Age-related breast cancer risk estimates for the general population based on sequencing of cancer predisposition genes in 19,228 breast cancer patients and 20,211 matched unaffected controls from US based cohorts in the CARRIERS study

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Germline hereditary cancer genetic testing

- Identify individuals and family members at increased risk of cancer
  - Increased risk for second primary cancer
  - Multiple organ systems may be involved
- Prevention or early detection of cancer
  - Mammographic and MRI screening
  - Surgical intervention
- Potential therapeutic benefit – PARP inhibitors, platinum agents

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Germline hereditary cancer genetic testing

- Breast cancer risk estimates for predisposition gene mutations apply to high-risk patients qualifying for clinical genetic testing
  - Family history of cancer
  - Young age at diagnosis
  - Multiple primary cancers
- Risk estimates for women in the general population remain to be defined

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Breast cancer risk estimates by panel gene

Gene	Relative Risk	
	Literature (Easton et al 2015)	Clinical testing (Couch et al 2017)
ATM	2.8 (90% C.I. 2.2-3.7)	2.8 (95%C.I. 2.2-3.6)
BARD1	Insufficient data	2.2 (95%C.I. 1.3-3.6)
BRIP1	No evidence of association	1.6 (95%C.I. 1.1-2.4)
CHEK2 (truncating)	3.0 (90% C.I. 2.6-3.5)	2.3 (95%C.I. 1.9-2.9)
CHEK2 (missense)	1.58 (95% C.I. 1.42-1.75) for I157T	1.5 (95%C.I. 1.3-1.7)
MRE11A	Insufficient data	0.9 (95%C.I. 0.5-1.6)
NBN	2.7 (90% C.I. 1.9-3.7) for c.657del5	1.1 (95%C.I. 0.7-1.8)
PALB2	5.3 (90% C.I. 3.0-9.4)	7.5 (95%C.I. 5.1-11.2)
RAD50	Insufficient data	0.8 (95%C.I. 0.5-1.6)
RAD51C	No evidence of association	0.8 (95%C.I. 0.5-1.4)
RAD51D	No evidence of association	3.1 (95%C.I. 1.2-7.9)

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Research strategy

- Developed the CAnceR RIsk Estimates Related to Susceptibility "CARRIERS" study
  (Fergus Couch, David Goldgar, Katherine Nathanson, Peter Kraft, Jeffrey Weitzel, Susan Domchek, Eric Polley)
- Define the population-based frequencies of pathogenic mutations in cancer predisposition genes
- Estimate age-related and lifetime risks of breast cancer in the general population

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QIAseq Custom Hereditary Cancer Gene Panel

ATM	CHEK2	NBN	RECQL
BARD1	FANCC	NF1	TP53
BRCA1	FANCM	PALB2	BLM
BRCA2	MLH1	PMS2	128 risk SNPs
BRIP1	MRE11A	PTEN	
CDH1	MSH2	RAD51C	
CDKN2A	MSH6	RAD51D	

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Case/control status by study

Studies	Case	Control	Total
Black Womens Health Study (BWHS)	1464 (4.9%)	2867 (9.6%)	4331 (7.2%)
Cancer Prevention Study 3 (CPS3)	1534 (5.1%)	1724 (5.8%)	3258 (5.4%)
Cancer Prevention Study 2 (CPS2)	3958 (13.2%)	3903 (13.1%)	7861 (13.1%)
California Teachers Study (CTS)	2185 (7.3%)	2064 (6.9%)	4249 (7.1%)
Multiethnic Cohort (MEC)	4460 (14.9%)	3205 (10.7%)	7665 (12.8%)
Nurses Health Study (NHS)	3606 (12.0%)	3681 (12.3%)	7287 (12.2%)
Nurses Health Study 2 (NHS2)	2072 (6.9%)	2412 (8.1%)	4484 (7.5%)
Womens Health Initiative (WHI)	929 (3.1%)	1341 (4.5%)	2270 (3.8%)
Mayo Clinic Breast Cancer Study (MCBCS)	2154 (7.2%)	1658 (5.6%)	3812 (6.4%)
Womens Circle of Health Study (WCHS)	4905 (16.3%)	4479 (15.0%)	9384 (15.7%)
Wisconsin Women Health Study (WWHS)	2756 (9.2%)	2498 (8.4%)	5254 (8.8%)
Total	30023	29832	59855

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Phenotypic characteristics of CARRIERS participants

Phenotype	Control	Case	Total
AgeDiag			
Mean (SD)	62.5 (11.3)	62.4 (11.4)	62.4 (11.4)
Range	21.8 - 94.3	21.0 - 94.0	21.0 - 94.3
Case Status			
invasive	0 (0.0%)	25368 (84.5%)	25368 (42.4%)
in situ	0 (0.0%)	3656 (12.2%)	3656 (6.1%)
Race			
African American	4940 (16.6%)	4003 (13.3%)	8943 (14.9%)
Asian	1257 (4.2%)	1271 (4.2%)	2528 (4.2%)
White	22342 (74.9%)	23322 (77.7%)	45664 (76.3%)
Other	1227 (4.1%)	1251 (4.2%)	2478 (4.1%)
Unknown	66 (0.2%)	176 (0.6%)	242 (0.4%)

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Frequency of mutations for known breast cancer predisposition genes (all races and ethnicities)

Case mutation frequency	4.2%
Control mutation frequency	1.6%

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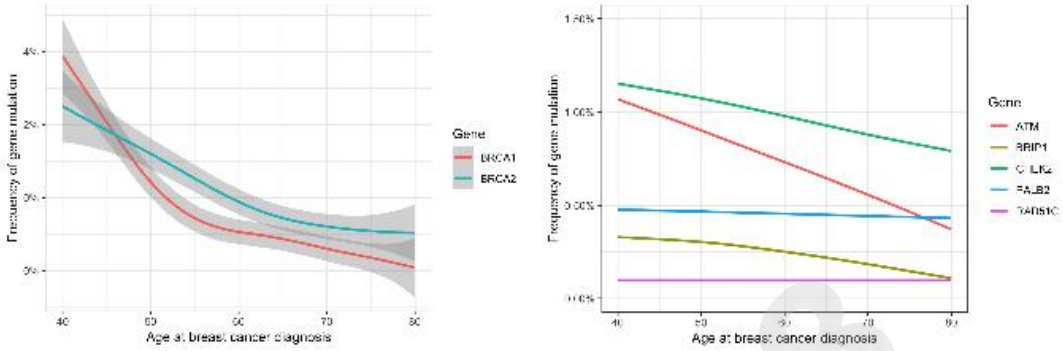
Age-related frequency of mutations in predisposition genes



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Frequency of mutations in cases =<50 years at diagnosis

Case mutation frequency	7.3%
Control mutation frequency	1.8%

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CARRIERS breast cancer risk estimates by panel gene

	Relative Risk	p-value
ATM	1.7	0.001
BARD1	1.1	0.80
BRCA1	7.9	<0.001
BRCA2	6.7	<0.001
BRIP1	2.1	0.01
CHEK2 (truncating)	2.5	<0.001
FANCM	1.0	0.95
MRE11A	1.0	0.90
NBN	0.6	0.16
PALB2	4.8	<0.001
RAD50	0.7	0.15
RAD51C	1.2	0.58
RAD51D	2.6	0.15
RECQL	1.0	0.89

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CARRIERS TNBC risk estimates by panel gene

BRCA1 OR=39.8; 95%CI=25.8-62.4

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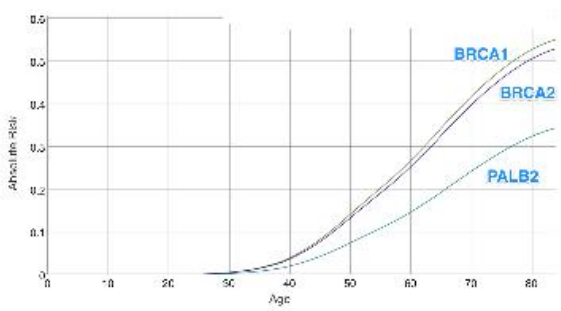
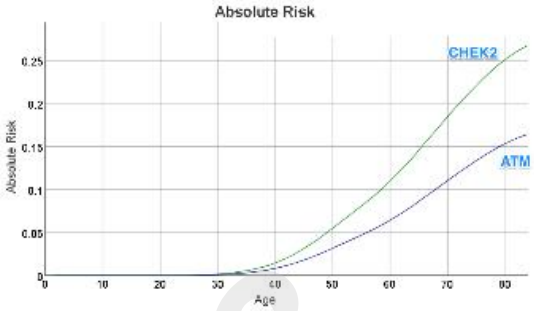
Lifetime risk estimates for overall breast cancer





Overall CARRIERS odds ratio extrapolated to SEER incidence rates

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Implications for Medical Management

Consider/Recommend Breast MRI	Discuss Option of RRM/ Consider based on family history	Unknown or insufficient evidence for BC risk	No increased BC Risk
ATM	*ATM*	*MLH1*	*BRIP1* ←
BRCA1	*BRCA1*	*MSH2*	
BRCA2	*BRCA2*	*MRE11A*	
CDH1	*CDH1*	*MSH6*	
CHEK2	*CHEK2*	*PMS2*	
NBN ←	*NBN* ←	*RAD50*	
NF1	*NF1*	*RAD51C* ←	
PALB2	*PALB2*	*RAD51D* ←	
PTEN	*PTEN*		
STK11	*TP53*		
TP53			
BARD1 ←			

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Summary for Panel Testing

- Testing of BRCA1, BRCA2, and moderate risk predisposition genes may result in improved clinical management of patients
- Accurate population-based and family history-based risk estimates for each gene are needed
- Age-related risks must be defined for improved medical management of mutation carriers

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