SPECTRUM OF MUTATIONS IDENTIFIED IN A 25-GENE HEREDITARY CANCER PANEL FOR PATIENTS WITH BREAST CANCER

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BACKGROUND

- Breast cancer is recognized as a component tumor in several well-described hereditary cancer syndromes, including Hereditary Breast and Ovarian Cancer (HBOC). Current National Comprehensive Cancer Network (NCCN) guidelines help identify patients with personal and/or family histories that should be tested for individual hereditary cancer syndromes; however, complex and limited patient histories can make it difficult to identify appropriate genetic testing.
- Advancements in next-generation sequencing allow health care providers to test for mutations in multiple cancer-predisposing genes simultaneously. This approach is especially useful in breast cancer patients, as there are many genes associated with increased breast cancer risk.
- The focus of this analysis was to determine the spectrum of gene mutations observed in patients with a personal history of breast cancer.

METHODS

- A commercial laboratory database was analyzed for patients with a personal diagnosis of breast cancer who underwent a 25-gene hereditary cancer panel between September 2013 and March 2015.
- The panel included *BRCA1*, *BRCA2*, *TP53*, *PTEN*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *APC*, *BMPR1A*, *CDH1*, *CDKN2A*, *MUTYH*, *SMAD4*, *STK11*, *CHEK2*, *PALB2*, *ATM*, *NBN*, *BARD1*, *BRIP1*, *CDK4*, *RAD51C* and *RAD51D*.
- Sequencing and large rearrangement were performed for all genes in the panel except *EPCAM*, for which only large rearrangement analysis was performed. All patient data regarding clinical history was obtained by health care provider report on the test requisition forms.
- HBOC testing criteria as defined by NCCN in 2013 were applied, excluding the contribution from prostate cancer, as we were unable to document the Gleason score. This may have resulted in an underestimate of the number of patients meeting HBOC testing criteria.
- Patients were included as meeting criteria for Lynch syndrome if the patient or a first- or second-degree relative met revised Bethesda criteria or had a diagnosis of endometrial cancer under age 50. These criteria may overestimate the number of patients determined to meet Lynch syndrome testing criteria.

RESULTS

- A total of 27,994 patients with a personal history of breast cancer were identified with 9.5% of females (2,638/27,669) and 16.6% of males (54/325) being positive for at least one deleterious or suspected deleterious mutation (Table 1).
  - 48.6% of mutations were detected in HBOC genes (*BRCA1* and *BRCA2*).
  - 42.9% of mutations were detected in other genes associated with breast cancer (Table 1).
  - 6.3% of mutations were detected in Lynch syndrome (LS) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*).
  - 2.1% of mutations were detected in other genes not associated with breast cancer (*APC*, *MUTYH*, *RAD51D*, *CDKN2A*, *SMAD4*).
- 73 patients were identified with two mutations. *BRCA1* or *BRCA2* accounted for at least one of the mutations in 50 patients.
- The majority of patients were diagnosed between the ages of 40 and 59.
- Figure 3 shows the distribution of mutations corresponding to patient age at diagnosis in 10-year intervals.
  - The majority of mutation-positive patients diagnosed with breast cancer before age 40 were identified as having a mutation in *BRCA1* or *BRCA2*.
  - Patients diagnosed between ages 40 and 59 had similar likelihoods of having a mutation in *BRCA1*/*BRCA2* or one of the 10 other breast cancer-predisposing genes on the panel.
  - Patients diagnosed over the age of 60 were more likely to have a mutation in a gene other than *BRCA1* or *BRCA2*.

TABLE 1. Mutation Distribution in Patients With a Personal History of Breast Cancer*

	Mutations in Females (N=2,710)		Mutations in Males (N=55)	
	n	%	n	%
Genes Associated with Breast Cancer				
BRCA1	653	24.1%	4	7.3%
BRCA2	644	23.8%	44	80.0%
CHEK2	329	12.1%	2	3.6%
ATM	276	10.2%	1	1.8%
PALB2	253	9.3%	1	1.8%
BRIP1	84	3.1%	1	1.8%
BARD1	54	2.0%	1	1.8%
TP53	52	1.9%	0	0%
RAD51C	50	1.8%	0	0%
NBN	45	1.7%	1	1.8%
CDH1	19	0.7%	0	0%
PTEN	15	0.6%	0	0%
STK11	2	0.1%	0	0%
Genes Not Associated with Breast Cancer				
PMS2	76	2.8%	0	0%
MSH6	52	1.9%	0	0%
MSH2	29	1.1%	0	0%
CDKN2A (p16)	24	0.9%	0	0%
RAD51D	17	0.6%	0	0%
MLH1	16	0.6%	0	0%
APC	11	0.4%	0	0%
Biallelic *MUTYH*	5	0.2%	0	0%
EPCAM	2	0.1%	0	0%
CDKN2A (p14)	1	0.04%	0	0%
SMAD4	1	0.04%	0	0%

*Includes pathogenic variants from 73 patients who have 2 mutations. Does not include 112 *APC* I1307K mutations.

FIGURE 1. NCCN Testing Criteria Adherence for Patients with a Personal History of Breast Cancer

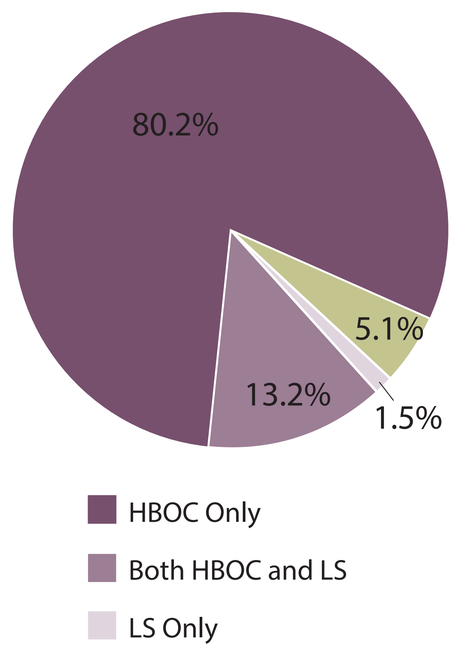
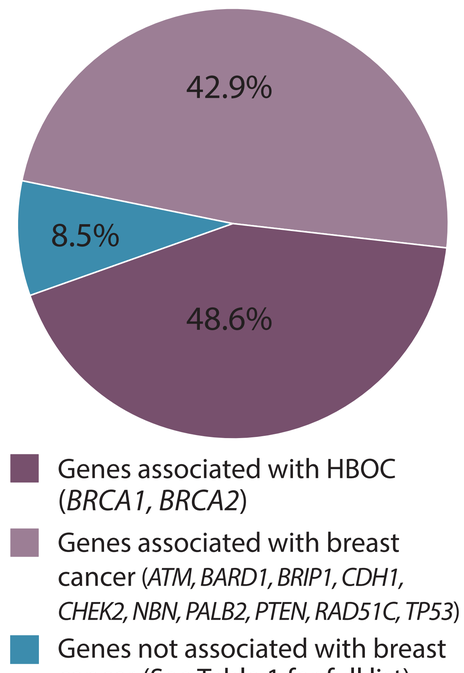
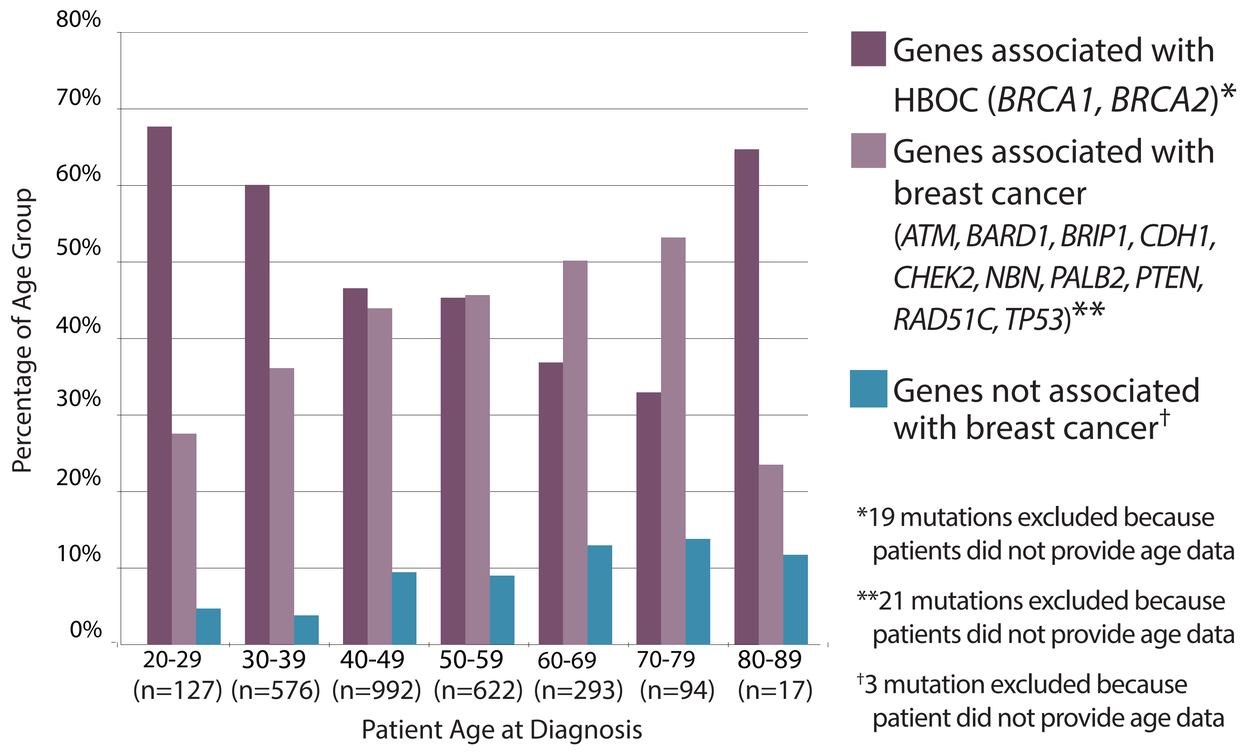


FIGURE 2. Mutations Identified in Patients with a Personal History of Breast Cancer*



*Includes patients with 2 mutations

FIGURE 3. Age at Diagnosis by Gene Mutation Type



*19 mutations excluded because patients did not provide age data

**21 mutations excluded because patients did not provide age data

†3 mutation excluded because patient did not provide age data

CONCLUSIONS

- Testing of patients with a personal history of breast cancer using a 25-gene panel identified 51.4% of mutations in genes other than *BRCA1* and *BRCA2*. This represents a 105.6% increase in mutations identified by *BRCA1* and *BRCA2* testing only.
- 8.5% of patients had a mutation in a gene not associated with breast cancer, but with significant other cancer risks that can now be addressed. This includes genes with a significant colorectal cancer risk (LS genes and *APC*) that would have been missed in a breast cancer-specific panel.
- 73 patients were found to have more than one mutation, providing the opportunity to appropriately modify medical management for these patients and their family members.

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