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Predisposing Germline Mutations in an Unselected Academic Breast Cancer (BC) Cohort

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BACKGROUND

- Evaluation of women with breast cancer (BC) for germline mutations associated with hereditary breast and ovarian cancer (HBOC) has become increasingly common due to its impact on management.
- Guidelines for genetic evaluation indicate testing for cases with early onset, triple negative disease or family cancer history.
- However, the majority of breast cancer occurs in patients without these high risk characteristics.
- The prevalence of mutations associated with HBOC has not been well characterized in a cohort unselected for these traits.

METHODS

Patients

- We performed a cross sectional study using DNA from blood samples from consecutive new invasive BC patients seen at the Dana-Farber Cancer Institute (01/01/2010 to 07/31/2012) who consented to research.
- Patients with a previous breast cancer were excluded.
- Subjects were otherwise unselected.

Genetic Testing

- Mutations in 25 cancer genes were identified using a next generation sequencing based panel.
- Germline sequence variations and large rearrangements were classified for pathogenicity (Deleterious or Suspected Deleterious).
- Analyzed genes were categorized into 3 groups.
  - *BRCA1, BRCA2*
  - Breast Cancer Susceptibility Genes: *ATM, BARD1, BRIP1, CDH1, CHEK2, NBN, PALB2, PTEN, STK11, TP53*
  - Other Cancer Susceptibility Genes: *APC, BMPR1A, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6,* biallelic *MUTYH, PMS2, RAD51C, RAD51D, SMAD4*

Statistical Analysis

- Participant characteristics and sequencing results were summarized with descriptive statistics, including medians, means, and standard deviations for continuous data.
- For categorical data, proportions with 95% confidence intervals were calculated by the Clopper-Pearson method.
- Demographic, clinical, and pathologic characteristics were compared using the chi-square test (categorical variables) and the t-test/ANOVA (continuous variables). P-values less than 0.05 were considered significant.

RESULTS

Table 1. Clinical and Tumor Characteristics in Study Cohort (n=488)

Study Characteristic	Value	N	%
Age at Diagnosis	Mean (SD)	50.3 (11.3)	
	Median	49	
	Range	28-88	
Age at Diagnosis	≤45 years	180	36.9
	46-60 years	199	40.8
	>60 years	109	22.3
Race/Ethnicity	Ashkenazi Jewish (AJ)	38	7.8
	Non-Hispanic White (not AJ)	397	81.4
	Hispanic	17	3.5
	African-American	12	2.5
	Asian	10	2.0
	Other	14	2.9
Jewish Ashkenazi Ethnicity	Yes	38	7.8
	No	450	92.2
Breast Cancer Subtypes: Receptor Status	TNBC	87	17.8
	HR+/HER2–	301	61.7
	HR–/HER2+	37	7.6
	HR+/HER2+	63	12.9
Histology	Ductal	357	73.2
	Lobular	36	7.4
	Ductal & Lobular	68	13.9
	Other	27	5.5
Grade	1	60	12.3
	2	181	37.2
	3	246	50.5
Stage	I	185	37.9
	II	218	44.7
	III	85	17.4
Bilateral Disease	Yes	9	1.8
	No	479	98.2
Patient History of Prior Cancer*	Yes	41	8.4
	No	447	91.6
FDR with Any Cancer*^	Yes	271	56.7
	No	207	43.3
FDR/SDR with Any Cancer*^	Yes	403	84.3
	No	75	15.7
FDR/SDR with Breast or Ovarian Cancer*^	Yes	234	49.0
	No	244	51.0
FDR/SDR with Breast Cancer <50yrs, Male Breast Cancer, or Ovarian cancer (any age)*^	Yes	89	18.6
	No	389	81.4

SD: standard deviation; FDR: first degree relative; SDR: second degree relative
*Excludes in situ cancers and non-melanoma skin cancers.
^10 Patients were missing family history information. These patients are excluded from analysis. If age at diagnosis was unavailable, it was conservatively considered to be >50 years.

Table 2. Germline Mutations Identified (n=488)

Genes	# of Patients with DM	% with DM	95% CI
Any Deleterious Mutation*	52 (55 total)	10.7	8.1-13.7
All Genes Related to Breast Cancer*	49	10.0	7.5-13.1
BRCA1 or *BRCA2*	30	6.1	4.2-8.7
*BRCA1**	18	3.7	2.2-5.8
*BRCA2**	12	2.5	1.3-4.3
Other Genes Related to Breast Cancer*	20 (21 total)	4.1	2.5-6.3
*ATM**	4	0.8	0.2- 2.1
BRIP1	4	0.8	0.2- 2.1
CHEK2^*	10	2.1	1.0- 3.7
NBN	1	0.2	0.01-1.1
PALB2	1	0.2	0.01-1.1
PTEN	1	0.2	0.01-1.1
Genes Unrelated to Breast Cancer*	4	0.8	0.2-2.1
MSH6	1	0.2	0.01-1.1
*PMS2**	1	0.2	0.01-1.1
RAD51C	1	0.2	0.01-1.1
RAD51D	1	0.2	0.01-1.1

CI: confidence interval
*Three patients had DMs in two different genes (*BRCA2* and *ATM*, *BRCA1* and *PMS2*, *ATM* and *CHEK2*.
^8 of 10 DMs in *CHEK2* were 1100delc.
No DMs were identified in the following genes: *BARD1; CDH1; STK11; TP53; APC; BMPR1A; CDK4; CDKN2A p14; CDKN2A p16; EPCAM; MLH1; MSH2; MUTYH* (biallelic); *SMAD4*.

- 488 samples from eligible subjects were included (Table 1).
  - The mean age of breast cancer diagnosis was 50.3 years.
- A total of 55 deleterious mutations (DMs) were identified in 52/488 women tested (Table 2).
- 49/488 (10.0%, 95% CI 7.5-13.1%) women tested had at least one DM in a gene associated with breast cancer.
  - *BRCA1/2* mutations were found in 6.1% [95% CI 4.2-8.7%].
- Mutations in other BC-associated genes were found in 4.1% [95% CI 2.5-6.3%], particularly *CHEK2* (2.0%, 95% CI 1.0, 3.7%)
  - Two women were found to have 2 mutations in breast cancer-predisposing genes (*BRCA2* and *ATM*, *CHEK2* and *ATM*).
- 4 women had a mutation in another cancer susceptibility gene (Table 2).
  - One woman had a mutation in both *PMS2* and *BRCA1*.
- Of the 49 women with BC-related mutations, 20 (40.8%) had BC diagnosed after age 45 (Table 3).
  - For *BRCA1/2*, the prevalence of DMs decreased with age at breast cancer diagnosis.
  - The prevalence of DMs in other breast cancer genes did not change with age.
  - *BRCA1/2* mutations were found in 18.4% of Ashkenazi Jewish patients and 5.1% of non-Ashkenazi patients.
- Among 87 women with TNBC, 15 (17.2%) had a deleterious germline mutation, with 12 (13.8%) in *BRCA1/2* (Table 4).
- Among 243 women with no first or second degree relative with breast or ovarian cancer, 20 (8.2%) had a mutation.

Table 3. Frequency of Deleterious Mutation by Age at Breast Cancer Diagnosis

	≤45 years (N=180)		46-60 years (N=199)		>60 years (N=109)	
Genes	# of Patients with DM	% with DM (95% CI)	# of Patients with DM	% with DM (95% CI)	# of Patients with DM	% with DM (95% CI)
Any Deleterous Mutation*	30	16.7% (11.5%-22.9%)	15	7.5% (4.3%-12.1%)	7	6.4% (2.6%-12.8%)
All Genes Related to Breast Cancer*	29	16.1% (11.1%-22.3%)	14	7.0% (3.9%-11.5%)	6	5.5% (2.1%-11.6%)
BRCA1 or *BRCA2*	22	12.2% (7.8%-17.9%)	6	3.0% (1.1%-6.5%)	2	1.8% (0.2%-6.5%)
Other Genes Related to Breast Cancer*	8	4.4% (1.9%-8.6%)	8	4.0% (1.8%-7.8%)	4	3.7% (1.0%-9.1%)
Genes Unrelated to Breast Cancer*	2	1.1% (0.1%-4.0%)	1	0.5% (0.01%-2.8%)	1	0.9% (0.02%-5.0%)

*Three patients diagnosed <45 years old had DMs in two different genes (*BRCA2* and *ATM*, *BRCA1* and *PMS2*, *ATM* and *CHEK2*).

Table 4. Deleterious Mutations by Breast Cancer Subtype (N=488)

	TNBC (N=87)		HR+/HER2– (N=301)		HR–/HER2+ (N=37)		HR+/HER2+ (N=63)	
Genes	# of Patients with DM	% with DM (95% CI)	# of Patients with DM	% with DM (95% CI)	# of Patients with DM	% with DM (95% CI)	# of Patients with DM	% with DM (95% CI)
Any Deleterious Mutation*	15	17.2% (10.0%-26.8%)	26	8.6% (5.7%-12.4%)	4	10.8% (3.0%-25.4%)	7	11.1% (4.6%-21.6%)
All Genes Related to Breast Cancer*	14	16.1% (9.1%-25.5%)	24	8.0% (5.2%-11.6%)	4	10.8% (3.0%-25.4%)	7	11.1% (4.6%-21.6%)
BRCA1 or *BRCA2*	12	13.8% (7.3%-22.9%)	15	5.0% (2.8%-8.1%)	2	5.4% (0.7%-18.2%)	1	1.6% (0.04%-8.5%)
Other Genes Related to Breast Cancer*	2	2.3% (0.3%-8.1%)	9	3.0% (1.4%-5.6%)	2	5.4% (0.7%-18.2%)	7	11.1% (4.6%-21.6%)
Genes Unrelated to Breast Cancer*	2	2.3% (0.3%-8.1%)	2	0.7% (0.1%-2.4%)	0	0.0% (0.0%-9.5%)	0	0.0% (0.0%-5.7%)

TNBC: triple negative breast cancer; HR: hormone receptor; HER2: human epidermal growth factor receptor
*One TNBC patient had DMs in both *BRCA1* and *PMS2*. One HR+/HER2+ patient had DMs in both *BRCA2* and *ATM*. One HR–/HER2+ patient had DMs in both *BRCA1* and *PMS2*.

CONCLUSIONS

- In a single academic institution, 10.7% of new breast cancer patients had a germline mutation in a breast cancer predisposition gene, with 6.1% in *BRCA1/2* and 4.1% in another breast cancer-predisposition gene.
- The prevalence of non-*BRCA* mutations is similar to series of patients from high risk clinics and with family cancer history.
- Expanded testing identifies additional predisposing mutations, the utility of which are being defined for the care of breast cancer patients and their families. Carriers will often not be identified by factors predicting mutations in more established genes.

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