Women with breast and uterine cancer are at increased risk for hereditary cancer predisposition

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Objectives: The purpose of this study is to explore the germline mutation spectrum and prevalence among women with breast and uterine cancer (BUC) who were clinician-referred for multi-gene hereditary cancer panel testing.

Methods: Clinical histories for patients who underwent multi-gene panel testing 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 (with no additional cancers). Patients underwent comprehensive analysis of 23-67 genes, depending on the panel ordered. Gene-specific mutation frequencies were calculated. The combined frequency of mutations in breast and uterine cancer genes was compared between BUC cases and three control groups with (1) no personal cancer history; (2) breast cancer only; and (3) uterine cancer only using Chi-square analysis.

Results: 767 women with BUC were identified from July 2013 to December 2016. The majority of the patients were Caucasian (70.7%; 542/767). The average age at first breast cancer diagnosis was 55 years (range 27-92 years) and the average age at uterine cancer diagnosis was 57 years (range 22-84 years). Breast cancer was diagnosed prior to uterine cancer in 52.3% (n=401) of BUC cases. Fifteen percent (n=115) of BUC cases tested positive for mutations in breast and uterine cancer genes. Analysis of gene-specific mutation frequencies revealed that *MSH6 (2.5%), CHEK2 (2.1%), BRCA1 (1.8%), BRCA2 (1.8%), ATM (1.8%), PMS2 (1.3%), PALB2 (1.2%)* and *MSH2 (0.9%)* were most frequently mutated among BUC cases. All of these most commonly mutated genes have published management guidelines to guide clinical care. BUC cases were significantly more likely to test positive for breast and/or uterine cancer gene mutations than breast cancer only controls (9.6%, OR=1.66, 95% CI=1.35-2.03, P<0.05), uterine cancer only controls (11.9%, OR=1.30, 95% CI=1.01-1.69, P<0.05), and unaffected controls (7.0%, OR=2.34, 95% CI=1.91-2.88, P<0.05).

Conclusions: In this multi-gene panel testing cohort, women with BUC are at greater risk of hereditary cancer gene mutations, therefore expanded genetic testing should be considered 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.

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