VANDERBILT UNIVERSITY
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Discovering novel breast cancer susceptibility loci and genes and improving risk prediction among African-ancestry females

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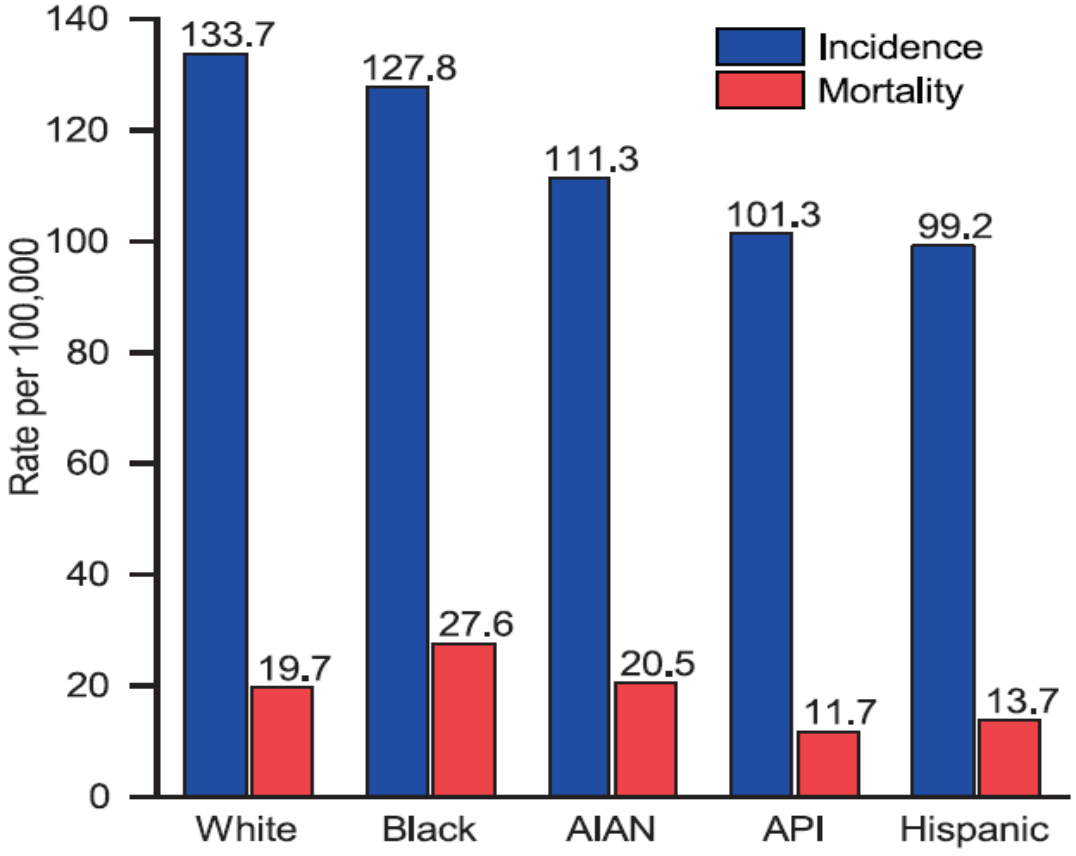
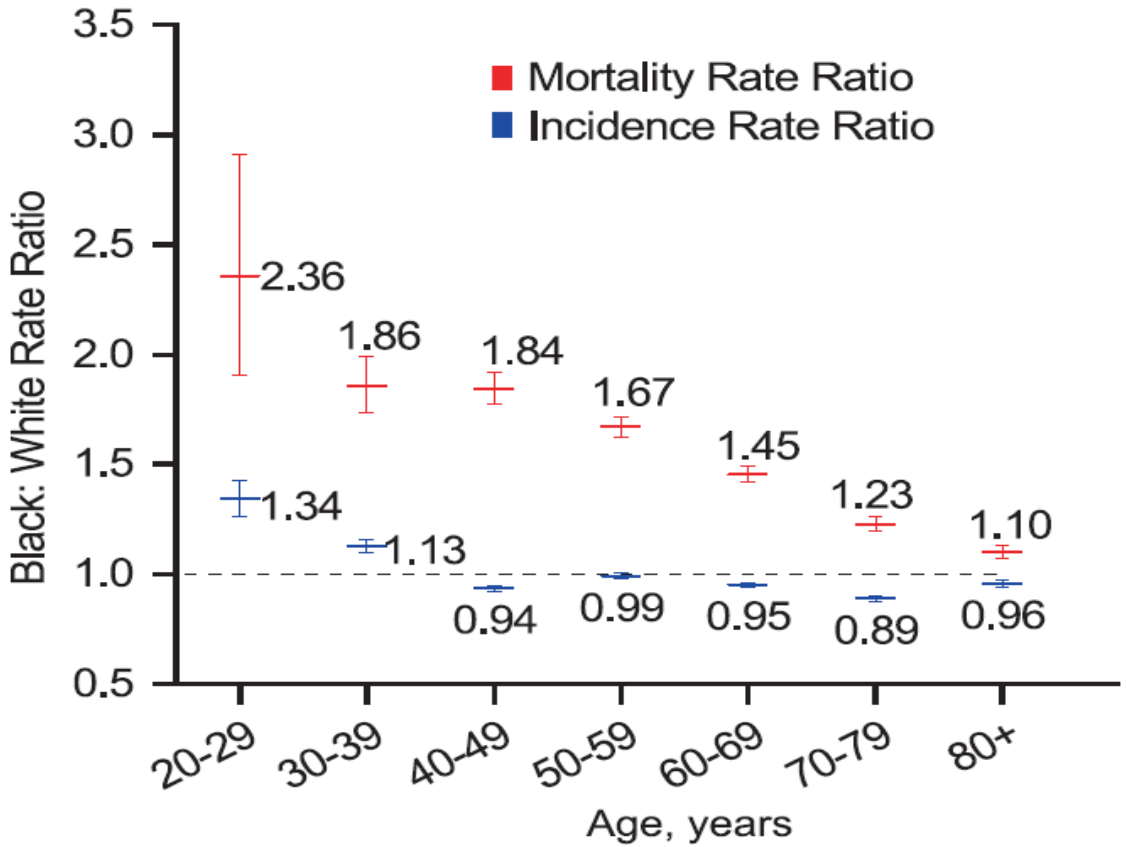
Female breast cancer incidence and mortality by race/ethnicity in the United States during 2015 to 2020



AIAN = American Indians/Alaska Natives
API = Asian/Pacific Islander



Giaquinto AN et al, , CA Cancer J Clin (2022)

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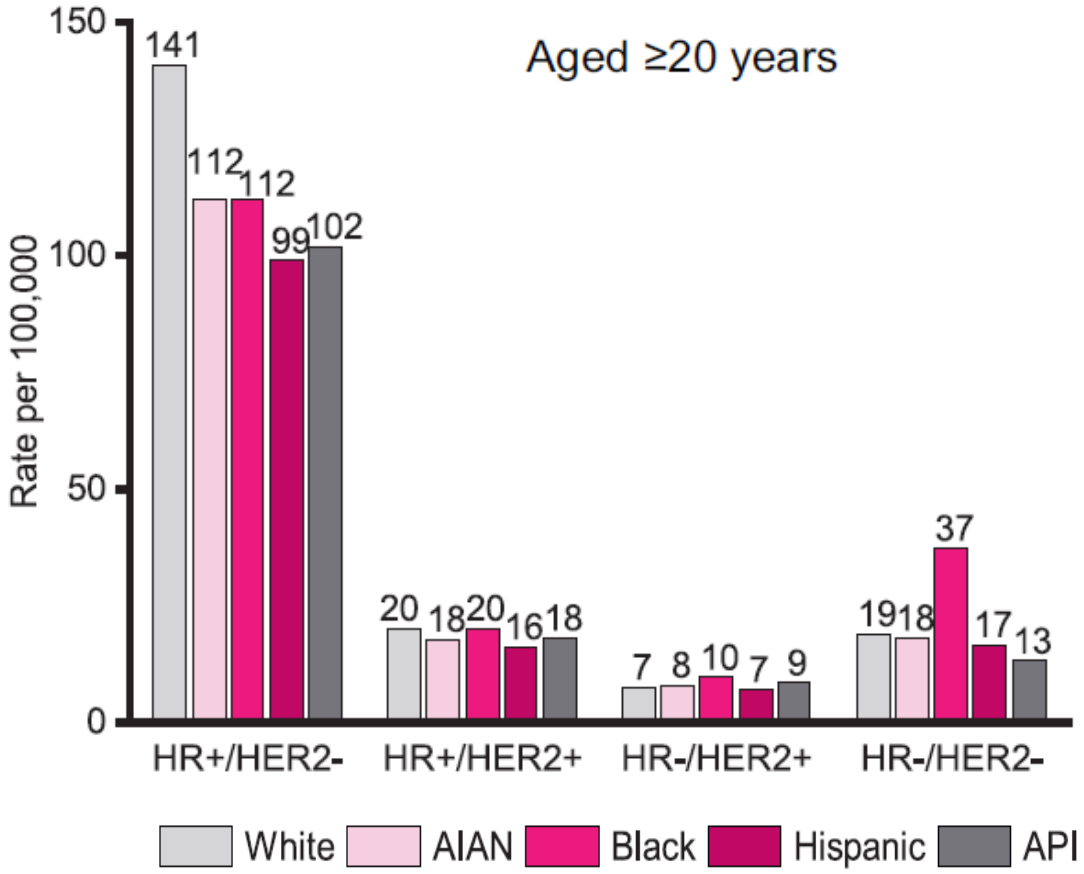

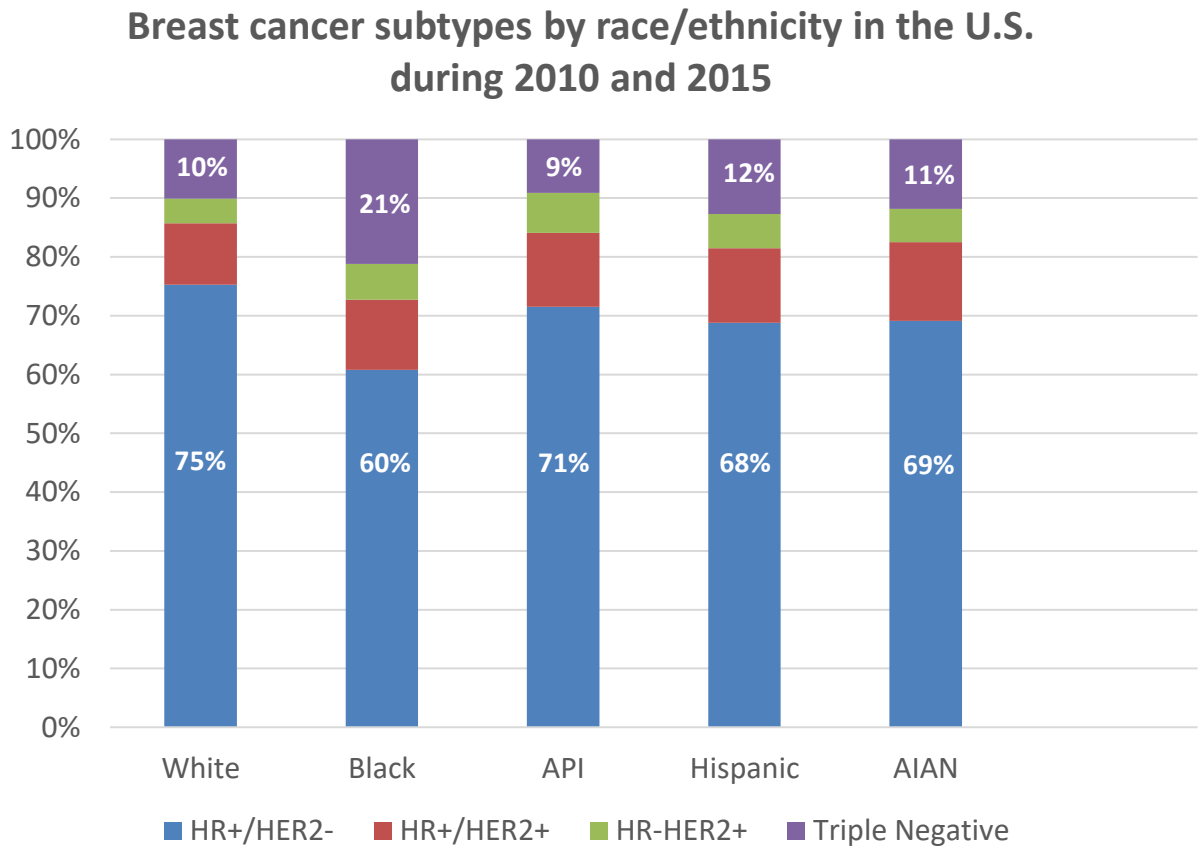

Giaquinto AN et al, , CA Cancer J Clin (2022)
Kong X et al. *JAMA Netw Open* (2020

African-ancestry Breast Cancer Genetics Consortium

- Funded by R01CA202981, an NCI Signature Project
- Initiated in 2016
- Targeted sample size:
  20,000 cases and 20,000 controls
- PIs: Wei Zheng (contact),
  Chris Haiman and Julie Palmer

nature medicine 2016

NEWS: Largest Genetic Study of Breast Cancer in African Americans Launches

NEWS

Largest genetic study of breast cancer in African Americans launched

African-ancestry Breast Cancer Genetics Consortium

13 Institutions/26 studies that contributed samples

- Vanderbilt University (NBHS, SCCS, STSBHS, Wei Zheng)
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Dataset	Array/Platform	All cases	Controls	ER-neg	TNBC
WGS	Illunima HiSeq X Ten, BGISEQ-500	1,408	2,297	641	354
New GWAS	MEGA	7,952	7,300	1,785	1,085
Existing GWAS	MEGA, Omni2.5, Human1M-Duo, 3 others	8,674	12,507	2,498	1,421
Total		18,034	22,104	4,924	2,860

Participants from **26 studies** (85.3% from the US) with a mean African ancestry of 78% in Black Americans.

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An Official Journal of the ACMG

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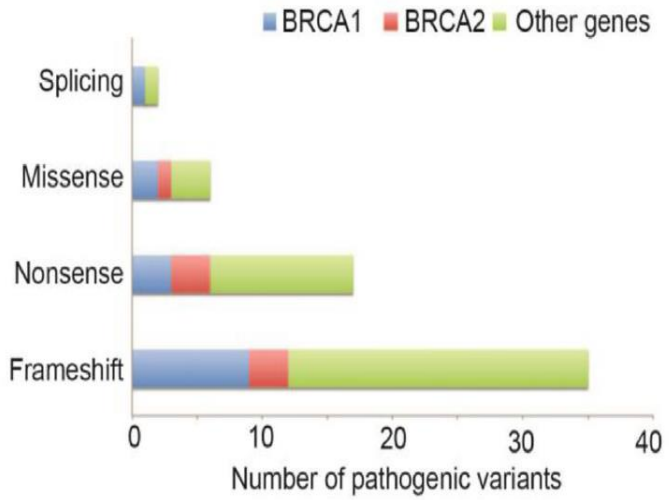
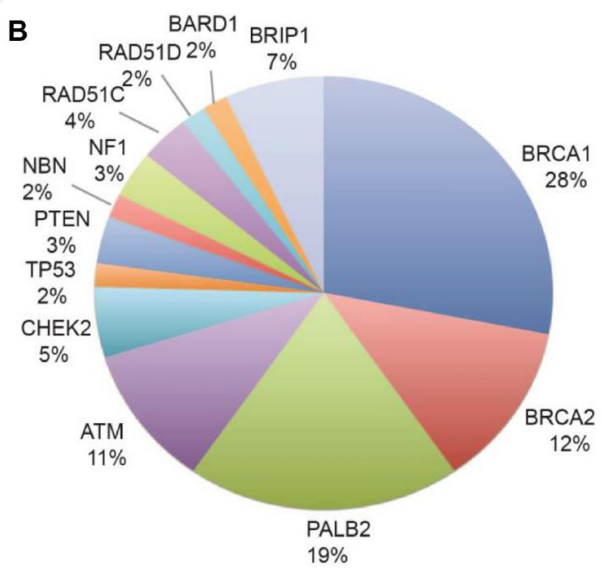
Evaluating breast cancer predisposition genes in women of African ancestry

Héctor Díaz-Zabala • Xingyi Guo • Jie Ping • ... Julie R. Palmer • Maureen Sanderson • Wei Zheng

Hector Diaz-Zabala

- Case-control study of 1,117 cases and 2,169 controls
- Meta-analysis of data from 7,096 cases and 8,040 controls included in 3 studies





Genes	OR	P-value
BRCA1	33.48	2.2×10^{-16}
BRCA2	10.75	2.2×10^{-16}
PALB2	11.76	2.2×10^{-16}
ATM	2.73	1.22×10^{-4}
CHEK2	3.73	1.4×10^{-3}
TP53	11.34	4.2×10^{-3}
PTEN	-	-
NF1	10.21	8.1×10^{-3}
BARD1	1.26	0.65
RAD51C	3.18	0.02
RAD51D	4.54	0.02

Based on 15,000 cases & controls

- Detected 61 pathogenic variants in 12 breast cancer predisposition genes, including 11 novel pathogenic variants
- Provided new evidence to extend findings from European- to African-ancestry populations
- Demonstrated significant different associations by ER status for multiple genes

GWAS of Breast Cancer Risk in African-ancestry Females

Guochong Damon Jia

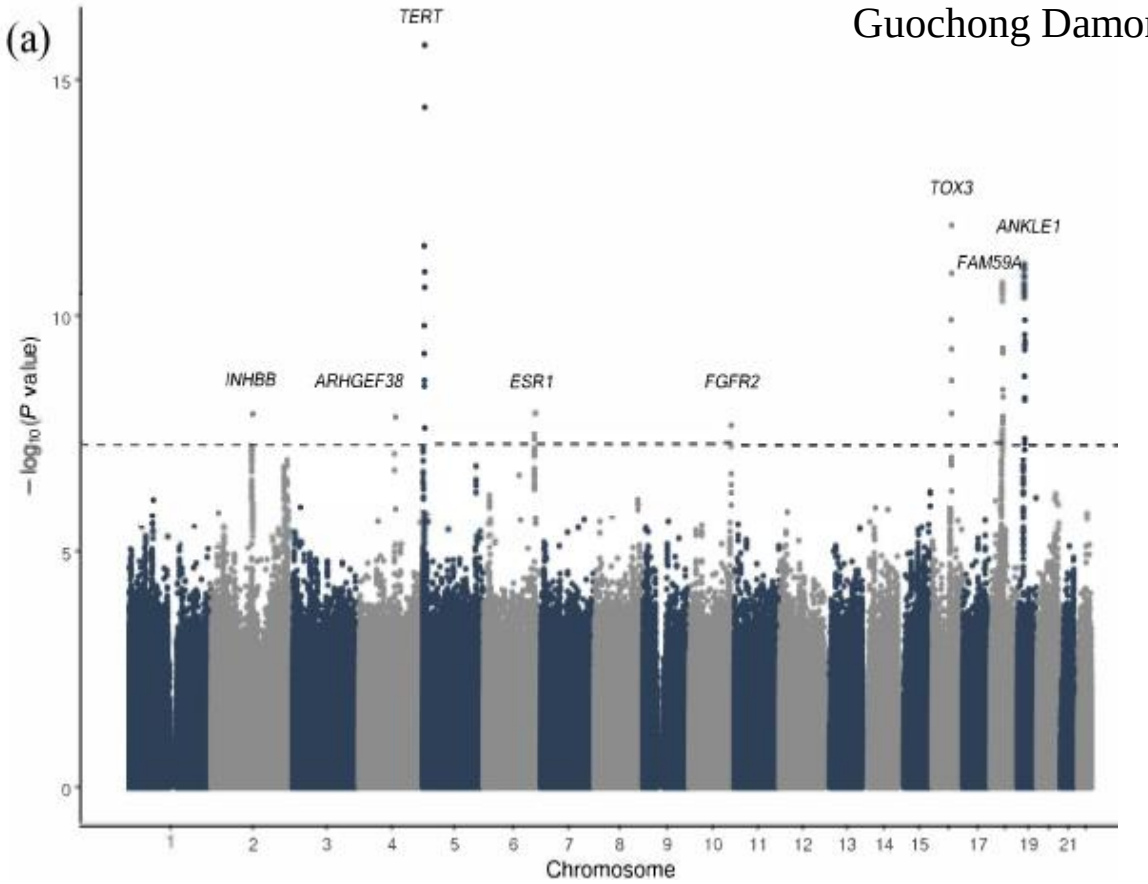
Study participants: 18,034 cases/22,104 controls from 26 studies, including 2,860 TNBC cases

Methods:

- Genotyping data were QC-ed and imputed using TOPMed data as the reference;
- 15,336,307 variants were included in the association analysis.

Major findings:

- Associations identified at **12** risk loci for overall breast cancer and **6** additional risk loci by subtypes at $P < 5\times10^{-8}$, including a missense allele in the *ARHGEF38* (OR = 1.69, $P=1.26\times10^{-10}$, MAF = 1%)
- 58 risk variants reported in previous GWAS were replicated at P < 0.05



Jia G, et al *Nat Genet* (2024)

Risk variants for TNBC in African-ancestry women

Risk loci identified for TNBC in Black women

	African-ancestry			European-ancestry	
Variant	EAF	OR	P-value	EAF	OR
rs76664032	0.81	1.30	3.64×10^{-10}	1.00	NA
rs10069690	0.59	1.38	1.15×10^{-23}	0.26	1.26
rs12974508	0.59	1.38	1.29×10^{-23}	0.48	1.21

2q14.2 (*RP11-18E11.1*), 5p15.33(*TERT*) 19P13.11 (*ABHD8*)

Genes	Estimated RR (95% CI)	Absolute risk by age 80 (%)[b]
NFI	2.6 (2.1-3.2)	26
ATM	2.8 (2.2-3.7)	27
CHEK2	3.0 (2.6-3.5)	29
NBN[e]	2.7 (1.9-3.7)	23

Risk of TNBC by numbers of risk variants in Black women

Risk allele count *	TNBC, n (%)	Controls, n (%)	OR (95% CI)
0	1 (0.04)	12 (0.07)	1.00 (Reference)
1	19 (0.7)	240 (1.5)	
2	123 (4.4)	1,260 (7.8)	1.30 (0.80, 2.21)
3	411 (14.8)	3,688 (22.7)	1.48 (0.94, 2.46)
4	907 (32.8)	5,487 (33.8)	2.19 (1.40, 3.63)
5	882 (31.9)	4,226 (26.0)	2.79 (1.78, 4.73)
6	425 (15.4)	1,317 (8.1)	4.21 (2.66, 7.03)
P for trend			8.51×10^{-53}

* Risk alleles of three risk variants A, T and C for rs76664032, rs10069690, and rs12974508, respectively

Jia G, et al *Nat Genet* (2024)

Easton DF, et al *N Engl J Med* (2015)

Developing and validating breast cancer PRS for African-ancestry females

PRS and AUROC[a]	PRS_{AFR}	PRS_{EUR}
	OR (95% CI)[b]	OR (95% CI)[b]
<20%	0.64 (0.52–0.79)	0.65 (0.53–0.81)
20–39%	0.74 (0.60–0.91)	0.87 (0.72–1.07)
40–59%	1.00 (Ref.)	1.00 (Ref.)
60–79%	1.05 (0.87–1.27)	1.25 (1.03–1.51)
80–89%	1.31 (1.05–1.64)	1.17 (0.93–1.48)
90–94%	1.74 (1.32–2.28)	1.44 (1.08–1.92)
≥95%	2.32 (1.80–2.99)	1.77 (1.35–2.31)
Per s.d. increase	1.42 (1.33–1.51)	1.31 (1.24–1.40)
AUROC	0.60 (0.58–0.62)	0.58 (0.56–0.60)

$PRS_{LDpred2}$: AUC = 0.58, OR per SD = 1.20

- PRS construction: 94 risk variants (12 sentinel, 36 known index, 46 ancestry-shift, excluding 5 with poor imputation quality)
- Training set: 15,680 cases and 17,362 controls)
- Testing set (2,354 cases and 4,742 controls).

	ER-positive [a]		ER-negative [b]	
	PRS_{AFR_ER+}	PRS_{EUR_ER+}	PRS_{AFR_ER-}	PRS_{EUR_ER-}
Per SD OR (95% CI)	1.36 (1.26, 1.47)	1.37 (1.27, 1.48)	1.67 (1.49, 1.87)	1.42 (1.27, 1.60)
AUC (SCCS+BWHS)	0.60 (0.58, 0.63)	0.59 (0.56, 0.61)	0.62 (0.59, 0.66)	0.60 (0.56, 0.63)

No of variants for PRS: 44 for ER (+) and 24 for ER (-): Testing samples: 1,413 ER(+) cases, 617 ER(-) cases and ~4200 controls

Breast cancer risk prediction using polygenic risk score (PRS) in African-ancestry women

PRS	OR (95% CI)
<20%	0.64 (0.52, 0.79)
20-39%	0.74 (0.60, 0.91)
40-59%	1.00 (Reference)
60-79%	1.05 (0.87, 1.27)
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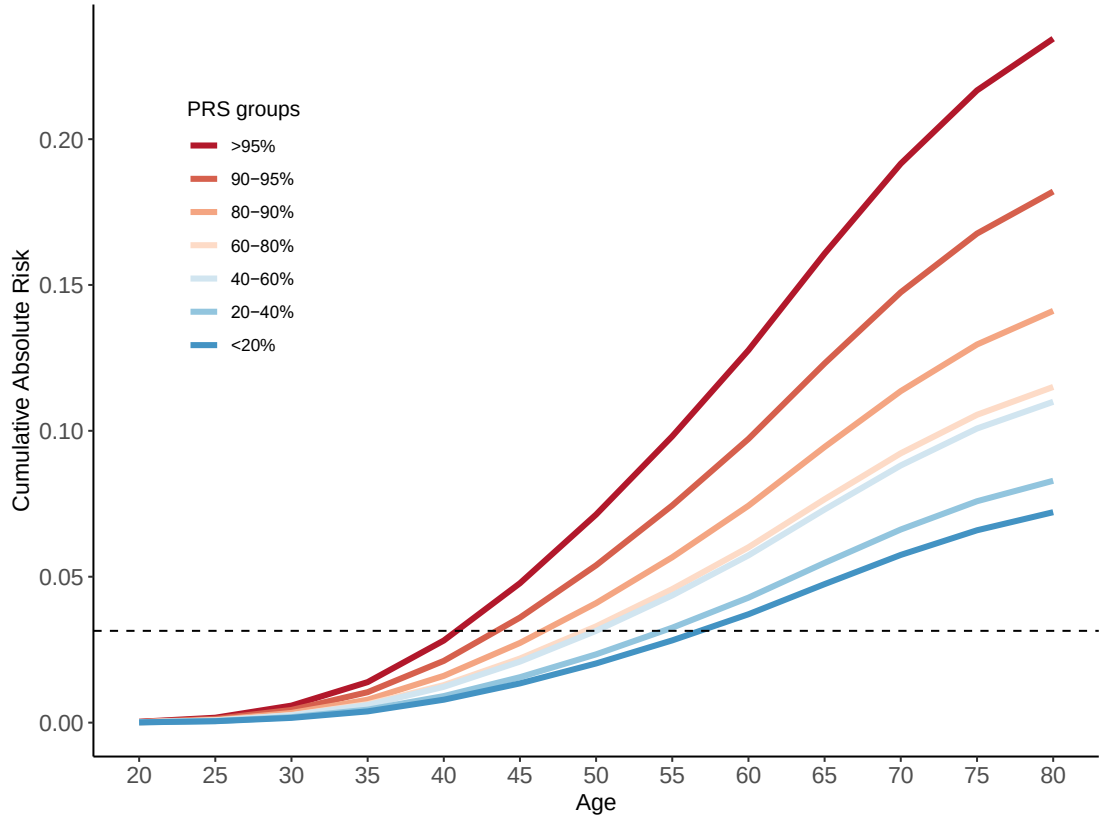
90-94%	1.74 (1.32, 2.28)
≥95%	2.32 (1.80, 2.99)



94 risk variants used to construct the PRS in a training set (15,680 cases and 17,362 controls) and evaluated in a testing set (2,354 cases and 4,742 controls). AUC = 0.60.

Summary

- Black/African Americans have a higher breast cancer mortality and TNBC risk
- Genetic studies in African-ancestry women can help to identify breast cancer risk variants that are more specific for this population or more difficult to identify in other populations
- Genetic factors may explain some of the elevated risk of TNBC in African-ancestry women
- PRS derived for African-ancestry females had a performance in breast cancer risk prediction approaching the level observed for other populations

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- **Study participants and staff**
- **National Institutes of Health for funding (R01CA202981)**

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- Chris Haiman (MPI), University of Southern California
- Julie Palmer (MPI), Boston University
- Co-Investigators at Vanderbilt: Jirong Long, Qiuyin Cai, Xingyi Guo, Ran Tao, Bingshan Li, Thomas Stricker, Carlos Arteaga, William Blot
- Trainees at Vanderbilt: Guochong Damon Jia, Jie Ping, Zhishan Chen, Hector Diaz-Zabala, Lili Larry Liu

What next?

We plan to significantly expand the African-ancestry Breast Cancer Consortium.

Please contact Dr. Wei Zheng at Wei.zheng@vanderbilt.edu

If you have collected genomic DNA samples from African-ancestry breast cancer patients and are interested in joining the consortium.