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Women with breast and uterine cancer are more likely to harbor germline mutations than women with breast or uterine cancer alone: A case for expanded gene testing

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HIGHLIGHTS

- Germline mutations are more frequent among women with breast and uterine cancer compared to women with either cancer alone.
- Genes most frequently mutated in women with breast and uterine cancer have published management guidelines that impact care.
- Multigene panel testing is warranted for women with breast and uterine cancer.

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ABSTRACT

Objective. We explored the germline mutation spectrum and prevalence among 1650 women with breast and uterine cancer (BUC) who underwent multi-gene hereditary cancer panel testing at a single commercial laboratory.

Methods. The combined frequency of mutations in 23 BC and/or UC genes was compared between BUC cases and control groups with (1) no personal cancer history; (2) BC only; and (3) UC only using logistic regression.

Results. Fourteen percent (n = 231) of BUC cases tested positive for mutations in BC and/or UC genes and were significantly more likely to test positive than individuals with BC only ($P < 0.001$), UC only ($P < 0.01$), or unaffected controls ($P < 0.001$). Analysis of gene-specific mutation frequencies revealed that *MSH6*, *CHEK2*, *BRCA1*, *BRCA2*, *ATM*, *PMS2*, *PALB2* and *MSH2* were most frequently mutated among BUC cases. Compared to BC only, *BRCA1*, *MLH1*, *MSH2*, *MSH6*, *PMS2* and *PTEN* mutations were more frequent among BUC; however, only *ATM* mutations were more frequent among BUC compared to UC only. All of the more commonly mutated genes have published management guidelines to guide clinical care. Of patients with a single mutation in a gene with established testing criteria (n = 152), only 81.6% met their respective criteria, and 65.8% met criteria for multiple syndromes.

Conclusions. Women with BUC are more likely to carry hereditary cancer gene mutations than women with breast or uterine cancer alone, potentially warranting expanded genetic testing for these women. Most mutations found via multi-gene panel testing in women with BUC have accompanying published management guidelines and significant implications for clinical care.

1. Background

Breast cancer (BC) and uterine cancer (UC) are the first and fourth most common cancers diagnosed in women, respectively, with a combined total of approximately 314,000 cases diagnosed in the United States in 2017 [1]. Identifying women who may be at increased risk for developing these relatively common cancers remains one of the primary goals of the oncology community, and recent advances in genetic testing for hereditary cancers are improving the detection of high-risk women [2].

Over twenty genes have been associated with increased risk for BC in published literature [3,4], and several have been associated with

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increased risk for UC [5]. Multi-gene panel testing was developed to allow clinicians to test multiple genes with overlapping phenotypes simultaneously. Next-generation sequencing, or massively parallel sequencing, significantly decreased the cost of DNA sequencing leading to the availability of multi-gene panel testing. Utilization of multi-gene panel testing has enabled the identification of mutations in previously well-defined cancer predisposition syndromic genes such as *CDH1*, *PTEN*, *TP53*, and others in patients with atypical phenotypes who did not meet testing guidelines [6]. This both improves understanding of the true phenotypic spectrum of these syndromes and provides diagnostic answers for more patients.

Many studies have shown that multi-gene panel testing is able to identify additional actionable mutations in BC cohorts that would not have been detected with traditional single-syndrome testing strategies [7–9]. A recent study found similar results in a UC cohort. Using multi-gene panel testing, they found deleterious mutations in 9.2% of their EC patients, and approximately one third of these mutations were in genes not associated with either Lynch syndrome or Cowden syndrome [10]. Despite the fact that genetic testing for hereditary syndromes associated with BC and/or UC has been available for over two decades and, more recently, that multi-gene panel testing has been shown to be feasible and to have good clinical utility for both of these cancer types, very little literature exists on the genetic testing outcomes for patients with both BC and UC (BUC). To date, the only well-established shared link between breast and uterine cancer susceptibility is through mutations in the *PTEN* gene, implicated in Cowden syndrome [11], and knowledge remains limited regarding the prevalence of genetic mutations among women diagnosed with BUC despite a recent national survey demonstrating patient interest [12].

The aim of the current study was to assess the overall mutation detection rate and mutation spectrum found in BUC patients who underwent multi-gene panel testing compared to women with BC only, UC only, or no personal cancer history. To investigate the genetic contribution to BUC, we assessed a cohort of BUC patients who underwent multi-gene panel testing for hereditary cancer susceptibility at one commercial laboratory from July 2013 to December 2016. This BUC cohort was compared to control groups consisting of women diagnosed with BC only, UC only, or no personal history of cancer who were also sent to the same laboratory for multi-gene panel testing. Expanded testing for patients with BUC can help guide management by identifying more patients who may benefit from additional surveillance, along with at-risk family members.

2. Methods

2.1. Study population

Clinical histories for a cohort of 51,918 patients who underwent multi-gene panel testing encompassing BC and/or UC indications at a single commercial laboratory (Ambry Genetics, Aliso Viejo, CA) were retrospectively reviewed to select cases with a history of both BC and UC and three female comparison groups consisting of unrelated women with (1) no reported personal cancer history; (2) personal history of BC only; and (3) personal history of UC only. This study was exempted from review by Western Institutional Review Board.

2.2. Laboratory methods

Patients underwent comprehensive analysis of 5–49 cancer susceptibility genes, depending on the panel ordered (Supplemental Table S1). With the exception of *GREM1*, *EPCAM*, and *MITF* (Supplemental Table S1), all genes were analyzed by Sanger or next-generation sequencing analysis of all coding domains, as well as at least five nucleotides into the flanking 5′ and 3′ ends of all the introns and untranslated regions, along with gross deletion/duplication analysis of covered exons and untranslated regions.

All variants, with the exception of previously characterized benign alterations, underwent thorough assessment and review of available evidence (e.g., population frequency information, published case reports, case/control and functional studies, internal co-occurrence and co-segregation data, evolutionary conservation, and in silico predictions). Variants were further classified per Ambry's five-tier variant classification protocol (pathogenic mutation; variant, likely pathogenic; variant of unknown significance; variant, likely benign; and benign) which is based on published recommendations/guidelines by the American College of Medical Genetics and Genomics and the International Agency for Research on Cancer [13–15]. Individuals with suspected somatic interference or mosaicism based on lower-than-expected allelic frequency on next-generation sequencing and Sanger sequencing results consistent with a mosaic variant call were excluded from analysis [16].

2.3. Clinical history analysis

Clinical histories of BUC cases were reviewed for personal and family history of cancer, age at cancer diagnoses, estrogen receptor status for BC diagnoses, and uterine histopathology. Sources of clinical data included clinician-completed test requisition forms and, in some cases, clinic notes and/or pedigrees submitted by the ordering clinician. BUC cases and UC controls were excluded if a non-epithelial histopathology was reported ($n = 29$). BUC cases harboring mutations in genes with established testing criteria (National Comprehensive Cancer Network criteria for *BRCA1/2*, *TP53*, Lynch syndrome, and Cowden syndrome testing) were reviewed to determine whether the respective testing criteria were met [17].

2.4. Statistical analysis

Gene-specific mutation frequencies were calculated for 23 genes implicated in hereditary BC and/or UC (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *EPCAM*, *MLH1*, *MRE11A*, *MSH2*, *MSH6*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11* and *TP53*) among BUC cases and all three female comparison groups. Due to the heterogeneity of multigene panel tests ordered and performed among patients, women were only included in the analyses if their multigene panel testing included all 23 genes. For each gene and all genes combined, we compared mutation frequencies in BUC cases with each comparison group (BC-only, UC-only, and cancer-free controls) using logistic regression, adjusted for race/ethnicity (self-reported), personal history of multiple primary BCs and family history of cancers (breast, ovarian, colorectal, endometrial, thyroid, gastric, pancreatic, and prostate cancers) among first- and second-degree relatives. In the comparison of BUC cases versus BC-only and UC-only groups, we additionally controlled for BC and UC diagnosis age, respectively.

3. Results

3.1. Clinical characteristics

In total, 1650 women with BUC were analyzed in this study after excluding 4 with mosaic variant calls. BUC cases were primarily Caucasian (70.5%) and age 50 years or older at the time of testing (94.4%, Table 1). Multiple primary BCs were reported in 17.4% of BUC cases and 24.5% reported additional cancer primaries beyond BC and UC (Table 1, Supplemental Table S2). Regarding the timing of BC and UC diagnoses, 48.4% of patients were diagnosed with BC before UC, 39.6% were diagnosed with UC prior to BC, 8.4% reported synchronous BC and UC diagnoses, and the remaining 3.6% were unclear regarding the order of cancer diagnoses due to missing information on the test requisition form (Table 1). The median age at first BC diagnosis was 56 years (IQR 48, 65) and the median age at UC diagnosis was 58 years (IQR 50, 65) (Table 1). Of patients diagnosed with BC first, estrogen receptor status was reported as positive for 28.7%, negative for 9.9%, and was not reported for 61.5%

(Table 1). Of the 13.9% of BUC cases for whom UC pathology was provided, 88% were adenocarcinomas or other epithelial cancers and 12% were mixed epithelial and mesenchymal cancers. Demographic information for BC, UC, and cancer-free control groups is provided in Supplemental Table S3.

3.2. Diagnostic yield

Overall, 231 (14.0%) BUC patients were identified to carry at least one pathogenic mutation/likely pathogenic variant including 219 (13.3%) with a single mutation or biallelic *MUTYH* mutations and 12 (0.7%) with mutations in two different genes. Furthermore, 146 (8.9%) had a mutation in a BC gene (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *MRE11A*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *RAD50*, *RAD51C*, and *RAD51D*), and 78 (4.7%) had a mutation in a UC gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*). Seven (0.4%) BUC patients tested positive for a mutation in *PTEN*, the only gene with well-described associations with both BC and UC. *MSH6*, *CHEK2*, *BRCA1*, *BRCA2*, and *ATM* were the most frequently mutated genes among BUC cases, even when separating those with BUC only and BUC with additional cancer types (Table 2, Fig. 1). Additionally, six mutations were detected in genes not known to be associated with either BC or UC. Gene-specific mutation frequencies for other genes tested not currently associated with BC and/or UC are shown in Supplemental Table S4. Overall diagnostic yield ranged from 8.3% to 17.8% depending on the panel ordered, and also varied based on personal history of other primary cancer diagnoses (Supplemental Table S5).

For individuals with a single mutation in any of the genes with established testing/diagnostic criteria (n = 152), clinical histories were assessed to determine whether such criteria were met for the respective hereditary cancer syndrome. Overall, 92.8% of patients met criteria for any of these syndromes, however, only 81.6% (n = 124) of these mutation-positive patients met their respective testing criteria, and 65.8% met criteria for multiple syndromes (Table 3). Of BUC patients with a mutation in *BRCA1* or *BRCA2*, 90.5% met hereditary breast and ovarian cancer testing criteria. The percentage of patients meeting Lynch syndrome criteria was 80.8% for those with mutations in a mismatch repair gene, and only 42.9% of BUC patients with *PTEN* mutations met Cowden syndrome diagnostic criteria. All BUC patients with mutations in *MLH1*, *PTEN* and *TP53* met criteria for at least one syndrome, while *PMS2* mutation carriers were least likely to meet any criteria.

3.3. Gene-phenotype association analysis

Among 730 BUC patients tested for all 23 BC and UC genes, mutations were more frequently detected in established BC genes compared to established UC genes ($P < 0.001$). Overall, mutations were significantly more frequent among BUC cases (14.0%) compared to women with BC only (9.3%), UC only (11.5%), or no personal history of cancer (6.8%) (Table 4). Mutations in *ATM*, *BARD1*, *BRCA2*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, and *PTEN* were more frequent among BUC cases than controls who did not report a personal history of cancer. Compared to women with BC only, *BRCA1*, *MLH1*, *MSH2*, *MSH6*, *PMS2* and *PTEN* mutations were more frequent among those with BUC; notably, women with BUC were twice as likely to have a mutation in *BRCA1* as those with BC only (OR = 2.01, 95% CI = 1.08–3.39, P = 0.016). However, compared to women with UC, only *ATM* mutations were more frequent among BUC (OR = 5.27, 95% CI = 1.73–19.48, P = 0.01), although sample size was more limited for these comparisons.

4. Discussion

Recent studies have demonstrated the importance of genetic testing in identifying BC and UC patients at risk for hereditary cancer syndromes as more clinicians are now ordering multi-gene panel testing for their patients with either of these relatively common cancer types [10,18]. To our knowledge this is the first study examining the frequency of genetic mutations in patients with BUC. In this study population of patients undergoing multi-gene panel testing at a single commercial laboratory, those with BUC were more likely to be mutation carriers than BC only patients, UC only patients, or those without a personal diagnosis of cancer. There was no overlap in the genes found to be more frequently mutated in the BUC group when compared to either BC or UC. This lack of overlap between genes showing significant associations with BUC compared to BC or UC suggests that BC, UC or their interaction may be responsible for the positive result. Mutations in *BRCA1* (a BC gene), *MLH1*, *MSH2*, *MSH6*, *PMS2* (UC genes) and *PTEN* (a BC and UC gene) demonstrated a stronger association with UC in this study while only *ATM* mutations were found to have a stronger association with BC. Comparisons with UC should be interpreted with caution based on the limited sample size relative to the other two groups.

When assessing BUC patients for underlying hereditary cancer susceptibility, it may be difficult to predict which gene(s) may be positive in the absence of other personal or family history suggestive of a specific cancer predisposition syndrome. Nearly 20% of mutation-positive BUC patients did not meet testing criteria for the respective gene/syndrome. One recent study found that >27% of patients who underwent multi-gene panel testing for common cancer types were found to carry mutations in genes for which they did not meet testing criteria [19]. With regards to Cowden syndrome, the ability to assess for clinical testing criteria was limited, as clinical documentation of non-cancerous features of Cowden syndrome such as macrocephaly and mucocutaneous lesions was not documented or performed in most cases. However, for the other hereditary cancer syndromes investigated, genetic testing criteria are based on personal and family history of cancers that are typically reported with a high level of completeness and accuracy on test requisition forms [20].

Conversely, patients may present with clinical histories suggestive of multiple cancer predisposition syndromes, supporting a multi-gene panel testing approach for BUC patients. In the current study, 65.8% of patients met testing criteria for more than one of the following syndromes: hereditary breast and ovarian cancer, Lynch syndrome,

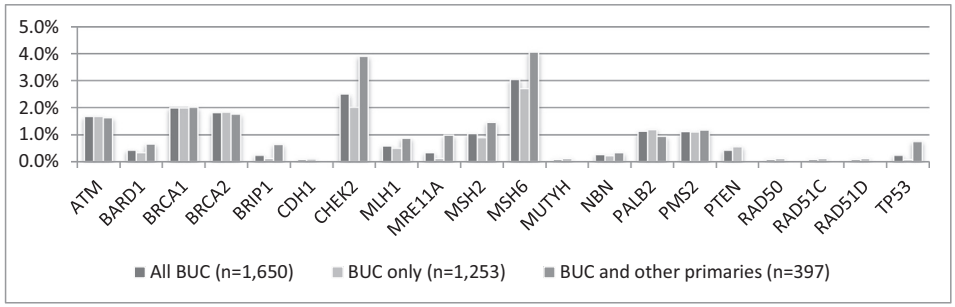

Fig. 1. Gene-specific mutation frequency stratified by history of additional cancer primaries.

Table 1
Demographics and clinical history of BUC cases.

Characteristic	n	%
Ethnicity		
African American/Black	92	5.6
Ashkenazi Jewish	102	6.2
Asian	54	3.3
Caucasian	1163	70.5
Hispanic	66	4.0
Other/Mixed Ethnicity	86	5.2
Unknown	87	5.3
Age at testing		
Under 30	1	0.1
30–39	11	0.7
40–49	80	4.8
50–59	346	21.0
60–69	670	40.6
70–79	428	25.9
80 or over	114	6.9
Age at BC/UC cancer diagnosis		
Median age at BC diagnosis (IQR)	56 (48,65)	
Median age at UC diagnosis (IQR)	58 (50,65)	
Timing of BC and UC diagnoses		
Synchronous BC & UC diagnosis	139	8.4
Diagnosed with BC first	799	48.4
Median (IQR) time between BC and UC diagnosis (years)	10 (5,16)	
Diagnosed with UC first	653	39.6
Median (IQR) time between UC and BC diagnosis (years)	8 (4,17)	
Unknown	59	3.6
Estrogen receptor status (if diagnosed with BC first)		
Estrogen receptor-positive BC	229	28.7
Estrogen receptor-negative BC	79	9.9
Estrogen receptor status unknown	491	61.5
UC pathology		
Adenocarcinoma - endometrioid	70	4.2
Adenocarcinoma - serous	52	3.2
Adenocarcinoma - clear cell	11	0.7
Adenocarcinoma - mixed	8	0.5
Adenocarcinoma - mucinous	3	0.2
Adenocarcinoma - NOS	55	3.3
Epithelial - other	2	0.1
Mixed epithelial and mesenchymal	28	1.7
Not Provided	1421	86.1
Personal cancer history		
Multiple primary BCs	287	17.4
Other primary cancers	405	24.5
Ovarian	92	5.6
Colorectal	88	5.3
Pancreatic	7	0.4
Thyroid	56	3.4
Gastric	4	0.2
Family cancer history[a]		
BC	952	57.7
Ovarian	202	12.2
UC	273	16.5
Colorectal	485	29.4
Pancreatic	186	11.3
Prostate	309	18.7
Thyroid	73	4.4
Gastric	207	12.5
Prior *BRCA1/2* testing		
Yes	248	15.0
No	1402	85.0

BC: breast cancer; UC uterine cancer.
[a] First- and second-degree relatives only.

Table 2
Gene-specific mutation frequencies among all BUC cases.

Associated cancer type	Gene	n, mutation carrier(s)	n, tested	Mutation frequency (%)
Breast	*ATM*	20	1201	1.67
	BARD1	5	1179	0.42
	BRCA1	33	1650	2.00
	BRCA2	30	1650	1.82
	BRIP1	3	1202	0.25
	CDH1	1	1369	0.07
	CHEK2	30	1201	2.50
	MRE11A	4	1179	0.34
	MUTYH	1	1179	0.08
	NBN	3	1179	0.25
	NF1	0	1129	0.00
	PALB2	14	1245	1.12
	RAD50	1	1179	0.08
	RAD51C	1	1202	0.08
	RAD51D	1	1152	0.09
	STK11	0	1185	0.00
	TP53	4	1650	0.24
Uterine	*EPCAM*	0	1341	0.00
	MLH1	8	1341	0.60
	MSH2	14	1341	1.04
	MSH6	41	1341	3.06
	PMS2	15	1341	1.12
Both	*PTEN*	7	1650	0.42

Cowden syndrome, and Li-Fraumeni syndrome. In addition, some patients who undergo multi-gene panel testing with larger panels will be found to carry mutations in genes that are not known to be associated with the cancer(s) the patient presented with. Therefore, genetic counseling to discuss the implications of these likely unexpected results is an important component of any clinical multi-gene panel testing protocol. Mutations detected in genes that appear unrelated to the patient's personal and/or family history of cancer can lead to the discovery of additional cancer risks, potential additional screening recommendations, and a discussion of genetic testing recommendations for the patient's relatives.

Cowden syndrome is the one hereditary cancer syndrome that encompasses well-documented increased risk for both BC and UC [11]. Increased UC risk has been well established as part of the cancer spectrum of Lynch syndrome [10,21], but the link between Lynch syndrome and BC remains controversial. As demonstrated by a large meta-analysis assessing BC risk in Lynch syndrome, several studies found no increased risk for BC in Lynch syndrome cohorts while others reported between a two- and 13-fold increase in BC risk for women with mutations in the mismatch repair genes [22]. Additionally, a recent study found an increase in BC risk associated with mutations in the *MSH6* and *PMS2* mismatch repair genes, but no such association with *MLH1* or *MSH2* mutations [23]. The current study did not find an association between any of the mismatch repair genes and BC, as there was no significant difference in the prevalence of mismatch repair gene mutations between the BUC group and UC controls.

In addition, the possible link between UC and hereditary breast and ovarian cancer is not well established. Some studies have reported increased risk for UC, especially serous/serous-like endometrial carcinoma, in *BRCA1* mutation carriers [24,25], while others have found that the increase in UC seen in *BRCA1/2* mutation carriers is largely, but not completely, accounted for by the development of endometrioid carcinomas in women who received tamoxifen for BC treatment or prophylaxis [26–28]. Although the use of tamoxifen is recommended as an option for breast cancer risk reduction, limited data is available regarding it's efficacy among BRCA carriers [29–30]. In the current study, breast cancer diagnosis preceded uterine cancer in 48% of patients, and information regarding Tamoxifen use was not provided by ordering clinicians for the majority of these patients. In addition, histologic subtype was only provided for 8.9% of BUC patients in this cohort, limiting the ability to stratify results by subtype. Despite these limitations, this study found that women with BUC were twice as likely to have a mutation in *BRCA1* as those with BC only.

This study is limited by its retrospective nature and the use of genetic tests that varied in the number of analyzed genes. To minimize potential biases introduced by the heterogeneity of the testing population, analysis was limited to patients tested for at least 23 genes associated with BC and/or UC. Other potential confounders in this dataset include history of prior genetic testing (e.g. previous *BRCA1/2* testing or MSI/

Table 3
Mutation-positive BUC cases meeting criteria for hereditary breast and/or uterine cancer syndromes.

Gene	Mutation-positive cases	Hereditary breast and ovarian cancer syndrome (*BRCA1/2*)	Cowden syndrome (*PTEN*)[a]	Li-Fraumeni syndrome (*TP53*)	Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM)	Met respective criteria	Met any criteria	Met multiple criteria
						n,%	n,%	n,%
BRCA1	33	31	0	9	22	31 (93.9)	31 (93.9)	23 (69.7)
BRCA2	30	26	0	6	18	26 (86.7)	29 (96.7)	17 (56.7)
EPCAM	0	0	0	0	0	0 (0.0)	0 (0.0)	0 (0.0)
MLH1	8	8	0	0	8	8 (100.0)	8 (100.0)	8 (100.0)
MSH2	14	11	0	2	13	13 (92.9)	13 (92.9)	11 (78.6)
MSH6	41	31	0	2	32	32 (78.0)	38 (92.7)	25 (61.0)
PMS2	15	8	0	0	10	10 (66.7)	11 (73.3)	7 (46.7)
PTEN	7	5	3	0	5	3 (42.9)	7 (100.0)	5 (71.4)
TP53	4	4	0	1	4	1 (25.0)	4 (100.0)	4 (100.0)
Total	152	124	3	20	112	124 (81.6)	141 (92.8)	100 (65.8)

[a] In most cases, comprehensive evaluation for mucocutaneous features of Cowden syndrome was either not documented or not performed.

IHC to screen for Lynch syndrome), tamoxifen and other environmental exposures influencing cancer risk, and personal/family history suggestive of particular cancer syndromes. While personal and family cancer history and prior genetic testing are requested from ordering clinicians via the test requisition form, this information is not provided in all cases. Information on tamoxifen and other environmental exposures is available for a proportion of cases through clinic notes submitted to the laboratory; however, these are not routinely ascertained.

While these limitations exist, the study population is representative of the wide range of referrals and indications for multi-gene panel testing, and these findings support using expanded genetic testing of BUC patients to identify those with underlying germline mutations and consequently help guide therapy and cancer surveillance. Mutations associated with hereditary breast and ovarian cancer, Lynch Syndrome, Cowden syndrome, and Li-Fraumeni syndrome have clear guidelines regarding management and surveillance for other cancers [2,17,31], which can benefit patients and their at-risk family members. The findings of the current study, that women with BUC are more likely to carry genetic mutations than women with either BC or UC alone and that the majority of these mutations are clinically actionable, support the conclusion that women with BUC should be offered expanded genetic testing. Future studies are needed that can further assess the frequency and spectrum of underlying hereditary mutations in women with BUC, such as a prospective study of a large number of women with BUC who are all tested with multi-gene panel testing inclusive of a broad spectrum of BC and UC predisposition genes. Additionally, studies analyzing the cost-effectiveness of a multi-gene panel testing strategy for BUC patients would be helpful.

Table 4
Gene-specific mutation frequencies in BUC cases with no additional cancer diagnoses compared to BC, UC, and cancer-fee controls.

Gene	BUC only[a] (n = 730)	No cancer[a] (n = 19,597)	BUC vs. no cancer			BC only[a] (n = 30,148)	BUC vs. BC			UC only[a] (n = 1307)	BUC vs. UC only (n = 1307)		
	n, positive	n, positive	P-value	OR[b]	95% CI	n, positive	P-value	OR[b]	95% CI	n, positive	P-value	OR[b]	95% CI
ATM	13	162	**0.01**	**2.33**	**[1.17,4.19]**	350	0.07	1.71	[0.90,2.93]	5	**0.01**	**5.27**	**[1.73,19.48]**
BARD1	3	16	**0.02**	**4.84**	**[1.08,15.54]**	74	0.37	1.71	[0.41,4.65]	1	0.12	6.22	[0.78,126.69]
BRCA1	13	172	0.05	2.08	[0.92,4.07]	416	**0.02**	**2.01**	**[1.08,3.39]**	8	0.06	2.63	[0.93,7.45]
BRCA2	13	206	**0.01**	**2.27**	**[1.14,4.06]**	421	0.12	1.56	[0.85,2.63]	12	0.12	2.07	[0.82,5.19]
BRIP1	1	56	0.75	0.72	[0.04,3.43]	81	0.53	0.53	[0.03,2.42]	1	0.56	2.30	[0.09,60.17]
CDH1	1	7	0.33	2.84	[0.15,16.31]	18	0.71	1.50	[0.08,8.40]	0	–	–	–
CHEK2	12	336	0.96	1.01	[0.52,1.78]	671	0.42	0.79	[0.42,1.34]	14	0.10	2.01	[0.86,4.62]
MLH1	4	17	0.03	4.23	[0.93,13.89]	14	**2.12–5**	**11.96**	**[3.31,34.61]**	13	0.45	0.61	[0.14,1.96]
MRE11A	1	17	0.40	2.42	[0.13,12.48]	33	0.78	1.33	[0.07,6.38]	1	0.55	2.38	[0.09,64.56]
MSH2	6	25	<**0.001**	**5.72**	**[2.03,14.00]**	12	<**0.001**	**27.65**	**[9.25,75.22]**	24	0.91	0.95	[0.34,2.27]
MSH6	16	34	<**0.001**	**18.18**	**[9.05,35.24]**	41	<**0.001**	**12.42**	**[6.47,22.73]**	35	0.65	1.16	[0.60,2.16]
MUTYH[c]	1	8	0.97	0.00	NA	7	0.15	4.71	[0.25,27.94]	1	0.98	2.95–6	[6.36–90,3–28]
NBN	1	47	0.96	0.00	[4.03–43,0.18]	54	0.82	0.79	[0.04,3.64]	6	0.98	–	–
PALB2	7	60	<**0.001**	**4.49**	**[1.81,9.59]**	261	0.72	1.15	[0.49,2.28]	4	0.06	3.34	[0.98,13.04]
PMS2	7	45	**0.01**	**3.37**	**[1.14,8.00]**	77	**4.17 × 10^{-3}**	**3.21**	**[1.32,6.67]**	13	0.52	0.71	[0.22,1.92]
PTEN	2	5	**0.02**	**8.31**	**[1.12,42.67]**	22	**0.02**	**5.70**	**[0.90,20.01]**	4	0.63	1.53	[0.21,8.22]
RAD50	0	47	0.97	–	–	76	0.94	–	–	4	0.99	–	–
RAD51C	1	28	0.59	1.73	[0.10,8.43]	73	0.64	0.62	[0.04,2.84]	2	0.69	1.67	[0.07,18.65]
RAD51D	1	19	0.46	2.17	[0.12,11.35]	31	0.74	1.40	[0.08,6.69]	2	0.82	1.34	[0.06,14.29]
TP53	1	6	0.11	6.38	[0.31,44.19]	37	0.65	1.59	[0.09,7.47]	0	–	–	–
Total	104	1329	<**0.001**	**2.54**	**[1.99,3.21]**	2793	<**0.001**	**1.85**	**[1.48,2.28]**	150	**4.63 × 10^{-3}**	**1.55**	**[1.14,2.09]**

BC, breast cancer; UC, uterine cancer; BUC, breast and uterine cancer.
Values in bold indicate cases where the p-value was <0.05.
[a] Cases and controls were limited to 730 patients who were tested for all 23 BC and/or UC susceptibility genes. Case-control results for *EPCAM*, *NF1*, and *STK11* are not shown, as no mutations were detected in these genes among BUC cases. Individuals with mutations in multiple genes were excluded from analysis, including 7 BUC cases with multiple mutations.
[b] Adjusted for ethnicity, personal history of multiple primary breast cancers, family history of breast, ovarian, colorectal, endometrial, thyroid, gastric, pancreatic, and prostate cancers; additionally adjusted for BC and UC diagnosis age in the comparison of BUC vs. BC and BUC vs. UC, respectively.
[c] Biallelic only.

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Author contributions

Kelly Fulk, MS, CGC; Holly LaDuca, MS, CGC; and Elizabeth C. Chao, MD, FACMG contributed to the drafting of this manuscript and the interpretation of data.

Michael R. Milam, MD, MPH and Michael P. Stany, MD, FACOG contributed to the drafting of this manuscript.

Shuwei Li, PhD and Mary Helen Black, PhD, MS contributed to the data analysis and interpretation for this study.

Amal Yussuf, BS contributed to the data acquisition for this study.

All authors participated in critical revisions of this manuscript.

Conflict of interest statement

Kelly Fulk, MS, CGC; Shuwei Li, PhD; Amal Yussuf, BS; Mary Helen Black, PhD, MS; Elizabeth C. Chao, MD, FACMG; and Holly LaDuca, MS, CGC are paid employees of Ambry Genetics, a commercial laboratory.

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