

Supplemental Online Content

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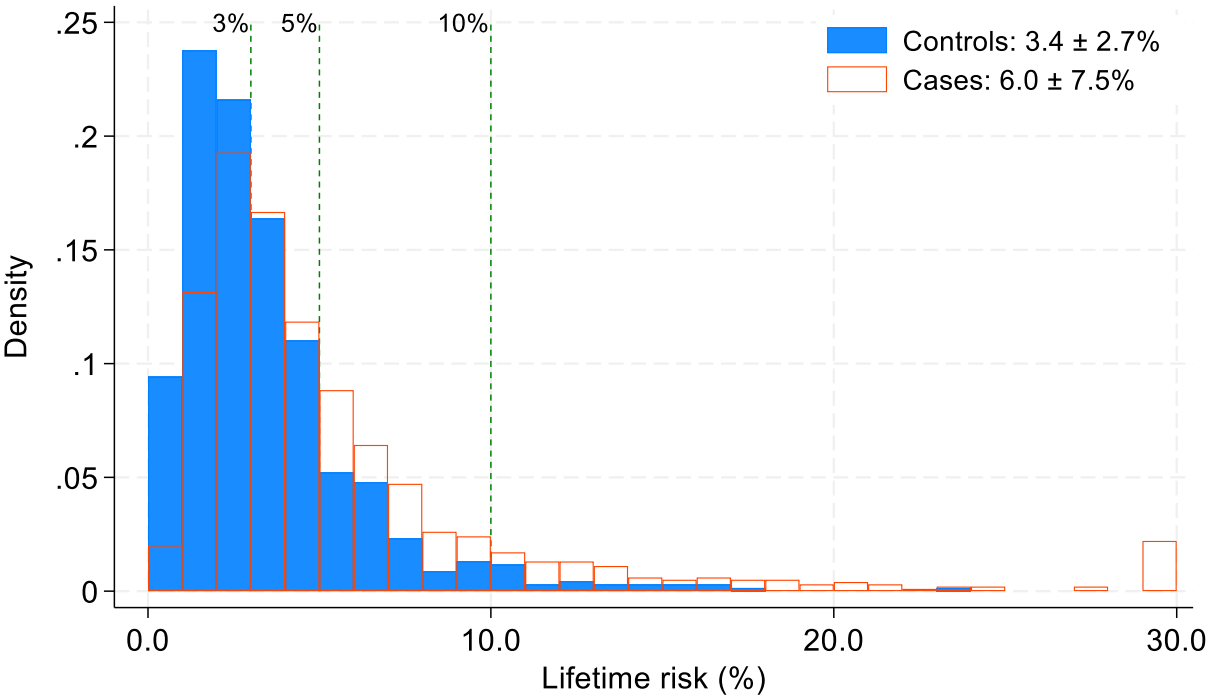
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This supplemental material has been provided by the authors to give readers additional information about their work.

eFigure. The Distribution of Lifetime Predicted Absolute Risks for Breast Cancer Cases and Controls in the Combined Model



Green dotted lines represent the 3%, 5%, and 10% lifetime absolute risk thresholds for breast cancer

eTable 1. Models Without Mean Imputation for the Epidemiological Risk Factors (n = 1,532)

	Unadjusted AUC (95% CI)	Age-adjusted AUC (95% CI)
Epidemiological RFs only	0.634 (0.606-0.661)	0.709 (0.682-0.736)
PRS only	0.572 (0.544-0.601)	0.579 (0.548-0.610)
PRS + PVs	0.599 (0.571-0.627)	0.608 (0.578-0.639)
Epidemiological RFs + PRS + PVs	0.662 (0.635-0.689)	0.727 (0.702-0.753)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PVs, pathogenic variants, AUC, area under receiver operating characteristic curve; CI, confidence interval.

eTable 2. Models Restricted to Participants From Nigeria (n = 1,551)

	Unadjusted AUC (95% CI)	Age-adjusted AUC (95% CI)
Epidemiological RFs only	0.637 (0.609-0.666)	0.719 (0.693-0.745)
PRS only	0.573 (0.544-0.603)	0.584 (0.552-0.616)
PRS + PVs	0.600 (0.571-0.629)	0.614 (0.582-0.645)
Epidemiological RFs + PRS + PVs	0.666 (0.639-0.694)	0.739 (0.714-0.763)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PVs, pathogenic variants, AUC, area under receiver operating characteristic curve; CI, confidence interval.

eTable 3. Models With Participants in Whole Dataset, Excluding Participants With Missing Values in the High to Moderate Penetrance Pathogenic Variants (n=1,950)

	Unadjusted AUC (95% CI)	Age-adjusted AUC (95% CI)
Epidemiological RFs only	0.637 (0.612-0.661)	0.642 (0.617-0.667)
Epidemiological RFs + PVs	0.675 (0.651-0.698)	0.682 (0.658-0.706)

Abbreviations: RF, risk factor; PVs, pathogenic variants, AUC, area under receiver operating characteristic curve; CI, confidence interval.

eTable 4. Performance of the Absolute Risk Prediction Models in Premenopausal Study Participants, n=979

	Unadjusted AUC (95% CI)	Age-adjusted AUC (95% CI)
Epidemiological RFs only	0.658 (0.624-0.692)	0.721 (0.688-0.754)
PRS only	0.553 (0.517-0.589)	0.541 (0.499-0.583)
PRS + PVs	0.586 (0.550-0.621)	0.571(0.529-0.614)
Epidemiological RFs + PRS + PVs (combined model)	0.676 (0.642-0.709)	0.724 (0.690-0.758)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PVs, pathogenic variants; AUC, area under receiver operating characteristic curve; CI, confidence interval.

eTable 5. Performance of the Absolute Risk Prediction Models in Postmenopausal Study Participants, n=682

	Unadjusted AUC (95% CI)	Age-adjusted AUC (95% CI)
Epidemiological RFs only	0.697 (0.651-0.743)	0.698 (0.652-0.744)
PRS only	0.627 (0.580-0.675)	0.629(0.582-0.676)
PRS + PVs	0.643 (0.597-0.690)	0.642 (0.594-0.690)
Epidemiological RFs + PRS + PVs (combined model)	0.735 (0.692-0.778)	0.738 (0.694-0.781)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PVs, pathogenic variants; AUC, area under receiver operating characteristic curve; CI, confidence interval.

eTable 6. Proportion of Premenopausal Participants Identified as High Risk Based on Different Thresholds of Lifetime Risk (n=979)

	Lifetime risk (to age 80)			
	<0.03	0.03-	0.05-	≥0.1
	N (%)	N (%)	N (%)	N (%)
Epidemiological RFs only				
controls (n=505)	289 (57.23%)	143 (28.32%)	66 (13.07%)	7 (1.39%)
cases (n=474)	163 (34.39%)	163 (34.39%)	119 (25.11%)	29 (6.12%)
PRS only				
controls (n=505)	137 (27.13%)	320 (63.37%)	48 (9.50%)	0
cases (n=474)	104 (21.94%)	298 (62.87%)	72 (15.19%)	0
PRS + PVs				
controls (n=505)	151 (29.90%)	312 (61.78%)	39 (7.72%)	3 (0.59%)
cases (n=474)	112 (23.63%)	278 (58.65%)	55 (11.60%)	29 (6.12%)
Epidemiological RFs + PRS + PVs (combined model)				
controls (n=505)	243 (48.12%)	154 (30.50%)	86 (17.03%)	22 (4.36%)
cases (n=474)	127 (26.79%)	136 (28.69%)	129 (27.22%)	82 (17.30%)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PV, pathogenic variants

eTable 7. Proportion of Postmenopausal Participants Identified as High Risk Based on Different Thresholds of Lifetime Risk (n= 682)

	Lifetime risk (to age 80)			
	<0.03	0.03-	0.05-	≥0.1
	N (%)	N (%)	N (%)	N (%)
Epidemiological RFs only				
controls (n=176)	139 (77.22%)	33 (18.33%)	7 (3.89%)	1 (0.56%)
cases (n=488)	278 (55.38%)	136 (27.09%)	80 (15.94%)	8 (1.59%)
PRS only				
controls (n=176)	68 (37.78%)	101 (56.11%)	11 (6.11%)	0
cases (n=488)	118 (23.51%)	313 (62.35%)	71 (14.14%)	0
PRS + PVs				
controls (n=176)	80 (44.44%)	89 (49.44%)	10 (5.56%)	1 (0.56%)
cases (n=488)	126 (25.10%)	293 (58.37%)	64 (12.75%)	19 (3.78%)
Epidemiological RFs + PRS + PVs (combined model)				
controls (n=176)	132 (73.33%)	34 (18.89%)	13 (7.22%)	1 (0.56%)
cases (n=488)	212 (42.23%)	141 (28.09%)	114 (22.71%)	35 (6.97%)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PV, pathogenic variants

eTable 8. Performance of the Absolute Risk Prediction Models With 313 PRS (n = 1,686)

	Unadjusted AUC (95% CI)	Age-adjusted AUC (95% CI)
Epidemiological RFs only	0.628 (0.601-0.655)	0.702 (0.676-0.729)
PRS only	0.550 (0.522-0.577)	0.553 (0.521-0.584)
PRS + PVs	0.578 (0.551-0.605)	0.585 (0.554-0.617)
Epidemiological RFs + PRS + PVs (combined model)	0.650 (0.624-0.677)	0.720 (0.694-0.745)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PVs, pathogenic variants; AUC, area under receiver operating characteristic curve; CI, confidence interval.

eTable 9. Proportion of Participants Identified as High Risk Based on Different Thresholds of Lifetime Risk, With 313 PRS (n=1,686)

	Lifetime risk (to age 80)			
	<0.03	0.03-	0.05-	≥0.1
	N (%)	N (%)	N (%)	N (%)
Epidemiological RFs only				
controls (n=690)	431 (62.46%)	176 (25.51%)	75 (10.87%)	8 (1.16%)
cases (n=996)	449 (45.08%)	306 (30.72%)	204 (20.48%)	37 (3.71%)
PRS only				
controls (n=690)	306 (44.35%)	384 (55.65%)	0	0
cases (n=996)	368 (36.95%)	627 (62.95%)	1 (0.10%)	0
PRS + PVs				
controls (n=690)	351 (50.87%)	335 (48.55%)	4 (0.58%)	0
cases (n=996)	403 (40.46%)	535 (53.71%)	6 (0.60%)	52 (5.22%)
Epidemiological RFs + PRS + PVs (combined model)				
controls (n=690)	429 (62.17%)	174 (25.22%)	78 (11.30%)	9 (1.30%)
cases (n=996)	437 (43.88%)	286 (28.71%)	190 (19.08%)	83 (8.33%)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PV, pathogenic variants.

eTable 10. Reclassification Table for Controls and Cases: The Epidemiological Risk Factors Only Model (Rows) and the Combined Risk Factors Model (Columns), With 313 PRS

Epidemiological risk factors only model	Combined risk factors model^a			
	No. (%)	No. (%)	No. (%)	No.
	<u>Controls</u>			
	<3%	3-10%	≥10%	Column total
<3%	397 (92.11)	32 (7.42)	2 (0.46)	431
3-10%	32 (12.7)	215 (85.7)	4 (1.6)	251
≥10%	0	5 (62.5)	3 (37.5)	8
Row total	429	252	9	690
	<u>Cases</u>			
	<3%	3-10%	≥10%	Column total
<3%	391 (87.1)	45 (10.0)	13 (2.9)	449
3-10%	46 (9.0)	423 (82.9)	41 (8.0)	510
≥10%	0	8 (21.6)	29 (78.4)	37
Row total	437	476	83	996

^aThe combined risk factors model contains epidemiological risk factors, polygenic risk score, and pathogenic variants

eTable 11. Performance of the Absolute Risk Prediction Models in Study Participants, With Information on Pathogenic Variants Restricted to BRCA1 and BRCA2 Versus With Information on Pathogenic Variants of All High/Moderate Penetrance Genes (n = 1,686)

	Unadjusted AUC (95% CI)	Age-adjusted AUC (95% CI)
PRS only	0.572 (0.544-0.599)	0.579 (0.548-0.611)
PRS + PVs of BRCA1/2	0.591 (0.563-0.618)	0.601 (0.572-0.631)
PRS + PVs of all high and moderate penetrance genes	0.598 (0.571-0.625)	0.609 (0.579-0.638)
PRS + PVs of BRCA1/2 + Epidemiological RFs (combined model 1)	0.654 (0.627-0.680)	0.719 (0.694-0.744)
PRS + PVs of all high and moderate penetrance genes + Epidemiological RFs (combined model 2)	0.657 (0.631-0.684)	0.723 (0.698-0.748)

Abbreviations: PRS, polygenic risk score; RF, risk factor; PVs, pathogenic variants; AUC, area under receiver operating characteristic curve; CI, confidence interval.

eTable 12. Reclassification Table for the Combined Model With Information on Pathogenic Variants Restricted to BRCA1 and BRCA2 Versus the Combined Model With Information on Pathogenic Variants of All High/Moderate Penetrance Genes (n = 1,686)

Combined model with BRCA1/2 ^a	Combined model with all high/moderate penetrance genes ^a			
	No. (%)	No. (%)	No. (%)	No.
	Controls ^b			
	<3%	3-10%	≥10%	Column total
<3%	378 (100)	0	0	378
3-10%	0	289 (100)	0	289
≥10%	0	0	23 (100)	23
Row total	378	289	23	690
	Cases			
	<3%	3-10%	≥10%	Column total
<3%	343 (98.56)	5 (1.44)	0	348
3-10%	0	528 (98.51)	8 (1.5)	536
≥10%	0	0	112 (100)	112
Row total	343	533	120	996

^a The combined model contains epidemiological risk factors, polygenic risk score, and pathogenic variants

^b None of controls have pathogenic variants in genes other than BRCA1/2 so no reclassification..