Positive Predictors of Inherited Cancer Susceptibility Among Women with Ovarian and Endometrial Cancer

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Background
- Ovarian and endometrial cancer are known to be associated with hereditary breast and ovarian cancer syndrome (HBOC), caused by mutations in the BRCA1 and BRCA2 genes, and hereditary non-polyposis colorectal cancer (HNPPC), caused by mutations in MLH1, MSH2, MSH6, PMS2, and/or EPCAM.
- Multigene panel testing (MGPT) allows simultaneous analysis of dozens of genes.
- Factors that predispose a positive MGPT result for women affected with ovarian and/or endometrial cancer are unclear.

Methods
- Clinical histories and test results were reviewed for all ovarian and/or endometrial cancer patients undergoing MGPT from March 2012 to June 2015.
- Clinical and demographic information including personal history of cancer, age at testing, and ethnicity was obtained from the requisition forms.
- Statistical analyses were performed using Fisher’s exact test. The significance level was set at 0.05.

Results
- 7318 ovarian and/or endometrial cancer patients were identified among nearly 70,000 MGPT patients.
- 13.5% (7,189/53,352) of ovarian and 12.8% (3,010/23,599) of endometrial cancer patients were positive on MGPT.
- 12.3% (4,636/37,932) of women affected with both cancers were positive on MGPT.
- MGPT positive rates were not significantly different between women with ovarian, endometrial, or both cancers.

Table 1. Multiple Primaries

<table>
<thead>
<tr>
<th>Total Number of Primaries</th>
<th>All Patients (N)</th>
<th>Positive % (N)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4872</td>
<td>12.2% (593)</td>
<td>n/a</td>
</tr>
<tr>
<td>2 or more</td>
<td>2446</td>
<td>15.6% (381)</td>
<td>6.9 x 1.01</td>
</tr>
<tr>
<td>3 or more</td>
<td>438</td>
<td>19.9% (82)</td>
<td>2.5 x 10^4</td>
</tr>
</tbody>
</table>

*Women with additional primary cancers were more likely to test positive on MGPT, and the size of this effect increased with the number of additional primaries.
*However, there were no significant differences in positive rates between women with both ovarian and endometrial cancer and women with one primary cancer (p = 0.64).

Ethnicity-Specific Positive Rates
- For ovarian cancer, positive rates were lowest among African American/Black women (0.00%) and highest among women of mixed ethnicity (17.8%).
- For endometrial cancer, positive rates were lowest among women of mixed ethnicity (11.0%) and highest among Ashkenazi Jewish women (19.7%, p = 0.002, OR = 1.74, 95% CI = 1.05, 2.73). This effect appears to be largely driven by the founder mutation MSH2 c.4683G>A, found in 6/25 Ashkenazi women.
- No other significant differences among ethnic groups were observed.

Table 2. Age at Diagnosis

<table>
<thead>
<tr>
<th>Diagnosis Age</th>
<th>Positive (%)</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>&lt; 5 years</td>
<td>15.1% (248)</td>
<td>1.21 (1.02, 1.44)</td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>12.8% (460)</td>
<td>1.31 (1.02, 1.69)</td>
</tr>
</tbody>
</table>

*Women diagnosed before age 50 years were more likely to receive a positive result.

Take-Home Points
- Additional cancer primaries and a younger age at diagnosis increased the likelihood of a positive result on MGPT for women with ovarian and/or endometrial cancer.
- Other than founder effects in Ashkenazi Jewish women, no significant ethnicity-related differences in positive rates were observed.
- 512 women (50%) tested with MGPT with a history of ovarian and/or endometrial cancer harbored pathogenic mutations in genes other than BRCA1, BRCA2, and the HNPPC genes.
- MGPT should be considered for all ovarian and endometrial cancer patients, particularly those diagnosed before age 50 or with additional cancer primaries.