Learning Objectives

- Explore the data on cervical cancer screening in postmenopausal women and whether it decreases the incidence of cervical cancer.
- Investigate the risks and benefits of screening in the postmenopausal women.
- Evaluate the optimal age for a woman’s last cervical cancer screening test.
- Analyze the importance of Atypical Glandular Cells and risk of cervical cancer in the postmenopausal women.

Cervical Cancer Screening Is It Ever Safe to Stop in Postmenopausal Women?

What’s the Risk of Atypical Glandular Cells?

NAMS 2015 Annual Meeting

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Associate Chief of Gyn Services
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Atlanta, GA

Current Cervical Cancer Screening Recommendations

- Cervical Cytology screening every three years ages 21-65
- Co-testing with cytology and HPV testing every five years ages 30 to 65
- Primary HPV testing every 3 years: 25-65 years of age
- End date of age 65 if 3 negative Pap tests or 2 negative co-tests in the preceding 10 years and no history of CIN 2+ disease in the last 20 yrs

Lisa Flowers MD
Personal/Professional Financial Relationships with Industry

<table>
<thead>
<tr>
<th>External Industry Relationships</th>
<th>Company Name</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equity, stock, or options in biomedical industry companies or publishers</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Board of Directors or officer</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Royalties from Emory or from external entity</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Industry funds to Emory for my research</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

The overall population-based weighted estimate of high-risk HPV prevalence by hc2 was 6.0% (95% confidence interval [CI] = 4.5 to 7.9).

A nationally-representative probability sample of community-dwelling adults aged 57–85 was generated from US households screened in 2004 for the Health and Retirement Study (HRS).

Source: Prevalence of High-Risk Human Papillomavirus Among Older Women; Stacy Tessler Lindau, MD, MAPP,1 Melinda L. Drum, PhD,2 Elyzabeth Gaumer, MA,3 Hanna Surawska, BA,4 and Jeanne A. Jordon, PhD5; Obstet Gynecol. 2008 Nov; 112(5): 979–989. doi: 10.1097/AOG.0b013e31818b0df2

Why the Peak in Cervical Cancer Rates in Women 60-69 year of age?

- Under or never screened populations comprise up to 40% of cervical cancer cases.
- However 60% of the cases are in a screened population.
  - Compliance with screening decreases with age
  - Protection from screening is time-limited
  - Efficacy of screening in the older women may be lower

Natural History of High-Risk HPV Infection and Potential Progression to Cervical Cancer

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Why the Peak in Cervical Cancer Rates in Women 60-69 year of age?

Sawaya et al. Review of 455 women from 1988-1995 diagnosed with ICC in the KPNC plan under the same insurance for ≥30 of the 36 months prior to diagnosis.
- No Pap test 6-36 months prior to dx
  - 53%
- Normal Pap tests
  - 28%
- 1 abnormal Pap test with adequate follow-up
  - 9%
- 1 abnormal Pap test with inadequate f/u.
  - 4%

Screening and Future Risk of ICC

What Needs to be Considered?

Are well-screened women with a history of negative tests and no history of high grade dysplasia at a sufficiently low risk of cervical cancer that screening can stop at age 65?

If so, how low is their risk and does it change as they age?

Are women who regularly engage in screening at 50-64 years of age at a reduced risk of ICC at age 65-83?
Is There Data Demonstrating that Screening Older Women Decreases the Incidence of ICC?

<table>
<thead>
<tr>
<th>Study</th>
<th>Screening Interval</th>
<th>% Incidence Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamineni et al USA</td>
<td>Screening ages 55-79</td>
<td>77</td>
</tr>
<tr>
<td>Sasieni et al UK</td>
<td>Screening at age 62-64</td>
<td>80</td>
</tr>
<tr>
<td>Andrae et al Sweden</td>
<td>Screening age 60 and older</td>
<td>64</td>
</tr>
<tr>
<td>Lonnberg et al Finland</td>
<td>Screening age 60 and older</td>
<td>51</td>
</tr>
</tbody>
</table>

Is There Data Demonstrating that Screening Older Women Significantly Impacts Mortality from ICC?


506 CC deaths and 3,306 controls age-matched between 2000-2009
54% of deaths were in cancers diagnosed more than 5 years after last screening
CC risk reduction was seen in the 55-69 age group (OR 0.29; CI 0.16-0.54)


1052 women with CC age matched with 10,494 between the ages of 20-69 between 1998-2008
Women 65-69 risk of dying from cervical cancer was reduced (OR 0.53 CI 0.35-0.79) (p< 0.05) if screening occurred within the prior 3 yrs.

How Long Will a Negative Screening Test Protect a Woman from Cervical Cancer?

<table>
<thead>
<tr>
<th>Study</th>
<th>Age Group</th>
<th>Time (yrs) Since Last Negative Test</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kamineni et al USA</td>
<td>55-79</td>
<td>3 to &lt;5</td>
<td>0.15 (0.04-0.58)</td>
</tr>
<tr>
<td>Sasieni et al UK</td>
<td>55-69</td>
<td>5.5 to 6.6</td>
<td>0.33 (0.14-0.79)</td>
</tr>
<tr>
<td>Vicus et al Canada</td>
<td>65-69</td>
<td>3-5</td>
<td>0.37 (0.15-0.92)</td>
</tr>
<tr>
<td>Castanon et al UK</td>
<td>65-83</td>
<td>≤5</td>
<td>0.25 (0.21-0.30)</td>
</tr>
</tbody>
</table>

In general a negative cytology test provides 5 years of protection in women over 60 yrs of age from cervical cancer.

The Balance of Harms, Benefits and Costs of Screening the Older Women

- Anxiety from false positive tests
- Difficulty tolerating the colposcopy
- Distress about have HPV and an abnormal Pap test
- Perception of increased risk of cervical cancer in the future.
- Screening even to age 90 years prevents only
  - 1.6 cancer cases per 1000 women.
  - 0.5 cancer deaths per 1000 women.
The Balance of Harms, Benefits and Costs of Screening the Older Women

- Extends life expectancy by only 1 year per 1000 women, while resulting in
  - 58 extra false-positive results
  - 127 extra colposcopies
  - 13 extra diagnoses of CIN2/3 requiring treatment.

- Compared to breast and colorectal cancer, risk of cervical cancer is significantly less at and after the recommended age of screening.

So What About Atypical Glandular Cells?

Significance of Atypical Glandular Cells

Schnatz et al Obstet Gynecol 2006;107:701-8
Meta analysis of 3,890 AGC Paps +/- ASC-US with f/u

Follow-up diagnosis
- LSIL 8.5%
- HSIL 11.1%
- AIS 2.9%
- Endometrial hyperplasia 1.4%
- Malignancy 5.2%
- AGC favor neoplasia
  - AIS 13%
  - Malignancy 21%

Previous HR HPV Testing and Pap Testing Results in Women with CC

Zhao et al. retrieved 70 cases of CC from multiple institutions with hrHPV testing and Pap test results 5 yrs prior to the cancer diagnosis.

<table>
<thead>
<tr>
<th>Negative hrHPV Testing</th>
<th>Negative Pap Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>9%  &lt; 1yr</td>
<td>3.4%  &lt; 1yr</td>
</tr>
<tr>
<td>23% 1-3 yrs</td>
<td>33% 1-3 yrs</td>
</tr>
<tr>
<td>25% 3-5 yrs</td>
<td>40% 3-5 yrs</td>
</tr>
</tbody>
</table>

- KPNC study also reported 31% (27/87) of patients with CC had a negative baseline hrHPV test result within 5 years preceding the diagnosis of cervical cancer.

Zhao et al. Arch Pathol Lab Med Vol 139, February 2015
Katki et al. Lancet Oncol 2011; 12(7): 663-672

Cancers found:
- Endometrium 58%
- Cervical AdenoCa 24%
- SCC 5%
- Ovary/Fallopian 6%
- Colon/breast
**Atypical Glandular Cells**

- AGC was most likely to lead to histologic diagnosis of adenocarcinoma
  - AGC: 1.5%; (31/2074)
  - ASC-H: 0.2%
  - HSIL: 0.6%
- AIS risk was similar between all groups
  - AGC: 1.8%
  - ASC-H: 1.1%
  - HSIL: 1.5%

**Most Likely Disease with AGC is Squamous in Origin**

Cancer may be squamous or adeno.

Endometrial cancer not related to HPV status and more common in older women.

Castle et al Obstet Gynecol, 2010

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**Atypical Glandular Cells**

- HPV positivity declined with age
  - 30-34: 44%
  - 60-64: 17%
- AGC though uncommon is linked with substantial risk of cervical adenoCA or AIS when hrHPV is positive.

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**Atypical Glandular Cells**

- KPNC cohort of 965,360 women, 2003-2010
- 30-64 yrs of age undergoing co-testing
- Estimated 5-yr risk of cervical cancer and CIN3+
- All HPV negative high grade Pap results had cancer risks high enough to warrant colposcopy.

<table>
<thead>
<tr>
<th>Pap Results</th>
<th>HPV positivity</th>
<th>5 year Risk of CIN 3+</th>
<th>P value</th>
<th>5 year Risk of CC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGC 2,074</td>
<td>25%</td>
<td>33% 0.93%</td>
<td>&lt;0.0001</td>
<td>9.0% 0.37%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ASC-H 1,647</td>
<td>71%</td>
<td>25% 3.5%</td>
<td>&lt;0.0001</td>
<td>2.5% 2.1%</td>
<td>0.8</td>
</tr>
<tr>
<td>HSIL 2,019</td>
<td>94%</td>
<td>49% 30%</td>
<td>0.006</td>
<td>6.6% 6.8%</td>
<td>0.7</td>
</tr>
</tbody>
</table>
A neg HPV with AGC is not Necessarily Reassuring

In women of 50y and older, a hrHPV-negative result was linked with a 18% chance of extra-cervical malignancy.

Summary

- Cervical cancer screening in older women does decrease incidence and mortality.
- The optimum age of stopping screening is heavily dependent on screening patterns and results prior to screening cessation.
- Sexual history or activity does not alter the screening guidelines.
- The cessation of screening at age 65 is not based on data from randomized trials.
- However risks from harms versus benefits suggest that cessation at 65 yrs of age is safe.
- AGC/HPV positive carries the highest cervical cancer risk of any co-test result except for SCC pap result.
References


