Breast & Cervical Cancer Screening:
Updates and Controversies

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I have no financial interests to disclose
Part I

Cervical Cancer Screening

1. Why USPSTF and other organizations changed guidelines (interval, start and stop ages)
2. HPV co-testing
3. What to do with HPV +, pap –
4. Which is better: pap or liquid-based cytology
Part II

Breast Cancer Screening

1. Why USPSTF changed guidelines for 40-49 yo women from B to C

2. Risk estimation for 40-49yo

3. Evidence on newer screening techniques: U/S, MRI, digital mammography
Don’t be alarmed, Ms. Jones, but from now on we’ll need to wheel you out on to the floor of Congress to perform your routine pelvic exams, so that law-makers can take notes and offer advice as they see fit.
Q1: 19 yo brought in by mom for pap. Sexually active since age 15. 4 male sexual partners. In addition to STI screening & counseling on safe sex and birth control, what else would you do?

1. Traditional Pap smear
2. Liquid-based cytology (eg thin prep)
3. HR-HPV only (without cytology)
4. HR-HPV with cytology (ie co-test)
5. Nothing more
Pap smears are the most effective screening test ever invented....

Cervical Cancer in US

Incidence

Mortality

per 100,000

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 many marketed directly to the public eg Thin Prep), 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.
Potential adverse effects of LEEP

- Preterm delivery: 70% ↑
- Low birth weight: 82% ↑
- PPROM: 169% ↑

*Lancet* 2006 367:489-98

Potential adverse effects of cold knife cone

- Perinatal mortality: 187% ↑
- Severe preterm delivery: 178% ↑
- Extreme low birthweight: 186% ↑

*BMJ* 2008 Sep 18;337

Caution: No randomized trials.
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)
Other US Guidelines very similar

**ACS/ASCCP/ASCP (2012)**

- **Begin**: age 21
- **Interval**: Age 21-29: Q 3yr, HPV as a reflex test not as primary screen. **After 30**: preferred = cyto + HPV q 5 yrs; cyto alone q 3yrs also ok.
- **End**: age 65 if 3 nl paps or 2 nl HPV within 10 yrs, most recent within 5yrs. Continue to screen for 20yr after CIN 2/3. Do not resume even if new sex partner

**ACOG (2009):**

- Same
- 21-29: Q 2yr. **After 30**, Q 3 yrs if 3 consecutive, satisf norms & not immunocompromised. Co-screen with HPV q 3yr approp if >30yo.
- **End**: 65-70yo if 3 conseq nls and no abnormals in last 10 yrs
What’s 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: 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
Ala Kahakai Trail

- Ancient Hawaiian Trail
- Access it at left side of beach—walk inland along rocks and you will see it
- Not sure how far it goes from Hapuna
Why is it ok to delay screening until age 21?

- Cervical cancer extremely rare in younger women
- HPV infection very common immediately after onset of intercourse and 90% is cleared by host within 2 yrs
- When dysplasia does occur in adolescents, it tends to be low grade and transient (90% regression at 3 yr).
  - If persists, plenty of time to detect and treat because long progression time of pre-invasive lesions to invasive cancer
- Excision of dysplasia associated with preterm birth
- Labels adolescent with a sexually transmitted infection
- **Bottom Line:** HPV infection typically cleared without help from us. Screening in adolescents therefore leads to treatment that is largely over-treatment. Harms>>>Benefits
Why is it ok to lengthen the screening interval?

• After several normal tests, very small likelihood of missed disease

• If newly acquired infection, high likelihood of regression and long time to invasion

• The more tests you do, the more false +’s. Mathematical reality: prevalence is low, tests not extremely specific.
21-29yo: The evidence for q 3 yr interval

- ACS/ACSSP: “Annual screening leads to a very small increment in cancers prevented at cost of large excess of unnecessary procedures and treatments.”

- 3 vs 1 yr screening (21-29 yo)
  - Lifetime risk of cancer death: 0.03/1000 vs 0.05/1000 (decrease of 2 per 100,000)
  - Lifetime colposcopy rates 2000/1000 vs 760/1000 women (increase of 1240 per 1000)
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 testing

- Better sensitivity, lower specificity, better reproducibility than pap/cytology
- HPV tests may better forecast which women will develop CIN3+
- 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
### Modeling

<table>
<thead>
<tr>
<th></th>
<th>False +</th>
<th>Colposcopies</th>
<th>CIN 2-3</th>
<th>Cancers</th>
<th>Cancer deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytology q3 years, ages 21-65</td>
<td>350</td>
<td>758</td>
<td>80</td>
<td>8.5</td>
<td>1.55</td>
</tr>
<tr>
<td>Cytology q3 years until age 30 then co-testing q5 years</td>
<td>281</td>
<td>625</td>
<td>85</td>
<td>7.1</td>
<td>1.29</td>
</tr>
</tbody>
</table>

Per 1000 women screened over a lifetime.

Modeling studies support similar benefits of co-testing every 5 years and cytology every 3 years, demonstrating small differences in expected cancer cases and cancer deaths.
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?
Cotesting: what to do with HPV positive/Pap normal women?

About 8-11% of women ages 30-55 in the US will have a positive HPV test (HC2) and a normal Pap test (Ann Int Med April, 2008)

At Kaiser Northern CA, about 3-7% of women ages 30-55 have a positive HPV test (HC2) and a normal Pap test (Obstet Gynecol March 2009)
HPV positive/Pap normal women

Recommendations by ASCCP and ACOG:

• Repeat co-test at 12 months.
  – If negative $\rightarrow$ q 5yr screening
  – If still HPV+ or if $\geq$ LSIL AS-CUS $\rightarrow$ colposcopy.

2012 ASCCP Guidelines; ObstetGynecol, Apr 2013

Alternate recommendation by ASCCP:

• Perform HPV genotype-specific typing for 16 or 16/18.
  – if positive, perform colposcopy.
  – If negative, repeat co-test at 12 months.
What’s Better: Pap or LBC?

Comparison of Liquid-Based Cytology With Conventional Cytology for Detection of Cervical Cancer Precursors
A Randomized Controlled Trial

Siebers, 2009

- N=89,784, cluster RCT
  - No difference in detection rate (sensitivity) or PPV, fewer unsatisfactory tests with LBC
  - Conclusion: no difference

- 2nd RCT, different design, similar findings

- Evidence based practice center & 2 reviews conclude: no difference in relative or absolute sensitivity or specificity
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
  – Return to traditional pap smear?
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
Part II

Breast Cancer Screening

1. Why USPSTF changed guidelines for 40-49 yo women from B to C
2. Risk estimation for 40-49yo
3. Evidence on newer screening techniques: U/S, MRI, digital mammography
Q2: 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.

1. Wait until age 50 and then get mammo
2. Regular (film) mammo
3. Digital mammo
4. Mammo plus ultrasound
5. 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 RRs for Breast Cancer Mortality From Mammography Screening Trials for All Ages

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

Nelson, Annals Int Med, 2009
40-49 yo women


Criticism: Most of these trials include benefits that may have accrued to women due to screening that occurred after the age of 50.

On other side: Most were done long ago and mammography technology improved today so benefits may be underestimated. However, modeling studies using updated sensitivity/specificity show same magnitude of benefit.
Ratio of Benefits vs Harms

- **Benefits** = decreased mortality, increase in # life years gained
- **Harms** (USPSTF doesn’t include financial costs in their analysis)
  - screening (radiation risk, pain, inconvenience)
  - diagnostic work-up for false positive (49% over 10 mammos, anxiety, 1/3 of total screening cost)
  - over-diagnosis (harms assoc with overtreatment, 10-25% of invasive, 34% of DCIS)

- Benefit/Harm ratio varies significantly by patient age
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></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&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 days</td>
</tr>
</tbody>
</table>

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

<sup>a</sup> 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.
Why the change from B to C for 40-49 yo’s from 2003 to 2009?

**USPSTF Assessment**

The USPSTF has reached the following conclusions:

For biennial screening mammography in women aged 40 to 49 years, there is moderate certainty that the net benefit is small. Although the USPSTF recognizes that the benefit of screening seems equivalent for women aged 40 to 49 years and 50 to 59 years, the incidence of breast cancer and the consequences differ. The USPSTF emphasizes the adverse consequences for most women—who will not develop breast cancer—and therefore use the number needed to screen to save 1 life as its metric. By this metric, the USPSTF concludes that there is moderate evidence that the net benefit is small for women aged 40 to 49 years.

For biennial screening mammography in women aged 50 to 74 years, there is moderate certainty that the net benefit is moderate.

For screening mammography in women 75 years or older, evidence is lacking and the balance of benefits and harms cannot be determined.

**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...
Screening frequency 1 vs 2 yrs

- Similar reduction in mortality with screening every one or two years

- Every two years (compared to annually) maximizes benefits of screening & minimizes harms
Given the lack of consensus, involve patient in the decision-making. 

<table>
<thead>
<tr>
<th>Organization</th>
<th>Year 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>
</tr>
<tr>
<td>American Cancer Society</td>
<td>2010</td>
<td>Age ≥40 yr, annually†</td>
</tr>
<tr>
<td>National Comprehensive Cancer Network</td>
<td>2011</td>
<td>Age ≥40 yr, annually†</td>
</tr>
<tr>
<td>National Cancer Institute</td>
<td>2010</td>
<td>Age ≥40 yr, every 1–2 yr†</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>
</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>
</tr>
<tr>
<td>American College of Radiology</td>
<td>2008</td>
<td>Age ≥40 yr, annually†</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>
</tr>
<tr>
<td>National Health Service, United Kingdom</td>
<td>2011</td>
<td>Age 47–73 yr, every 3 yr</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.
Tipping the balance toward benefit in 40-49yo

- Digital mammography
  - Increased sensitivity in 40-49yo and women with dense breasts c/w film
  - Studies conflict on specificity—likely slightly lower than film

- Risk based screening
  - If can limit the screened population to one with similar prevalence of cancer as older women, ratio of benefit to harm becomes more favorable
Risk-based approach

• Modeling by CISNET to determine the elevated risk necessary in 40-50yo to achieve same risk/benefit ratio as in >50yo with biennial screening (risk=false +, benefit=life years gained)

• Elevated risk of breast cancer necessary to achieve parity:
  – Biennial film $\rightarrow$ RR=1.6, annual $\rightarrow$ 3.6
  – Biennial digital $\rightarrow$ RR=2.0, annual $\rightarrow$ 4.3

van Ravesteyn NT, Ann Intern Med, 2012
New Meta-analysis of risk factors 40-49yo

- Compared to average risk US popln
- **Protective**: Overwt/obese (0.80), fatty on mammo (0.46), late menarche (0.8), >3 births (0.73), menopause (0.60), ERT (no ut, 0.70)

New Technologies

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

- **Sensitivity:**
  - Most studies show higher sensitivity in 40-49.
  - One large study (DMIST) showed lower sensitivity in women >65yo

- **Specificity:**
  - Very mixed: some show no difference, most show decreased specificity
2 largest US studies: <50yo

DMIST (research study)
- N=42,760 women, 14,335 <50yo
- All women got both digital and film mammo
- One year f/u
- Sensitivity: 51% (F) vs 78% (D)
- Specificity: both 90%
- Calculated PPV based on 2.8/1000 prevalence: 1.4 vs 2.1%

BCSC (community based)
- N= 329,260 women, in <50yo: 77,392 digital, 221,696 film
- Women got either digital or film depending on site
- One year f/u
- Sensitivity: 76(F) vs 82%(D)
- Specificity: 89.7 vs 88%
- Calc PPV: 2.1 vs 1.9%

Pisano, NEJM, 2005
Kerlikowske, Ann Int Med, 2011
Bottom Line: Digital

- 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
Q2: 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
Caution: comparing detection rates….

- Studies of new techniques typically compare detection rates
- **Key q is**: does improved detection lead to overall benefit (decreased mortality/morbidity)
- Observational studies prone to lead-time and length bias
- Earlier treatment may not be better than later
  - Ex: 10,000 50 yo’s followed for 20 yrs. Without mammo, 260 will die of breast cancer. With biennial mammo: 223 will 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

• In very high risk women (dense + 1 RF), U/S detected additional 3.7-5/1000, 7-10% biopsy rate

Nothacker BMC Cancer 2009
Berg, JAMA, 2012
MRI + Mammo

• 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%

Conclusions: Breast Cancer

• **40-49 informed decision**
  – Risk evaluation—recommend if risk 2x greater than general popln; 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
Perspective: Days of life gained and compliance with screening

Smoking cessation = 240 days gained
Last words

- Preventive interventions require a high burden of proof: the “do no harm” principle.
- Want to know that early detection improves outcomes. Comparing detection rates of newer technologies is insufficient b/c of lead-time and length bias.
- Guidelines are designed to maximize population screening benefits and minimize population screening harms—this is hard to explain to individual patient
Enjoy The Big Island!