Ancestry-specific risk of triple-negative breast cancer associated with germline pathogenic variants in hereditary cancer predisposition genes

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Abstract # 10517

BACKGROUND

- Triple-negative breast cancer (TNBC) represents ~15% of invasive breast cancer (BC).
- Ancestry-specific variabilities in TNBC risk are well-described, with African American women experiencing higher incidence and mortality from TNBC than women of other ancestries.
- Increased risk of TNBC has been associated with both rarer (e.g. *RAD51C/D, BARD1*) and more commonly detected (e.g. *BRCA1/2, PALB2*) germline pathogenic variants (PV) in hereditary cancer predisposition genes, but less is known about ancestry-specific TNBC risks for PV carriers.

METHODS

COHORT

- We examined clinical and genetic records from women referred for multigene cancer panel testing (9/2013-5/2020).

STATISTICAL ANALYSIS

- TNBC rates were characterized for each self-reported ancestry as percentages with 95% confidence intervals (CIs).
- Multivariable logistic regression was used to test associations of PV in 6 genes with risk of TNBC after accounting for age, ancestry, and personal/family cancer history.
- We analyzed each gene in the full cohort, and in subcohorts defined by self-reported ancestry. Effect sizes are expressed as odds ratios with 95% CIs.

RESULTS

- Out of 627,219 women referred for multigene panel testing, 114,205 (18.2%) had a personal history of invasive BC, of which,17,951 (15.6%) reported TNBC (Table 1).
- Among women with invasive breast cancer, TNBC was reported more frequently in women of African ancestry (3,443/12,572; 27.4%, 95% CI 26.6% to 28.2%) than in women of Hispanic (1,414/9,361; 15.1%, 95% CI 14.4% to 15.9%), European (8,909/63,693; 14.0%, 95% CI 13.7% to 14.3%) or Asian (472/4,021; 11.7%, 95% CI 10.8% to 12.8%) ancestry.
- Ancestry-stratified risks of TNBC associated with germline PVs are seen in Table 2 (data not shown for ancestries with ≤4 TNBC cases).

Table 1. Patient Demographics

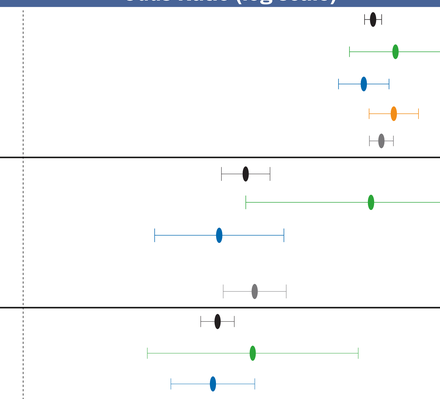
	All Patients	All Invasive BC	TNBC
Total Patients	627,219	114,205	17,951
Age at testing, years			
Range	18-90	18-90	20-90
Median	46	54	54
Family History* of Breast Cancer	430,392 (68.6%)	64,321 (56.3%)	8,295 (46.2%)
Ancestry			
Ashkenazi Jewish	4,328 (0.7%)	586 (0.5%)	56 (0.3%)
Asian	15,074 (2.4%)	4,021 (3.5%)	472 (2.6%)
African	56,035 (8.9%)	12,572 (11%)	3,443 (19.2%)
Hispanic	53,834 (8.6%)	9,361 (8.2%)	1,414 (7.9%)
Middle Eastern	3,537 (0.6%)	759 (0.7%)	89 (0.5%)
Native American	4,985 (0.8%)	783 (0.7%)	118 (0.7%)
Pacific Islander	540 (0.1%)	110 (0.1%)	15 (0.1%)
European	362,768 (57.8%)	63,693 (55.8%)	8,909 (49.6%)

Percentages calculated from column totals. Patients with multiple ancestries not listed, so totals may not equal 100.

*First- or second-degree relative

Table 2. Association between Pathogentic Variants in Cancer Predisposition Genes and Risk of Triple-Negative Breast Cancer

Gene	Ancestry	N positive	N positive w/TNBC	Odds Ratio (log scale)	OR	95% CI	p
BRCA1	All	7,228	1,193		21.57	(20.01, 23.25)	$<10^{-260}$
	Asian	275	49		26.26	(17.53, 39.32)	$1.2x10^{-56}$
	African	688	161		19.88	(15.92, 24.81)	$7.7x10^{-154}$
	Hispanic	958	155		25.87	(20.83, 32.13)	$3.3x10^{-190}$
	European*	3,625	582		23.20	(20.88, 25.78)	$<10^{-260}$
BARD1	All	898	125		7.05	(5.70, 8.73)	$4.3x10^{-72}$
	Asian	29	7		21.18	(7.06, 63.57)	$5.2x10^{-08}$
	African	94	22		5.59	(3.17, 9.86)	$2.7x10^{-09}$
	Hispanic	49	4		-	-	-
	European*	549	71		7.63	(5.79, 10.06)	$4.8x10^{-47}$
PALB2	All	2,604	231		5.51	(4.75, 6.38)	$8.1x10^{-114}$
	Asian	65	7		7.50	(2.97, 18.93)	$2.0x10^{-05}$
	African	284	43		5.29	(3.66, 7.64)	$8.0x10^{-19}$
	Hispanic	298	15		3.65	(2.10, 6.34)	$4.3x10^{-06}$
	European*	1,398	115		5.92	(4.82, 7.27)	$8.8x10^{-65}$
RAD51C	All	846	86		4.87	(3.82, 6.21)	$2.3x10^{-37}$
	Asian	22	0		-	-	-
	African	78	22		9.37	(5.23, 16.77)	$4.9x10^{-14}$
	Hispanic	88	9		5.63	(2.64, 12.04)	$8.0x10^{-06}$
	European*	483	47		5.17	(3.74, 7.14)	$2.4x10^{-23}$
RAD51D	All	506	45		4.68	(3.36, 6.52)	$6.0x10^{-20}$
	Asian	25	2		-	-	-
	African	64	14		6.28	(3.13, 12.58)	$2.2x10^{-07}$
	Hispanic	33	3		-	-	-
	European*	269	21		5.18	(3.23, 8.31)	$9.4x10^{-12}$
BRCA2	All	8,077	488		4.64	(4.21, 5.13)	$4.9x10^{-203}$
	Asian	294	14		4.19	(2.32, 7.55)	$1.9x10^{-06}$
	African	850	101		5.25	(4.15, 6.64)	$1.7x10^{-43}$
	Hispanic	732	44		6.01	(4.31, 8.39)	$5.7x10^{-26}$
	European*	4,407	243		4.88	(4.25, 5.60)	$1.5x10^{-111}$



*Includes White/Non-Hispanic, but not Ashkenazi Jewish

CONCLUSIONS

- Among women affected by BC undergoing genetic testing, TNBC was reported more frequently in women of African ancestry.
- PVs in *BRCA1/2*, *PALB2*, *RAD51C/D*, and *BARD1* are associated with substantial risk of TNBC.
- PV-associated TNBC risks were comparable across ancestries.

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