Cancer Screening 2019

New Recommendations, New Controversies

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I have no conflicts of interest

Overview

• Background
• Breast Cancer Screening
  – Implications of “dense breasts”
  – New screening technologies
• Colorectal Cancer
  – When to start?
• Lung Cancer Screening
  – Who to screen with low dose CT?
• Prostate Cancer Confusion
• Cervical Cancer and HPV

What is new

• Tomosynthesis for breast cancer
• ACS recommends colon cancer screening starting at 45
• Cervical cancer HPV screening
  – Move towards primary with reflex Pap
  – Self-collection in low resource settings
Trends in 5-Year Survival (%)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>All</td>
<td>49</td>
<td>55</td>
<td>69</td>
</tr>
<tr>
<td>Breast (F)</td>
<td>75</td>
<td>84</td>
<td>91</td>
</tr>
<tr>
<td>Colorectal</td>
<td>50</td>
<td>60</td>
<td>66</td>
</tr>
<tr>
<td>Lung</td>
<td>12</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Cervical</td>
<td>68</td>
<td>-</td>
<td>69</td>
</tr>
<tr>
<td>Prostate</td>
<td>68</td>
<td>-</td>
<td>99</td>
</tr>
</tbody>
</table>

Rates of screening in 2015 (%)

<table>
<thead>
<tr>
<th>Site</th>
<th>2005</th>
<th>2015</th>
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</thead>
<tbody>
<tr>
<td>Breast (F)</td>
<td>66</td>
<td>64</td>
</tr>
<tr>
<td>Colorectal</td>
<td>43</td>
<td>63</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Cervical</td>
<td>85</td>
<td>82</td>
</tr>
<tr>
<td>Prostate</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>
USPSTF

- Rigorous review of existing peer-reviewed evidence for the average person
- Ratings reflect the strength of the evidence on the benefits and harms of a preventive service
- No consideration of costs
- ACA: Must cover A or B ratings

USPSTF Grades

<table>
<thead>
<tr>
<th>Grade</th>
<th>Evidence</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High certainty of substantial net benefit</td>
<td>Provide</td>
</tr>
<tr>
<td>B</td>
<td>High certainty of moderate net benefit Moderate certainty of moderate/substantial net benefit</td>
<td>Provide</td>
</tr>
<tr>
<td>C</td>
<td>Moderate certainty that net benefit is small</td>
<td>Selectively offer/provide</td>
</tr>
<tr>
<td>D</td>
<td>No net benefit or harms outweigh benefits</td>
<td>Do not provide</td>
</tr>
<tr>
<td>I</td>
<td>Insufficient evidence regarding balance of benefits and harms</td>
<td></td>
</tr>
</tbody>
</table>

Breast Cancer

Breast Cancer Screening

- Maggie Graham is a 50 year old woman with no family history of breast cancer. She has been reading news articles about the "increased accuracy" of screening ultrasound or MRI in women with dense breasts.
- You perform a clinical breast examination, which is normal.
Breast Cancer Screening

- What do you recommend to Maggie?
  - Add ultrasound
  - Add breast MRI
  - Mammogram alone
  - Add ultrasound and MRI

U.S. screening guidelines: no agreement

<table>
<thead>
<tr>
<th>Organization</th>
<th>Starting age</th>
<th>Stopping age</th>
<th>Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States Preventive Services Task Force (USPSTF)</td>
<td>50</td>
<td>74</td>
<td>Biennial</td>
<td>Screening for age 40-49 = Grade C recommendation</td>
</tr>
<tr>
<td>American Cancer Society (ACS)</td>
<td>45</td>
<td>As appropriate based on life expectancy</td>
<td>Annually, then biennially after age 55</td>
<td>Continue screening as long as good health life expectancy &gt; 10 years</td>
</tr>
<tr>
<td>American College of Obstetricians and Gynecologists (ACOG)</td>
<td>40</td>
<td>As appropriate based on life expectancy</td>
<td>Annually</td>
<td>Consider cessation of screening at age 75</td>
</tr>
</tbody>
</table>

New ACOG Guidelines: July 2017

- 40-49: Informed consent
- Annual ages 40-54 years if screening
- Biennial for ages 55+ years
- Stop when life expectancy < 10 years

Harms Of Screening

- **Over-diagnosis**
  - Cancers diagnosed that never would cause symptoms: patients receive all the costs and harms of treatment
  - Estimates: 10% to 30% of invasive breast cancers plus the majority of DCIS
- **False positives**
  - Anxiety
  - Additional tests including biopsies
  - One-third of total screening cost
- **Radiation exposure**
  - One breast cancer for 3000 women screened annually for 10 years

Jorgensen, BMJ, 2009
Impact of mammographic screening in U.S.

Breast Cancer Deaths
Randomized Trials, all ages

<table>
<thead>
<tr>
<th>Age, years</th>
<th>Deaths Averted Screening 1,000 Women Over 10 Years</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 to 49</td>
<td>0.3</td>
<td>-0.1 to 0.9</td>
</tr>
<tr>
<td>50 to 59</td>
<td>0.8</td>
<td>0.2 to 1.7</td>
</tr>
<tr>
<td>60 to 69</td>
<td>2.1</td>
<td>1.1 to 3.2</td>
</tr>
<tr>
<td>70 to 74</td>
<td>1.3</td>
<td>-1.7 to 3.2</td>
</tr>
<tr>
<td>75+</td>
<td>Unknown</td>
<td>--</td>
</tr>
</tbody>
</table>

Bottom line: Greatest screening benefit in women aged 60-69; smaller, and possibly no, screening benefit in women aged 40-49

False-Positive Results and Breast Biopsies per 1000 women

Estimated annual mammography screening costs in the US 2010

- Screening the 40 million women in the US aged 50-74 costs
  - $4.72 billion per year
- Screening the 22 million women in the US aged 40-49 costs
  - $1.32 billion per year
**Summary 40 to 49 years of age**

- Small, non-significant reduction in mortality
- Greatest harms
- Expensive

Shared decision-making

**State breast density legislation**

- Requires notification of women with heterogeneously dense or extremely dense breasts
- Exact wording specified by law: decreased sensitivity and increased risk for BC
- No mandate for insurance coverage of supplemental screening in most states
- FDA considering national guidelines

**Newish Breast Technologies**

- Digital Mammography
- Digital Breast Tomosynthesis
- Breast MRI
- Breast Ultrasound

**Digital mammography**

- Higher sensitivity, same specificity in women < 50 years old, dense breasts
  - Sensitivity 78% versus 51% film
  - Specificity 90%
- Worse in women 65 and older
  - Sensitivity 53% versus 69% film
T omosynthesis

- 71% of facilities in US in 2019
- Add-on to digital mammography
- Covered by CMS since 2016
- TMIST RCT: Tomo versus digital since 2017
  - 165,000 women in US and Canada
  - Annual if premenopausal, biennial x 5 years

Tomosynthesis results by age and density

For every 1000 mammograms
- 5.5 breast cancers detected
- 52 versus 22 false positive biopsy recommendations
**MRI Screening**

- MRI is very sensitive
- Not influenced by breast density
- Specificity is variable
- Expensive
- Limited to hereditary syndromes for now
  - e.g. BRCA mutation carriers

**Summary: Women with Dense Breasts**

- Tomosynthesis is becoming standard
- Ultrasound – high false positives and cost, little proven benefit
- MRI may be useful in screening very high risk women (BRCA carriers)
- The effect of MRI screening on mortality is not known

**Bottom Line: Breast Cancer**

- 40-49 informed consent
  - Digital if decide to screen: now standard
- 50-74 screen every 2 years
- 75+ informed consent - don’t if life expectancy less than 10 years
- Don’t promote SBE, promote breast awareness
- BRCA risk equivalent: MRI starting age 30

**Colorectal Cancer**
**Question?**

- What do you most commonly recommend for colorectal cancer screening?
  - Fecal occult blood test (FOBT)
  - Fecal immunochemical Test (FIT)
  - Fecal DNA
  - Sigmoidoscopy
  - Colonoscopy
  - Air contrast barium enema
  - Virtual Colonoscopy
  - Other

**New ACS Guideline 2018**

- Begin screening at age 45 – qualified recommendation
- Begin screening at 50 – strong recommendation
- Screen through 75 if life exp >10 years
- Shared decision making 76-85 years
- Discourage after age 85

**Why ACS change?**

- Increasing incidence of colon cancer for ages < 50
- Increasing mortality < 50
- Modeling per 1000 screened: 25 extra life-years for 810 extra colonoscopies starting at 45

**Why not start at 45?**

- No direct evidence of benefit for ages 45-49 years
  - Most RCTs enrolled participants starting at age 50
  - 3 enrolled at age 45, but no subgroup data published for 45-49
- Cost / resource allocation issues that could exacerbate current disparities
**USPSTF 2016**

- **USPSTF: “A” recommendation (2016)**
  - Routine screening from age 50 until 75
- **USPSTF “C” recommendation (2016)**
  - Individualized decisions age 76 to 85
    - Greater benefit in those not previously screened
- **No screening after 85**

**Colorectal Cancer Screening: Conclusions**

- Any screening is better than no screening for reducing colorectal cancer mortality
- Increase awareness of the importance of colorectal cancer screening
- Beginning at age 45 is controversial

**Lung Cancer Screening**

**What is your practice?**

- A. I recommend lung cancer screening for my patients who qualify.
- B. I am still trying to decide whether to recommend lung cancer screening to my patients.
- C. I do not think we should be recommending lung cancer screening.
PLCO: Lung Cancer Screening CXR

- 154,901 adults ages 55 to 74 randomized to annual CXR for 4 years vs. usual care
- Followed for 13 years
- Cumulative lung cancer mortality
  - Rate ratio: 0.99 (95% CI 0.87-1.22)
- 7 prior studies: summary RR 1.11

Oken MM. JAMA 2011;306:1865

Low Dose Spiral Computed Tomography

- Scans lung in < 20 seconds (single breath)
- No IV contrast
- More radiation exposure than CXR but less than conventional CT
- Can detect much smaller lesions than chest X-ray

The National Lung Screening Trial (NLST)

53,454 participants randomized to CT or CXR
- Current or former heavy smokers: ≥ 30 pack-years
- Ages 55 to 74
- Annual CT scans x 3 years. 6.5 years follow-up

RR (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Lung cancer death</th>
<th>Any death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>.80 (.73-.93)</td>
<td>.93 (.86-.98)</td>
</tr>
</tbody>
</table>

20% reduction in lung cancer death; 7% all deaths!

Number needed to invite to screen

- NNI to prevent one lung cancer death in 6.5 years = 320
- NNI to prevent one death from any cause in 6.5 years = 218
**NLST Harms**

- False positives
  - At least 1 positive test in 39%
- Possible over diagnosis
  - Higher cancer incidence with CT
    - 1060 vs. 941 cancers
  - Rate ratio 1.13 (95% CI 1.03-1.23)
- Radiation exposure
- Incidental findings

**The NELSON Trial**

- 15,792 participants in Netherlands randomized to CT or usual care
- CT at baseline, 1, 3, and 5.5 years
- 10 year follow-up
  - Reduction in lung cancer death
    - Men: 26% (9% - 41%)
    - Women: 61%

**Medicare Coverage Decision**

- Annual LDCT for ages 55-77, at least 30 pack year history and currently smoking or quit within past 15 years
- Order for lung cancer screening written during lung cancer screening shared decision making visit by physician or certified non-physician practitioner
- USPSTF Grade B
Lung cancer screening decision tool

- www.shouldiscreen.com
- Free – for patients
- Shared decision making
  - Bring printed results to visit
- Benefits and harms
- Graphical
- English / Spanish

Primary Prevention Of Lung Cancer

- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation!!!!!
  – And prevent initiation in adolescents
- Smokers who quit x 7 years = 20% reduction in risk for lung cancer (=NLST)

Summary Lung Cancer Screening

- Smoking cessation
- Strict adherence to NLST entry criteria
  – 55-74 years, 30+ pack years
- Target highest risk patients
- Use experienced centers
- Shared decision making
Prostate Cancer Screening

Recent US Guidelines

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>USPSTF – average risk man</td>
<td>Shared decision making starting at age 55; stop at age 70.</td>
</tr>
<tr>
<td>ACS</td>
<td>Shared decision-making starting at age 50; 45 if African descent or 1st degree relative &lt; 65. Q2 if &lt; 2.5; Q1 otherwise. Stop if life expectancy &lt; 10 years.</td>
</tr>
<tr>
<td>AUA</td>
<td>Shared decision making starting at age 55; stop at age 70. Q2. Ages 40-54 if African descent or family history of metastatic adenocarcinomas (breast, prostate, ovarian, pancreatic)</td>
</tr>
</tbody>
</table>

PLCO PSA Screening Trial, USA, 15+ years FU

HR 1.03 (0.87-1.23)
PSA: Red line

Pinsky, Cancer, 2017

European Trial (ERSPC)

RR 0.79 (0.69-0.91)
NNS 781
PSA blue line

Schroder, Lancet, 2014
Why the difference in outcomes?

- Usual care with high rates of PSA screening in the US PLCO?
- PSA trigger for biopsy 3.0 versus 4.0?
- Differential co-intervention in ERSPC?
  - Intervention group treated at academic centers
  - More prostatectomy (RR 2.8) / aggressive tx
- Cause of death not blinded to treatment
  - Prior studies: death less likely to be adjudicated as PC if aggressive treatment

Harms of screening

- Overdiagnosis (23% to 60%)
  - Unnecessary treatment
    - Impotence, incontinence, urethral stricture, rectal injury, death in 20% to 67% of treated patients
- False positive (>10% of tests, 80% of + tests)
  - Biopsy
    - Infection / sepsis, pain, hematuria
    - 1/200 with serious infection or urinary retention
  - Anxiety

Bottom Line: Prostate Cancer

- Shared decision-making
- Optimum benefits, if any, ages 55-69
- High risk: African Americans, relatives < 65, relatives with metastatic disease
- Frequency: Q 1, 2, or 4 years?
- Biopsy: At PSA 2.5, 3, or 4?
- Don’t screen age > 70 years, LE < 10

Cervical Cancer
Guideline concordance: USPSTF, ACS, ACOG, …

- Start at 21
- Ages 21-29 Pap every 3 years
- Ages 30-65 Pap plus HPV co-test every 5 years
  - Pap every 3 years acceptable
- Stop at 65 if normal testing x 10 years and no advanced cervical pathology in past 20 years
- HPV vaccination for all starting at age 11-12
  - Catch up through age 26, maybe through 45 (9 valent)
  - Prevents cervical, vaginal, anal, penile, and oropharyngeal cancer

HPV testing


Cervical Cancer

- 50% never screened
- 10% no screen in past 5 years
- No regular source of healthcare
- Recent immigrants to the US

... so screen! And vaccinate!

Cancer Screening Summary

- Breast: Every 2 years at 50
- Colon: Screen at 50
- Lung: Informed consent, NLST criteria
- Prostate: Informed consent
- Cervical: Consensus + HPV vaccine
Men and Women: Incidence 2019

Questions?

**USPSTF Guidelines**

**Mammography**
- Age 50-74: screening mammography every 2 years
- Age 40-49: individualize decision to begin biennial screening according to patient’s context and values
- Age ≥75: no recommendation (insufficient evidence)

**Breast Exam**
- Clinical breast examination alone – insufficient evidence
- Recommend against teaching women to perform routine breast self-examination
  - No mortality benefit
  - Higher rates of benign breast biopsies

**USPSTF Guidelines**

- Evidence is insufficient to assess the balance of benefits and harms for digital breast tomosynthesis (DBT)
- The evidence is insufficient to assess the risks and benefits of adjunctive screening (ultrasound, MRI or DBT) for women with dense breasts and an otherwise negative screening mammogram
  
  – January, 2016
ACS Recommendations: Average Risk Women

- Begin mammography at age 45
  - Women aged 45-54 should be screened annually
  - Women aged 55 and older should be screened every two years or have the opportunity to continue annual screening
  - Continue screening as long as overall health is good and 10 year life expectancy
- Clinical breast exam not recommended for average risk women at any age

ACS Recommendations: High Risk Women

- Women at high risk for breast cancer based on certain factors should get an MRI and a mammogram every year
  - Lifetime risk 20 to 25% or greater
  - BRCA1 or BRCA2 gene mutation
  - First degree relative with BRCA mutation and have not had genetic testing
  - Had XRT to chest between ages 10-30
  - Have certain high risk breast cancer syndromes
- Women with lifetime risk of breast cancer of <15% should not receive MRI screening

Supplemental screening: better outcomes?

<table>
<thead>
<tr>
<th>Tomosynthesis (DBT)</th>
<th>Ultrasound (US)</th>
<th>MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Slightly higher cancer detection rate, fewer false positives</td>
<td>Well-tolerated, relatively inexpensive</td>
<td>Most sensitive, no radiation</td>
</tr>
<tr>
<td><strong>Limitations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not as sensitive as MRI, limited evidence base (newer), limited availability</td>
<td>High false positive rate (low PPV), operator-dependent</td>
<td>High false positive rate, oversensitivity, IV contrast, claustrophobia, expensive</td>
</tr>
</tbody>
</table>

Newer Tests

- Virtual Colonoscopy
- Stool-based molecular testing
  - Fecal DNA
- Fecal immunochemical tests
- Septin 9
Computed Tomographic Colonography (Virtual Colonoscopy)

- Non-invasive radiological technique
  - Radiation dose similar to barium enema
- Bowel preparation similar to colonoscopy
  - Prep-less technique is being evaluated
- Does not require sedation
- Colon distended with carbon dioxide or air
- Colonoscopy to remove polyps

Potential Harms

- Radiation Exposure
  - 1/1000 could develop solid cancer or leukemia
- Procedure related harms
  - Perforation rate low
- Extra-colonic findings (27%-69%)
- Need for repeat prep if findings

Fecal Immunochemical Testing (FIT)

- Uses labeled antibodies that attach to antigens of any human globin present in the stool
- Globin does not survive passage of the upper GI tract
- No dietary restrictions (easier than FOBT)

Fecal Immunochemical Testing

- FIT is more sensitive in detecting CRC and large adenomas (>1 cm) than FOBT
- FIT is a little less specific than FOBT
American College of Physicians 2015

- Annual high sensitivity FOBT or FIT
- Flex sigmoidoscopy every 5 years
- High sensitivity FOBT or FIT every 3 years plus flex sigmoidoscopy every 5 years
- Colonoscopy every 10 years

Wilt et al., Annals IM, 2015

USPSTF 2016

- Screening for CRC in average risk patients age 50-75 is of substantial net benefit
- Multiple screening strategies available
  - Different levels of evidence
  - No evidence that any strategy provides greater net benefit

USPSTF JAMA 2016

Lung cancers on subsequent screens

<table>
<thead>
<tr>
<th>Screening round</th>
<th>N</th>
<th>Lung cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>26,309</td>
<td>270</td>
</tr>
<tr>
<td>Second</td>
<td>24,715</td>
<td>168</td>
</tr>
<tr>
<td>Third</td>
<td>24,102</td>
<td>211</td>
</tr>
</tbody>
</table>

No significant drop off in lung cancer incidence with annual screening

Summary from NLST for shared decision

<table>
<thead>
<tr>
<th></th>
<th>Low-dose CT 20,732 people</th>
<th>Chest X-ray 21,710 people</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefit: How did CT scans help compared to chest X-ray, an ineffective screening test?</td>
<td>13 in 1,000</td>
<td>17 in 1,000</td>
</tr>
<tr>
<td>4 in 1,000 fewer died from lung cancer</td>
<td>75 in 1,000</td>
<td>75 in 1,000</td>
</tr>
<tr>
<td>Harm: What problems did CT scans cause compared to chest X-ray?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>223 in 1,000 more had at least one false alarm</td>
<td>365 in 1,000</td>
<td>142 in 1,000</td>
</tr>
<tr>
<td>18 in 1,000 more with a false alarm leading to an invasive procedure, such as bronchoscopy, biopsy, or surgery</td>
<td>25 in 1,000</td>
<td>7 in 1,000</td>
</tr>
<tr>
<td>2 in 1,000 more had a major complication</td>
<td>3 in 1,000</td>
<td>1 in 1,000</td>
</tr>
</tbody>
</table>
USPSTF Recommendation

- USPSTF recommends annual screening for lung cancer with low-dose computed tomography (LDCT) in persons at high risk for lung cancer based on age and smoking history
  – Grade B recommendation

Impact of 2012 USPSTF D Rec?