1513: Risks of Triple Negative Breast Cancer Associated with Cancer Predisposition Gene Mutations

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Abstract

Background: Multigene panel testing for hereditary cancer includes genes identified as hereditary breast and/or ovarian cancer (HBOC) genes despite limited data regarding the precise cancer risks associated with mutations in these genes. Here we report on risks of breast cancer and separately risks of triple negative breast cancer associated with mutations in 20 predisposition genes.

Methods: A cohort of 10,091 individuals with breast cancer, including 2,400 with triple negative breast cancer, were tested for mutations with the BreastNext and OvaNext clinical genetic testing panels. A further 2,100 individuals with triple negative breast cancer were tested for the same genes by custom capture-based sequencing. Case-control analyses were performed comparing the frequencies of pathogenic mutations from Caucasian breast cancer cases with frequencies from Caucasian study matched controls, and Caucasian, non-Finnish, non-TCGA controls from the ExAC database.

Results: Pathogenic mutations were identified in 9.6% of the BreastNext and OvaNext breast cancer cases. Mutations in the *ATM* and *CHEK2* genes were associated with moderate risks (OR>2) and mutations in *PALB2* were associated with high-risks (OR>5) of breast cancer. Pathogenic mutations in *MSH6* and *RAD51D* were associated with moderate risks of breast cancer. Predicted pathogenic missense mutations in *CHEK2*, *MSH2*, and *MSH6* were associated with moderate risks of breast cancer. In contrast, pathogenic mutations were observed in 13% of 4,500 triple negative breast cancers from the two studies. Mutations in the *PALB2*, *RAD51D*, and *BARD1* homologous recombination repair (HRR) genes were associated with high risks of triple negative breast cancer, whereas mutations in *BRIP1*, *RAD51C*, and *NBN* were associated with moderate risks.

Conclusion: This large breast and ovarian cancer case-control analysis provides useful data for predisposition genes previously lacking risk estimates, that will be useful for clinical risk management of patients. The study of triple negative breast cancer suggests that several HRR genes, previously excluded as moderate or high risk breast cancer genes, all have higher, clinically relevant risks of triple negative breast cancer.

Objectives

To estimate the risks of overall breast cancer and triple negative breast cancer associated with pathogenic mutations in cancer predisposition genes.

Background

Clinical genetic testing of individuals with a personal or family history of breast cancer using panels for *BRCA1/2* and other candidate cancer predisposition genes have become routine clinical practice. While the cumulative lifetime and age specific risks associated with mutations in *BRCA1/2* in high-risk families and in the general population are well understood, the risks of breast cancer associated with mutations in many of the other panel genes are not well defined.

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer that is defined as any breast cancer that does not express the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) genes.[2] Women diagnosed with TNBC are likely under the age of 40, which is lower than the median diagnosis age in the US of 61 years.[3,14] About 15% of women with TNBC are reported to be Caucasian, while nearly 25-55% are likely African American or Mexican.[1] Compared to other breast cancer subtypes, there is an increased risk of recurrence within 4 years of diagnosis and an increased mortality rate.

Mutations in *BRCA1/2* account for approximately 10% of unselected TNBC cases and up to 20% of TNBC from high-risk families. However, the contribution of mutations in other cancer predisposition genes to TNBC is not well defined. Couch, et al recently reported that 14% of 1824 unselected TNBC patients harbored germline mutations in *BRCA1/2, PALB2, BARD1, RAD51C, RAD51D, XRCC2,* and several other genes. Here we combined data from this unselected series of TNBC cases and panel testing data from Ambry Genetics to assess the influence of mutations in predisposition genes on TNBC.

Methods

Ambry Genetics Breast Next and OvaNext Study population

Study subjects included a nationwide sample of 15,087 patients referred for BreastNext or OvaNext panel testing between March 2012 and December 2014 by Ambry Genetics (Aliso Viejo, CA). Demographic and clinical history information was provided by the ordering clinician (Table 1), using test requisition forms, clinic notes or pedigrees. Rigorous clinical data curation standards were applied, with clinical notes and pedigree data taking precedent.

Ambry Genetics TNBC Study population

Study subjects included a nationwide sample of 4,049 TNBC patients referred for clinical hereditary panel testing between March 2012 and December 2015 by Ambry Genetics (Aliso Viejo, CA).

TNBCC Study population

Study subjects included 2149 TNBC cases obtained from general oncology clinics that were unselected for age of diagnosis or family history of cancer.

Multigene panel testing

BreastNext is comprised of genes implicated in breast cancer predisposition; OvaNext includes genes associated with ovarian, breast, or uterine cancer. Because BRCA1/2 were only included in the BreastNext and OvaNext panels after 06/13/2013, 1,885 individuals were not tested for BRCA1 or BRCA2 on the panels. Similarly, 2,503 individuals were not tested for RAD51D and NF1 before October 2013. BreastNext and OvaNext targeted custom capture and sequencing and targeted chromosomal microarray analysis were used to identify mutations. A five-tier variant classification system was applied to all alterations. Pathogenic mutations and likely pathogenic variants (VLPs) in each gene were pooled and compared between caucasian cases and ExAc non-TCGA NFE controls to estimate relative risks of breast cancer.

Table 1

Overall Triple Negative Cohort Demographics: TNBCC + Ambry

	Overall		TNBCC Cohort		Ambry TN Cohort	
	N	%	N	%	N	%
Total patients	6198		2149		4049	
Gender						
Female	5462	88.1	1417	65.9	4045	99.9
Male	2	0.03	-	-	2	0.05
Unknown	734	11.8	732	34.1	2	0.05
Ethnicity						
African-American	673	10.9	34	1.6	639	15.8
Ashkenazi-Jewish	119	1.9	-	-	119	2.9
Asian	163	2.6	10	0.5	153	3.8
Caucasian	4151	67.0	1785	83.1	2366	58.4
Hispanic	281	4.5	7	0.3	274	6.8
Other/Unknown	590	9.5	313	14.6	277	6.8
Age at Dx						
<50	2916	47.1	1008	46.9	1908	47.1
>50	3194	51.5	1076	50.1	2118	52.3
Unknown	65	1.05	65	3.02	23	0.57

*Ethnicity counts do not include Middle Eastern, Mixed, and Native American.
TNBCC: Triple Negative Breast Cancer Consortium

Table 2

Relative Risks for Breast Cancer by Gene in the Ambry Genetics Cohort

Gene	Case Mutation Carriers	Case AN	Control Mutation Carriers	Control AN	RR	95% CI-Lower	95% CI - Upper	P value
ATM	48	8330	88.0	53845	3.5	2.4	5.1	$8.2x10^{-11}$
BARD1	7	8330	27.0	54114	1.7	0.6	4.0	$2.1x10^{-1}$
BRIP1	14	8330	54.0	52856	1.6	0.8	3.0	$1.1x10^{-1}$
CDH1	4	8330	3.0	54339	8.7	1.5	59.4	$7.8x10^{-3}$
CHEK2	112	8330	244.0	48202	2.7	2.1	3.4	$1.1x10^{-15}$
MRE11A	7	8330	23.0	54029	2.0	0.7	4.8	$1.1x10^{-1}$
NBN	12	8330	41.0	52238	1.8	0.9	3.6	$7.1x10^{-2}$
NF1	10	7268	18.0	49396	3.8	1.6	8.6	$1.7x10^{-3}$
PALB2	30	8330	30.0	53394	6.4	3.7	11.0	$1.4x10^{-11}$
RAD50	17	8330	158.0	50997	0.7	0.4	1.1	$1.1x10^{-1}$
RAD51C	7	8330	32.0	54161	1.4	0.5	3.3	$3.5x10^{-1}$
RAD51D	4	7268	8.0	53574	3.7	0.8	13.7	$4.6x10^{-2}$

Results

Table 3

Relative Risks for Triple Negative Breast Cancer in Combined TNBCC and Ambry Genetics Studies

	TNBCC Cohort								Ambry TNBC Cohort								TNBCC & Ambry TNBC Cohorts							
Gene	Case Mutation Carriers	Case AN	Control Mutation Carriers	Control AN	RR	95% CI - Lower	95% CI - Upper	P-value	Case Mutation Carriers	Case AN	Control Mutation Carriers	Control AN	RR	95% CI - Lower	95% CI - Upper	P-value	Case Mutation Carriers	Case AN	Control Mutation Carriers	Control AN	RR	95% CI - Lower	95% CI - Upper	P-value
ATM	3	3930	88	53845	0.5	0.1	1.4	0.29	4	3558	88	53845	0.7	0.2	1.8	0.66	7	7488	88	53845	0.6	0.2	1.2	0.20
BARD1	10	3930	27	54114	5.1	2.2	10.9	$1.29x10^{-4}$	15	3558	27	54114	8.4	4.2	16.5	$1.42x10^{-8}$	25	7488	27	54114	6.7	3.7	12.0	$2.21x10^{-10}$
BRCA1	153	3930	83	53373	25.3	19.3	33.6	$1.50x10^{-116}$	183	5502	83	53373	21.6	16.6	28.4	$1.20x10^{-122}$	336	9432	83	53373	23.2	18.2	29.9	$1.30x10^{-194}$
BRCA2	48	3930	136	53345	4.7	3.3	6.6	$8.70x10^{-4}$	66	5502	136	53345	4.6	3.4	6.3	$6.91x10^{-20}$	114	9432	136	53345	4.7	3.6	6.0	$3.68x10^{-30}$
BRIP1	8	3930	54	52856	2.0	0.8	4.2	$7.50x10^{-2}$	4	3558	54	52856	1.1	0.3	3.0	0.79	12	7488	54	52856	1.6	0.8	3.0	0.19
CHEK2	1	3930	244	48202	0.1	0.0	0.3	$3.72x10^{-7}$	6	3560	244	48202	0.3	0.1	0.8	$4.63x10^{-3}$	7	7490	244	48202	0.2	0.1	0.4	$2.61x10^{-8}$
MRE11A	4	3930	23	54029	2.4	0.60	7.0	0.11	1	3558	23	54029	0.7	0.02	4.1	1.00	5	7488	23	54029	1.6	0.5	4.2	0.38
PALB2	21	3930	30	53394	9.5	5.2	17.2	$5.45x10^{-12}$	33	3654	30	53394	16.1	9.5	27.3	$5.19x10^{-23}$	54	7584	30	53394	12.7	8.0	20.5	$1.42x10^{-28}$
RAD50	5	3930	158	50997	0.3	0.1	0.8	$8.10x10^{-3}$	3	3558	158	50997	0.2	0.0	0.7	$2.02x10^{-3}$	8	7488	158	50997	0.3	0.1	0.6	$3.15x10^{-5}$
RAD51C	7	3930	32	54161	3.0	1.1	7.0	$1.47x10^{-2}$	4	3558	32	54161	1.9	0.5	5.4	0.28	11	7488	32	54161	2.5	1.1	5.1	$1.57x10^{-2}$
RAD51D	7	3930	8	53574	11.9	3.7	37.6	$2.74x10^{-6}$	5	3436	8	53574	9.7	2.5	33.8	$6.79x10^{-4}$	12	7366	8	53574	10.9	4.1	30.8	$4.77x10^{-7}$
TP53	2	3930	18	53777	1.5	0.2	6.4	0.64	8	5502	18	53777	4.3	1.6	10.5	$1.86x10^{-3}$	10	9432	18	53777	3.2	1.3	7.2	$5.40x10^{-3}$

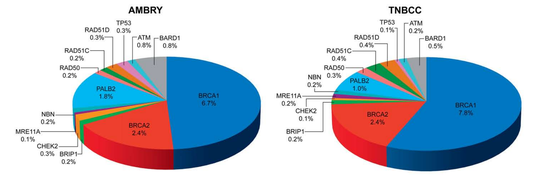
Table 4

Relative Risks of TNBC in combined TNBCC and Ambry Genetics Studies – Excluding cases with personal or family history of ovarian cancer

Gene	Case Mutation Carriers	Case AN	Control Mutation Carriers	Control AN	RR	95% CI-Lower	95% CI-Upper	P-value
ATM	7	6740	88	53845	0.6	0.3	1.4	0.25
BARD1	24	6740	27	54114	7.1	4.1	12.3	$<1.0X10^{-4}$
BRCA1	265	8338	83	53373	19.8	16.0	25.4	$<1.0X10^{-4}$
BRCA2	95	8338	136	53345	4.4	3.4	5.8	$<1.0X10^{-4}$
BRIP1	12	6740	54	52856	1.7	0.9	3.3	0.082
CHEK2	2	6742	244	48202	0.1	0.0	0.2	$<1.0X10^{-4}$
MRE11A	5	6740	23	54029	1.7	0.7	4.6	0.26
PALB2	48	6824	30	53394	12.5	7.9	19.8	$<1.0X10^{-4}$
RAD50	7	6740	158	50997	0.3	0.2	0.7	0.005
RAD51C	9	6740	32	54161	2.3	1.1	4.7	0.031
RAD51D	10	6642	8	53574	10.1	4.0	25.6	$<1.0X10^{-4}$
TP53	8	8338	18	53777	2.9	1.2	6.6	0.013

Figure 1

Mutation frequency in TNBCC and Ambry TNBC studies



Conclusions

- 14% of unselected TNBC cases in TNBCC and 14% of TNBC cases receiving clinical panel testing from Ambry Genetics have mutations in predisposition genes.
- Mutations in *BRCA1* and *BRCA2* account for 9.1%-10.2% of TNBC cases.
- *PALB2* and *CDH1* are high-risk breast cancer genes (RR>5.0), whereas *ATM, CHEK2, BRIP1, MRE11A, NF1,* and *RAD51D* may be moderate risk breast cancer genes (RR>2.0)
- *BRCA1, PALB2, BARD1,* and *RAD51D* may be high risk TNBC genes, whereas *BRCA2* and *RAD51C* may be moderate risk TNBC genes.
- Accounting for ovarian cancer personal and family history does not substantially alter these results.

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