Clinical outcomes after conservative management of CIN1/2, CIN2, and CIN2/3 in women ages 21-39 years

Michelle I. Silver, PhD, ScM
Cancer Prevention Fellow
National Cancer Institute
Division of Cancer Epidemiology & Genetics
Rockville, MD, USA
Disclosures

- No financial relationships or conflict of interest to disclose
Management of Abnormal Results

• ASCCP Guidelines\(^1\):
  • When \textbf{CIN3} is found in women of \textit{any age}, \textit{treatment is recommended}
  • When \textbf{CIN2/3} is found in young women, \textit{observation or treatment is acceptable}
  • When \textbf{CIN2} is found in \textit{young women}, \textit{observation is preferred but treatment is acceptable}

• Conservative management = intensive observation/repeated testing instead of immediate treatment
  • Monitor for regression vs progression

\(^1\)Massad et al. JLGTD 2013
Study Aim

Assess clinical outcomes among younger women (ages 21-39 years) with conservatively managed CIN2
Kaiser Permanente Northern California (KPNC)

• NCI Collaboration: following over 1 million women in cervical cancer screening since 2003

Large integrated healthcare system
• 2003: began cotesting with 3-year screening intervals
• 2007: implemented HPV vaccination

• Demonstration project of real world clinical effectiveness
Study Population

Women ages 21-39 enrolled at KPNC since 2003

• First abnormal biopsy result of CIN1/2, CIN2, CIN2/3 (baseline histology)
• Not immediately referred for treatment (no treatment for >4 months after abnormal result)
• Remained in KPNC for cervical cancer screening for at least 22 months after histology result

2,417 women included

• Median follow-up: 48 month (IQR: 31-71 months)
## Outcome Definitions

<table>
<thead>
<tr>
<th>Outcome Category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Progressed to cancer</td>
<td>Cancer histology from biopsy or treatment</td>
</tr>
<tr>
<td>2. Treated</td>
<td>LEEP (loop electrocautery excision procedure) Cold knife cone (cone biopsy) Hysterectomy</td>
</tr>
<tr>
<td>3. Return to routine screening</td>
<td>2 negative cytologies and/or colposcopies at 6 and 12 months AND negative cotest at 24 months</td>
</tr>
<tr>
<td>4. Persistent high grade lesion</td>
<td>CIN2/3/AIS detected at LEEP CIN2/3/AIS detected at biopsy without subsequent regression</td>
</tr>
<tr>
<td>5. Persistent low grade lesion</td>
<td>Remaining women who did not fit into 4 groups above. All had at least 1 abnormal biopsy, HPV or Pap test</td>
</tr>
</tbody>
</table>
### Baseline histology results

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Age 21-24</th>
<th>Age 25-29</th>
<th>Age 30-34</th>
<th>Age 35-39</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (N)</strong></td>
<td>2417</td>
<td>757</td>
<td>848</td>
<td>556</td>
<td>256</td>
</tr>
<tr>
<td><strong>CIN1/2</strong></td>
<td>17.7</td>
<td>18.1</td>
<td>15.3</td>
<td>22.1</td>
<td>17.2</td>
</tr>
<tr>
<td><strong>CIN2</strong></td>
<td>69.0</td>
<td>71.2</td>
<td>71.1</td>
<td>65.5</td>
<td>64.0</td>
</tr>
<tr>
<td><strong>CIN2/3</strong></td>
<td>13.2</td>
<td>11.6</td>
<td>13.6</td>
<td>12.4</td>
<td>18.8</td>
</tr>
</tbody>
</table>

Majority of results are CIN2
Somewhat higher CIN2/3, lower CIN2 for older age groups
Clinical outcomes by baseline diagnosis

<table>
<thead>
<tr>
<th>Baseline histology</th>
<th>Total (N)</th>
<th>Cancer</th>
<th>Treated</th>
<th>Exit colposcopy</th>
<th>High-grade lesion</th>
<th>Low-grade lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Total (N)</td>
<td>2417</td>
<td>100</td>
<td>428</td>
<td>1670</td>
<td>319</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>6</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Treated</td>
<td>717</td>
<td>29.7</td>
<td>23.1</td>
<td>30.0</td>
<td>37.0</td>
<td></td>
</tr>
<tr>
<td>Exit colposcopy</td>
<td>474</td>
<td>19.6</td>
<td>21.5</td>
<td>18.3</td>
<td>24.1</td>
<td></td>
</tr>
<tr>
<td>High-grade lesion</td>
<td>172</td>
<td>7.1</td>
<td>7.9</td>
<td>7.2</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Low-grade lesion</td>
<td>1048</td>
<td>43.4</td>
<td>47.2</td>
<td>44.4</td>
<td>32.6</td>
<td></td>
</tr>
</tbody>
</table>

- Treatment increased with worse disease
- Less than 20% exited colposcopy
- Half remained in follow-up
  - 55% of CIN1/2
  - 51% CIN2
  - 38% CIN2/3
- Low-grade persistence highest in CIN1/2 and CIN2
Clinical outcomes by age

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<td>7.9</td>
<td>4.5</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Low-grade lesion</strong></td>
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<td>48.9</td>
<td>41.8</td>
<td>41.9</td>
<td>35.6</td>
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- Higher treatment among older women and more exit colposcopy
- Low-grade persistence in half of women under 25
Screening history of cancer cases

**Case 1:** 2 year gap from CIN2 to next visit where cone biopsy detected SCC

**Case 2:** 2 year gap from CIN1/2 to next visit where HPV+/HSIL led to cone biopsy and detection of SCC

**Case 3:** 3 year gap from CIN2 to next visit where HPV+/HSIL led to cone biopsy and detection of SCC

**Case 4:** Sequential HPV+ cotests led to biopsy which detected SCC

**Case 5:** CIN2 biopsy led to LEEP which detected microinvasive SCC

**Case 6:** Persistent HPV+ and then HSIL led to LEEP which detected microinvasive SCC

- All cancers were preceded by at least 1 high-grade abnormal result (CIN2+ or HSIL) and/or patient failure to return
- No cancers after negative co-test
Conclusions

• 30% of women required treatment in the future (esp. CIN2/3, age 35+)

• No cancers occurred after a negative cotest

• Less than 20% met criteria to exit intensive follow-up despite average of 4 years of follow-up

• 40-60% remained in intensive colposcopy protocol in the absence of continued CIN2+
  • Failure to ‘clear’ or return to normal, but no progression either
  • Continued cycle frequent tests
Prolonged surveillance is required to return to routine screening in the absence of continued CIN2+, many women fall into this category.

How can we identify which women can return to routine screening after fewer follow-ups without increasing cancer risk?
  - Age? Genotype? Other markers?

How can we review clinical practices guidelines to better target which women need follow-up?
KPNC Post-biopsy Guidelines: CIN1/2

- **Summary**: management depends on age and preceding Pap result

- After HPV-positive ASCUS, LSIL or sequential HPV positive
  - Ages 21-24: retest in 12 months
  - Ages 25+: retest in 12 months; CIN1/2 may be followed indefinitely or treated after at least 24 months of follow-up

- After ASC-H or HSIL
  - Ages 21-24: Observation with colposcopy and cytology at 6 month intervals for up to 24 months
  - Ages 25+: Diagnostic excisional procedure or cotesting at 12 and 24 months

- CIN1/2 should not be treated in women 21-24 regardless of prior Pap result
KPNC Post-biopsy Guidelines: CIN2 or CIN2/3

Ages 21-24: Observation with colposcopy and cytology at 6 month intervals for at least 12 months, up to 24 months

Ages 25+: Excision preferred if childbearing complete; observation as described above if childbearing not completed

Treat if CIN2+ persists at 24 months

Caveat: Manage appropriate to age, reproductive ambitions, and histology, and patient preference
KPNC Post-biopsy Guidelines: CIN3

Immediate precursor to invasive cancer and should be treated regardless of age or reproductive concerns

‘Observation is unacceptable if cancer prevention is the goal’