Women with Breast and Uterine Cancer Have Increased Risk for Genetic Mutations: A Case-Control Analysis (Abstract # 1549)

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BACKGROUND

- In 2015, the most common cancers that will impact women are breast and uterine cancer with an estimated 250, 000 cases to be diagnosed in the United States.[1]
- Multi-gene panels have given clinicians more options regarding genetic testing for patients with both breast and uterine cancer (BUC).[2]
- Expanded genetic testing for patients with BUC may help guide management by identifying patients who may benefit from additional surveillance, including at-risk family members.[3,4]

METHODS

- Clinical histories for patients who underwent comprehensive analysis of 6-28 genes, depending on the panel ordered, at a single commercial laboratory (Ambry Genetics, Aliso Viejo, CA) were retrospectively reviewed to select cases with a history of both breast and uterine cancer.
- Gene-specific mutation frequencies were calculated for BUC cases and compared with matched female controls from two groups: 1) no reported personal cancer history (n=3,149) and 2) personal history of breast cancer only (BC) who were also referred for multi-gene panel testing (n=10,154).
- For selected genes, Fisher's exact tests were used to examine the association between case/control status and mutation carrier status. Wilcoxon rank-sum tests were used to compare personal/family histories of case/control groups and evaluate potential confounding factors. Multivariate regression analysis was also performed to test associations after controlling for the personal/family history (such as a history of breast, ovarian, colorectal, thyroid, gastric, pancreatic, and/or prostate cancer).

TABLE 1. DEMOGRAPHICS OF 319 BUC CASES

Ethnicity	n	%	Panel Ordered	n	%	Additional Personal Cancer History	n	%	Family Cancer History[3]	n	%
African American/Black	16	5.0	BRCAplus	93	29.2	breast<50[1]	110	35.7	breast	125	39.2
Alaskan Native	0	0.0	BreastNext	31	9.7	endometrial<50[2]	86	28.1	breast<50	49	15.4
Ashkenazi Jewish	12	3.8	GynPlus	28	8.8	ovarian	14	4.4	uterine	31	9.7
Asian	8	2.5	ColoNext	12	3.8	colorectal	26	8.2	uterine<50	14	4.4
Caucasian	257	80.6	CancerNext	85	26.6	colorectal<50	8	2.5	ovarian	11	3.5
Hispanic	11	3.4	OvaNext	66	20.7	thyroid	17	5.3	colorectal	51	16.0
Middle Eastern	3	0.9	PancNext	2	0.6	gastric	2	0.6	colorectal<50	8	2.5
Mixed Ethnicity	12	3.8	RenalNext	2	0.6	pancreatic	3	0.9	thyroid	12	3.8
Native American	0	0.0							gastric	11	3.5
Other	0	0.0							pancreatic	18	5.7
									prostate	32	10.1

[1] ages not provided for 11 patients; [2] ages not provided for 13 patients; [3] family history not provided for 1 patient

FIGURE 1. BUC MUTATION SPECTRUM

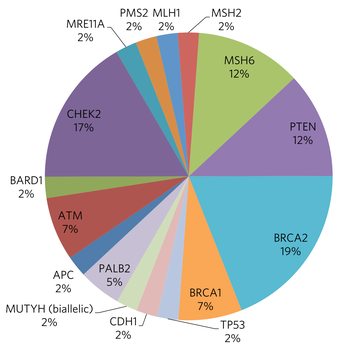
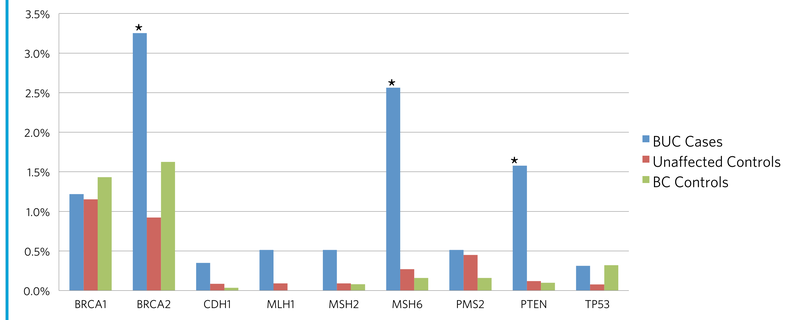


TABLE 2. BUC PATIENTS COMPARED TO CONTROLS

	BUC vs. NO-CANCER CONTROLS						BUC vs. BC CONTROLS					
	Mutation Frequency		Fisher's Exact Results			Multivariate	Mutation Frequency		Fisher's Exact Results			Multivariate
Gene	Cases % (N)	Controls % (N)	Odds Ratio	Odds Ratio (95% CI)	P-value	P-value	Cases % (N)	Controls % (N)	Odds Ratio	Odds Ratio 95% CI	P-value	P-value
BRCA1	1.2% (3/246)	1.2% (25/2170)	1.06	[0.20,3.51]	0.759	0.894	1.2% (3/246)	1.4% (111/7747)	0.85	[0.17,2.58]	1	0.723
BRCA2	3.3% (8/246)	0.9% (20/2170)	3.61	[1.36, 8.67]	0.005*	0.015*	3.3% (8/246)	1.6% (126/7747)	2.03	[0.85,4.20]	0.069	0.187
CDH1	0.3% (1/287)	0.1% (2/2317)	4.04	[0.07,77.78]	0.296	1	0.3% (1/287)	0.03% (3/8755)	10.2	[0.19,127.24]	0.121	6.97e-4*
MLH1	0.5% (1/195)	0.1% (1/1114)	5.73	[0.07,449.02]	0.276	0.994	0.5% (1/195)	0% (0/1247)	-	-	-	-
MSH2	0.5% (1/195)	0.1% (1/1114)	5.73	[0.07,449.02]	0.276	0.994	0.5% (1/195)	0.1% (1/1247)	6.41	[0.08,502.38]	0.252	0.05*
MSH6	2.6% (5/195)	0.3% (3/1114)	9.72	[1.87,63.15]	0.003*	0.022*	2.6% (5/195)	0.2% (2/1247)	16.32	[2.65,172.39]	7.2e-4*	3.88e-4*
PMS2	0.5% (1/195)	0.4% (5/1114)	1.14	[0.02,10.30]	1	0.127	0.5% (1/195)	0.2% (2/1247)	3.21	[0.05,61.89]	0.354	0.251
PTEN	1.6% (5/317)	0.1% (3/2509)	13.36	[2.59,96.41]	0.0007*	0.03*	1.6% (5/317)	0.1% (9/9050)	16.08	[4.21,53.76]	6.7e-5*	1.23e-7*
TP53	0.3% (1/319)	0.1% (2/2576)	4.05	[0.07,77.77]	0.296	0.983	0.3% (1/319)	0.3% (29/9068)	0.98	[0.02,5.95]	1	0.371

*Statistically significant

FIGURE 2. GENE-SPECIFIC MUTATION FREQUENCIES



*Statistically significant association between BUC and at least one control group

RESULTS

- 319 women with BUC were identified and approximately 13% (n=42) were found to have gene mutations. Additional personal and family history information is available in Table 1.
- Analysis of gene-specific mutation frequencies revealed that mutations in *BRCA2*, *MSH6*, and *PTEN* were more frequent among BUC cases than controls who did not report a personal history of cancer (Table 2, Figure 2).
- When comparing BUC cases to BC controls, *MSH6* and *PTEN* mutations were also observed at an increased frequency; however, mutations in *BRCA2* were not (Table 2, Figure 2). *BRCA2* mutations were significantly more common in the BUC group when compared to matched BC controls who may have had other cancers, but not uterine canner (p=0.037, data not shown).
- Of the 18 BUC cases with *BRCA2*, *MSH6*, or *PTEN* mutations, the majority (n=14, 77.8%) had clinical histories suggestive of the respective genetic syndromes. The remaining four patients (2 *PTEN*, 1 *BRCA2*, 1 *MSH6*) did not meet testing criteria for the respective syndromes based on the clinical history information provided.

CONCLUSIONS

- It is important to consider Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Lynch syndrome, and Cowden syndrome when evaluating women with a history of both breast and uterine cancer.
- Multi-gene hereditary cancer panels are an efficient way to test BUC patients for all relevant hereditary cancer syndromes.
- While it was not surprising that women with BUC were at an increased risk of Cowden Syndrome, statistically significant increased frequencies of mutations in genes associated with Lynch Syndrome and HBOC were observed as well. Further studies are needed to explore these potential links.

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