Multi-gene testing in a male breast cancer cohort: insights and unexpected results.

INTRODUCTION: The role of *BRCA2* and *BRCA1* in male breast cancer is well established, however, there is limited data regarding the role of other genes in male breast cancer. The aim of this study was to assess the clinical characteristics and genetic testing outcomes in men diagnosed with breast cancer undergoing multi-gene testing.

METHODS: Test results were reviewed for male breast cancer patients who underwent analysis of breast cancer-associated genes via multi-gene testing from March 2012 to March 2015. Panels consisted of 5-49 genes, depending on the test ordered. Clinical histories provided on test requisition forms were assessed. Statistical analysis was performed using the Wilcoxon Rank Test and the Fisher's exact test.

RESULTS: Approximately 12% (33/280) of men diagnosed with breast cancer were identified to carry a pathogenic mutation/likely pathogenic variant, ~2% (5/280) were identified to carry a moderate risk mutation (*APC* p.I1307K or *CHEK2* p.I157T), ~1% (2/280) were identified to carry a monoallelic *MUTYH* mutation, ~18% (51/280) had variant of unknown significance but were otherwise negative, and ~67% (189/280) tested negative. The mutation rate was highest for *BRCA2*, at 7.3% (18/247 tested), followed by *CHEK2*, at 5.1% (10/196 tested). Of note, 3 men tested positive for multiple mutations: one man had *BRCA2* and *ATM* mutations, one man had *BRCA2* and *TP53* mutations, and one man, with a clinical diagnosis of ataxia-telangiectasia, had two *ATM* mutations.

The average age at diagnosis for mutation-positive men (62.5 years) was not significantly different from negative men (59.6 years) (p=0.269). However, the average age of diagnosis for men with *CHEK2* 1100delC mutations (46.0 years) was significantly lower than the average age of diagnosis for men who were otherwise positive (p=0.012). Fourteen of the mutation-positive men were found to have multiple cancers; colon polyps, melanoma, and cancers of the bladder, prostate and pancreas were reported in more than one individual. Based on the family history provided, two men who tested positive for *BRCA2* mutations would not otherwise have met NCCN criteria for testing. The majority of men in this cohort with a family history of male breast cancer (10/19) tested negative for a mutation. Five mutation-positive patients were found to have a family history of male breast cancer: three with *CHEK2* mutations; one with a *BRCA2* and a *TP53* mutation; and one with two *ATM* mutations. Men with *CHEK2* mutations were significantly more likely to have a family history of male breast cancer compared to other positive men (p=0.020) as were men with multiple mutations (p=0.008).

CONCLUSION: In this cohort of male breast cancer patients, multi-gene testing identified mutations in patients that would not previously have been identified with a single gene testing approach and allowed for identification of families with multiple mutations. Age at diagnosis and family history were not predictive of positive test results in general, although men with *CHEK2* 1100delC mutations were diagnosed at a significantly younger age. Although 30% of this cohort was not tested for *CHEK2*, the *CHEK2* mutation rate in the men tested was second in frequency to *BRCA2*, suggesting a role for *CHEK2* testing in male breast cancer patients.