Breast and Prostate Cancer Risks for Male BRCA1 and BRCA2
Pathogenic Variant Carriers Using Polygenic Risk Scores

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Abstract

Background: Recent population-based female breast cancer and prostate cancer polygenic risk scores (PRS) have been developed. We assessed the associations of these PRS with breast and prostate cancer risks for male BRCA1 and BRCA2 pathogenic variant carriers.

Methods: 483 BRCA1 and 1,318 BRCA2 European ancestry male carriers were available from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). A 147-single nucleotide polymorphism (SNP) prostate cancer PRS (PRSPC) and a 313-SNP breast cancer PRS were evaluated. There were three versions of the breast cancer PRS, optimized to predict overall (PRSBC), estrogen-receptor (ER) negative (PRSER-) or ER-positive (PRSER+) breast cancer risk.

Results: PRSER+ yielded the strongest association with breast cancer risk. The odds ratios (ORs) per PRSER+ standard deviation estimates were 1.40 (95% confidence interval [CI] =1.07-1.83) for BRCA1 and 1.33 (95% CI = 1.16-1.52) for BRCA2 carriers. PRSPC was associated with prostate cancer risk for both BRCA1 (OR=1.73, 95% CI =1.28-2.33) and BRCA2 (OR=1.60, 95% CI =1.34-1.91) carriers. The estimated breast cancer ORs were larger after adjusting for female relative breast cancer family history. By age 85 years, for BRCA2 carriers, the breast cancer risk varied from 7.7% to 18.4% and prostate cancer risk from 34.1% to 87.6% between the 5th and 95th percentiles of the PRS distributions.

Conclusions: Population-based prostate and female breast cancer PRS are associated with a wide range of absolute breast and prostate cancer risks for male BRCA1 and BRCA2 carriers. These findings warrant further investigation aimed at providing personalized cancer risks for male carriers and to inform clinical management.
Key words: $BRCA1$, $BRCA2$, male breast cancer, prostate cancer, PRS, polygenic, genetics
*BRCA1* and *BRCA2* pathogenic variants are associated with increased male breast cancer and prostate cancer risks\textsuperscript{1-4}. A recent prospective study estimated the lifetime risk of developing prostate cancer to be 29\% for *BRCA1* and 60\% for *BRCA2* carriers\textsuperscript{5}. The risks of developing male breast cancer compared with the general population have been estimated to be 15-18-fold higher for *BRCA1* and 80-fold higher for *BRCA2* carriers\textsuperscript{6,7}. Up to one in ten *BRCA2* carriers develop breast cancer\textsuperscript{8-12} and display potentially more aggressive disease relative to sporadic cases\textsuperscript{8,12,13}.

Polygenic risk scores (PRS) that combine the effects of multiple disease-associated single nucleotide polymorphisms (SNPs), provide marked cancer risk stratification in both the general population\textsuperscript{14,15} and *BRCA1* and *BRCA2* carriers\textsuperscript{16-18}. Our previous findings suggested the joint effects of PRS and *BRCA1* and *BRCA2* pathogenic variants may identify men at clinically meaningful breast and prostate cancer risk levels\textsuperscript{17}. Recent studies have identified additional breast and prostate cancer susceptibility variants\textsuperscript{15,19,20}, and have refined PRS for these cancers\textsuperscript{15,21}.

The Breast Cancer Association Consortium recently developed and validated a 313-SNP PRS in European ancestry women, which was further optimized to predict Estrogen-Receptor (ER)-specific disease\textsuperscript{21}. The estimated per standard deviation (SD) odds ratio (OR) for the most predictive (ER-positive) PRS was OR=1.68 (95\%CI:1.63-1.73)\textsuperscript{21}. A recent evaluation of this PRS in unselected male breast cancer cases showed similar associations with breast cancer risk in men\textsuperscript{22}. The most recent prostate cancer PRS was developed using 147-SNPs associated with prostate cancer risk in European-ancestry men from the general population\textsuperscript{15}. The estimated per SD OR for the prostate cancer PRS was OR=1.86 (95\%CI:1.83-1.89)\textsuperscript{15}. 


Male *BRCA1* and *BRCA2* carriers are likely to benefit from more personalized breast and prostate cancer risk estimates. Investigating the extent to which these PRS modify cancer risks may lead to more precise and gender-specific cancer risk assessment and could assist in optimizing cancer screening.

Here, we assessed the associations of the newly developed 313-SNP breast cancer PRS and 147-SNP prostate cancer PRS derived using population-based data, with breast and prostate cancer risks, respectively, for male *BRCA1* and *BRCA2* carriers. We investigated whether cancer family history influences the associations and if breast cancer associations differed by ER-status or tumor grade. Furthermore, we assessed whether associations vary by age or *BRCA1* and *BRCA2* pathogenic variant characteristics (location; functional effect). We used the results to estimate age-specific absolute risks of developing breast and prostate cancers for male carriers by PRS distribution percentiles.

**Methods**

Statistical analyses were performed using R-3.6.3 (commands can be found in the Supplementary Methods).

**Study participants and genotyping**

Male *BRCA1* and *BRCA2* pathogenic variant carriers were recruited through 40 studies from 19 countries participating in the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA). The majority of male carriers were ascertained through families attending cancer genetic clinics (96.9%, Supplementary Tables 1-2). In this setting, individuals are referred to clinical genetics because of strong family or personal cancer history. The first individual in a family, screened for mutations,
tends to be an affected individual diagnosed at a young age, most often female relative with a young age at breast cancer diagnosis. When a pathogenic variant is identified, then other family members are tested for the same variant. All participants were aged ≥18 years and provided written informed consent. All studies were approved by local ethical review committees. A total of 1,989 male BRCA1 and BRCA2 carriers of European ancestry were included the present study, by selecting all available men with a breast or prostate cancer diagnosis and matched controls. Details of matching, genotyping and quality control processes have been described previously and in Supplementary Table 2.

Data collected included breast or prostate cancer diagnoses, age at diagnosis or interview, prostate cancer Gleason score, breast cancer ER-status and grade, and family history of: prostate; male breast; and female breast cancers among first- and second-degree relatives. BRCA1 and BRCA2 pathogenic variants (detailed pathogenicity description: http://cimba.ccge.medschl.cam.ac.uk/files/CIMBA_Mutation_Classification_guideline_s_May16.pdf) were categorized according to their known or predicted effect on protein function: “class I” included loss-of-function variants expected to yield unstable or no protein; “class II” included variants likely to produce stable mutant proteins.

Pathology data were obtained from pathology reviews, medical, pathology or tumor registry records, or immunohistochemical staining of tissue microarrays.

Polygenic risk scores

PRS were constructed as the weighted sums of alleles (Supplementary Methods) for 313-SNPs for breast cancer and 147-SNPs for prostate cancer (Supplementary Tables 3-4). Three breast cancer PRS were evaluated, optimized
to predict: overall (PRS\textsubscript{BC}); ER-negative (PRS\textsubscript{ER-}); and ER-positive (PRS\textsubscript{ER+}) breast cancer\textsuperscript{21}. These PRS were scaled to the female population-based control PRS SDs\textsuperscript{21}. The prostate cancer PRS (PRS\textsubscript{PC}) was scaled to the SD calculated from population-based controls\textsuperscript{15}.

**Associations between PRS and cancer risks**

PRS associations with breast and prostate cancer risks were assessed simultaneously using multinomial logistic regression to estimate per SD ORs. Men without breast or prostate cancer diagnoses were considered controls. Breast and prostate cancer cases were defined by considering the first occurring cancer. Instances in which breast and prostate cancers were diagnosed simultaneously were considered as breast cancer cases. Statistical models were adjusted for three ancestry informative principal components (proxy adjustment for study/country, as a direct adjustment would result in too few controls and cases within each study/country, **Supplementary Table 1**) and age. Models using the combined sample of carriers were adjusted for \textit{BRCA1}/\textit{BRCA2} status. To account for relatedness, we estimated robust variances by clustering on family membership\textsuperscript{27,28}. The primary analyses assumed a continuous PRS. Categorical PRS associations were evaluated using the quartiles of the PRS distributions in the combined \textit{BRCA1}/2 carrier controls.

Since the distribution of tumor ER-status in male carriers may differ from the distributions in the general population\textsuperscript{26}, we assessed the associations between all three versions of the breast cancer PRS with overall breast cancer risk and ER-specific disease. Associations with ER-positive and ER-negative breast cancer were assessed simultaneously by considering “ER-negative”, “ER-positive” or “unknown”
as distinct multinomial outcomes. We also assessed the associations with breast cancer grade-specific risk by considering “grade 1”, “grade 2”, “grade 3”, or “unknown grade” as separate multinomial outcomes. A case-only logistic regression also was undertaken that considered grades 1 and 2 as “controls”, and grade 3 as “cases”.

To assess the PRS<sub>PC</sub> association with disease aggressiveness, we partitioned prostate cancers into those with Gleason scores <7, ≥7, or “unknown”, and these were used as distinct multinomial outcomes. A case-only logistic regression assessed differences in the associations with Gleason scores <7 (“controls”) and Gleason scores ≥7 (“cases”).

Discriminatory ability of each PRS was assessed by calculating the area under the receiver operator characteristic (ROC) curve (AUC). Under the sampling design, the majority of male carriers were identified through clinical genetics. Therefore, the majority of both affected and unaffected carriers are expected to have family history of cancer. To determine whether this introduces any biases in the PRS associations, we fitted models that were adjusted for family history in first- and second-degree relatives.

To determine whether PRS associations varied by age (continuous), pathogenic variant location or pathogenic variant effects on protein function (“class I” or “class II” variants), we estimated interaction terms between these factors with the PRS and statistical significance was assessed using likelihood ratio tests (LRT). Pathogenic variants were categorized based on previously-reported nucleotide position differences in breast/ovarian or prostate cancer risks<sup>29-31</sup>.

We undertook a sensitivity analysis to test for PRS heterogeneity across study-countries (<b>Supplementary Methods</b>).
All statistical tests were 2-sided and a P value of less than 0.05 was considered statistically significant.

**Predicted age-specific absolute and ten-year cancer risks by PRS**

We predicted absolute risks up to age 85 years and ten-year risks of developing breast and prostate cancers by PRS distribution percentiles, assuming the estimated PRS OR follows a log-linear model across the entire PRS range (Supplementary Methods)\(^32\).

**Results**

**Study participants and genotyping**

After quality control, the analyses included 483 \(BRCA1\) (33 breast and 70 prostate cancer cases) and 1,318 \(BRCA2\) (244 breast and 141 prostate cancer cases) carriers of European ancestry (Supplementary Tables 1-2).

All SNPs from both PRS were well imputed \((r^2≥0.76; \text{Supplementary Tables 3-4, Supplementary Figures 1-2})\). Average PRS were larger for cases compared with controls (Supplementary Table 2).

**Associations with breast cancer risk**

The associations between the breast cancer PRS and male breast cancer risk for carriers are shown in Table 1 and Supplementary Tables 5-6. The PRS\(_{ER^+}\) yielded the strongest associations with overall breast cancer risk for \(BRCA1\) (OR=1.40, 95%CI = 1.07-1.83) and \(BRCA2\) (OR=1.33, 95%CI = 1.16-1.52) carriers. The PRS\(_{BC}\) resulted in nearly identical associations as the PRS\(_{ER^+}\). There was no statistically
significant evidence that the PRS_{ER^+} associations differed by country (P_{heterogeneity} \geq 0.48, Supplementary Figure 3). In the joint analysis of BRCA1 and BRCA2 carriers, men in the uppermost PRS_{ER^+} quartile had approximately twofold increased breast cancer risk (OR=2.10, 95%CI = 1.43-3.08) compared with men in the lowest quartile (Supplementary Table 6).

Most breast cancers amongst the male carriers were ER-positive (95.7%). The OR for the association between the PRS_{ER^+} and ER-positive breast cancer risk for BRCA1 carriers (OR=1.79, 95%CI = 1.30-2.48; Table 1) was somewhat higher compared to the OR for overall breast cancer. The number of ER-negative cancers was too small to assess associations with ER-negative disease. There was no statistically significant evidence for differences in the associations of any of the PRS by grade (Table 1; Supplementary Table 6).

The ability of PRS_{ER^+} to discriminate between controls and breast cancer cases was estimated as an AUC of 0.60 (95%CI = 0.51-0.69) for BRCA1 and 0.59 (95%CI = 0.55-0.63) for BRCA2 carriers.

Associations with prostate cancer risk

The estimated associations between the PRS_{PC} and prostate cancer risk for male carriers are reported in Table 2 and Supplementary Tables 5 and 7. The ORs per PRS_{PC} SD were estimated to be 1.73 (95%CI = 1.28-2.33) for BRCA1 and 1.60 (95%CI = 1.34-1.91) for BRCA2 carriers. There was no statistically significant evidence that the PRS_{PC} associations differed by country (P_{heterogeneity} \geq 0.14; Supplementary Figure 4). In the joint analysis of BRCA1 and BRCA2 carriers, men in the top PRS_{PC} quartile had a prostate cancer OR of 3.35 (95%CI = 2.06-5.42) compared with men in the lowest quartile (Supplementary Table 7).
There was a suggestion of higher risk for aggressive disease for BRCA1 carriers (Gleason score ≥7: OR=2.09, 95%CI = 1.27-3.46; Gleason score <7: OR=1.11, 95%CI = 0.70-1.77), also supported by the case-only analysis (OR=1.87, 95%CI = 1.01-3.44, P=0.05; Table 2). There were no differences in the PRS<sub>PC</sub> associations with high- or low-Gleason score among BRCA2 carriers (Table 2).

The PRS<sub>PC</sub> discriminatory ability was estimated as an AUC of 0.62 (95%CI = 0.54-0.69) for BRCA1 and 0.62 (95%CI = 0.57-0.67) for BRCA2 carriers.

Adjusting for cancer family history
Adjusting for family history of male breast cancer did not influence the PRS<sub>ER+</sub> associations with breast cancer risk (Table 1, Supplementary Table 8). However, the OR estimates were somewhat larger when adjusting for female breast cancer family history (Table 1, Supplementary Table 9).

The associations of PRS<sub>PC</sub> with prostate cancer risk remained similar after adjusting for prostate cancer family history (Table 2, Supplementary Table 10).

PRS interactions with age and gene pathogenic variants characteristics
There was little evidence for OR estimate variability with age, for both the breast and prostate cancer PRS (P<sub>LRT</sub>≥0.43; Table 3).

The PRS<sub>ER+</sub> and PRS<sub>PC</sub> ORs with breast or prostate cancer risks appeared to be larger for “class II” variant (pathogenic variants likely to yield stable mutant proteins) carriers compared with “class I” BRCA1 and BRCA2 variant carriers (Table 3). However, these differences were not statistically significant (P<sub>LRT</sub>≥0.26).
There was no statistically significant evidence that the PRS<sub>ER+</sub> (P<sub>LRT</sub>≥0.61) or PRS<sub>PC</sub> (P<sub>LRT</sub>=0.52) associations differed by the pathogenic variant location in the gene (Table 3).

**Absolute risks of developing breast and prostate cancer**

The absolute risks of developing breast cancer by age 85 years for BRCA2 carriers was predicted to be 7.7% at the 5<sup>th</sup> and 18.4% at the 95<sup>th</sup> PRS<sub>ER+</sub> distribution percentiles (Figure 1). The ten-year risks of developing breast cancer at 50 years were 0.8% at the 5<sup>th</sup> and 2.0% at the 95<sup>th</sup> PRS<sub>ER+</sub> distribution percentiles for BRCA2 carriers (Figure 2). The corresponding risks at age 75 years were 3.7% and 9.3%, respectively.

The predicted absolute risks of developing prostate cancer by age 85 years were 13.1% at the 5<sup>th</sup> and 50.4% at the 95<sup>th</sup> PRS<sub>PC</sub> distribution percentiles for BRCA1 carriers (Figure 1). The corresponding risks for BRCA2 carriers were 34.1% and 87.6%. BRCA2 carriers had ten-year risks of 2.1% and 10.1% at the 5<sup>th</sup> and 95<sup>th</sup> PRS<sub>PC</sub> percentiles at age 50 years, respectively. The corresponding risks at age 75 years were 25.5% and 77.0% (Figure 2).

**Discussion**

We evaluated the associations of the most recently developed breast and prostate cancer PRS with site-specific cancer risks in the largest case-control study of male BRCA1 and BRCA2 carriers available to date. Our findings showed that these PRS, developed using population-based data, are associated with breast and prostate cancer risks for male BRCA1 and BRCA2 carriers. Despite the modest estimated AUCs, our results demonstrate that since male carriers are already at elevated risks
of developing breast and prostate cancers, these PRS can lead to large differences in the absolute cancer risks for carriers across PRS percentiles.

Both PRS_{BC} and PRS_{ER+} were associated with larger OR estimates than PRS_{ER-} in predicting breast cancer risk, consistent with the fact that most breast cancers in men are ER-positive, including those harboring BRCA1 and BRCA2 pathogenic variants\(^\text{26}\). Similarly, when assessing associations with ER-positive breast cancer risk, PRS_{BC} and PRS_{ER+} showed the strongest associations for both BRCA1 and BRCA2 carriers. There were no differences in PRS associations by breast cancer grade.

The 147-SNP PRS_{PC}\(^\text{15}\) yielded larger per SD OR estimates than a previously evaluated 103-SNP prostate cancer PRS\(^\text{17}\). There was some evidence that PRS_{PC} may be associated with a higher OR for more aggressive disease (Gleason score \(\geq 7\)) for BRCA1 carriers. This pattern was not observed for BRCA2 carriers, who tend to develop more aggressive disease\(^\text{5}\). If this finding is replicated by larger studies, the PRS may prove to be useful in cancer prevention and surveillance by identifying BRCA1 carriers at greater risk of developing aggressive prostate cancers.

PRS associations with breast or prostate cancer risk, adjusted for family history of male breast or prostate cancer, were similar to unadjusted estimates, suggesting that cancer family history in male relatives does not alter PRS associations. Adjusting for family history of female breast cancer resulted in somewhat larger OR estimates for the breast cancer PRS compared with unadjusted estimates. This observation is consistent with male carriers being identified and recruited into our studies mostly based on their female relatives’ breast cancers.
There was little evidence supporting variability in PRS associations by age or pathogenic variant characteristics. However, larger sample sizes are required to reliably assess such differences and the current analyses were likely underpowered.

Previous studies\(^{18,33}\), suggest the magnitude of the breast cancer PRS associations are attenuated in female \textit{BRCA}1 and \textit{BRCA}2 carriers compared with associations seen in the general population\(^{21}\). As seen for female carriers, the estimated breast cancer ORs for male carriers were attenuated compared with estimates for women in the general population\(^{21}\). Similarly, the estimated prostate cancer OR estimate for male carriers was attenuated compared with population-based data\(^{15}\). Taken together, these observations suggest there is a deviation from the multiplicative model for the joint effects of \textit{BRCA}1 and \textit{BRCA}2 pathogenic variants and the PRS for both male and female carriers. These observed attenuations for \textit{BRCA}1 and \textit{BRCA}2 carriers are unlikely to be an overestimation of the effects in the general population ("winner’s curse"\(^{34}\)), as they have been validated in independent prospective cohorts\(^{21}\). The lower ORs for the breast and prostate cancer PRS in male \textit{BRCA}1 and \textit{BRCA}2 carriers, compared with the general population, may reflect a general attenuation of the effect sizes of common variants on genetic risk in the presence of a pathogenic variant in a high-risk gene\(^{35,36}\). This supposition may also explain the larger PRS ORs for \textit{BRCA}1 carriers, who are at lower risk compared to \textit{BRCA}2 carriers\(^{37}\). However, given the current study design, we cannot rule out that the observed attenuations in effect size are related to ascertainment biases. Although adjusting for family history did not change the OR estimates substantially, residual confounding may still remain. Large-scale population studies will be required to address this. If the attenuations in the PRS effect size are real, they would result in a smaller range of cancer risks for \textit{BRCA}1
and BRCA2 carriers compared to using the PRS effect sizes estimated from general population data.

Whilst breast cancer risk stratification might not currently be feasible for men in the general population, male BRCA1 and BRCA2 carriers may represent a group likely to benefit from a more refined stratification of their individual breast and prostate cancer risks, to better inform their clinical management. At present, limited recommendations based on low-level evidence or expert opinion are available for male carriers. Current guidelines recommend clinical breast examinations beginning at ages 30-35 years and suggest mammographic screening on an individual basis, whereas clinical prostate cancer screening, particularly for BRCA2 carriers, is recommended from ages 40-45 years\(^{38-40}\).

The PRS percentile-specific absolute risks varied substantially over the PRS distribution, consistent with previous studies in male\(^{17}\) and female\(^{16,18}\) BRCA1 and BRCA2 carriers. At least twofold increased risk is often considered a clinically actionable level for breast and prostate cancers\(^{41}\). Our findings may inform the development of age-specific clinical recommendations and provide guidance on when to start risk-adapted screening, based on their PRS percentile-specific ten-year risks. Overall, refined risk estimates may be useful to distinguish male carriers at higher risk, who may benefit from enhanced and/or earlier screening; and identify carriers at lower risk, who may opt for more limited or postponed surveillance. Identification of men at lower risk of prostate cancer by PRS stratification has been shown to be useful in reducing overdiagnosis in the general population, resulting in a reduction in the harms associated with prostate-specific antigen (PSA) testing\(^{42}\). Similar arguments may apply to male carriers, in whom PRS prediction may further improve screening efficacy.
Strengths of this study include the fact that this is an independent validation of the most recently derived breast\(^{21}\) and prostate\(^{15}\) cancer PRS derived from population-based data. We benefitted from the availability of Gleason scores and breast cancer ER-status and grade; hence, we could assess subtype-specific associations. Finally, we assumed recent prospectively estimated prostate cancer incidence rates\(^{5}\) to predict absolute prostate cancer risks, which may be more representative of risks for carriers currently seen in clinical genetics centers.

Study limitations include the limited sample size to assess PRS associations with cancer risks for subgroups of male carriers. However, these data remain the largest male \(BRCA1\) and \(BRCA2\) carrier case-control study with available genotype data. The breast\(^{21}\) and prostate\(^{15}\) cancer PRS do not include male breast cancer-specific risk associated SNPs or SNPs which may specifically be associated with prostate cancer risk for carriers. If such SNPs exist, further improvement may be gained in risk prediction by including them in PRS. The absolute risk calculations assumed that the PRS OR behaves log-linearly over the PRS range. It was difficult to evaluate this assumption in the present analyses due to the limited sample size of male carriers. However, empirical evidence based on larger sample sizes of female carriers\(^{18}\) or in the general population\(^{15,21}\) suggests that this assumption is plausible. Additionally, the absolute breast and prostate cancer risk predictions by PRS will require validation in large prospective studies of male carriers with long-term follow-up, although such studies remain a challenge. Finally, the PRS that we investigated were derived using European ancestry data, hence our estimated associations and predicted risks may not be applicable to non-European ancestry carriers.

PRS are now used in cancer risk-stratified screening trials and implementation studies in the general population\(^{43-47}\). They are commercially
available and are used in multifactorial cancer risk prediction models for women\textsuperscript{48,49}. We found that PRS derived from population-based data are associated with breast and prostate cancer risks and lead to meaningful risk stratification for male carriers. These findings may potentially be used to provide more personalized cancer risk predictions and therefore assist clinical management decisions. Future implementation studies should determine if optimal strategies exist for incorporating these PRS into genetic counselling and risk assessment to clarify whether they can influence the clinical management decisions of male \textit{BRCA1} or \textit{BRCA2} carriers.

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**Data Availability**
The complete dataset is not publicly available due to restraints imposed by the ethical committees of individual studies. Requests to access the complete dataset which is subject to GDPR rules can be made to the Data Access Coordinating Committee (DACC) of CIMBA, following the process described on the CIMBA website (http://cimba.ccge.medschl.cam.ac.uk/projects/data-access-requests/). Submitted applications are reviewed by the CIMBA DACC every three months.

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### Tables

**Table 1.** Breast cancer PRS associations with breast cancer risk for BRCA1 and BRCA2 carriers.

| PRS investigated and outcome | No. of Controls | No. of Cases | OR (95% CI) | P<sup>a</sup> | No. of Controls | No. of Cases | OR (95% CI) | P<sup>a</sup> |
|-----------------------------|-----------------|--------------|-------------|--------------|-----------------|--------------|-------------|--------------|
| **PRS<sub>BC</sub>** association with breast cancer risk |                 |              |             |              |                 |              |             |              |
| Continuous<sup>b</sup>                | 380             | 33           | 1.40 (1.06-1.85) | 0.02        | 933             | 244         | 1.32 (1.15-1.52) | <0.001       |
| Continuous: adjusted for male relative breast cancer FH<sup>c</sup> | 380             | 33           | 1.39 (1.05-1.84) | 0.02        | 933             | 244         | 1.33 (1.15-1.52) | <0.001       |
| Continuous: adjusted for female relative breast cancer FH<sup>c</sup> | 380             | 33           | 1.44 (1.07-1.95) | 0.02        | 933             | 244         | 1.36 (1.18-1.57) | <0.001       |
| **PRS<sub>BC</sub>** association with grade-specific breast cancer risk<sup>d</sup> |                 |              |             |              |                 |              |             |              |
| Controls                      | 380             | --           | 1.00 (reference) |             | 933             | --           | 1.00 (reference) |             |
| Grade 1                       | --              | 1            | 1.03 (0.63-1.67)<sup>g</sup> | 0.92        | --              | 11           | 1.33 (0.74-2.36) | 0.34         |
| Grade 2                       | --              | 6            | 1.17 (0.63-2.17)<sup>g</sup> | 0.92        | --              | 68           | 1.29 (1.04-1.60) | 0.02         |
| Grade 3                       | --              | 12           | 1.56 (1.03-2.37) | 0.04        | --              | 98           | 1.23 (1.00-1.50) | 0.05         |
| Grade unknown                 | --              | 14           | 1.47 (0.93-2.32) | 0.10        | --              | 67           | 1.51 (1.18-1.93) | 0.001        |
| Case-only: grade 1+2 vs grade 3<sup>e</sup> | 7               | 12           | 6.30 (0.88-44.87) | 0.07        | 79              | 98           | 0.95 (0.71-1.27) | 0.73         |
| **PRS<sub>ER</sub>-** association with breast cancer risk |                 |              |             |              |                 |              |             |              |
| Continuous<sup>b</sup>                | 380             | 33           | 1.12 (0.79-1.59) | 0.52        | 933             | 244         | 1.23 (1.07-1.41) | 0.004        |
| Continuous: adjusted for male relative breast cancer FH<sup>c</sup> | 380             | 33           | 1.12 (0.79-1.59) | 0.53        | 933             | 244         | 1.23 (1.07-1.42) | 0.004        |
| Continuous: adjusted for female relative breast cancer FH<sup>c</sup> | 380             | 33           | 1.14 (0.80-1.63) | 0.48        | 933             | 244         | 1.25 (1.09-1.45) | 0.002        |
| **PRS<sub>ER</sub>-** association with ER-specific breast cancer risk<sup>f</sup> |                 |              |             |              |                 |              |             |              |

*Note:* FH = family history, PRS = polygenic risk score, OR = odds ratio, CI = confidence interval, P = p-value.
a P value was calculated using a 2-sided Wald test. \( \text{PRS}_{\text{BC}} \) = overall breast cancer \( \text{PRS} \); \( \text{PRS}_{\text{ER}} \) = \( \text{ER} \)-negative breast cancer \( \text{PRS} \); \( \text{PRS}_{\text{ER}+} \) = \( \text{ER} \)-positive breast cancer \( \text{PRS} \); \( \text{FH} \) = family history; \( \text{OR} \) = odds ratio per \( \text{PRS} \) standard deviation, estimated from a multinomial logistic regression (unless otherwise stated); \( \text{CI} \) = confidence interval.
The continuous test shows the per PRS standard deviation associations, estimated from a multinomial logistic regression model assuming a continuous PRS.

Association estimates adjusted for family history of (male and female) breast cancer in first- and second-degree relatives. FH was coded as no family history, one or more relative diagnosed with breast cancer, unknown FH or missing FH. Supplementary Table 8 (male breast cancer FH adjusted) and Supplementary Table 9 (female breast cancer FH adjusted) describe the breast cancer FH adjusted analyses in greater detail.

The breast cancer grade specific ORs were estimated by partitioning breast cancer status into multinomial outcomes for grade 1, grade 2, grade 3, or grade unknown.

The case-only breast cancer grade analysis was a logistic regression considering grade 1 and grade 2 breast cancers combined as “controls” and grade 3 breast cancers as “cases”.

The ER-specific breast cancer ORs were estimated by partitioning breast cancer status into distinct multinomial outcomes for ER-negative, ER-positive, or ER-status unknown.

Grade 1 and grade 2 combined for BRCA1 carriers (to ensure adequate sample size to estimate associations).
Table 2. Prostate cancer PRS associations with prostate cancer risk for BRCA1 and BRCA2 carriers.

| PRS investigated and outcome | BRCA1 carriers | BRCA2 carriers |
|-----------------------------|----------------|---------------|
|                             | No. of Controls | No. of Cases | OR (95% CI) | P<sup>a</sup> | No. of Controls | No. of Cases | OR (95% CI) | P<sup>a</sup> |
| Continuous<sup>b</sup>      | 380            | 70           | 1.73 (1.28-2.33) | <0.001 | 933            | 141          | 1.60 (1.34-1.91) | <0.001 |
| Continuous: adjusted for FH<sup>c</sup> | 380 | 70 | 1.74 (1.29-2.35) | <0.001 | 933 | 141 | 1.59 (1.32-1.90) | <0.001 |
| PRS<sub>PC</sub> association with Gleason score (GS) specific prostate cancer risk<sup>d</sup> | | | | |
| Controls                    | 380            | --           | 1.00 [reference] | 933 | -- | 1.00 [reference] | |
| GS < 7                      | --             | 26           | 1.11 (0.70-1.77) | 0.66 | -- | 27 | 1.83 (1.29-2.58) | <0.001 |
| GS ≥ 7                      | --             | 21           | 2.09 (1.27-3.46) | 0.004 | -- | 82 | 1.68 (1.32-2.13) | <0.001 |
| GS unknown                  | --             | 23           | 2.38 (1.49-3.80) | <0.001 | -- | 32 | 1.26 (0.95-1.68) | 0.11 |
| Case-only analysis: GS ≥ 7 vs GS < 7<sup>e</sup> | 26 | 21 | 1.87 (1.01-3.44) | 0.05 | 27 | 82 | 0.93 (0.63-1.37) | 0.72 |

<sup>a</sup> P value was calculated using a 2-sided Wald test. PRS<sub>PC</sub> = prostate cancer PRS; GS = Gleason score; FH = family history. OR = odds ratio per PRS standard deviation, estimated from a multinomial logistic regression (unless otherwise stated); CI = confidence interval.

<sup>b</sup> The continuous test shows the per PRS standard deviation associations, estimated from a multinomial logistic regression model assuming a continuous PRS.

<sup>c</sup> Association estimates adjusted for family history of prostate cancer in first- and second-degree relatives. FH was coded as no family history, one or more diagnosed relative, unknown FH or missing FH. Supplementary Table 10 describes the prostate cancer FH adjusted analyses in greater detail.

<sup>d</sup> The Gleason score prostate cancer ORs were estimated by partitioning prostate cancer status into distinct multinomial outcomes for GS < 7, GS ≥ 7, or GS unknown.
The case-only prostate cancer analysis was a logistic regression considering GS < 7 prostate cancers as "controls" and GS ≥ 7 prostate cancers as "cases".
Table 3. PRS interactions with age and BRCA1 and BRCA2 pathogenic variant characteristics for BRCA1 and BRCA2 carriers with breast cancer risk and prostate cancer risk.

| Model and Category | Breast cancer (PRS<sub>ER+</sub>)<sup>a</sup> | Prostate cancer (PRS<sub>PC</sub>) |  |
|-------------------|-------------------------------------------|---------------------------------|---|
|                   | BRCA1 carriers | BRCA2 carriers | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| PRS x Age interaction<sup>c</sup> | | | 1.88 (0.68-5.18) | 0.22 | 1.34 (0.71-2.53) | 0.37 | 0.64 (0.20-2.04) | 0.45 | 2.03 (0.91-4.52) | 0.08 |
| PRS                | 1.00 (0.98-1.01) | 0.56 | 1.00 (0.99-1.01) | 0.98 | 1.02 (1.00-1.03) | 0.09 | 1.00 (0.98-1.01) | 0.55 |
| PRS x Age          | 0.90 | 0.86 | 0.43 | 0.79 |  |
| Gene pathogenic variant class<sup>e</sup> | | | 1.38 (1.03-1.84) | 0.03 | 1.31 (1.13-1.52) | <0.001 | 1.57 (1.13-2.19) | 0.008 | 1.57 (1.31-1.89) | <0.001 |
| Class I            | 1.71 (0.72-4.07) | 0.23 | 1.39 (0.67-2.86) | 0.38 | 3.00 (1.36-6.60) | 0.006 | 2.04 (0.63-6.55) | 0.23 |
| Class II           | 0.76 | 0.69 | 0.26 | 0.97 |  |
| BRCA1 pathogenic variant location (OCCR) | | | 1.50 (1.00-2.26) | 0.05 | NA | NA | NA | NA |  |
| 5' to c.2281       | 1.17 (0.79-1.72) | 0.44 | NA | NA | NA | NA | NA |  |
| c.2282 to c.4071   | 1.61 (0.87-2.98) | 0.13 | NA | NA | NA | NA | NA |  |
| c.4072 to 3'       | 0.85 |  |
| BRCA2 pathogenic variant location (OCCR) | | | 1.43 (1.09-1.88) | 0.009 | NA | NA | NA | NA |  |
| 5' to c.2830       | NA | 1.24 (0.99-1.55) | 0.06 | NA | NA | NA | NA |  |
| c.2831 to c.6401   | NA | 1.33 (1.04-1.70) | 0.02 | NA | NA | NA | NA |  |
| c.6402 to 3'       | 0.61 |  |
| BRCA2 pathogenic variant location (PCCR) | | | 1.67 (1.06-2.62) | 0.03 | 1.77 (1.07-2.95) | 0.03 | 1.49 (1.18-1.89) | <0.001 | 1.76 (1.24-2.50) | 0.002 |
| 5' to c.755        | NA | NA | NA | NA | NA | NA | NA |  |
| c.756 to c.1000    | NA | NA | NA | NA | NA | NA | NA |  |
| c.1001 to c.7913   | NA | NA | NA | NA | NA | NA | NA |  |
| c.7914 to 3'       | 0.52 |  |
The associations with breast cancer risk are reported for the ER-positive breast cancer PRS (PRS<sub>ER+</sub>). OR = odds ratio per PRS standard deviation, estimated from a multinomial logistic regression; CI = confidence interval; OCCR = ovarian cancer cluster region; PCCR = prostate cancer cluster region.

b P value was calculated using a 2-sided Wald test, unless otherwise indicated.

c The PRS term is applicable at age 0-years and the PRSxAge interaction term is a per-year effect. Age in years.

d P values were calculated using a 2-sided likelihood ratio test. The likelihood ratio test compared the model that estimated the interaction term with a nested model that omitting the interaction term.

e “Class I” pathogenic variant = loss-of-function pathogenic variants expected to result in unstable or no protein; “class II” pathogenic variant = pathogenic variants likely to yield stable mutant proteins.
Figure Legends

Figure 1: The predicted absolute risks of developing breast cancer and prostate cancer by PRS percentile. Risks were calculated assuming the per SD OR estimates in the combined sample of \textit{BRCA1} and \textit{BRCA2} carriers (Tables 1 and 2). (A) The absolute risks of developing breast cancer for \textit{BRCA2} carriers by PRS\textsubscript{ER+} percentiles. (B) The absolute risks of developing prostate cancer for \textit{BRCA1} carriers by PRS\textsubscript{PC} percentiles. (C) The absolute risks of developing prostate cancer for \textit{BRCA2} carriers by PRS\textsubscript{PC} percentiles. PRS\textsubscript{ER+} = ER\textsuperscript{+}-positive breast cancer PRS.

Figure 2: The predicted ten-year risks of developing breast cancer and prostate cancer by PRS percentile. Ten-year risks were calculated from the absolute risks of developing breast cancer or prostate cancer (Figure 1). (A) The ten-year risks of developing breast cancer for \textit{BRCA2} carriers by PRS\textsubscript{ER+} percentiles. (B) The ten-year risks of developing prostate cancer for \textit{BRCA1} pathogenic variant carriers by PRS\textsubscript{PC} percentiles. (C) The ten-year risks of developing prostate cancer for \textit{BRCA2} pathogenic variant carriers by PRS\textsubscript{PC} percentiles. PRS\textsubscript{ER+} = ER\textsuperscript{+}-positive breast cancer PRS.
Figure 1

(A) BRCA2 carriers: absolute risk of breast cancer (PRS_{ER+})

(B) BRCA1 carriers: absolute risk of prostate cancer

(C) BRCA2 carriers: absolute risk of prostate cancer

50th (median) percentile
10th and 90th percentiles
5th and 95th percentiles
Figure 2

(A) BRCA2 carriers: ten-year risk of breast cancer (PRS_{ER+})

(B) BRCA1 carriers: ten-year risk of prostate cancer

(C) BRCA2 carriers: ten-year risk of prostate cancer

Ten-year risk (%) vs Age (years)