PREVENTIVE SERVICES IN WOMEN’S HEALTH

U.S. PREVENTIVE SERVICES TASK FORCE

WOMEN’S HEALTH TOPICS

- Cervical cancer screening
- Calcium + Vitamin D to prevent fractures
- Breast cancer
- BRCA
- Preventive meds

VITAMIN D AND CALCIUM SUPPLEMENTATION TO PREVENT FRACTURES

POLL: WHAT DO YOU DO NOW?

A. Recommend all post-menopausal women take 500 mg of calcium carbonate with 200 IU vitamin D twice daily
B. Recommend all post-menopausal women take 1000 mg of calcium carbonate with 1000 IU or more of vitamin D daily
C. Recommend all post-menopausal women get their vitamin D from the sun and calcium from food
D. None of the above
WHAT DO YOU DO NOW?

• Conventional wisdom
  • Post-menopausal women need 1000-1500 mg of calcium daily
  • Very few women get this much calcium from their diet
  • We recommend a supplement of 500 mg of calcium carbonate twice daily with vitamin D (usual formulation has 200 IU)

USPSTF

• Recommends against daily supplementation with 400 IU or less of vitamin D₃ and 1,000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women
  • D recommendation

WHI DRIVES RECOMMENDATION

• High quality, large RCT
  • No bone density measurements at baseline
  • 1000 mg calcium and 800 IU vitamin D
  • No reduction in fractures

http://www.uspreventiveservicestaskforce.org/uspstf12/vitamind/vitdartfig2.htm
WHAT DO YOU DO NOW?

• Conventional wisdom
  • Post-menopausal women need 1000-1500 mg of calcium daily
  • Very few women get this much calcium from their diet
  • I recommend a supplement of 500 mg of calcium carbonate twice daily with vitamin D (the formulation has 200 IU)

CALCIUM AND HEART DISEASE?

• Reason for caution (not part of USPSTF evidence review)

WHAT DO I DO NOW?

• I think you should get your calcium from food and your vitamin D from the sun.

CERVICAL CANCER SCREENING
MARCH 15, 2012

- The USPSTF and the ACS (in conjunction with ASCCP and ASCP) released updated cervical cancer screening recommendations
- Not a coincidence
- Independently developed
- Remarkably similar conclusions/guidelines

CERVICAL CANCER SCREENING

BACKGROUND

CERVICAL CANCER

- Histologic types
  - Squamous cell
    - 70% of all cases (primary target of cytological screening)
    - Arises at squamocolumnar junction (transformation zone)
    - Primary target of cytology screening
  - Adenocarcinoma
    - ~18%
  - Mixed adenosquamous and other

A reminder: squamocolumnar junction
HPV INFECTION

• “It is well recognized that infection with oncogenic HPV types is a necessary, although not sufficient, cause of virtually all cervical cancer.”

• Results from a large international collection of cervical tumor specimens revealed the presence of HPV DNA in 99.7 percent of cases.

HPV INFECTION AND PERSISTENCE

• A high proportion of sexually active women become infected with HPV, but only a small proportion of HPV infections become persistent.

• 91 percent of prevalent HPV infections clear within 24 months (including infections with high risk subtypes).

PREVALENCE OF HPV INFECTION

BURDEN OF ILLNESS

• SEER data:

  • “It is estimated that 12,710 women will be diagnosed with and 4,290 women will die of cancer of the cervix uteri in 2011.”

  • For comparison, for every woman who will die of cervical cancer:
    • 5 will die of colon cancer
    • 8 will die of breast cancer
    • 15 will die of lung cancer
INADEQUATE SCREENING

- About half of all cervical cancer deaths are in women who have not been screened or who have had incomplete follow-up to screening and treatment.
- If we could assure adequate screening of the entire population, the residual preventable burden would be small.

POSSIBLE GOALS FOR NEW CERVICAL CANCER PREVENTION STRATEGIES

- Further reduction in mortality?
- Reduction in the burden and/or harms of screening and treatment of screen-detected disease.

CERVICAL CANCER SCREENING RECOMMENDATIONS

- Age under 21 years
  - Do not screen
- Age 21-30 years
  - Screen with cytology every 3 years
  - Do not screen with HPV
- Age 30-65 years
  - Screen with cytology every 3 years or...
  - Co-testing with cytology and HPV every 5 years
- Women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer
  - Do not screen
- Women older than age 65 years who have not had adequate prior screening
  - screen with cytology every 3 years or...
  - Co-testing with cytology and HPV every 5 years

CERVICAL CANCER SCREENING RECOMMENDATIONS
WHY NOT SCREEN BEFORE AGE 21?

- Cervical cancer is rare in this age range (1 in a million)
- HPV infection is common and results in transient abnormalities of the cervix
- Detection and Rx of those abnormalities leads to harm

WHAT ABOUT SEXUAL HISTORY?

- Young women with multiple sexual partners are the most susceptible to the harms of screening
- The possibility of benefit is vanishingly close to zero
- Just say no to screening for cervical cancer before age 21.

SCREENING INTERVAL FOR CYTOLOGY IN WOMEN AGE 21-65

- RCTs of screening programs at different intervals never exist
- e.g. no one has done an RCT comparing colonoscopy for colon cancer screening every 5 years to every 10 years or 20 years (decided to leave in the typo)
- Task Force has used modeling

MODEL: ENORMOUSLY COMPLICATED – EVEN IF YOU LIKE MATH

Table 8. Survival Analyses: Sensitivity Analysis: Relative Risk of Positive/Positive Colonoscopy, CIN2+ Cancers, Cancer Cases, and Cancer Specific Mortality Associated with Screening Beginning at Age 10 Years and Increased in Five-Year increments to Age 55 Years, Among Women Followed for 5 Years

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<tr>
<th>Strategy</th>
<th>Age 10</th>
<th>Age 15</th>
<th>Age 20</th>
<th>Age 25</th>
<th>Age 30</th>
<th>Age 35</th>
<th>Age 40</th>
<th>Age 45</th>
<th>Age 50</th>
<th>Age 55</th>
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</tbody>
</table>

USPSTF Update on Women’s Health Issues
Family Medicine Winter Symposium
December 6, 2014
CYTOLOGY STARTING AGE 21, FOLLOWED FOR LIFE (PER 1000)

ANNUAL CYTOLOGY
- 951 false positive
- 1931 colposcopies

CYTOLOGY EVERY THREE YEARS
- 350 false positive
- 738 colposcopies

“All models are wrong, some are useful.”

HARMS: COLPOSCOPIES

- Pain, bleeding
- Sentinel measure for downstream harms
- Similar to using number of colonoscopies as sentinel measure of harm in modeling of colon cancer screening

HARMS: OVER-DIAGNOSIS

- CIN2 can/does regress – over-diagnosis and over-treatment are real risks
- CIN3 can also regress
- Standard of care currently to Rx all CIN2+

OBSERVATIONAL STUDY

- Lancet Oncology, vol 12, July 2011
- Katki et al followed 313,818 women in Kaiser Permanente Northern California
OBSERVATIONAL STUDY ON INCIDENCE

• 319,177 (96.2%) of women had normal Pap at baseline
• CIN3+ at:
  • 3 years 0.17%
  • 5 years 0.36%
• Risk of invasive cancer at five years after normal cytology was 7.5 per 100,000 women (0.0075%)

SCREENING INTERVAL FOR CYTOLOGY IN WOMEN AGE 21-65

• Cytology every 3 years demonstrates a good balance of benefits and harms
• “Pap smears every three years are safe and effective at reducing cervical cancer, while minimizing the risks of false positive results and the harms associated with treating disease that will go away without treatment.”

USE OF HPV TO SCREEN FOR CERVICAL CANCER

HPV SCREENING BEFORE AGE 30

• Recommend against
  • Prevalence is high, therefore false positive rate is high
  • False positive means identifying someone "in need of intervention" to prevent cervical cancer who does not need that intervention because her disease will regress spontaneously

Just say no to screening for cervical cancer with HPV before age 30.
HPV SCREENING FOR CERVICAL CANCER FOR AGE > 30 YEARS

- Multiple studies of varied design demonstrate that HPV testing is...
- More sensitive than cytology for CIN2+
- Less specific than cytology
- The Task Force had the challenge of being “moderately certain” about the balance of benefits and harms.

RCTS OF HPV SCREENING FOR CERVICAL CANCER

- EPC reviewed and presented the results of 6 European RCTs that included HPV in some way in the experimental group
- Inconsistent design, varying protocols, incomplete reporting and perhaps most importantly incomplete follow-up through two rounds of testing

CYTOLOGY EVERY 3 YEARS VS CO-TESTING EVERY 5 YEARS

- Kaiser observational data
- Further exploration in the model to try to fill in gaps in evidence

KAISER DATA

- Cumulative incidence of CIN3+ the same (0.17%) ...
- three years after normal cytology and
- five years after double negative co-testing
- Other analyses confirm increased sensitivity and decreased specificity of HPV testing relative to cytology
- Did not report total colposcopies
### MODEL DATA

<table>
<thead>
<tr>
<th>False positives</th>
<th>Colposcopies</th>
<th>CIN2-3</th>
<th>Cancers</th>
<th>Cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology q3 years</td>
<td>350</td>
<td>758</td>
<td>80</td>
<td>8.5</td>
</tr>
<tr>
<td>Cytology q3 years until age 30 then co-testing q5 years</td>
<td>255</td>
<td>575</td>
<td>84</td>
<td>7.44</td>
</tr>
</tbody>
</table>

Note: model assumed women with normal colposcopy immediately returned to usual screening

### CERVICAL CANCER SCREENING RECOMMENDATIONS

- **Age 30-65 years**
  - Screen with cytology every 3 years or...
  - Co-testing with cytology and HPV every 5 years

### AGE 65 YEARS OR OLDER

- Potential for benefit in those adequately screened in the past whose screening tests are normal is very low, potential for harm at least small
- Note women who have had CIN2+ should continue to be screened for 20 years
- Consider screening women who do not have a history of adequate screening

http://fcm-algo.umh.edu/Algorithms/CervicalCancerScreening.htm
BREAST CANCER

BRCA SCREENING

• The USPSTF recommends that primary care providers screen women who have family members with breast, ovarian, tubal, or peritoneal cancer with 1 of several screening tools designed to identify a family history that may be associated with an increased risk for potentially harmful mutations in breast cancer susceptibility genes (BRCA1 or BRCA2).
• Women with positive screening results should receive genetic counseling and, if indicated after counseling, BRCA testing.

BRCA

• A woman’s risk for breast cancer increases to 45% to 65% by age 70 years if there are clinically significant mutations in either BRCA gene
• Mutations in the BRCA1 gene increase ovarian cancer risk to 39% by age 70 years, and BRCA2 mutations increase ovarian cancer risk to 10% to 17% by age 70 years
BRCA MANAGEMENT

• Cohort studies of risk-reducing surgery
  • Breast cancer risk was reduced by 85% to 100% with mastectomy and by 37% to 100% with oophorectomy
  • Ovarian cancer risk was reduced by 69% to 100% with oophorectomy or salpingo-oophorectomy

SCREENING TOOLS

• For women who have at least 1 family member with breast or ovarian cancer
  • Several brief familial risk stratification tools to determine the need for in-depth genetic counseling

WEB SITE

BREAST CANCER: MEDICATIONS FOR RISK REDUCTION

• A systematic review of clinical trials found that tamoxifen and raloxifene reduced the incidence of invasive breast cancer by 7 to 9 events per 1000 women over 5 years.

• In general, women with an estimated 5-year risk of 3% or greater are, on the basis of model estimates, more likely to benefit from tamoxifen or raloxifene.

QUESTIONS?