Hyperplasia & Cancer Risk

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City of Hope
Duarte, CA
NCI-Designated Comprehensive Cancer Center
When EH is Diagnosed …

• What is the risk of concurrent cancer?

• What is the risk of future cancer?
Endometrial Hyperplasia

Normal Endometrium → Proliferative Lesion → Carcinoma Precursor → Carcinoma

↑ ↑ ↑ ↑ ↑

Endometrial Hyperplasia (EH)
WHO Histologic Distinctions for Endometrial Hyperplasia (EH)

- **Normal Endometrium**
- **Proliferative Lesion**
- **Carcinoma Precursor**
- **Carcinoma**

**Benign / Anovulatory / Proliferative Endometrium**

**Simple Hyperplasia**

**Complex Hyperplasia**

**Atypical Hyperplasia**

**Well-Differentiated Carcinoma**

*Primarily complex atypical hyperplasia (CAH)*
Concurrent Cancer at EH Diagnosis

Normal Endometrium → Proliferative Lesion → Carcinoma Precursor → Carcinoma

Benign / Anovulatory / Proliferative Endometrium
Simple Hyperplasia
Complex Hyperplasia
Atypical Hyperplasia
Well-Differentiated Carcinoma

Sampling:
Biopsy / curettage only samples a portion of the endometrium
Concurrent Cancer at EH Diagnosis

Normal Endometrium → Proliferative Lesion → Carcinoma Precursor → Carcinoma

Benign / Anovulatory / Proliferative Endometrium

Simple Hyperplasia → Complex Hyperplasia → Atypical Hyperplasia → Well-Differentiated Carcinoma

Diagnosis / Classification:

Under-diagnose carcinoma as EH
How Often?

Normal Endometrium → Proliferative Lesion → Carcinoma Precursor → Carcinoma

Benign / Anovulatory / Proliferative Endometrium

Simple Hyperplasia → Complex Hyperplasia → Atypical Hyperplasia → Well-Differentiated Carcinoma

SH or CH: 1% - 2% of biopsies were up-graded to cancer by experts

How Often?

Normal Endometrium → Proliferative Lesion → Carcinoma Precursor → Carcinoma

Benign / Anovulatory / Proliferative Endometrium → Simple Hyperplasia → Complex Hyperplasia → Atypical Hyperplasia → Well-Differentiated Carcinoma

AH: 40% - 50% biopsies were cancer at hysterectomy

Risk of Progression to Carcinoma

- Benign / Anovulatory / Proliferative Endometrium
- Simple Hyperplasia: <10%
- Complex Hyperplasia: 10%-30%
- Complex Atypical Hyperplasia: >25%
- Well-Differentiated Carcinoma

Percent of EH lesions that progress to carcinoma “after 1 to 20 years”

Key Questions

What factors predict progression from EH to carcinoma?

- SH and CH often over-diagnosed
- AH often an under-diagnosis of carcinoma
- AH often prompts hysterectomy
EH Progression Study

- **Objective:**
  - Determine risk of progression from EH to carcinoma

- **Nested case-control study at large health plan**
  - Kaiser Permanente Center for Health Research
  - Linked and computerized:
    - Pathology archive since 1971
    - Medical records since ~1990
    - Pharmacy data since 1985
    - Tumor registry since the 1960s

Study Participants

• Cases
  – 214 women diagnosed with cancer at least 1 year after a diagnosis of EH, 1970-2003
    • Specific KPNW pathology code for “EH”
    • EH via biopsy or curettage
    • Index biopsy: 1st diagnosis of incident EH

• Controls
  – 404 women diagnosed with EH who remained at-risk for an equivalent interval
    • Individually matched to case on age at EH & date of EH
    • Risk-free progression interval similar to their index case

Study Data

Index Biopsy | Follow-up Biopsies | Diagnosis Date | Censor Date
---|---|---|---

2/17/1988
1/12/2003 |

Tissue blocks from biopsies & cancer

All slides from cases & controls

• Original diagnoses
• Pathology panel diagnoses for WHO
• Diagnoses for other classification systems

Risk factor data via medical records
Medication data via pharmacy records

Cancer Risk among Women Diagnosed with EH

Normal Endometrium → Proliferative Lesion → Carcinoma Precursor → Carcinoma

Benign / Anovulatory / Proliferative Endometrium → Simple Hyperplasia → Complex Hyperplasia → Atypical Hyperplasia → Well-Differentiated CA

RRs adjusted for age, date, progression interval, BMI, repeat biopsies, & MPA treatment

Panel Diagnosis of Index Biopsy

Absolute Risks of Progression

1000 EH Patients

% Undergoing Hysterectomy

SH <5%
CH 15%
AH 80%
% Hysterectomies Showing Cancer

SH  15%-20%
CH  15%-20%
AH  50%
% Patients with Undetected Cancer

- SH: 1%
- CH: 2%
- AH: ~30%
% At Risk for Progressing to CA

- SH: 94%
- CH: 83%
- AH: 14%
Absolute Risks of CA over 20 Years

- SH: 5%
- CH: 5%
- AH: 30%
Total # of Cancers by EH Type

- SH: 21%
- CH: 16%
- AH: 63%
Conclusions (1)

- AH has a high risk of concurrent & future cancer
  - A bona fide surrogate endpoint

- Risks are lower among non-AH, but they account for 1/3\textsuperscript{rd} of prevalent & incident cancers
  - Need better risk prediction & stratification
Conclusions (2)

• High percentage of AH patients who undergo hysterectomy represents effective censoring
  – True burden of uterine cancer is higher than current rates of invasive cancer indicate

• EH is a model of effective cancer control
  – “Prevent” cancer by detecting it early and offering curative treatment
Conclusions (3)

• EIN & WHO
  – In a direct comparison, RRs for EIN were slightly lower than the RRs for AH
  – Fewer data on relative and absolute risks of progression among patients with EIN

Cancer Risks Among Women Diagnosed with EIN

Panel EIN and Panel WHO:

Panel EIN = *Benign*
- 71 cases, 159 ctrls
- RR = 1.0 (Ref.)

Panel EIN = *EIN*
- 42 cases, 65 ctrls
- RR = 7.8 (3.4-17.9)

Panel EIN = *Cancer*
- 21 cases, 43 ctrls
- RR = 2.2 (1.1-4.7)

Panel WHO = *SH*
- 41 cases, 67 ctrls
- RR = 9.2 (3.9-21.8)

Panel WHO = *CH*
- 13 cases, 10 controls, RR = 17.1 (4.2-70.1)

Panel WHO = *AH*
- 43 cases, 34 ctrls
- RR = 14.2 (5.3-38.0)

Panel WHO = *DPEM, SH, or CH*
- 95 cases, 207 ctrls
- RR = 1.0 (Ref.)

Panel WHO = *Normal or Negative*
- Not included

Panel WHO = *Carcinoma*
- Not included

**Increasing Severity**

Collapsed EIN and WHO Categories:

Panel EIN = *Benign*
- 71 cases, 159 ctrls
- RR = 1.0 (Ref.)

Panel EIN = *EIN or Cancer*
- 55 cases, 75 ctrls
- RR = 9.0 (4.1-19.7)

Panel WHO = *Normal or Negative*
- Not included

Panel WHO = *Carcinoma*
- Not included

Panel WHO = *DPEM, SH, or CH*
- 95 cases, 207 ctrls
- RR = 1.0 (Ref.)

Panel WHO = *AH*
- 43 cases, 34 ctrls
- RR = 9.2 (3.9-21.8)

Area of categories is proportional to the total number of cases & controls in each category, relative to 138 eligible cases & 241 eligible controls.

*Lacey JV, et al. Cancer 2008;113:2073*
Collaborators and Study Team

- **NCI – DCEG / HREB**
  - Mark Sherman, MD
  - Nilanjan Chatterjee, PhD
  - Victoria Chia, PhD
  - Douglas Richesson, MPH
- **Brigham & Women’s Hosp.**
  - George Mutter, MD
- **Kaiser Permanente Center for Health Research**
  - Andrew Glass, MD
  - Brenda Rush, RN
- **University of Southern Cal.**
  - Bryan Langholz, PhD
- **Cleveland Clinic**
  - Charis Eng, MD, PhD
- **University of Calgary**
  - Maire Duggan, MD
- **University of Calgary**
  - Maire Duggan, MD
- **Stavanger Hospital**
  - Jan P.A. Baak, MD, PhD
EIN & D-score vs. WHO

- D-score analysis nearly complete
  - RRs markedly less than 45

- AH vs. all non-AH
  - Sensitivity = 31% and specificity = 86%

- EIN vs. benign
  - Sensitivity = 37% and specificity = 71%

- Neither EIN nor D-score outperformed WHO
## Classification of Index Biopsies: Original vs. Pathology Panel

<table>
<thead>
<tr>
<th>Pathology Panel EH Classification</th>
<th>Normal</th>
<th>DPEM</th>
<th>SH</th>
<th>CH</th>
<th>AH</th>
<th>CA</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Original Classification</td>
<td></td>
<td></td>
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<tr>
<td>Cases</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPEM</td>
<td>35</td>
<td>6</td>
<td>8</td>
<td>2</td>
<td>5</td>
<td>0</td>
<td>56</td>
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<tr>
<td>SH</td>
<td>20</td>
<td>8</td>
<td>11</td>
<td>4</td>
<td>16</td>
<td>2</td>
<td>64</td>
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<tr>
<td>CH</td>
<td>19</td>
<td>8</td>
<td>14</td>
<td>9</td>
<td>7</td>
<td>4</td>
<td>69</td>
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<tr>
<td>AH</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>6</td>
<td>7</td>
<td>25</td>
</tr>
<tr>
<td>Follow-up</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>8</td>
<td></td>
<td></td>
<td>25</td>
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<tr>
<td>Total</td>
<td>76</td>
<td>33</td>
<td>42</td>
<td>21</td>
<td>42</td>
<td>13</td>
<td>214</td>
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<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SH</td>
<td>62</td>
<td>33</td>
<td>18</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>123</td>
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<tr>
<td>CH</td>
<td>53</td>
<td>41</td>
<td>29</td>
<td>20</td>
<td>10</td>
<td>0</td>
<td>153</td>
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<tr>
<td>AH</td>
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<td>23</td>
<td>20</td>
<td>16</td>
<td>21</td>
<td>3</td>
<td>128</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
<td>97</td>
<td>67</td>
<td>43</td>
<td>34</td>
<td>3</td>
<td>404</td>
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Clinical Data

<table>
<thead>
<tr>
<th>Age at EH (yrs)</th>
<th>Cases (N=138)</th>
<th>Controls (N=241)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;44</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>45-48</td>
<td>20%</td>
<td>22%</td>
</tr>
<tr>
<td>49-52</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>53-58</td>
<td>21%</td>
<td>21%</td>
</tr>
<tr>
<td>59+</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Mean:</td>
<td>52.1 yrs</td>
<td>51.5 yrs</td>
</tr>
<tr>
<td>Progression interval (yrs)</td>
<td>6.7 (1-25)</td>
<td>6.4 (1-25)</td>
</tr>
</tbody>
</table>

## Follow-up Data

<table>
<thead>
<tr>
<th>Follow-up biopsies</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1</td>
<td>75%</td>
<td>86%</td>
</tr>
<tr>
<td>At least 1 w/in 6 mos.</td>
<td>22%</td>
<td>53%</td>
</tr>
<tr>
<td>Median</td>
<td>2 (0-12)</td>
<td>2 (0-13)</td>
</tr>
<tr>
<td>Mean if at least 1</td>
<td>2.9</td>
<td>2.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment after EH</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Any MPA</td>
<td>86%</td>
<td>92%</td>
</tr>
<tr>
<td>Injectable MPA</td>
<td>21%</td>
<td>17%</td>
</tr>
<tr>
<td>Oral MPA</td>
<td>72%</td>
<td>86%</td>
</tr>
</tbody>
</table>

*Lacey JV, et al. Br J Cancer 2008;98:45*
Major Knowledge Gaps

- Misclassification and low inter-observer reproducibility
- Minimal understanding of risk factors for precursors
- Suboptimal ability to predict subsequent cancer risk
- Over-diagnosis and over-treatment
- Poorly understood natural history
Relative Risks by Time Since EH

<table>
<thead>
<tr>
<th>Panel Classification</th>
<th>1-5 years</th>
<th>5+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPEM</td>
<td>1.0 (ref)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>SH or CH</td>
<td>3.2 (0.5 – 22.2)</td>
<td>1.1 (0.4 – 3.2)</td>
</tr>
<tr>
<td>AH</td>
<td>48.0 (7.8 – 294.2)</td>
<td>3.5 (1.3 – 9.6)</td>
</tr>
</tbody>
</table>

No change after accounting for tamoxifen use.
No difference after excluding cases with 2-, 3-, or 4-year progression intervals.
No change after adjusting for # of MPA prescriptions or menopausal status.

Test EIN & D-score

**EIN**
- Blinded review of all original index biopsies from cases and controls
- 2 BWH pathologists
  - GL Mutter, MD
  - M Nucci, MD
- Consensus EIN

**D-score**
- Blinded computerized morphometric analysis of original index biopsies from cases & controls
- Stavanger Hospital
  - JPA Baak, MD
- D-score & components

*Estimate RR for progression, compared with WHO*