**Positive predictors of inherited cancer susceptibility among women with ovarian and endometrial cancer**

Rachel McFarland, BS, Holly LaDuca, MS, CGC, Shuwei Li, PhD, Jill S. Dolinsky, RN, MS, CGC

Ambry Genetics, Aliso Viejo, CA

Objectives: This study assessed potential factors influencing the likelihood of a positive result in ovarian and/or endometrial cancer patients undergoing hereditary cancer multi-gene panel testing (MGPT).

Methods: A total of 4,511 ovarian and/or endometrial cancer patients (3,043 with ovarian, 1,227 with endometrial, and 241 with both) were identified from a cohort of over 41,000 individuals undergoing MGPT at one clinical diagnostic laboratory. Rates of pathogenic and likely pathogenic alterations (mutations) were calculated and comparisons were made using Fisher’s exact test based on the available clinical and demographic information from test requisition forms.

Results: 13.2% of ovarian and 12.2% of endometrial cancer patients harbored a mutation in one or more genes analyzed, as listed in Table 1. Mutation rates were higher among non-Caucasians (15.0%) than in Caucasians (12.6%), but the difference was not significant (p = 0.1). 20.3% of women of mixed ethnicity (p = 0.007 compared to Caucasians) carried a mutation. Other ethnicities were examined and not found to significantly influence likelihood of a mutation.

Women diagnosed with either ovarian or endometrial cancer < 50 years were not significantly more likely to receive positive results than women diagnosed at age 50 or over (p = 0.3 for ovarian cancer, p = 0.08 for endometrial). Women diagnosed between ages 40-59 had the highest rate of mutation (16.3%).

More than one-third of women tested (n = 1593) had >1 primary cancer, including 5.3% with both ovarian and endometrial cancer. Among probands with both ovarian and endometrial cancer, mutation rates were lower (10.8%) than those with only one cancer (11.8%), although this difference was not significant (p = 0.3). Mutations were significantly more common (15.7%, p = 0.03) among those with other combinations of multiple primaries, and mutation rates were highest (19.1%, p = 0.0001) among probands with 3 or more primary cancers.

Conclusions: Among ovarian and endometrial cancer patients referred for MGPT, positive results were more prevalent among women of mixed ethnicity, those diagnosed in their 40s and 50s, and those with additional primary cancers, suggesting that the likelihood of positive results may be influenced by ethnicity, age at diagnosis, and the presence of multiple cancers.

**Table 1: Genes Tested and Positive Results Identified**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  | | --- | --- | --- | --- | |  | % of Individuals Tested with Pathogenic or Likely Pathogenic Alteration | | | | Gene | **Ovarian Cancer** | **Endometrial Cancer** | **Ovarian & Endometrial Cancer** | | BRCA1 | 4.22 | 1.19 | 0.91 | | BRCA2 | 2.69 | 1.11 | 0.46 | | CHEK2 | 1.89 | 2.43 | 2.45 | | MSH6 | 0.91 | 3.27 | 3.91 | | BRIP1 | 1.17 | 0.40 | 0.62 | | MSH2 | 0.40 | 2.16 | 1.74 | | RAD51C | 1.09 | 0.00 | 0.00 | | APC | 0.53 | 0.96 | 0.00 | | ATM | 0.62 | 1.06 | 1.23 | | PALB2 | 0.54 | 0.93 | 0.61 | | PMS2 | 0.34 | 0.96 | 0.43 | | RAD51D | 0.59 | 0.00 | 0.00 | | MLH1 | 0.10 | 1.12 | 0.00 | | PTEN | 0.31 | 0.48 | 0.00 | | NBN | 0.33 | 0.13 | 0.62 | | TP53 | 0.30 | 0.14 | 0.00 | | CDKN2A | 0.00 | 0.48 | 0.00 | | RAD50 | 0.29 | 0.00 | 0.00 | | NF1 | 0.23 | 0.00 | 0.00 | | MUTYH\* | 0.08 | 0.44 | 0.00 | | MRE11A | 0.13 | 0.13 | 0.00 | | SMAD4 | 0.27 | 0.00 | 0.00 | | BARD1 | 0.08 | 0.13 | 0.00 | | CDH1 | 0.00 | 0.09 | 0.00 | | EPCAM | 0.03 | 0.00 | 0.00 |   \*Carriers were not included. |  |