Genetic Susceptibility to Endometrial Cancer: an update

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Outline

• Part 1: GWAS

• Part 2: EXWAS

• Part 3: Future
Part 1: GWAS

**Genome-wide association study of endometrial cancer in E2C2**

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Epidemiology of Endometrial Cancer Consortium (E2C2)
Discovery – Main Results

N = 5,472
Epidemiology of Endometrial Cancer Consortium (E2C2)
Fast track replication*  
(participants of European non-Hispanic ancestry**, N=4238)

<table>
<thead>
<tr>
<th>SNP</th>
<th>CHR</th>
<th>A</th>
<th>GWAS</th>
<th>Replication</th>
<th>GWAS + Replication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Beta</td>
<td>StdErr</td>
<td>Q</td>
</tr>
<tr>
<td>RS10739046</td>
<td>9p24.2</td>
<td>C</td>
<td>-0.1949</td>
<td>0.0416</td>
<td>2.10</td>
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<tr>
<td>RS10822320</td>
<td>10q21.3</td>
<td>T</td>
<td>-0.2849</td>
<td>0.0641</td>
<td>5.67</td>
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<tr>
<td>RS11651755 (HNF1B)</td>
<td>17q12</td>
<td>C</td>
<td>-0.0684</td>
<td>0.0434</td>
<td>5.98</td>
</tr>
<tr>
<td>RS1352075</td>
<td>11q13.3</td>
<td>C</td>
<td>-0.2011</td>
<td>0.0442</td>
<td>2.29</td>
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<tr>
<td>RS4430796 (HNF1B)</td>
<td>17q12</td>
<td>G</td>
<td>-0.0845</td>
<td>0.0399</td>
<td>9.02</td>
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<td>RS4697273</td>
<td>4p15.2</td>
<td>A</td>
<td>-0.2487</td>
<td>0.0534</td>
<td>5.47</td>
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<tr>
<td>RS9344</td>
<td>11q13.3</td>
<td>A</td>
<td>0.1840</td>
<td>0.0397</td>
<td>2.66</td>
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<tr>
<td>RS9369262</td>
<td>6p24.1</td>
<td>C</td>
<td>-0.4497</td>
<td>0.0986</td>
<td>0.00</td>
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<tr>
<td>RS941990</td>
<td>6p22.3</td>
<td>G</td>
<td>0.2090</td>
<td>0.0469</td>
<td>3.69</td>
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</tbody>
</table>

Note: Highlighted SNPs corresponds to the published hits by *Spurdle et al. 2011*

* by taqman  
** Contributing studies: AHS, EDGE, FHCRC, MEC, CPSII, Turin, Wise
Conclusions from the GWAS

- No novel common variants were associated with EC risk
- HNF1B locus was replicated

Limitations:
- Sample size
- Tumor heterogeneity
Part 2: EXWAS

Exome Genotyping Arrays

**Exome**: parts of the genome that encode proteins

- Genotyping costs < sequencing costs
  - Permits larger sample sizes
- Focus: Protein altering variants
  - Non-synonymous (260,054 candidates)
  - Splicing (12,662 candidates)
  - Stop altering (7,137 candidates)
- Additional variation
  - GWAS hits, ancestry informative markers, random synonymous variants, etc.
- Custom content
  - 2000 SNPs from E2C2 GWAS discovery phase
Epidemiology of Endometrial Cancer Consortium (E2C2)
MAF within reported ethnicities

![Histograms showing the distribution of MAF within reported ethnicities (Asian, Black, Hawaiian, Latina, Caucasian, Other). Each histogram represents the number of variants across different MAF intervals (0, >0 - 0.01, >0.01 - 0.05, >0.05).]
Single Variant Association Analysis
(all Ethnicities)

N = 2,833
Single Variant Association Analysis (only Caucasian)
### Single Variant Association Analysis

<table>
<thead>
<tr>
<th>Variant</th>
<th>Gene/Locus</th>
<th>MAF</th>
<th>OR</th>
<th>P-value (all ethnicities)</th>
<th>P-value (only Caucasians)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs1953358</td>
<td>LINC00520</td>
<td>0.49</td>
<td>1.36 (1.20, 1.53)</td>
<td>4.76E-07</td>
<td>3.35E-06</td>
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<tr>
<td>rs8178648</td>
<td>PROS1</td>
<td>0.09</td>
<td>1.71 (1.37, 2.12)</td>
<td>1.53E-06</td>
<td>3.00E-05</td>
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<tr>
<td>rs9399840</td>
<td>n/a</td>
<td>0.47</td>
<td>0.75 (0.67, 0.85)</td>
<td>3.01E-06</td>
<td>5.18E-05</td>
</tr>
<tr>
<td>exm1401784</td>
<td>ATP8B3</td>
<td>0.23</td>
<td>0.72 (0.61, 0.83)</td>
<td>1.92E-05</td>
<td>6.49E-05</td>
</tr>
<tr>
<td>rs6926980</td>
<td>KIAA1586</td>
<td>0.23</td>
<td>0.75 (0.65, 0.87)</td>
<td>7.95E-05</td>
<td>6.56E-05</td>
</tr>
</tbody>
</table>
Conclusions from the EXWAS

• No rare variants reach significance with risk of EC

• Limitations:
  – small sample size
  – predominantly designed for those with European ancestry
  – incomplete coverage of all functional variants in exome

• Strengths:
  – first exome chip analysis of endometrial cancer
  – comprehensive study of a multi-ethnic population
Part 3: Future

• Meta-analysis

• Gene-environment-wide interaction studies (GEWIS)

• Genetic susceptibility by subtype
Thanks!

Epidemiology of Endometrial Cancer Consortium