Ovarian Cancer Risk Associated with Mutations Detected by Multiple-Gene Germline Sequencing in 95,561 Women

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Background

• Multi-gene panel testing approximately doubles mutation detection rate
  – *BRCA1/2*, Lynch Syndrome genes, *ATM*, *CHEK2*, *PALB2*, *STK11*, *TP53*, *NBN*, *CDH1*, etc.

• Uncertainty about magnitude of ovarian cancer risk with unfamiliar genes

• Recommendations (e.g., salpingo-oophorectomy) depend on risk level

• Most penetrance studies to date are relatively under-powered
Patients and Methods

• Patient population: 95,561 women, tested clinically
  – September 2013-2015 (period of availability of multiple-gene panel)
  – Exclusions: missing data fields on requisition form, prior testing

• Data collection: Clinical testing requisition forms
  – Completed by ordering clinician
  – Queried personal and family cancer history, racial/ethnic ancestry

• Genetic testing: 25-gene hereditary cancer panel (Myriad)
  – Full sequencing and comprehensive rearrangement analysis
  – Standard variant classification approach (Am. College of Med. Genetics)
Statistical Analysis

- **Primary method:** Multivariable logistic regression
  - Dependent variable: Ovarian cancer
  - Independent: Age, race/ethnicity, personal and family cancer history
  - Wald statistic used to calculate odds ratios with 95% confidence interval
  - Interpretation: Risk due to mutation, after accounting for other variables

- **Secondary method:** Case-control study matched on age, race, family hx
  - Exact McNemar’s test used to estimate odds ratios, 95% CI
  - Intended as a sensitivity analysis on results of logistic regression
### Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Patients (%)</th>
<th>OC Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Patients</strong></td>
<td>95,561 (100)</td>
<td>5,020 (5)</td>
</tr>
<tr>
<td><strong>Age at Genetic Testing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>11-98</td>
<td>20-97</td>
</tr>
<tr>
<td>Median</td>
<td>48</td>
<td>62</td>
</tr>
<tr>
<td>% Age ≤ 50 years</td>
<td>57</td>
<td>20</td>
</tr>
<tr>
<td><strong>Ancestry</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western/Northern European</td>
<td>54,372 (57)</td>
<td>3,359 (67)</td>
</tr>
<tr>
<td>Central/Eastern European</td>
<td>13,134 (14)</td>
<td>543 (11)</td>
</tr>
<tr>
<td>Latin American/Caribbean</td>
<td>8,915 (9)</td>
<td>405 (8)</td>
</tr>
<tr>
<td>African</td>
<td>8,829 (9)</td>
<td>254 (5)</td>
</tr>
<tr>
<td>Native American</td>
<td>3,925 (4)</td>
<td>174 (3)</td>
</tr>
<tr>
<td>Asian</td>
<td>3,195 (3)</td>
<td>169 (3)</td>
</tr>
<tr>
<td>Ashkenazi</td>
<td>2,211 (2)</td>
<td>80 (2)</td>
</tr>
<tr>
<td>Near or Middle Eastern</td>
<td>980 (1)</td>
<td>35 (1)</td>
</tr>
<tr>
<td><strong>Family Cancer History</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One or More FDR with OC</td>
<td>11,396 (12)</td>
<td>392 (8)</td>
</tr>
</tbody>
</table>

FDR, First-degree relative; OC, Invasive epithelial ovarian cancer.
Distribution of Pathogenic Mutations

- 7% (6,626) had ≥1 mutation
- 14% (701) of OC patients
  - 63.5% were in BRCA1/2
  - 9.4% Lynch genes
  - 27.2% other genes

Mutations in Ovarian Cancer Patients

- BRCA1: 35.7%
- BRCA2: 27.8%
- Lynch Syndrome Genes: MLH1, MSH2, MSH6, PMS2
- Other Ovarian Cancer Genes: BRIP1, RAD51C, RAD51D, STK11, TP53
- Other Breast Cancer Genes: ATM, BARD1, CDH1, CHEK2, NBN, PALB2, PTEN
- Other Panel Genes: APC, BMPR1A, CDK4, CDKN2A, MUTYH, SMAD4
Multivariable Regression Results

- Significant associations detected for 11 genes
- 2-fold to 40-fold elevations in ovarian cancer risk

<table>
<thead>
<tr>
<th>Gene</th>
<th>OR</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>STK11</td>
<td>41.9</td>
<td>5.55, 315</td>
<td>2.9×10⁻⁴</td>
</tr>
<tr>
<td>BRCA1</td>
<td>11.8</td>
<td>9.99, 14.0</td>
<td>6.2×10⁻¹⁸¹</td>
</tr>
<tr>
<td>BRCA2</td>
<td>5.26</td>
<td>4.38, 6.31</td>
<td>1.0×10⁻⁷⁰</td>
</tr>
<tr>
<td>RAD51C</td>
<td>4.98</td>
<td>3.09, 8.04</td>
<td>4.6×10⁻¹¹</td>
</tr>
<tr>
<td>RAD51D</td>
<td>4.78</td>
<td>2.13, 10.7</td>
<td>1.4×10⁻⁰⁴</td>
</tr>
<tr>
<td>MLH1</td>
<td>3.11</td>
<td>1.47, 6.59</td>
<td>0.0031</td>
</tr>
<tr>
<td>BRIP1</td>
<td>2.62</td>
<td>1.72, 3.98</td>
<td>6.4×10⁻⁰⁶</td>
</tr>
<tr>
<td>MSH2</td>
<td>2.04</td>
<td>1.08, 3.84</td>
<td>0.028</td>
</tr>
<tr>
<td>MSH6</td>
<td>1.92</td>
<td>1.19, 3.10</td>
<td>0.0076</td>
</tr>
<tr>
<td>NBN</td>
<td>1.85</td>
<td>1.05, 3.24</td>
<td>0.032</td>
</tr>
<tr>
<td>ATM</td>
<td>1.69</td>
<td>1.19, 2.40</td>
<td>0.0032</td>
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</table>

OR, Odds ratio; CI, Confidence interval

Odds Ratios, Logistic Regression

Confidential - Do Not Distribute
Odds Ratios, Comparing Approaches

- Multivariate Regression
- Matched Case-Control

- BRCA1
- BRCA2
- RAD51C
- RAD51D
- MLH1
- BRIP1
- MSH6
- NBN
- ATM
- BARD1
- CHEK2
- P16
- PALB2
- PMS2
Conclusions

• 11 genes associated with significant OC risk increase (2- to 40-fold)
  – STK11, BRCA1, BRCA2, RAD51C, RAD51D, MLH1, BRIP1, MSH2, MSH6, NBN, ATM
  – First report of OC risk with ATM (~0.5%-1% of breast cancer patients)

• 14% of all OC patients had at least one pathogenic mutation

• Nearly 1/3 were in non-BRCA1/2, non-Lynch Syndrome genes
  – 15.4% in “breast cancer genes”, 11.2% in “ovarian cancer genes”
  – Panel testing may reveal a broader spectrum of associated cancers
Limitations and Questions Raised

• Data collection
  – Clinical testing sample; not accrued prospectively for research purposes
  – Patient characteristics, family history were derived from clinician report

• Analytic approach
  – Could not use a kin-cohort approach (not a family study)
  – Two other methods (logistic regression, case-control) largely consistent

• Other patient populations
  – May not generalize to unselected cancer patients
  – However, does represent “real-world” testing scenarios
Future Directions

• Penetrance, prevalence in other populations
  – Unselected cancer patients (breast, ovarian, other)
  – Enriched for racial/ethnic minorities

• Complementary and confirmatory study designs
  – Validate report of patient and family cancer history
  – Testing of relatives, kin-cohort analysis
  – More clinical detail (tumor features, treatment, outcomes)