Cancer Screening for Women: Updates and Controversies

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Disclosures

I have no financial interests to disclose

However, I sometimes hike in Kapu areas….!
Lecture Plan

- Major cancers: Cervix, breast, colon, lung, ovary
- Not comprehensive: 1-2 questions for each one
- Cervix: Why did USPSTF and other organizations change guidelines (interval, start and stop ages)
- Colorectal: What is the best method for screening

Lecture Plan

- Breast
  1) Why USPSTF changed guidelines for 40-49 yo women from B to C
  2) Evidence on newer screening techniques: U/S, MRI, digital mammography
- Lung: Why does the USPSTF recommend screening even though there are so many false positives?
- Ovary: Why can’t we effectively screen for ovarian cancer?
Pap smears are the most effective screening test ever invented....
Why does pap screening work?

- Sensitivity and specificity of pap/cytology not great

  BUT

- The organ is easily accessible for screening
- Natural history is favorable:
  - precursor exists that is detectable and treatable;
  - time course before cancer develops is long
  - many opportunities to detect. Even if one test is false negative, get another chance.
- It is cost-effective because many years of life are saved because cancer is actually prevented.

Can we do better?

- Half of cervical cancers occur in women who are not screened or inadequately screened. These women tend to be poor, uninsured, with lack of access to care
  - A more sensitive test like HPV or Thin Prep (marketed directly to the public!) will not fix this

- In poor countries, cervical cancer remains a huge problem.
Can we do better? YES!

- **False +**: Although colposcopy is not that morbid, false +’s still cause anxiety, labeling, and are costly.
  - Spacing the screening interval, starting screening later and HPV typing used correctly in conjunction with cytology, will reduce false +’s and colposcopies

- **Over-treatment**: Only 30% of untreated CIN3 becomes invasive cancer (over 30 yrs). Destroying all CIN3 = over-treatment. Main harm is preterm delivery.
  - Smart screening, biomarkers, risk-based approaches and less aggressive (but still evidence-based) treatment guidelines can help.

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2012 USPSTF Cx Ca

- **STRONGLY RECOMMENDS (“A”)**
- **Who?** Women with cervix, regardless of sexual history
- **Begin:** Start age 21
- **Interval:** 21-29: cytology q 3yr; after 30: can do q 5yr with cyto+HPV or cont’d q 3 yr cyto alone
- **End:** Age 65 if adequate prior screening (as per ACS/ASCCP) and not at high risk for cx cancer (HIV, DES, immunocompromised)
- **Other:** Recommends against any HPV testing in <30yo (“D” grade)
All US guidelines similar

- All strongly recommend against starting before age 21
- None recommends annual screening
- All recommend against HPV alone or as a co-test in women <30 (ok as a reflex test after abnormal pap per ACS/ASCCP)
- All recommend no screening after hyst as long as no history of CIN2+
- All recommend stop at age 65
- None recommend changes in screening for those who’ve had HPV vaccine

What’s new/different?

- Co-test with HPV:
  - 1st time USPSTF has recommended co-testing with HPV (ok for women who want to extend interval to 5 yrs)
  - ACS/ASCCP/ASCP: prefers co-test with 5 yr interval; acceptable to do cyto alone q3yr
- F/U after CIN2+: ACS/ASCCP: 20 yrs ACOG: 10 yrs, USPSTF vague
- Criteria to end at age 65: ACS/ASCCP—clearer guidance than others
Why is less screening now recommended?

Why is it ok to delay screening until age 21

- Cervical cancer extremely rare; HPV infection very common immediately after onset of intercourse. 90% cleared by host within 2 yrs
- If persistent, we will pick up at age 21, still with plenty of time to treat because long progression time of pre-invasive lesions to invasive cancer

Why is it ok to lengthen the screening interval

- Large population based study showed safety of this approach. 1yr vs 3yr screening: decrease lifetime risk of mortality by 2 per 100,000, increase in lifetime colpo rates from 760/1000 to 2000/1000
- The more tests you do, the more false positives.

Why the difference between <30 and >30 yo?

- HR-HPV co-testing becomes clinically useful after age 30
- In <30yo: HPV often positive, often transiently. Therefore, HPV testing not clinically useful.
- > Age 30: HPV positivity more likely to represent persistent HPV which is a significant risk factor for dysplasia/cancer. Conversely, HPV negativity is a strong negative predictor.
Role of HR-HPV co-testing

• Better sensitivity, worse specificity, better reproducibility than pap/cytology
• HPV tests may better forecast which women will develop CIN3+ and more sensitive for adeno-ca
• Has potential for increased detection (more sensitive) and increased interval of screening (more predictive of CIN3 risk)
• Harm=increased colpo/treatment. This can be mitigated by increasing interval to 5 yr

Co-testing caveats

• HPV has decreased specificity so if we co-screen more often than q5 years, patients will incur greater harm without benefit
  – Before doing co-test, ensure patient is willing to be screened every 5 years
• HPV-based strategies also lead to more positives
  – Some women will need prolonged surveillance
  – Some women who would otherwise be able to stop at age 65 will require continued screening beyond age 65
• What to do with HPV+, cytology negative?
ACS/ACSSP/ACP guidelines

- Co-testing “preferred” method
- Preferred by whom?
  - USPSTF: co-testing is an option “for women who want to lengthen the screening interval”
- Looking more deeply into the “preferred” recommendation…. Supplemental page

Co-testing “preferred”

- Weak recommendation
  - “substantial uncertainty surrounding the balance of benefits and harms, and further research is needed to increase confidence in the results, or that benefits and harms are closely balanced, with decisions based largely on individual preferences and values”
- Given these substantial reservations, it is puzzling that the guidelines did not disclose that the designation of co-testing as “preferred” was a weak recommendation.
Beware guideline bias

• ACS/ASCCP/ACSP: Approximately 25% of committee members reported financial conflicts of interests with companies that make HPV tests

Now what?

• FDA approved Roche Cobas HPV test as primary screen (no pap) in >25yo
Should we wait for more evidence?

• Downside of waiting… Missing cancer?
  – our screening programs already work very well
  – most cancers occur in under-screened or those not followed up well after abnormal pap
  – chance of cervical cancer in 5 yrs after neg pap is 7.5/100,000, after neg HPV test is 3.8/100,000.

• Downside of being early adopter?
  – Don’t know if it’s a better approach
  – Increased worry in women told they have hpv
  – Increased colposcopy in women who have no dysplasia

Conclusions: Cervical Cancer

• Cervical cancer screening in the US is already very successful at decreasing cervical cancer incidence and morbidity

• Now the goal is to decrease harm by decreasing false + and over-treatment:
  – Start screening later (age 21)
  – Screen less often (q 3yr)
  – Use HPV co-test to extend interval to 5yr in patients who desire this

Stout, Arch Int Med 2008
Path to Mauna Kea Resort

- Part of Ala Kahakai Trail
- 1.5 miles
- Access to the right of Hapuna property—up on grassy area (not down on beach)
- Mauna Kea=sister resort eg can use facilities, sign for Mai Tai’s
- Wear closed-toed shoes
Q1: 43 yo woman with normal mammo 2 yrs ago but with “extremely dense” breasts. No other breast cancer risk factors. She would like your recommendation re: screening.

A. Wait until age 50 and then get mammo
B. Regular (film) mammo
C. Digital mammo
D. Mammo plus ultrasound
E. Mammo plus MRI

2009 USPSTF recommendations

• 50-74 yo: RECOMMENDS (“B”)
• 40-49 yo: Individual decision (ie don’t offer routinely) (“C”) (was “B” in 2003)
• What? Mammography with or without clinical breast exam
• How often? Every 2 years (was every 1-2 years in 2003)
• When stop? After age 75, evidence is insufficient to make recommendation (“I”)

USPSTF Rec's: A=strongly recommends; B=recommends; C=no recommendation; D=Recommends against; I=insufficient evidence
2009 Meta-analysis by USPSTF

- 1 new trial specifically in women 40-49
- 1 trial with updated data

**Table 1. Pooled RR for Breast Cancer Mortality From Mammography Screening Trials for All Ages**

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Trials Included, n</th>
<th>RR for Breast Cancer Mortality (95% CrI)</th>
<th>NNI to Prevent 1 Breast Cancer Death (95% CrI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-49</td>
<td>8*</td>
<td>0.85 (0.75–0.96)</td>
<td>1904 (929–6378)</td>
</tr>
<tr>
<td>50-59</td>
<td>6†</td>
<td>0.86 (0.75–0.99)</td>
<td>1339 (322–7455)</td>
</tr>
<tr>
<td>60-69</td>
<td>2‡</td>
<td>0.68 (0.54–0.87)</td>
<td>377 (230–1050)</td>
</tr>
<tr>
<td>70-74</td>
<td>1§</td>
<td>1.12 (0.73–1.72)</td>
<td>Not available</td>
</tr>
</tbody>
</table>

Nelson, Annals Int Med, 2009

**Why the change? Conceptually…**

**In women 40-49 c/w older women…**

- Smaller number of deaths are prevented because:
  - Lower incidence of breast cancer
  - Lower sensitivity of mammography
  - Cancers often more aggressive, less treatable

- More false positives
  - Lower specificity and prevalence → lower positive predictive value & more false positives
Why the change? Numerically:

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Estimated benefits and harms of annual screening mammography for 10 years in 1000 average American women at age 40 or age 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected</td>
<td>Aged 40 Years</td>
</tr>
<tr>
<td>Mammograms</td>
<td>10,000</td>
</tr>
<tr>
<td>Positive test result</td>
<td>550</td>
</tr>
<tr>
<td>Biopsy</td>
<td>75</td>
</tr>
<tr>
<td>Invasive BC</td>
<td>14</td>
</tr>
<tr>
<td>DCIS</td>
<td>4</td>
</tr>
<tr>
<td>BC deaths</td>
<td>2</td>
</tr>
<tr>
<td>BC deaths averted</td>
<td>0.3</td>
</tr>
<tr>
<td>Gain in life expectancy*</td>
<td>3 days</td>
</tr>
</tbody>
</table>

**Abbreviations:** BC, breast cancer; DCIS, ductal carcinoma in situ.

*The gain in life expectancy represents the average gain for 1000 women screened. Some women diagnosed with breast cancer gain many days, but most women do not benefit.

**Bottom Line:** USPSTF uses absolute benefit, not relative benefit and strongly considers risk of harm to healthy women (which is subjective and debatable).

The USPSTF notes that a "C" grade is a recommendation against *routine* screening of women aged 40 to 49 years. The Task Force encourages individualized, informed decision making about when to start.
Other Guidelines

Given the lack of consensus, involve patient in the decision-making....

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year</th>
<th>Guidelines Issued</th>
<th>Mammography</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF</td>
<td>2009</td>
<td>Age 50–74 yr, every 2 yr; age 40–49 yr and age ≥75 yr; individualize the decision (every 2 yr, if performed)</td>
<td></td>
</tr>
<tr>
<td>American Cancer Society</td>
<td>2010</td>
<td>Age ≥40 yr, annually†</td>
<td></td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>2011</td>
<td>Age ≥40 yr, annually†</td>
<td></td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>2010</td>
<td>Age ≥40 yr, every 1–2 yr†</td>
<td></td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>2007</td>
<td>Age 50–74 yr, every 1–2 yr; age 40–49 yr, individualize the decision (every 1–2 yr, if performed)</td>
<td></td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists</td>
<td>2003</td>
<td>Age 40–49 yr, every 1–2 yr; age ≥50 yr, annually†</td>
<td></td>
</tr>
<tr>
<td>American College of Radiology</td>
<td>2008</td>
<td>Age ≥40 yr, annually†</td>
<td></td>
</tr>
<tr>
<td>Canadian Task Force on Preventive Health Care</td>
<td>1998–2001</td>
<td>Age 50–69 yr, every 1–2 yr; age 40–49 yr, individualize the decision (every 1–2 yr, if performed)</td>
<td></td>
</tr>
<tr>
<td>National Health Service, United Kingdom</td>
<td>2011</td>
<td>Age 47–73 yr, every 3 yr</td>
<td></td>
</tr>
</tbody>
</table>

* USPSTF denotes U.S. Preventive Services Task Force.
† No upper age limit was specified.
‡ These recommendations have not been updated since 1989.

New Technologies

- Digital Mammography
- Breast MRI
- Ultrasound plus Mammography
- Thermography?
Digital Mammography

- More sensitive for women<50, extremely dense breasts, ER negative breast cancer
- Easier access, transmission and storage of images, lower average dose of radiation
- Trade-off of slightly lower specificity
- From BCSC: in 10,000, 2 additional breast cancers for 170 additional false positive results

Tipping the balance toward benefit in 40-49yo

- Digital mammography
  - Increased sensitivity in 40-49yo and women with dense breasts c/w film
- Risk based screening
  - If limit the screened population to one with similar prevalence of cancer as older women, ratio of benefit to harm becomes more favorable
  - Who? women with ≥1 first degree relative w brst ca or brst density category ≥4
Caution: comparing detection rates….

- Studies of new techniques typically compare detection rates in observational studies.
- **Key q is:** does improved detection lead to overall benefit (decreased mortality/morbidity).
- Observational studies prone to lead-time and length bias.
- Earlier detection/treatment may not be better than later.
  - Ex: 10,000 50 yo’s followed for 20 yrs. Without mammo, 260 die of breast cancer. With mammo: 223 die. Screening averted 37 deaths per 10,000 over 20 years = 1 death saved/270 women for 20 years.

Ultrasound + Mammo

- Potentially useful in dense breasts?
- No RCT’s of normal risk women or women with only risk being dense breasts.
- Meta-analysis in women with dense breasts:
  - 6 cohort studies, only 2 included adeq f/u (nec to know false + and -)
  - Studies small; few cancers detected (results unstable)
  - CONCLUSION—more study necessary.

Nothacker, *BMC Cancer* 2009
MRI + Mammo

- Only for high risk women (BRCA, personal h/o brst ca, lifetime risk >20%)
- Systematic review
  - No RCT's, no studies with long term f/u or mortality
  - MRI more sensitive (80-100%) vs 25-59%, less specific 73-93% (3-5 fold higher recall rate)
  - Mammo more sensitive for DCIS therefore need both
  - Concl: more study needed, unknown if lead time/ length bias or real benefit, screening doesn’t detect nor cure 100% therefore consider risk reducing strategies
- ACS: Annual MRI + mammo for women with lifetime risk >20%

Q1: 43 yo woman with normal mammo 2 yrs ago but with “extremely dense” breasts. No other breast cancer risk factors. She would like your recommendation re: screening.

A. Wait until age 50 and then get mammo
B. Regular (film) mammo
C. Digital mammo
D. Mammo plus ultrasound (evid insuff, esp in women with dense breasts as only rf)
E. Mammo plus MRI (only for women with >20% risk of brst ca)
Conclusions: Breast Cancer

- **40-49 informed decision**
  - Risk evaluation—recommend if risk 2x greater than general popIn; Digital if decide to screen
- **50-74 screen every 2 years**
  - Best benefit/harm ratio from 50-65yo
- **Ultrasound + mammo for dense breasts…**
  - More study needed.
- **MRI + mammo for very high risk…**
  - May be useful, longer f/u necessary to confirm benefit, ACS recommends if>20% lifetime risk

Ala Kahakai Trail

- **Ancient Hawaiian Trail**
- Access it at left side of beach—walk inland along rocks and you will see it
- Nice beach with trees/coves about 25 min away
Q2: 55 yo woman with no symptoms or family history of colorectal cancer. What type of CRC screening do you typically recommend?

A. FOBT or FIT
B. Sigmoidoscopy
C. Colonoscopy
D. CT Colonography
E. Any of the above
F. None of the above

Colorectal cancer screening

3rd most common cause of cancer death in women

Similar in many ways to cervical cancer screening:

• Natural history is known:
  – Pre-invasive lesion exists (adenoma)
  – Orderly progression from simple adenoma to one with poor histologic features to carcinoma-in-situ to invasive cancer
  – Long time course for this progression (many years)

• Treatment of the pre-invasive lesions is effective (~100%) at PREVENTING cancer
Colorectal cancer screening: options

- FOBT: fecal occult blood test *
- Sigmoidoscopy *
- Colonoscopy
- Barium enema
- CT colonography (virtual colonoscopy)
- Various combinations of the above
- Fecal DNA
- FIT: Fecal immunochemical test

* RCT evidence of benefit

Evidence of benefit

- 4 large RCT’s of FOBT prove benefit (>320,000 people, up to 18 years follow-up)
  - Decreased CRC mortality of 16%
  - Absolute risk reduction: 0.8 - 4.6/1000
  - One trial also showed decreased cancer incidence of 17-20%
- 5 trials of sigmoidoscopy showed:
  - Decreased CRC mortality of 28%
  - Absolute risk reduction 1.6/1000
  - Decreased cancer incidence of 18%
Newer methods?

CT colonography:
- No sedation needed, need bowel prep
- Radiation exposure: 1/1000 risk of new cancer
- Colonoscopy to remove polyps seen
- Incidental extra-colonic findings in 27-69%
  - 5-15% require additional evaluation and medical or surgical intervention but few ultimately required definitive treatment

Fecal DNA:
- Detects more neoplasms than FOBT, but with more false positive results
- Expensive: $400 to $800 versus $3 to $20 for FOBT

Fecal Immunochemical Testing (FIT):
- Detects more neoplasms than FOBT, but with only slightly more false positive results
- ~$20, only one sample needed, no dietary restrictions
- Compliance improved compared with FOBT
How Are We Doing?

- FOBT in past 2 years: 27%
- Ever had a sigmoidoscopy or colonoscopy: 53%
- Colonoscopy after positive FOBT: 33%

BRFSS, 2004

CRC: slowly improving

Incidence: 28% decrease
Mortality: 44% decrease
What is the best test?

• Any test that the patient will accept is the best test!

• **USPSTF STRONGLY RECOMMENDS (“A”):**
  – All men and women 50-75 yo
  – FOBT (or FIT) q 1 year
  – Sigmoidoscopy: q 5 years
  – Colonoscopy q 10 years

• Joint ACS, ACR Task Force also recommends CT Colonography q5yr & fecal DNA (unknown timing)

Kawaihae Harbor: Lunch fish truck
Ovarian Cancer Screening

PLCO RCT: Annual screening with CA-125 + TVUS for 6 yrs, 12 yr f/u

(PLCO=pro, lung, colon, ovarian screening trial)

<table>
<thead>
<tr>
<th></th>
<th>Screen</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian Cancer (rate/10,000)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39,105</td>
<td>39,111</td>
<td>–</td>
</tr>
<tr>
<td>Ov Ca</td>
<td>212 (5.7)</td>
<td>176 (4.7)</td>
<td>1.2 (1.0-1.5)</td>
</tr>
<tr>
<td>Stage 3&amp;4</td>
<td>77%</td>
<td>78%</td>
<td>ns</td>
</tr>
<tr>
<td>Deaths</td>
<td>118 (3.1)</td>
<td>100 (2.6)</td>
<td>1.2 (0.8-1.7)</td>
</tr>
</tbody>
</table>

20% increase in diagnosis AND death

Buys S. JAMA 2011

PLCO Results

- 3285 women (8%) with false positive screens
  - 1080 surgical follow-up
  - 163 serious surgical complications (15%)
- PPV=6% (94% of those with + test did NOT have cancer)

Conclusion: “Annual screening for ovarian cancer…with simultaneous CA-125 and transvaginal ultrasound does not reduce disease-specific mortality in women at average risk for ovarian cancer but does increase medical procedures and associated harms.”
Why can’t we screen for ovarian cancer?

1. No known histologic precursor lesions
2. Unknown time for development or for progression from Stage 1 to Stage 4
   – mathematical models suggest 8 months for development which would be impossibly short to detect by screening
3. For false positives, about 1/3 undergo surgery as the confirmatory test which is more morbid than confirmatory tests for others types of cancer screening

Why can’t we screen for ovarian cancer?

4. Very low prevalence compared to other cancers
   – Peak prevalence (age 55), 50/100,000 (yearly incidence=14/100k)
   – Breast cancer: 6/1000; cervical dysplasia and colonic adenomas: ~4%
5. Given low prevalence, even if a test had a specificity of 99.5%, PPV would only be 7%.
   – Large number would undergo unnecessary surgery to detect 1 case of ovarian cancer
   – In practice, specificity always lower than in research studies
CT for Lung Cancer Screening

- National Lung Cancer Screening Trial (2011)
- Stopped early due to benefit
- 53,000 smokers (>30pack-yr), 55-74yo, helical CT (low dose) vs CXR annually for 3 yrs, f/u 7 yrs
- 354 vs 442 lung cancer deaths: ARR~3.3/1000
  RR 0.80 (0.73-0.93). Any death: RR 0.93 (0.86-98)
- 24% with positive CT during study—95% were false positives with requirement for various tests, mostly imaging but sometimes lung biopsy or surgery to rule-in/rule out lung ca

To prevent 62 deaths from lung cancer..

Among 53,000 participants over 7 yrs, there were 309 deaths in cxr group and 247 in CT group (diff=62). This required:

- 75,000 CT scans
- 18,146 positive tests
- 17,066 false positive tests
- 673 thoracotomy / mediastinoscopy
- 303 broncoscopies
- 99 needle biopsies
USPSTF 2013: B recommendation

Screening for Lung Cancer

This topic page summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on screening for lung cancer.

Current Recommendation

Release Date: December 2013

- The USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults ages 50 to 80 years who have a 30 pack-per-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.

Grade: B recommendation.

Why does the USPSTF recommend it even though there are so many false positives?

Why do you think a B recommendation?

Comparing it to mammography in 40-49yo….

<table>
<thead>
<tr>
<th></th>
<th>Mammo (C rec)</th>
<th>LDCT (B rec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decr mortality</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>False positives</td>
<td>10% per screening round</td>
<td>24% over 3 rounds, 96% false positive</td>
</tr>
<tr>
<td>Baseline risk in popln to be screened</td>
<td>Very low</td>
<td>High</td>
</tr>
<tr>
<td>ARR</td>
<td>0.5 per 1000</td>
<td>3 per 1000</td>
</tr>
<tr>
<td>NNS</td>
<td>1904</td>
<td>320</td>
</tr>
<tr>
<td>Case fatality (% with this cancer who die)</td>
<td>Very low</td>
<td>Very high</td>
</tr>
</tbody>
</table>
Bottom Line: Lung Cancer Screening

• The only cancer screening trial with a statistically significant decrease in total mortality
• “The personal and public health consequences of lung cancer are enormous, and even a small benefit from screening could save many lives.”  USPSTF

Health Policy not yet established

• ~ 94 million current or former smokers in the U.S.; ~ 7 million meet NLST criteria
• Specificity of CT in practice will be lower than in research setting ➔ increased false positive rates
• Instituting in practice more complex than other cancers: need primary care, radiology, IR, surgery, pulmonary to be involved.
• Expensive… $ $ $
Last words

• Preventive interventions require a high burden of proof: the “do no harm” principle.
• Comparing detection rates of newer technologies is insufficient b/c of lead-time and length bias. Need RCT showing better outcomes, not just more cancers detected.
• Choose your guidelines carefully: beware vested interests in guideline groups.
• Guidelines are designed to maximize population benefits and minimize population harms—this is hard to explain to individual patient.

Enjoy The Big Island!