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Original Research

Association and performance of polygenic risk scores for breast cancer among French women presenting or not a familial predisposition to the disease



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Abstract Background: Three partially overlapping breast cancer polygenic risk scores (PRS) comprising 77, 179 and 313 SNPs have been proposed for European-ancestry women by the Breast Cancer Association Consortium (BCAC) for improving risk prediction in the general population. However, the effect of these SNPs may vary from one country to another and within a country because of other factors.

Objective: To assess their associated risk and predictive performance in French women from (1) the CECILE population-based case-control study, (2) *BRCA1* or *BRCA2* (*BRCA1/2*) pathogenic variant (PV) carriers from the GEMO study, and (3) familial breast cancer cases with no *BRCA1/2* PV and unrelated controls from the GENESIS study.

Results: All three PRS were associated with breast cancer in all studies, with odds ratios per standard deviation varying from 1.7 to 2.0 in CECILE and GENESIS, and hazard ratios varying from 1.1 to 1.4 in GEMO. The predictive performance of PRS₃₁₃ in CECILE was similar to that reported in BCAC but lower than that in GENESIS (area under the receiver operating characteristic curve (AUC) = 0.67 and 0.75, respectively). PRS were less performant in *BRCA2* and *BRCA1* PV carriers (AUC = 0.58 and 0.54 respectively).

Conclusion: Our results are in line with previous validation studies in the general population

and in *BRCA1/2* PV carriers. Additionally, we showed that PRS may be of clinical utility for women with a strong family history of breast cancer and no *BRCA1/2* PV, and for those carrying a predicted PV in a moderate-risk gene like *ATM*, *CHEK2* or *PALB2*.

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1. Introduction

Prediction of cancer risk is an essential part of preventative medicine that can help guiding clinical management, in particular in hereditary breast and ovarian cancer (HBOC) families. Breast cancer risk prediction classically includes risk factors such as age, sex, family history of disease, lifestyle, hormonal and clinical features, breast density and genotype for pathogenic variants (PV) in the predisposition genes *BRCA1* and *BRCA2* (*BRCA1/2*) [1]. In recent years, some risk models have been updated to include additional genomic information, typically the effects of rare PV in other genes (*ATM*, *CHEK2* and *PALB2*) [2,3] and the joined effect of single nucleotide polymorphisms (SNPs) summarized in polygenic risk scores (PRS) [4–6]. Indeed, in the general population, some studies suggested that stratification of women according to their risk of breast cancer based on their PRS could personalize screening and prevention strategies [7–10]. Several PRS for breast cancer have been defined and validated in women of European ancestry from the large multi-centric and multi-country studies conducted by the Breast Cancer Association Consortium (BCAC). The establishment of the most recent PRS, which includes 313 SNPs, and its validation in independent prospective sample sets required almost all resources available before 2019 [11]. Therefore, few studies have independently benchmarked its performance. It was recently assessed in Asians [12,13] and African Americans [14,15] as well as in *BRCA1/2* PV carriers in international studies conducted by the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) [16]. However, even in European populations, the effect of some of these SNPs may vary from one country to another or within one country because of other factors, which may modify predictive performance of PRS. Here, we assembled a large dataset of women of European descent residing in France and representing three populations of women at different level of breast cancer risk to investigate in each group the performance of three partially overlapping PRS for breast cancer comprising 77 [10], 179 [17,18] and 313 SNPs [11]. Our goal was to assess whether these PRS modify breast cancer risk prediction in order to further assess if, when incorporated in predictive models, they could improve ability to predict breast cancer in the French population, and particularly in women attending family cancer clinics because of their personal or family history of breast cancer.

2. Material and methods

2.1. Study participants, genotyping and genotype imputation

The dataset comprised 7173 women of European ancestry from three studies on breast cancer conducted in France, namely CECILE, GEMO and GENESIS. The study designs are outlined in [Supplementary methods](#) and were described in detail previously [19–21].

CECILE is a population-based case-control study involving incident breast cancer cases and cancer-free controls that were frequency-matched to the cases by 10-year age group and study area [19,22]. Genotyping of samples was performed using the iCOGS beadchip (Illumina Inc. USA) in the context of genome-wide association studies (GWAS) conducted by BCAC [17]. iCOGS genotyping data were available for 1019 cases (of which 900 cases had invasive tumours and 119 had in situ tumour) and 999 controls [19]. After quality control (QC) procedures, we analysed data from 1015 cases and 996 controls.

GEMO is a resource to study genetic factors modifying cancer risk in HBOC families segregating *BRCA1/2* PV carriers. Participants are tested positive for a confirmed PV in *BRCA1/2* and are enrolled through the national network of cancer genetics clinics [20]. Genotyping of samples was performed using iCOGS or OncoArray beadchips in the context of GWAS conducted by CIMBA [23,24]. After QC, we analysed iCOGS data from 1883 *BRCA1/2* female carriers (1181 of whom had breast cancer) and OncoArray data from 756 *BRCA1/2* female carriers (428 of whom had breast cancer).

GENESIS is a case-control study [21] involving familial breast cancer cases tested negative for *BRCA1/2* and with at least one sister affected with breast cancer and unrelated controls (friends or colleagues) aged-matched (± 3 years) to cases at interview. Genotyping of samples was performed using the iCOGS beadchip. After QC, we analysed data from 1257 index cases and 1266 unrelated controls.

Detailed information about the design, genotyping and initial QC for iCOGS [25] and for OncoArray [17,18,26] can be found within the original publication of the consortia. We performed genotype calling, QC and genotype imputation of missing SNPs for iCOGS and OncoArray datasets separately. The different steps of the

process are summarized on [Supplementary Fig. S1](#). The number of SNPs in each PRS that are not present on the iCOGS and OncoArray chips are also provided on [Supplementary Fig. S1](#). We performed imputation of these missing SNPs in each study separately using a two-stage procedure, with SHAPEIT2 [27] to derive phased genotypes and IMPUTE2 [28] to perform imputation, using 1000 Genomes Project (Phase 3) data as the reference panel [29].

The modifier effect of PRS₃₁₃ in carriers of a predicted PV in *ATM*, *CHEK2* and *PALB2* was assessed in 974 cases and 1135 controls from GENESIS, for whom sequencing data were available [30] ([Supplementary methods](#)).

2.2. Statistical analyses

PRS is the weighted combined effect of uncorrelated SNPs calculated under the hypothesis of additivity of SNP effect. We used SNP effect size estimated by the BCAC as weight, as described in the [Supplementary data](#). We examined association with breast cancer and performance of the three following PRS: PRS₇₇ which includes 77 independent SNPs identified in early GWAS on breast cancer conducted by the BCAC [10], PRS₁₇₉ which includes 179 independent SNPs identified afterward in successive GWAS [17,18,31], and PRS₃₁₃ which was most recently developed and validated in women of European ancestry enrolled in 10 prospective cohorts and in the UK biobank [11] ([Supplementary Table S1](#)).

We assessed the association of the standardized PRS in CECILE and GENESIS using logistic regression models, adjusted for age (age at diagnosis of breast cancer for cases, age at interview for controls). In GEMO, to account for nonrandom sampling with respect to breast cancer status, we assessed association with risk of breast cancer using a weighted Cox proportional hazards regression model [32] (see [Supplementary methods](#)).

3. Results

3.1. Association and performance of PRS₃₁₃ in the three French studies

Demographic and clinical characteristics of women included in the three groups of the population with presumably different levels of breast cancer risk are presented in [Table 1](#). As anticipated, we found that PRS₃₁₃ was associated with breast cancer in all three groups, but the associated risk varied substantially from one group to another. In CECILE, the OR per SD was 1.71 (95% CI 1.57–1.86) and AUC was 0.67 (95% CI 0.64–0.69) ([Table 2](#)). These results were similar to those reported for overall breast cancer in BCAC (OR per SD, 1.65; 95% CI 1.59–1.72; AUC = 0.64). In GENESIS, the associated risk was higher (OR per SD, 1.84; 95% CI 1.70–1.99) and this PRS performed even better (AUC, 0.75; 95% CI 0.73–0.77) than in CECILE women ([Table 2](#)) [11].

As 85% of CECILE cases and 84% of GENESIS cases had developed ER-positive breast cancer, we also examined association and performance of the ER-positive breast cancer PRS₃₁₃ developed by BCAC in these two studies. Although the performance of this subtype-specific PRS was similar to that of the PRS for overall breast cancer in CECILE (AUC, 0.67; 95% CI 0.65–0.69) and in GENESIS (AUC, 0.76; 95% CI 0.74–0.77), point estimates of ORs were higher in both studies (OR per SD was 1.82 in CECILE and 2.00 in GENESIS) ([Table 2](#)).

In GEMO, risks associated with overall breast cancer or with breast cancer subtypes were similar and much lower than those observed in CECILE and GENESIS: for *BRCA1* PV carriers, HR per SD ranged from 1.15 (95% CI 1.05–1.26) for the overall breast cancer PRS₃₁₃ to 1.26 (95% CI 1.13–1.41) for the ER-negative PRS₃₁₃; for *BRCA2* PV carriers, HR per SD ranged from 1.28 (95% CI 1.15–1.42) for the overall breast cancer PRS₃₁₃

Table 1
Characteristics of women included in the analyses.

Study	Population	SNP array	Cases			Controls		
			N	Mean age at diagnosis (SE)	Mean year at birth (range)	N	Mean age at interview/censure (SE)	Mean year at birth (range)
CECILE	Cases selected from cancer registries and frequency-matched population controls (for age and area of residence)	iCOGS	1015	54.4 (0.3)	1951 (1930–1980)	996	54.7 (0.3)	1951 (1931–1981)
GENESIS	Index cases from HBOC families and unrelated controls (friends and colleagues)	iCOGS	1257	50.5 (0.3)	1951 (1918–1977)	1266	56.4 (0.3)	1953 (1926–1986)
GEMO	<i>BRCA1</i> carriers	iCOGS	697	41.0 (0.3)	1960 (1907–1986)	491	43.3 (0.6)	1964 (1913–1994)
		OncoArray	184	40.6 (0.7)		150	41.1 (1.1)	
GEMO	<i>BRCA2</i> carriers	iCOGS	484	43.8 (0.5)	1955 (1914–1985)	211	44.2 (0.9)	1963 (1913–1992)
		OncoArray	244	43.0 (0.6)		178	45.0 (1.1)	

SE, standard error.

Table 2
Association of PRS₃₁₃ with breast cancer.

Study	Cases	Controls	PRS ₃₁₃ ^a	OR ^b (95% CI)	P-value	AUC (95% CI)
CECILE	1015	996	BC	1.71 (1.57–1.86)	1.9×10^{-36}	0.67 (0.64–0.69)
			ER+	1.82 (1.66–2.00)	1.5×10^{-37}	0.67 (0.65–0.69)
			ER–	1.53 (1.39–1.70)	5.2×10^{-17}	0.61 (0.59–0.64)
GENESIS	1257	1266	BC	1.84 (1.70–1.99)	1.1×10^{-53}	0.75 (0.73–0.77)
			ER+	2.00 (1.83–2.18)	8.7×10^{-56}	0.76 (0.74–0.77)
			ER–	1.83 (1.66–2.02)	2.9×10^{-34}	0.72 (0.70–0.74)
<hr/>						
				HR ^c (95% CI)	P-value	AUC (95% CI)
GEMO – BRCA1	881	641	BC	1.15 (1.05–1.26)	0.01	0.54 (0.52–0.57)
			ER+	1.14 (1.03–1.26)	0.03	0.54 (0.51–0.57)
			ER–	1.26 (1.13–1.41)	5.0×10^{-4}	0.57 (0.54–0.60)
GEMO – BRCA2	728	389	BC	1.28 (1.15–1.42)	2.0×10^{-4}	0.58 (0.55–0.62)
			ER+	1.30 (1.16–1.46)	2.0×10^{-4}	0.58 (0.54–0.62)
			ER–	1.20 (1.04–1.37)	0.03	0.56 (0.52–0.59)

^a Three versions of PRS₃₁₃ were derived using per-allele log ORs from the BCAC: one for overall breast cancer (BC), one for ER-positive breast cancer (ER+), and one for ER-negative breast cancer (ER–). PRS were standardized using the mean PRS and standard deviation in BCAC controls.

^b Odds ratio per 1 unit of standard deviation.

^c Hazard ratio per 1 unit of standard deviation. CI, confidence interval. AUC, area under the receiver operating characteristic curve.

to 1.30 (95% CI 1.16–1.46) for the ER-positive PRS₃₁₃ (Table 2). Moreover, the discriminatory ability of PRS was at most 0.57 for *BRCA1* PV carriers and at most 0.58 for *BRCA2* PV carriers (Table 2).

3.2. Comparison of performance of PRS₇₇, PRS₁₇₉ and PRS₃₁₃

Although most genomic regions containing the SNPs included in the three PRS overlap, only a limited number of SNPs are identical or correlated (Supplementary Table S2). We therefore compared the effect size and performance of the three PRS in the different datasets. As PRS₃₁₃, PRS₇₇ and PRS₁₇₉ were associated with breast cancer risk in CECILE and GENESIS, with OR per SD varying from 1.67 to 2.01. However, we found that PRS₇₇ may confer a lower risk of breast cancer than PRS₁₇₉ and PRS₃₁₃ in GENESIS (Table 3).

In GEMO, the effect size was unchanged whatever the PRS, with HR per SD varying from 1.14 to 1.17 for *BRCA1* PV carriers and from 1.28 to 1.35 for *BRCA2* PV carriers (Table 3). Regarding their discriminative ability, all three PRS performed equally in each dataset.

3.3. Breast cancer risk modification by PRS₃₁₃ in carriers of a predicted pathogenic variant in a moderate-risk breast cancer gene

We next investigated the performance of PRS₃₁₃ in carriers of a predicted PV in *ATM*, *CHEK2* or *PALB2*. In a previous work, we confirmed that carriers of such variants in GENESIS were at increased risk of developing breast cancer [30]. In GENESIS participants with both sequencing and iCOGS genotyping data, women carrying an *ATM*, *CHEK2* or *PALB2* variant had a two-fold increased risk of breast cancer per unit of SD

of PRS₃₁₃ (Table 4). Risks associated with PRS₃₁₃ in carriers were higher than those for *BRCA1/2* PV carriers. However, we did not observe significant variation in the effect of the PRS according to the altered gene or the variant type (loss-of function or missense variant) (Table 4). We also observed a significant 8.7-fold increased risk of breast cancer for carriers of a predicted PV in the highest tertile of PRS₃₁₃ when compared with noncarriers with a PRS₃₁₃ in the middle tertile (Table 5). This associated risk was different from the risk of noncarriers with a PRS₃₁₃ in the highest tertile ($P_{\text{Het}} < 0.001$).

Finally, when women were binned by tertile of the PRS, we observed in CECILE and GENESIS significant risk modification for women in the lowest and highest tertiles of PRS₃₁₃ as compared to women in the middle tertile (Table 6). In GENESIS, point estimates for *ATM* and *PALB2* variant carriers in the highest tertile were substantially increased (OR, 5.65; 95% CI 1.82–17.5 for *ATM* and OR, 10.2; 95% CI 0.98–106 for *PALB2*). However, these observations should be interpreted with caution due to the limited number of variant carriers in GENESIS and consequently the large confidence intervals. In GEMO, we observed a significant increased risk of breast cancer for *BRCA1* PV carriers in the highest tertile of PRS₃₁₃ as compared to those in the middle tertile (OR, 1.39; 95% CI 1.11–1.75), and a significant reduced risk for *BRCA2* PV carriers in the lowest tertile as compared to those in the middle tertile (OR, 0.67; 95% CI 0.48–0.95).

4. Discussion

The three partially overlapping PRS investigated here had been defined using datasets composed of women of European ancestry from collaborative analyses

Table 3
Comparison of effect of PRS₃₁₃, PRS₁₇₉ and PRS₇₇ on breast cancer risk.

Study	PRS ₃₁₃ ^a			PRS ₁₇₉ ^a			PRS ₇₇ ^a		
	OR ^b (95% CI)	P-value	AUC (95% CI)	OR ^b (95% CI)	P-value	AUC (95% CI)	OR ^b (95% CI)	P-value	AUC (95% CI)
CECILE	1.84 (1.68–2.03)	1.9 × 10 ⁻³⁶	0.67 (0.64–0.69)	1.81 (1.65–1.99)	3.3 × 10 ⁻³⁵	0.66 (0.64–0.69)	1.67 (1.53–1.84)	9.5 × 10 ⁻²⁸	0.64 (0.62–0.67)
GENESIS	2.01 (1.84–2.19)	1.1 × 10 ⁻⁵³	0.75 (0.73–0.77)	2.01 (1.83–2.20)	1.3 × 10 ⁻⁵¹	0.75 (0.73–0.77)	1.71 (1.57–1.86)	2.8 × 10 ⁻³⁶	0.73 (0.71–0.74)
	HR ^c (95% CI)	P-value	AUC (95% CI)	HR ^c (95% CI)	P-value	AUC (95% CI)	HR ^c (95% CI)	P-value	AUC (95% CI)
GEMO – BRCA1	1.17 (1.06–1.30)	0.01	0.54 (0.52–0.57)	1.14 (1.04–1.26)	0.03	0.54 (0.51–0.56)	1.14 (1.03–1.26)	0.03	0.53 (0.50–0.56)
GEMO – BRCA2	1.32 (1.18–1.50)	2.0 × 10 ⁻⁴	0.58 (0.55–0.62)	1.35 (1.20–1.52)	2.0 × 10 ⁻⁵	0.59 (0.55–0.62)	1.28 (1.15–1.44)	3.0 × 10 ⁻⁴	0.58 (0.54–0.61)

AUC, area under the receiver operating characteristic curve.

^a PRS were standardized using the mean PRS and standard deviation in CECILE controls.

^b Odds ratio per 1 unit of standard deviation.

^c Hazard ratio per 1 unit of standard deviation.

involving heterogeneous populations from multiple countries. In these datasets, the vast majority of cases were unselected for their personal or family history of breast cancer. Because effect of SNPs on cancer risk may vary from one country to another due to other factors, there is some uncertainty on how the proposed PRS influence breast cancer risk in a given population. We thus sought to confirm their association with breast cancer in three groups of French women at different level of breast cancer risk: cases from the general population, cases with a family history of breast cancer in siblings and tested negative for *BRCA1/2*, and *BRCA1/2* PV carriers. Within each group, the effect of the three PRS on risk was similar with the exception of PRS₇₇ which was associated with a lower OR per SD than PRS₃₁₃ and PRS₁₇₉ in GENESIS. Since these PRS were constructed at different time using different approaches to select the SNPs, only a limited number of SNPs are shared or strongly correlated between the three PRS. Therefore, the choice of the PRS to use in risk prediction models may be driven by the efficiency of the genotyping technologies in order to minimize the number of missing SNP genotypes and imputations. Notably, using the OncoArray data, 71 out of 179 SNPs (39.7%) had to be imputed for PRS₁₇₉ and 204 out of 313 SNPs (65.2%) had to be imputed for PRS₃₁₃, and no significant improvement in either OR or AUC was observed for PRS₃₁₃.

Remarkably, we found the predictive value of PRS₃₁₃ for overall breast cancer in women with a familial predisposition and tested negative for *BRCA1/2* was higher than in women from the general population and women from BCAC (AUC = 0.75 in GENESIS versus 0.67 in CECILE versus 0.64 in BCAC [11]). Because GENESIS controls were not selected based on family history of breast cancer, it is possible that a residual familial effect correlated to the PRS would explain partially the higher performance. However, using the PRS to discriminate women at higher risk of breast cancer among those with a family history of breast cancer and no *BRCA1/2* PV may still be useful. In addition, although GENESIS cases were diagnosed at a younger age than CECILE cases, it is unlikely that a birth cohort effect could explain the difference in the performance of the PRS in the two studies (Supplementary Table S3). By contrast, PRS₃₁₃ was much less performant in *BRCA2* PV carriers (AUC = 0.58) and not predictive in *BRCA1* PV carriers (AUC = 0.54). In terms of associated risks, HR per SD obtained in GEMO are in line with those reported in the CIMBA retrospective cohort for overall breast cancer (HR per SD = 1.20 (1.17–1.23) for *BRCA1* PV carriers and 1.31 (1.27–1.36) for *BRCA2* PV carriers in CIMBA when no family adjustment was made) [16].

It should be mentioned that CECILE was one of the 69 BCAC studies contributing to the development of PRS₃₁₃ [11] and that GEMO contributed to the CIMBA study that assessed this PRS in *BRCA1/2* PV carriers [16]. However, CECILE samples only accounted for 1.2% of the BCAC

Table 4
Effect of predicted pathogenic variants in *ATM*, *CHEK2* or *PALB2*, and effect of PRS₃₁₃ on breast cancer risk.

GENESIS participants	Cases	Controls	Effect of rare variants		Effect of PRS ₃₁₃	
			OR (95% CI)	P-value	OR ^a (95% CI)	P-value
All ^b	974	1135	n/a	n/a	1.84 (1.69–2.00)	1.7×10^{-45}
Noncarriers	847	1067	n/a	n/a	1.84 (1.68–2.01)	1.7×10^{-41}
Carriers of a variant (any type) in:						
<i>ATM</i> or <i>CHEK2</i> or <i>PALB2</i>	127 ^c	68	2.18 (1.59–2.99)	1.5×10^{-6}	2.05 (1.48–2.83)	1.6×10^{-5}
<i>ATM</i>	58	38	1.79 (1.16–2.76)	0.008	2.15 (1.37–3.37)	8.5×10^{-4}
<i>CHEK2</i>	48	21	2.43 (1.43–4.15)	0.001	1.62 (0.92–2.85)	0.10
<i>PALB2</i>	26	9	3.08 (1.40–6.76)	0.005	2.07 (0.93–4.62)	0.08
Carriers of a loss-of-function variant in:						
<i>ATM</i> or <i>CHEK2</i> or <i>PALB2</i>	38	8	4.64 (2.12–10.15)	1.3×10^{-4}	2.69 (0.97–7.50)	0.06
Carriers of a missense variant in:						
<i>ATM</i> or <i>CHEK2</i> or <i>PALB2</i>	92	60	1.82 (1.29–2.58)	7.2×10^{-4}	1.94 (1.38–2.73)	1.5×10^{-4}

^a Overall breast cancer PRS₃₁₃ standardized using the mean PRS₃₁₃ and standard deviation in BCAC controls.

^b GENESIS participants with available multigene panel sequencing data and iCOGS genotyping data.

^c Five cases carried two variants: two cases carried an *ATM* loss-of-function variant and a *PALB2* missense variant, one case carried a *CHEK2* loss-of-function variant and a *PALB2* missense variant, one case carried an *ATM* missense variant and a *CHEK2* missense variant, and one case carried an *ATM* missense variant and a *PALB2* missense variant. These cases were included in each per gene analysis.

Table 5
Joint effect of PRS₃₁₃ and predicted pathogenic variants in *ATM*, *CHEK2* and *PALB2*.

	Cases	Controls	OR ^a (95% CI)	P-value
Noncarrier ^b & PRS ₃₁₃ in the middle tertile	213	349	Ref.	
Noncarrier ^b & PRS ₃₁₃ in the lowest tertile	99	352	0.49 (0.37–0.66)	1.3×10^{-6}
Noncarrier ^b & PRS ₃₁₃ in the highest tertile	535	366	2.43 (1.95–3.04)	4.3×10^{-15}
Carrier ^c & PRS ₃₁₃ in the middle tertile	36	29	1.92 (1.13–3.28)	0.02
Carrier ^c & PRS ₃₁₃ in the lowest tertile	14	26	0.97 (0.49–1.93)	0.94
Carrier ^c & PRS ₃₁₃ in the highest tertile	77	13	8.66 (4.65–16.13)	9.9×10^{-12}

^a Odds ratio per 1 unit of standard deviation.

^b Noncarrier of a predicted pathogenic variant in *ATM*, *CHEK2* or *PALB2*.

^c Carrier of a predicted pathogenic variant in *ATM*, *CHEK2* or *PALB2*.

Table 6
Odds ratios for developing breast cancer by PRS₃₁₃ tertile.

PRS ₃₁₃ tertile	≤33				>33 to ≤66			>66			
	Cases	Controls	OR (95% CI)	P-value	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	P-value
CECILE	143	332	0.46 (0.36–0.59)	1.5×10^{-9}	309	332	Ref.	563	332	1.82 (1.48–2.24)	1.1×10^{-8}
GENESIS											
All ^a	113	378	0.49 (0.37–0.64)	2.3×10^{-7}	249	378	Ref.	612	379	2.48 (2.01–3.06)	3.3×10^{-17}
<i>ATM</i>	7	15	0.62 (0.19–2.02)	0.43	16	17	Ref.	35	6	5.65 (1.82–17.5)	2.8×10^{-3}
<i>CHEK2</i>	4	8	0.33 (0.07–1.62)	0.17	14	7	Ref.	30	6	2.62 (0.69–9.96)	0.16
<i>PALB2</i>	4	3	1.01 (0.15–6.96)	0.99	7	5	Ref.	15	1	10.2 (0.98–106)	0.05
GEMO											
<i>BRCA1</i>	256	214	1.02 (0.80–1.30)	0.84	263	213	Ref.	362	214	1.39 (1.11–1.75)	4.4×10^{-3}
<i>BRCA2</i>	167	130	0.67 (0.48–0.95)	0.02	257	129	Ref.	304	130	1.32 (0.97–1.82)	0.08

^a GENESIS participants with available multigene panel sequencing data and iCOGS genotyping data.

dataset and GEMO samples accounted for 8% of *BRCA1* PV carriers and 9% of *BRCA2* PV carriers investigated by CIMBA. In absence of other available datasets, our study represents a unique opportunity to assess the relevance of the published PRS to improve breast cancer prediction in the French population.

Specific PRS have been described to predict risk of breast cancer subtypes, which could be useful to stratify women according to prognosis or for more beneficial treatments [11,33]. We confirmed the strongest association of ER-positive PRS in the French general population and in the high-risk population with no *BRCA1/2* PV, with OR per SD and AUC close to those reported by Mavaddat *et al.* (OR per SD, 1.74 (95% CI 1.66–1.82) and AUC = 0.65 in BCAC) [11]. On the other hand, the ER-negative PRS was more strongly associated in *BRCA1* PV carriers. However, the performance of this latter PRS was limited, which agrees with CIMBA results (AUC = 0.57 in GEMO and 0.58 in CIMBA) [16]. In *BRCA2* PV carriers, we confirmed the strongest associations for the overall and the ER-positive breast cancer PRS and their similar performance (AUC = 0.58 in GEMO and 0.60 in CIMBA) [16].

Interestingly, in women with a familial predisposition involving a moderate-risk gene, OR associated with PRS₃₁₃ are of the same magnitude that OR associated with rare predicted PV in *ATM*, *CHEK2* and *PALB2*. This indicates that adding PRS as a risk factor in risk prediction models may significantly improve management of women who receive genetic counselling.

Due to small numbers, we could not assess the effect of age or family history on the performance of PRS, nor assess PRS that have been recently developed in Asian [12,13] and African populations [14,15], and had to restrict our analyses to women of European descent according to genetic markers to assess PRS that had been constructed using per allele log OR obtained in the BCAC European population. Hence, further efforts should be conducted to assess and probably improve the discriminatory power of PRS in under-studied ethnic groups, as this could limit PRS adoption and applicability and exacerbate health disparities [34]. PRS have the potential to enhance disease risk prediction and diagnostic refinement, to predict progression and recurrence of disease and to improve the efficiency of population-level screening, however PRS cannot be used as a standalone tool, since as for other risk factors, they are estimates with a level of uncertainty that could affect risk stratification owing to statistical imprecision and the use of discrete cut-offs. Therefore, communication of PRS result to patients by healthcare professionals trained in genetics requires careful consideration as they may be incorrectly conflated with return of diagnostic test for high penetrance variants [34].

In conclusion, efforts should be pursued to develop and validate more specific PRS, especially in high-risk women with a known PV in a moderate-to high-risk gene in order

to integrate the effects of the common SNPs with family history, lifestyle/hormonal and other risk factors like mammographic density in risk prediction models that are applicable for each country. Indeed, the identification of groups of women with sufficiently different cancer risks will be informative in the genetic counselling process to allow female PV carriers to make more informed choices about the type and timing of cancer screening, prevention and possible risk reduction treatments.

Data accessibility

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics statement

Participants from CECILE, GEMO and GENESIS provided written informed consent. All three studies were approved by the relevant Advisory Committees on the Treatment of Health Research Information (*Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale* (CCPPRB) Kremlin-Bicêtre for CECILE, *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (CCTIRS) for GEMO, and CCPPRB Ile-de-France III for GENESIS) and by the National Data Protection authority (CNIL). Followed procedures were in accordance with the ethical standards of these committees.

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Fabienne Lesueur: Supervision.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

DS-L and LG coordinated the genotyping of SNPs included in the PRS of the MammoRisk® test commercialized by Predilife until December 2021. This

genotyping was performed in the Department of Genetics of the Institut Curie.

All other authors declare no conflicts of interest.

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Appendix A. Supplementary data

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