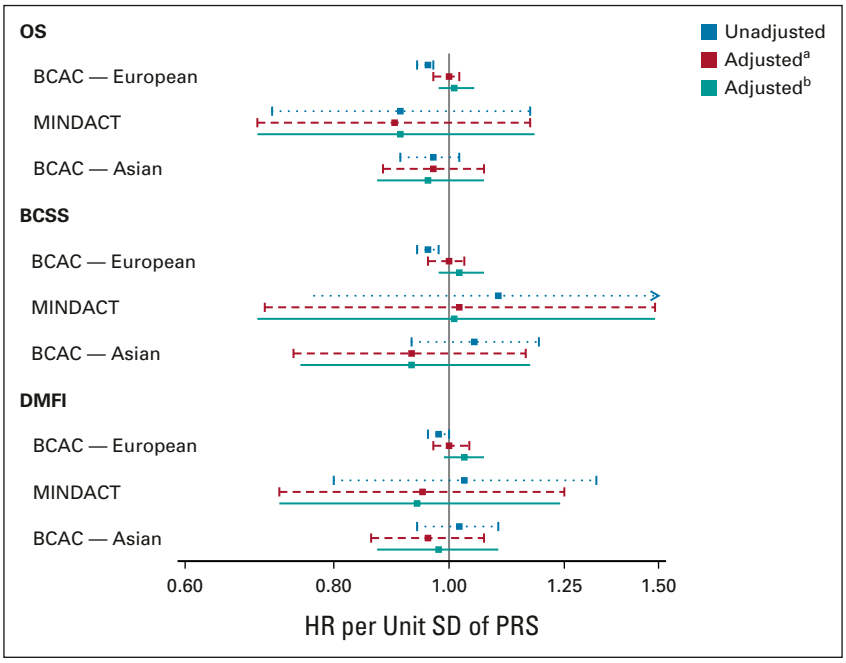


**FIG 2.** Association between $PRS_{313}$ and OS, breast cancer–specific survival, and distant metastasis-free interval in BCAC and MINDACT. See Table 3 for exact numeric estimates. Cox regression models: unadjusted analysis was stratified for country in BCAC. [a]Additionally adjusted for age (continuous), 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]

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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## 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.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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## APPENDIX

**TABLE A1.** Breast Cancer Association Consortium and Mindact Collaborators

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| Carl Blomqvist | Department of Oncology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland |
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**TABLE A1.** Breast Cancer Association Consortium and Mindact Collaborators (continued)

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

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

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

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

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| Ute Hamann | Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany |

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

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

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

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

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

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

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

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| Mary Beth Terry | Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY |
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**TABLE A1.** Breast Cancer Association Consortium and Mindact Collaborators (continued)

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

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