

Polygenic Risk Score Enhances Comprehensive Breast Cancer Risk Assessment and Modifies Clinical Actionability in Carriers of a Pathogenic Variant

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Abstract

Purpose

Breast cancer risk varies widely among women with a pathogenic variant (PV) in a breast cancer susceptibility gene; however, follow-up and prevention strategies are often homogeneous. Polygenic risk scores (PRS) may refine risk stratification. We evaluated changes in breast cancer risk categories and clinical actionability after incorporating PRS into classical risk factors in unaffected carriers.

Methods

This nationwide multicenter study conducted across Spain included unaffected women carrying a germline PV in a breast cancer susceptibility gene. Ten-year and lifetime breast cancer risk categories were estimated using the BOADICEA model before and after incorporation of the PRISMA-268 PRS. Risk categories were defined according to the NICE thresholds. The primary outcome was change in breast cancer risk category and clinical actionability.

Results

Among 1,205 women, 577 were non-*BRCA1/2* carriers and 628 were *BRCA1/2* carriers. PRS incorporation resulted in lifetime-risk reclassification in 31% of non-*BRCA1/2* carriers compared with 12% of *BRCA1/2* carriers. After PRS integration, 29%, 35%, and 36% of non-*BRCA1/2* carriers were classified as having average, moderate, and high lifetime breast cancer risk, respectively. At age 30 years, 61% of non-*BRCA1/2/PALB2* carriers would be eligible to initiate breast cancer surveillance.

Conclusions

Incorporating PRS into multifactorial breast cancer risk assessment significantly modifies risk stratification, particularly among non-*BRCA1/2/PALB2* carriers, and provides clinically relevant information to guide personalized prevention and screening strategies.

Introduction

Breast cancer is a multifactorial disease resulting from the complex interplay between genetic susceptibility and non-genetic risk factors. Established non-genetic determinants include age, body mass index, alcohol consumption, reproductive and hormonal exposures, mammographic breast density, and oncological family history. Genetic breast cancer susceptibility comprises both rare monogenic PVs^{1–8} and the cumulative effect of multiple common low-risk single nucleotide polymorphisms (SNPs) quantified in a PRS as a weighted sum of risk alleles.^{9–11} PVs in monogenic high-penetrance genes such

as *BRCA1* and *BRCA2* confer lifetime risks that frequently exceed 50%.^{12,13} In contrast, PVs in other breast cancer susceptibility genes, including *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D* and *BARD1*, are generally associated with lower lifetime risks, often in the range of 20%–30%.^{12,13} Even in the absence of a monogenic PV, women in the highest percentiles of the PRS distribution may reach lifetime risks exceeding 30%, approaching those observed in carriers of high-penetrance monogenic PVs in breast cancer susceptibility genes.

Historically, management of high- and moderate-penetrance gene carriers has relied largely on gene-specific average lifetime risk estimates, frequently resulting in uniform surveillance and prevention strategies. However, recent advances in risk prediction models have enabled more accurate multifactorial risk assessment, and contemporary guidelines increasingly advocate for individualized risk estimation incorporating polygenic and non-genetic risk factors to refine risk stratification and guide clinical management.^{14–17}

Current National Institute for Health and Care Excellence (NICE)¹⁸ guidelines stratify women into average-, moderate-, and high-risk categories according to estimated 10-year and lifetime breast cancer risk thresholds, with risk category informing recommendations for surveillance and preventive strategies. Consequently, changes in an individual's estimated risk may result in reclassification across risk categories and potentially influence clinical management, including eligibility for preventive interventions such as endocrine risk-reduction therapy in women with an estimated 10-year breast cancer risk greater than 5%.^{19,20} Multifactorial risk prediction models, such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA), integrate genetic and non-genetic risk factors within the CE-marked medical device CanRisk to generate individualized risk estimates, and have been validated in the general population and among *BRCA1/2* PV carriers.^{21,22} However, the potential impact of multifactorial risk assessment, particularly following incorporation of the PRS, remains less clearly defined among carriers of a moderate-penetrance PV.

Based on our previous work demonstrating that incorporation of mammographic density and the PRISMA-268 PRS into the BOADICEA model reclassified breast cancer risk categories in approximately one-third of women with a family history of breast cancer who were not carriers,²³ we sought to evaluate the impact of the PRS integration on risk stratification among unaffected carriers of breast cancer susceptibility genes (*BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, and *BARD1*). Specifically, we assessed reclassification across NICE risk thresholds for both 10-year and lifetime breast cancer risk estimates and explored the potential clinical implications of such reclassification for personalized screening and prevention strategies.

Materials and Methods

Study design and participants

This multicenter study was conducted in 17 centers across Spain. Participants were consecutively recruited from cancer genetics clinics between June 2023 and January 2026. Eligible participants were women aged 30–70 years with no personal history of cancer who carried a germline pathogenic or likely pathogenic variant in a breast cancer susceptibility gene, including *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, and *BARD1*.

Written informed consent was obtained at the inclusion visit. Baseline clinical and genetic information was collected at the inclusion visit or extracted from existing medical records when already available. In addition, a new blood sample was obtained for genotyping of the PRISMA-268 PRS.

PRS genotyping

PRISMA-268 PRS genotyping was performed using TaqMan OpenArray (ThermoFisher Scientific). The CanRisk tool has been adapted to incorporate PRISMA-268 PRS into breast cancer risk prediction, which comprises 231 SNPs and 37 surrogates in high linkage disequilibrium ($r^2 > 0.9$) with variants from the PRS313.^{23–25} Samples with call rates below 80% were excluded from the analysis.

Data collection

Variables collected included age, weight, height, alcohol consumption, age at menarche, menopausal status and age at menopause when applicable, parity, oral contraceptive use, hormone replacement therapy, mammographic breast density, family history of cancer, carrier status for pathogenic or likely PVs in breast cancer susceptibility genes and PRISMA-268 PRS.

Breast density was classified according to the Breast Imaging Reporting and Data System (BI-RADS) of the American College of Radiology (ACR). For women younger than 40 years without available mammographic breast density information, BI-RADS category C was assumed.²⁶

Breast cancer risk estimation

Individual breast cancer risk estimates were calculated using the CanRisk tool, incorporating all available non-genetic risk factors, country of residence (Spain), family history information, monogenic PV, and the PRISMA-268 PRS.

Risk estimates were first calculated without the PRS and subsequently updated after PRS incorporation. Participants were classified into average-, moderate-, or high-risk categories based on their 10-year and lifetime (ages 20–80 years) breast cancer risk estimates using NICE guidelines thresholds (< 3%, 3%–8%, and > 8% for 10-year risk; <17%, 17%–30%, and > 30% for lifetime risk).¹⁸

Study outcomes

The primary outcome was the proportion of participants whose breast cancer risk category changed after incorporation of the PRS into the multifactorial risk assessment model. Secondary outcomes included changes in breast cancer surveillance and risk reducing recommendations following the incorporation of the PRS, as measures of clinical actionability.

Statistical analysis

A descriptive analysis of all included variables in the study was performed. Continuous variables were expressed as median and interquartile range (IQR); categorical variables were expressed as absolute values and percentages. Differences in sociodemographic characteristics across PV types were assessed using the Kruskal–Wallis test for continuous variables, Fisher’s exact test for nominal categorical variables, and ordered logistic regression for ordinal categorical variables (R function *polr*). To assess whether the incorporation of PRS information resulted in significant changes in breast cancer risk categories, Fisher’s exact test was used. No clinical data imputation was performed. All statistical analyses were performed using R statistical software version 4.4.0.

Ethical considerations

All participants provided written informed consent. The study was approved by the Vall d’Hebron Hospital Ethics Committee (PR(AG)516/2019) and by the ethics committee of each participating institution.

Results

Study population

A total of 1,205 women were included in the study, of whom 96% were of European ancestry. PV carriers were distributed as follows: *BRCA2* (n = 378; 31%), *BRCA1* (n = 250; 21%), *ATM* (n = 214; 18%), *PALB2* (n = 138; 11%), *CHEK2* (n = 120; 10%), *RAD51C* (n = 56; 5%), *RAD51D* (n = 24; 2%), and *BARD1* (n = 25; 2%). The median age at enrollment was 46 years (IQR, 38–54). Overall, 44% of participants were premenopausal, and 32% were nulliparous. Breast density was predominantly classified as BI-RADS categories B (38%) and C (47%). The median PRS z-score was 0.226 (range, -3.418 to 3.960) (*Table 1*).

BRCA1/2 carriers

Among *BRCA1/2* carriers (n = 628), median estimated lifetime risk after incorporation of the PRS was 63% in *BRCA1* (IQR 50–73) and 47% in *BRCA2* (IQR 33–59) (*Fig. 1, Supplementary Fig. 1*). In a stepwise lifetime risk analysis in which breast density and the PRS were sequentially added to classical risk factors, these two variables substantially widened risk stratification (*Supplementary Fig. 2*). Following PRS integration, 1% of *BRCA1* carriers were classified as average risk, 3% were classified as moderate risk, and 96% as high risk. Among *BRCA2* carriers, 2% were classified as average risk, 17% as moderate

risk, and 81% as high risk (*Table 2*). Incorporation of the PRS resulted in a change in lifetime risk category in 12% of *BRCA1/2* carriers, with their risk category increasing in 3% ($n = 16$) and decreasing in 9% ($n = 55$) (Figs. 2 and 3A). Reclassification of lifetime risk category was more frequent among *BRCA2* carriers (17%) than among *BRCA1* carriers (4%) (Fig. 3A and *Supplementary Table 2*).

For 10-year breast cancer risk, the PRS incorporation resulted in a change in risk category in 11% of *BRCA1/2* carriers, with risk increasing in 2% ($n = 12$) and decreasing in 9% ($n = 56$) (Figs. 2 and 3B). Reclassification was more frequent among *BRCA2* carriers (15%) than *BRCA1* carriers (5%), driven by downward reclassification (Fig. 3B and *Supplementary Table 3*). As risk reclassification at younger ages is expected to have greater clinical actionability, we performed an additional analysis among the 241 women aged 30–40 years. Within this subgroup, 80% were classified as high 10-year risk and would be candidates for magnetic resonance imaging (MRI)-based surveillance and/or risk-reducing mastectomy, whereas 18% and 2% were classified as moderate- and average-risk, respectively, potentially allowing de-intensification of screening or avoidance of prophylactic mastectomy.

Non- *BRCA* carriers

In non-*BRCA1/2* carriers ($n = 577$), lifetime breast cancer risk estimates varied substantially following incorporation of the PRS (Fig. 1 and *Supplementary Fig. 1*). The median lifetime risk for *PALB2* heterozygous carriers was 42% (IQR, 30–55). Lower median risk estimates were observed among carriers of *ATM* (21%, IQR 14–30), *CHEK2* (21%, IQR 14–33), *RAD51D* (18%, IQR 12–28), *BARD1* (17%, IQR 13–22), and *RAD51C* (15%, IQR 10–25).

The majority (73%) of *PALB2* heterozygous carriers were classified as high risk. In contrast, among carriers of moderate-penetrance genes, only 24%, 31%, 14%, 25%, and 20% of *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, and *BARD1* carriers, respectively, were classified as high risk. A substantial proportion of carriers were categorized as average risk, including 34%, 32%, 55%, 46%, and 48% of *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, and *BARD1* carriers, respectively (*Table 2*).

In a univariate analysis, we observed statistically significant differences in mean PRS, the proportion of women with high breast density, and first-degree family history of breast cancer between women in the lowest and highest 15% of lifetime risk estimates among *BRCA1/2*, *PALB2*, *ATM* and *CHEK2* heterozygous carriers (*Supplementary Table 1*).

Like *BRCA1/2* carriers, the addition of breast density and the PRS progressively increased the spread of predicted lifetime breast cancer risks compared with the baseline assessment (*Supplementary Fig. 2*).

Overall, after PRS integration, 29% of women were classified as average risk, 35% as moderate risk, and 36% as high risk based on lifetime breast cancer risk estimates (*Table 2*). Incorporation of the PRS resulted in a change in lifetime risk category in 31% of participants, with risk increasing in 17% ($n = 99$) and decreasing in 14% ($n = 78$) (Figs. 2 and 3A). Lifetime risk reclassification was most frequent among

RAD51D (37%) and *ATM* (36%) carriers, followed by *CHEK2* (33%), *BARD1* (32%), *RAD51C* (27%), and *PALB2* (20%) carriers (Figs. 3A and Supplementary Table 2).

For 10-year breast cancer risk, incorporation of the PRS resulted in a change in risk category in 27% of participants, with risk increasing in 12% ($n = 67$) and decreasing in 15% ($n = 88$) (Figs. 2 and 3B). Reclassification was most frequent among *RAD51D* carriers (34%), followed by *RAD51C* (32%), *BARD1* (28%), *PALB2* and *ATM* (26% each), and *CHEK2* (25%). Both upward and downward shifts in risk category were observed in all gene groups (Fig. 3B and Supplementary Table 3).

Because *PALB2* carriers exhibited substantially higher risk estimates than carriers of moderate-penetrance genes, clinical actionability was evaluated separately for this subgroup. In the baseline assessment, 75% of *PALB2* heterozygous carriers were classified as being at a high 10-year risk category. Following incorporation of the PRS, this proportion decreased to 65% (Table 2 and Supplementary Table 3). Specifically, among the 47 women aged 30–40 years carrying a *PALB2* PV, 53% were classified as high risk based on their 10-year breast cancer risk, whereas 38% and 9% were classified as moderate- and average-risk, respectively, and may be eligible for less intensive screening and/or avoidance of risk-reducing mastectomy before age 40.

Among the remaining 439 carriers of moderate-risk susceptibility genes (*ATM*, *CHEK2*, *RAD51C*, *RAD51D*, and *BARD1*), baseline assessment classified 64 (15%) women as high risk, 279 (63%) as moderate risk, and 96 (22%) as average risk. After inclusion of the PRS, 89 (20%) were classified as high risk, 227 (52%) as moderate risk, and 123 (28%) as average risk. Of these 439 carriers, 109 (25%) were aged 30–40 years. In this subgroup, 61% ($n = 66$) exceeded a 3% 10-year breast cancer risk threshold following incorporation of the PRS, and 14% ($n = 15$) had a 10-year risk $> 8\%$. In terms of clinical actionability, 61% of these women would be eligible to initiate breast cancer surveillance at age 30, and 14% would qualify for MRI-based screening.

Implications for endocrine risk-reduction therapy

To evaluate the potential impact of integrating the PRISMA-268 PRS on recommendations for preventive endocrine risk-reduction therapy, we assessed the proportion of women aged 35–59 years whose estimated 10-year breast cancer risk exceeded the 5% threshold, consistent with ASCO recommendations²⁰ to discuss endocrine risk-reduction therapy with women in this age group who are at increased risk of breast cancer. The analysis included 744 non-carriers with a family history of breast cancer from the previously reported PRISMA-I²³ cohort and 238 carriers of *ATM* or *CHEK2* PVs from the present cohort. With the full risk assessment, 177 (24%) non-carriers and 128 (54%) carriers were classified as eligible for preventive endocrine therapy.

Discussion

This large multicenter study, including 1,205 unaffected women carrying a PV in a breast cancer susceptibility gene, evaluated the impact in clinical recommendations of incorporating the PRISMA-268

PRS into the multifactorial breast cancer risk prediction model BOADICEA. Our findings demonstrate that the addition of the PRS significantly refines breast cancer risk estimation and may influence risk-based surveillance recommendations, particularly among non-*BRCA1/2* carriers.

Over the past decade, efforts have been invested in investigating if addition of the PRS analysis modifies breast cancer risk in carriers of a PV in a breast cancer susceptibility gene.^{27,28} Several studies have shown that integrating monogenic, polygenic, and other risk factors within multifactorial risk prediction models improves risk stratification and may lead to clinically meaningful changes in screening recommendations.^{29–31} Importantly, Schreurs et al. demonstrated that the sequential incorporation of questionnaire-based risk factors, mammographic breast density and PRS resulted in successive and additive changes in risk stratification and thus, surveillance recommendations among women from germline *1100delC CHEK2* families, highlighting the incremental contribution of each component to risk stratification. However, data on the clinical impact of comprehensive multifactorial risk assessment incorporating monogenic PVs, family history, mammographic breast density, and polygenic risk across a broad range of breast cancer susceptibility genes remain limited. Our study extends this evidence by evaluating more than 1,200 unaffected carriers across high- and moderate-penetrance genes using a comprehensive risk assessment and by examining its potential implications for screening and preventive interventions. Among women carrying a germline PV in *BRCA1* incorporation of the PRS resulted in limited reclassification, but not in *BRCA2* PV carriers. For instance, 15% of *BRCA2* carriers had a change in their lifetime risk category with the addition of PRS with the multifactorial assessment, and most shifted downwards. More specifically in the range between 30 and 40 years, 32% were classified as having moderate or average risk. Given that decisions regarding intensive breast cancer surveillance and risk-reducing surgery are frequently initiated during this period of life,^{17,32} these findings may be particularly relevant for individualized risk counseling. If prospective validation confirms the calibration of these estimates, both age of onset of MRI-based surveillance or risk-reducing mastectomy could be delayed. Of note, the threshold for the high-risk category was defined as a lifetime breast cancer risk of 30% according to NICE guidelines, whereas US guidelines typically use a lower threshold ($\geq 20\%$) to recommend annual breast MRI screening. Consequently, a greater proportion of women may be considered eligible for MRI surveillance in the US.^{33,34}

Counseling women carrying a PV in a moderate-penetrance breast cancer susceptibility gene has historically been challenging because of the substantial heterogeneity in breast cancer risk estimates, tumor characteristics, and age-specific cancer risks.^{12,13,35} This uncertainty has translated into variability in recommendations regarding the age at initiation of screening and the use of risk-reducing interventions. Consequently, current international guidelines recommend incorporating multifactorial risk assessment to support personalized clinical management.^{14–16,36,37} Our findings strongly support this approach, demonstrating a wide distribution of both lifetime and 10-year breast cancer risk estimates among *ATM*, *CHEK2*, *RAD51C*, *RAD51D*, and *BARD1* PV carriers. The wide distribution captured by comprehensive risk assessment can be nicely illustrated by the distribution of *CHEK2* carriers across all risk categories following incorporation of the PRS. For lifetime risk, approximately one-third of women

were classified as average-, one-third as moderate-, and one-third as high-risk, respectively. Therefore, incorporation of the PRS may be of utmost relevance to avoid both over- and under-management by providing a more accurate assessment of individual breast cancer risk.

Another clinically relevant application of individualized risk assessment concerns women aged 30 to 40 years carrying a PV in a moderate-penetrance gene, for whom recommendations regarding the initiation of breast cancer screening remain uncertain. In our study, 61% of women in this age group had a 10-year breast cancer risk of at least 3%, the NICE threshold used to define moderate risk and guide recommendations to start screening with annual mammography, while 14% had a 10-year risk of 8% or greater and met criteria to start with annual MRI.

Our study and others demonstrate that carriers of a PV in the same susceptibility gene do not constitute a homogeneous risk group and may have markedly different risk profiles. This concept is further supported by the observation that women heterozygous for a PV in *BRCA1/2*, *PALB2*, *ATM*, and *CHEK2* at the extremes of the lifetime risk distribution differed significantly in the frequency of high mammographic breast density, family history of breast cancer, and mean PRS. The characterization of women with the lowest and highest lifetime risk estimates highlights the contribution of these factors and reinforces the importance of their systematic assessment in clinical practice. Detailed collection of family history, mammographic breast density, and obtaining polygenic risk should therefore be considered an essential component of individualized breast cancer risk assessment.

Incorporation of the PRS also substantially influenced eligibility for endocrine risk-reduction therapy. Preventive endocrine medications for breast cancer have shown to be effective,^{38–41} and ASCO guidelines recommend offering them in women whose breast risk exceeds 5% in the next 10 years.²⁰ Comprehensive risk assessment including the PRS identified 25% of women with family history and nearly half of the *ATM* and *CHEK2* carriers included in this study as eligible candidates for endocrine risk-reduction therapy, while indicating that many carriers of these genes would not meet treatment thresholds.

This study has several strengths, including its large sample size, collection of mammographic breast density among the non-genetic risk factors, and comprehensive gene-specific analysis. However, several limitations should be acknowledged. First, the PRISMA-268 PRS was originally developed in women of European ancestry, and its performance may slightly vary in multiethnic populations. Second, prospective validation of the calibration and discrimination of the BOADICEA algorithm with the PRS integration in our cohort is ongoing, and clinical implementation should therefore be approached with caution until this data becomes available. Moreover, although our findings support the potential value of individualized risk assessment, the effectiveness of clinical interventions aligned to PRS-based risk-stratified breast cancer screening programs remains to be demonstrated in prospective randomized clinical trials.^{42–44} Finally, the behavioral impact of PRS-informed risk disclosure requires further investigation. These ongoing studies will be critical to determine whether PRS-guided risk stratification

translates into improved clinical outcomes and will support its implementation in routine clinical practice.

In conclusion, these findings demonstrate that carriers of a PV in the same susceptibility gene can have markedly different risk profiles. Risk estimates based solely on average gene-specific risks and age may be inadequate and could lead to inappropriate clinical management. These results highlight the potential value of personalized risk assessment to refine screening and prevention strategies, paving the way toward more individualized care and more efficient use of healthcare resources.^{45,46}

Declarations

Data Availability Statement:

To protect patient privacy, the datasets generated and/or analyzed during the current study are not publicly available but may be made available from the corresponding author upon reasonable request.

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Ethical Approval:

All participants provided written informed consent. The study was approved by the Vall d'Hebron Hospital Ethics Committee (PR(AG)516/2019) and by the ethics committee of each participating institution.

Competing Interests:

The authors declare no conflicts of interest

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Authors' Contributions

Alejandra Rezkallah, Anna Moreno-Garcia, Judith Balmaña: Conceptualization, formal analysis, writing—original draft, writing—review and editing.

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

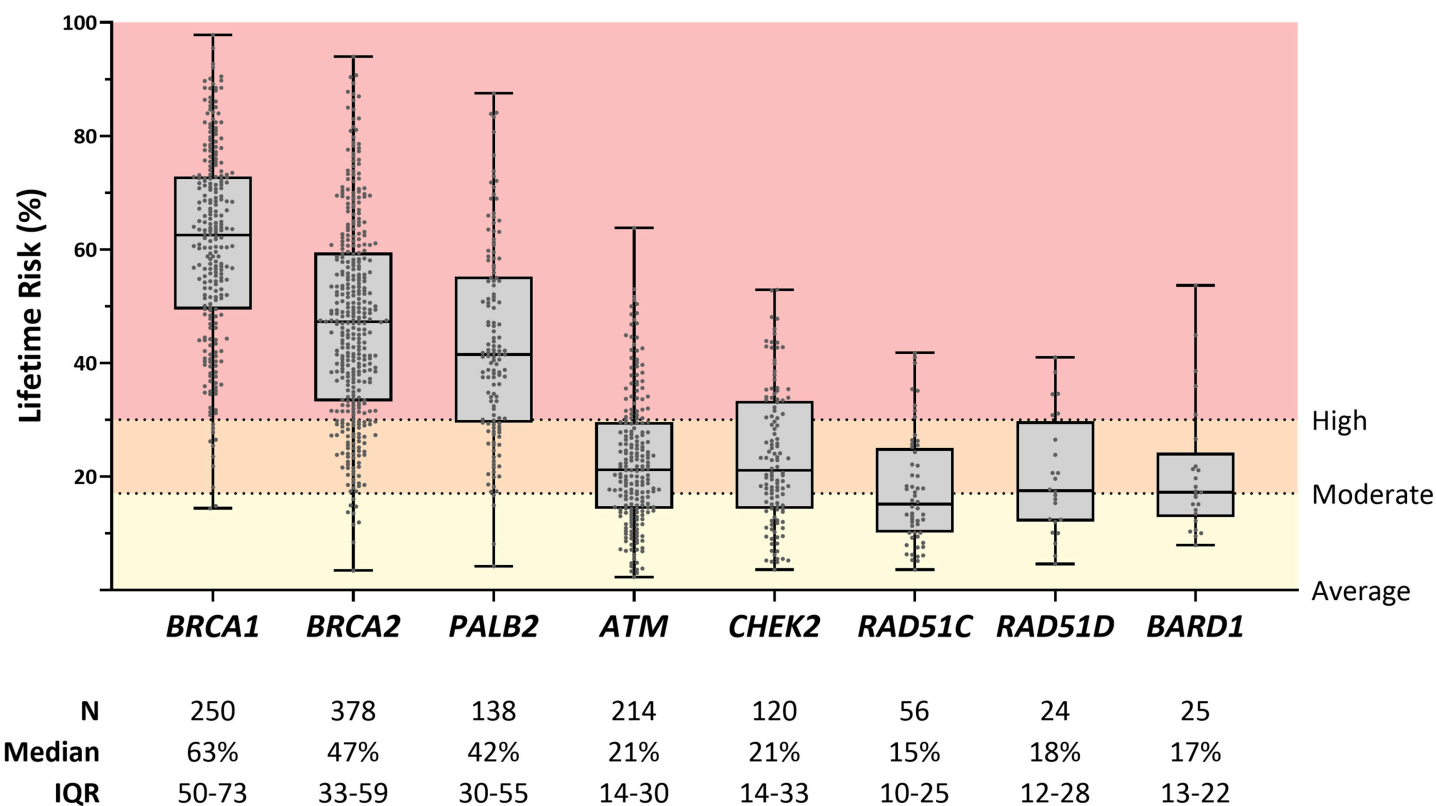


Figure 1

Distribution of lifetime breast cancer risk estimates across gene carriers using full assessment model. Shaded areas indicate average (<17%), moderate (17% to <30%), and high (≥30%) lifetime risk categories.

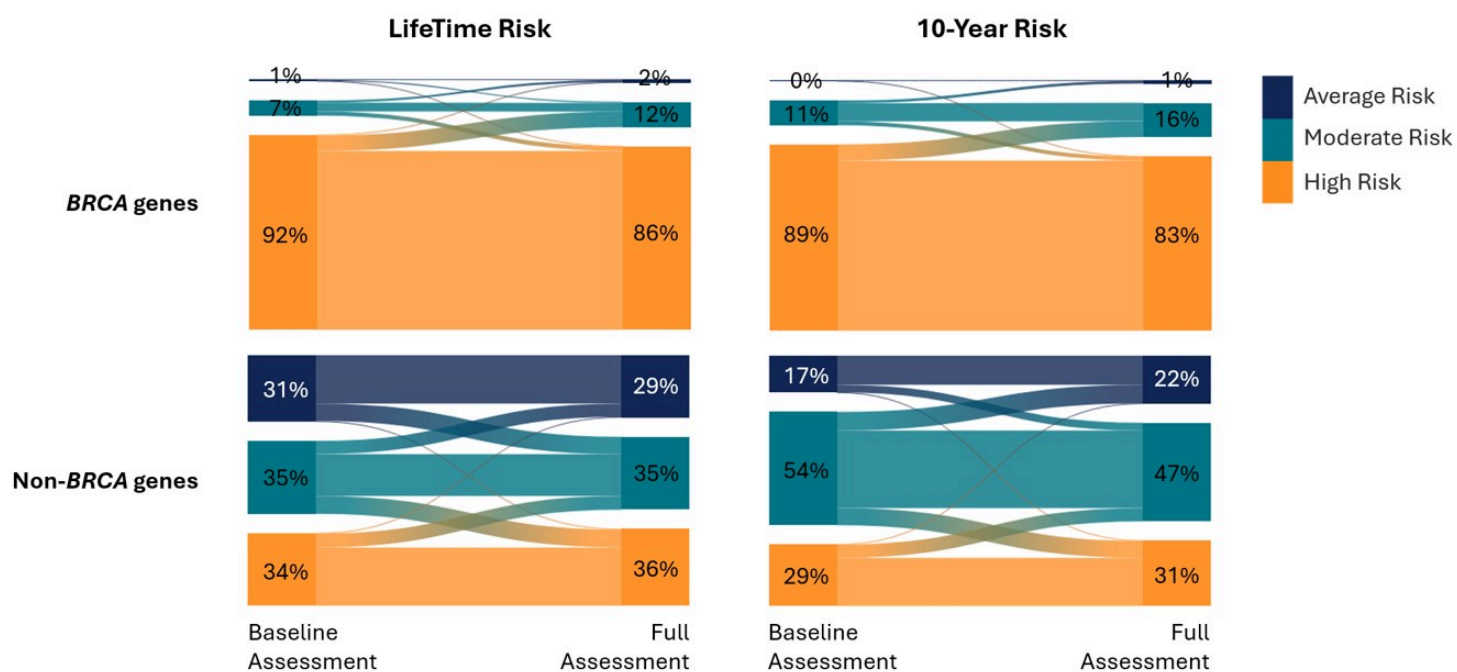


Figure 2

Reclassification of lifetime and 10-year breast cancer risk categories after incorporation of the polygenic risk score. Flows represent movement between average-, moderate-, and high-risk categories from baseline to full risk assessment among *BRCA1/2* and non-*BRCA1/2* carriers.

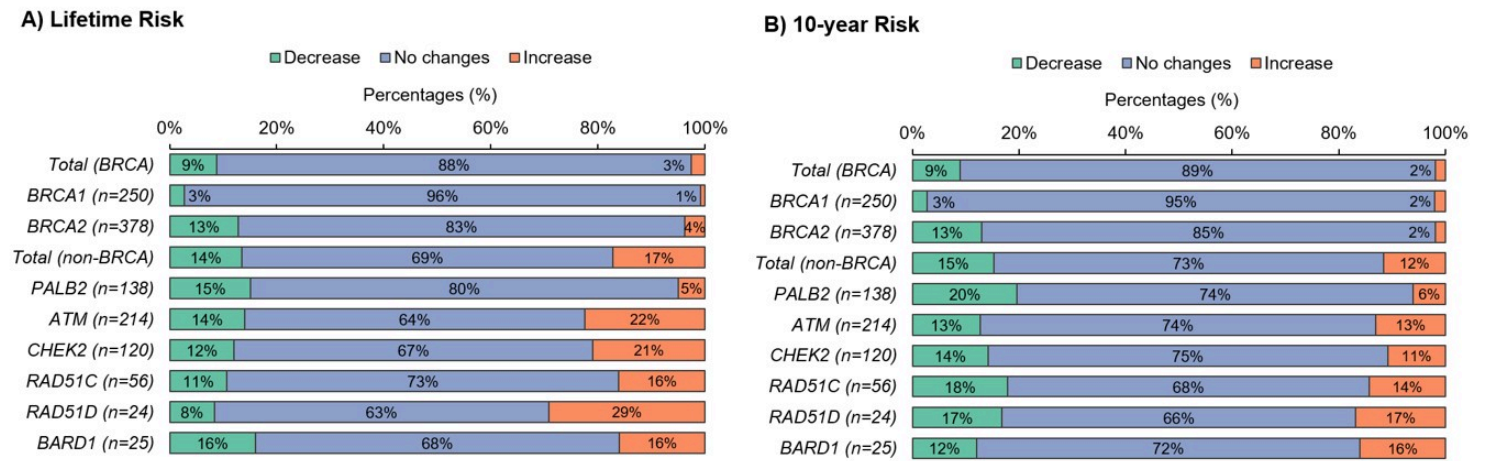


Figure 3

Changes in breast cancer risk category following polygenic risk score integration. Percentage of women whose breast cancer risk category decreased, remained unchanged, or increased after integration of the polygenic risk score into the full risk assessment model. Part A shows lifetime risk; Part B, 10-year risk.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.xlsx](#)
- [Table2.xlsx](#)
- [SupplementaryInformation.pdf](#)