Cancer Screening 2018

New Recommendations,
New Controversies

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Disclosures

I have no conflicts of interest

Selected Controversies in Screening

- Breast Cancer
- Colorectal Cancer
- Lung Cancer
- Prostate Cancer

Principles of screening

- Asymptomatic patients
  - High sensitivity, high true positive rate
  - High specificity, low false positive rate
  - Early detection reduces risk of death from the cancer
  - Reasonably high prevalence of disease
  - Test results in minimal harm
USPSTF

- Rigorous review of existing peer-reviewed evidence
- Strength of the evidence on the benefits and harms reflected in ratings
- No consideration of costs
- ACA: Must cover services with A or B ratings

Breast Cancer Screening

- The most common cancer in women, second leading cause of cancer death
- Screening mammography reduces breast cancer mortality
- Risk of breast CA increases with age, median age 62

USPSTF Grades

ACG Cancer Cases and Death Rates

Table 1. Estimated New Female Breast Cancer Cases and Deaths by Age, US, 2017

<table>
<thead>
<tr>
<th>Age</th>
<th>In Situ Cases</th>
<th>Invasive Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-40</td>
<td>1,610</td>
<td></td>
<td>11,103</td>
</tr>
<tr>
<td>40-49</td>
<td>12,448</td>
<td>36,765</td>
<td>3,440</td>
</tr>
<tr>
<td>50-59</td>
<td>17,680</td>
<td>58,620</td>
<td>7,590</td>
</tr>
<tr>
<td>60-69</td>
<td>17,500</td>
<td>68,075</td>
<td>9,430</td>
</tr>
<tr>
<td>70-79</td>
<td>10,370</td>
<td>47,800</td>
<td>8,220</td>
</tr>
<tr>
<td>80+</td>
<td>3,760</td>
<td>20,080</td>
<td>10,910</td>
</tr>
<tr>
<td>All ages</td>
<td>63,410</td>
<td>252,710</td>
<td>40,810</td>
</tr>
</tbody>
</table>

Note: Estimates are rounded to the nearest 10. Percentages may not sum to 100 due to rounding. ©2013, American Cancer Society, Inc., Surveillance Research
U.S. breast cancer screening guidelines: limited 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>Biennially</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 above age 75</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>

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 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>0 to 3.2</td>
</tr>
<tr>
<td>75+</td>
<td>Unknown</td>
<td>--</td>
</tr>
<tr>
<td>50 to 69</td>
<td>1.3</td>
<td>0.6 to 0.2</td>
</tr>
</tbody>
</table>

Harms Of Screening

- 1st mammogram at age 40, the 10-year cumulative risk of a false-positive biopsy result was higher (7.0%) for annual vs biennial (4.8%) screening.
- CBE adds no mortality benefit to mammography and has a higher false-positive rate
- False positives: Anxiety, biopsies, cost
- Radiation exposure: One breast cancer for 3000 women screened annually for 10 years

False-Positive Results and Breast Biopsies/1000 women

<table>
<thead>
<tr>
<th>Harms of One-Time Mammography Screening, by age</th>
<th>Outcome</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-74</th>
</tr>
</thead>
<tbody>
<tr>
<td>False-positive mammogram</td>
<td>121</td>
<td>93</td>
<td>81</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Breast biopsies recommended</td>
<td>16</td>
<td>16</td>
<td>17</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Biopsies per cancer diagnosed</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
Screening has led to large increase in detection of ductal carcinoma in situ (DCIS)

State breast density legislation

- Increased breast density IS a risk factor for BC
- Must notify women with dense breasts
- There is decreased sensitivity and increased risk for BC with mamm
- Insurance may not cover supplemental screening

Breast Cancer Screening

- Maggie 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.

What do you recommend to Maggie?

a) Add ultrasound
b) Add breast MRI
c) Mammogram alone
d) Add ultrasound and MRI
Newer Breast Technologies

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

Digital mammography

- Test of choice in asymptomatic women
- Higher sensitivity (78% vs 51%), same specificity (90%) in women < 50 years old, dense breasts
- Worse in women 65 and older
  - Sensitivity 53% versus 69% film

Digital Breast Tomography/3D Mamm

- Digital Breast Tomography (DBT) NOT a primary screening strategy

MRI Screening

- Highly sensitive breast imaging as a diagnostic tool in women with breast cancer
- Specificity is variable
- Useful in dense breasts
- Expensive
**Supplemental screening: better outcomes?**

<table>
<thead>
<tr>
<th>Advantage</th>
<th>MRI</th>
<th>Ultrasound (US)</th>
<th>Tomosynthesis (DBT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most sensitive</td>
<td></td>
<td>Well-tolerated</td>
<td>Similar cancer</td>
</tr>
<tr>
<td>No radiation</td>
<td></td>
<td>Relatively</td>
<td>detection rate,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>inexpensive</td>
<td>fewer false</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>positives</td>
</tr>
<tr>
<td>High false</td>
<td></td>
<td></td>
<td>Not as sensitive</td>
</tr>
<tr>
<td>positive rate</td>
<td></td>
<td>High false</td>
<td>as MRI</td>
</tr>
<tr>
<td>Overdiagnosis</td>
<td></td>
<td>positive rate</td>
<td>Limited evidence</td>
</tr>
<tr>
<td>IV contrast</td>
<td></td>
<td>(low PPV)</td>
<td>base (newer)</td>
</tr>
<tr>
<td>Expensive</td>
<td></td>
<td>Operator-</td>
<td>Limited availability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dependent</td>
<td></td>
</tr>
</tbody>
</table>

**Limitations**

- High false positive rate
- Overdiagnosis
- IV contrast
- Expensive
- High false positive rate (low PPV)
- Operator-dependent
- Not as sensitive as MRI
- Limited evidence base (newer)
- Limited availability

USPSTF Grade I: January 2017

**Impact For Clinical Practice**

- MRI may be useful in screening high risk women but mortality impact is not known
- MRI screening is not currently recommended for average risk women
- Ultrasound adds little to mammography for screening
- 3D mamm/BDT shows promise

**Conclusion: Breast Cancer**

- 40-49 informed consent
  - Digital mamm is standard
- 50-74 screen every 2 years
- 75+ informed consent – only if life expectancy > 10 years
- Don’t promote CBE/SBE

**Lung Cancer Screening**
Mr. Nico is a 69 year old man with a 50 pack-year history of smoking and COPD. You have previously been unsuccessful in encouraging him to quit smoking. He comes in for a check-up, is worried about developing lung cancer and wants to know what test you think he should have. What do you recommend?

a. Chest X ray  
b. Sputum cytology  
c. Low Dose CT chest  
d. None of these tests

**USPSTF 2013 Recommendation**

- Recommends annual screening for lung cancer  
- Use low-dose CT in age 55-80  
- With 30 pack year hx smoking  
- And currently smoke or quit within past year  
  - Grade B recommendation  
  - Published December, 2013

**Feb 2018 CHEST guidelines**

- Supports USPSTF recs  
- Low-dose CT screening should NOT be routinely performed for  
  – Smokers who do not meet the smoking and age criteria  
  – Comorbidities that adversely influence ability to tolerate the evaluation of findings, or tolerate treatment of an early stage lung cancer, or substantially limit life expectancy

**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)

- 50,000 people randomized to CT or CXR
  - Current or former heavy smokers: ≥ 30 pack-years
  - Ages 55 to 74
  - Annual CT scans x 3; 6.5 years follow-up
- 20% reduction in lung cancer death with screening CTs

NCI Risk-based Screening

- Individualized risk-based screening may be more effective at preventing lung cancer deaths than current USPSTF screening criteria.
- Lung Cancer Risk Assessment Tool would include high-risk moderate smokers with a history of 20 to 29 pack-years who are currently ineligible for screening.
- Smoking-cessation counseling remains a high priority for clinical attention in discussions with current smokers, who should be informed of their continuing risk of lung cancer; screening should not be viewed as an alternative to smoking cessation.

LDCT Screening Harms

- False positives
  - At least 1 positive test in 40% CTs
- Possible overdiagnosis of early cancers
- Radiation exposure
- Incidental findings

Medicare Coverage Decision

- Annual screening age 55-77, asymptomatic, at least 30 pack year history and currently smoking or quit within past 15 years
- Written order for lung cancer screening, shared decision making visit by physician or APN/PA

CMS, February, 2015
Primary Prevention Of Lung Cancer

Implications for Practice

- Smoking cessation
- Adherence to guidelines
  - 55-70 years, 30+ pack years
- Watch for better risk-based screening soon
- Use experienced centers to ensure quality and effectiveness of CT

Colorectal Cancer

Incidence and Mortality are Dropping
What do you most commonly recommend for colorectal cancer screening?

- a. Fecal occult blood test (FOBT)
- b. Fecal immunochemical test (FIT)
- c. Sigmoidoscopy
- d. Colonoscopy
- e. Virtual Colonoscopy
- f. Fecal DNA

Joint Guideline: ACS, ACR, Multi-Society Task Force

- FOBT annually
- Fecal immunochemical test annually
- Flexible sigmoidoscopy every 5 years
- DCBE every 5 years
- CT colonography every 5 years
- Colonoscopy every 10 years
- Stool DNA testing (interval uncertain)

Levin, Gastroenterology, 2008

All CRC Guidelines

- Discuss the menu of options with patients
- Offer a test that is effective at both cancer prevention AND early detection
- CRC prevention should be the primary goal of screening
2017 New Multi-Society Guidelines

- American College of Gastroenterology, American Gastroenterological Association, Society for Gastrointestinal Endoscopy
- Start screening at age 50 in average risk individuals
  - Limited evidence supports screening African Americans starting at age 45
- Consider discontinuing screening at age 75 or less than 10 years life expectancy

American College of Physicians 2015

- Age 50-75
- High sensitivity gFOBT or FIT q1 yr
- Flex sigmoidoscopy q5 yrs
- High sensitivity gFOBT or FIT q3 yrs plus flex sigmoidoscopy q5 yrs
- Colonoscopy q10 yrs
  - Ann Intern Med 2015

USPSTF 2016

- Screening for CRC in average risk patients age 50-75 is of substantial net benefit
- Multiple screening strategies available
  - Strategies reviewed include colonoscopy, FOBT, FIT, flex sig, CT colonography, fecal DNA and methylated SEPT9DNA test
  - No evidence that any strategy provides greater net benefit
  - USPSTF JAMA 2016

USPSTF JAMA 2016

Multi-Society Guidelines (July 2017)

The new guidelines include three “tiers” of testing
- First tier tests
  - Colonoscopy or FIT, with colonoscopy offered first
  - A risk stratified approach is also appropriate
- Second tier tests
  - CT colonography (CTC) every 5 years
  - FIT-fecal DNA every 3 years
  - Sigmodioscopy every 5-10 years
- Third tier
  - Capsule colonoscopy every 5 years
FIT vs colonoscopy outreach

- Mailed FIT outreach is more effective than colonoscopy outreach for colorectal cancer (CRC) screening. More people chose FIT.
- Primary outcome was screening process completion (adherence to colonoscopy completion, annual testing for a normal FIT result, diagnostic colonoscopy for an abnormal FIT result)
- BUT: completion rate 38% in the colonoscopy outreach group, 28% in the FIT outreach group, and 11% in the usual care group.

CONFIRM Trial Underway at VA

- Compare screening with colonoscopy vs. annual FIT in 50,000 average risk pts.
- Examines if screening colonoscopy is superior to FIT in the prevention of CRC mortality measured over 10 years.
- The primary endpoint is CRC mortality. The secondary endpoints are CRC incidence, quality and complications of colonoscopy

Newer Tests

- Virtual Colonoscopy
- Stool based molecular testing
  - Fecal DNA
- Combined FIT and Stool DNA
- Septin-9

Computed Tomographic Colonography (Virtual Colonoscopy)

- Non-invasive radiological technique
- Bowel preparation similar to colonoscopy
- Does not require sedation
- Colon distended with air
- Colonoscopy still needed to remove polyps
**Fecal DNA Testing**

- PCR test for DNA mutations in the stool
- Potential advantages
  - Non-invasive
  - No preparation
  - Detection along entire length of the colon

**Multi-target Stool DNA Testing**

- Multi-target DNA test, FIT, and colonoscopy for average risk adults
- Stool DNA detects more neoplasms than FIT, but with more false positive results
  - Sensitivity for CRC 92.3% vs 73.8%
  - Specificity for CRC 86.6% vs 94.9%

**Fecal Immunochemical Testing (FIT)**

- Labeled antibodies attach to antigens of human globin present in the stool
- Globin does not survive passage of the upper GI tract
- No dietary restrictions (easier than FOBT)
- FIT is more sensitive in detecting CRC and large adenomas (>1 cm) than FOBT

**Combined FIT-Stool DNA**

- Cologuard is the combined stool DNA with FIT test
- Colorectal cancer detection
  - Sensitivity 92%
  - Specificity 84%
- More sensitive than FIT but less specific
  - More false positives
Septin 9

- The only blood test for CRC
- Serum assay to detect circulating Septin 9
  - Septin 9 hypermethylates in CRC
  - FDA approved 2016
  - Not recommended in any guideline
  - Sensitivity/specificity lower than FIT

Screening Completion

Implications for Practice

- Screening for ave risk age 50-75
- Any screening is better than no screening for reducing colorectal cancer mortality
- Follow through is critical
- Increase population awareness of the importance of colorectal cancer screening

Prostate Cancer Screening
What is your usual practice for PSA screening for men aged 50-70?

a. Usually order PSA
b. Sometimes order PSA
c. Rarely order PSA
d. Never order PSA

SCREENING TESTS: PSA

- PSA testing has increased dramatically since 1988 in the USA
- Observational studies have shown conflicting findings on the benefits of screening
- Two large randomized controlled trials of PSA screening and mortality

USPSTF Recommendations 2012

- Recommended against PSA based screening for prostate cancer
  - Can detect early prostate CA, but inconclusive about improved health outcomes.
  - Harms (false positives, anxiety, biopsies)
  - Complications of treatment of some cases of cancer that may never have affected a patient’s health.
  - Grade “D” recommendation

Prostate Cancer: Should We Screen?

- High prevalence
  - 10% lifetime risk
  - 30% of men have asymptomatic prostate cancer at autopsy
- Disease may have serious consequences, but may also be a benign disease for many men
- Treatment for preclinical disease may not be effective
  - Complications of prostate cancer treatment
    - 0-1% incontinence
    - 30-60% impotence
- Unclear if screening reduces cancer mortality
### Cancer Screening Trial

- 76,693 men randomized to annual PSA for 6 years plus rectal examination for four years vs usual care
- High rates of screening in the control group
- No significant difference in death between the two groups at 7 year follow-up
  - 2.0 deaths per 10,000 person years in the screening group
  - 1.7 deaths per 10,000 person years in the controls
- Similar results after 10 years

  - Andriole, NEJM 2009

### European Randomized Study of Screening for Prostate Cancer (ERSPC)

- 182,000 men aged 50-74 in eight European countries
- PSA screening at least once every four years vs no screening
- Mortality lower in the screened group at 9 year follow up (7 fewer prostate cancers per 10,000)
- To prevent one prostate cancer death at 11 year follow up 1,410 men must be screened, 48 additional prostate cancers treated
- To prevent one prostate cancer death at 13 year follow up, 701 men screened

  - Schroder NEJM 2009; Schroder NEJM 2011; Schroder Lancet 2014

### USPSTF Draft Recommendations 2017

- Clinicians should inform men age 55-69 about the potential benefits and harms of PSA screening
  - Grade C
- Decision to screen should be individualized
- No specific recommendations for high risk men
  - Family history, African American
- No screening in men aged 70 and over
  - Grade D

### American Cancer Society

- Screening should not occur without an informed decision making process
- Men at average risk should receive the information beginning at age 50; and at age 45 for men at higher risk and age 40 for very high risk
- No age cut off: men with at least a 10 year life expectancy should have informed decision making

  - American Cancer Society, 2016
American Cancer Society

- For screening:
  - PSA with or without DRE
  - Screening yearly for PSA is 2.5 or greater
  - If PSA <2.5, screening can be extended to every 2 years
  - PSA of 4.0 or greater - referral
  - PSA of 2.5-4.0 ng/ml individualized risk assessment
  - Risks=Age, African American, FH, previous negative biopsy

ACS, 2016

ACP Guidance Statement

- Derived from an appraisal of available guidelines
  - ACPM, ACS, AUA, USPSTF
- Inform men aged 50-69 about limited potential benefits and substantial harms of screening for PSA
  - Base decision on risk, discussion of benefits and harms, health and life expectancy and preferences
  - Do not screen those who do not have a clear preference for screening

UCSF Smarter Screening

<table>
<thead>
<tr>
<th>Age</th>
<th>PSA</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-60</td>
<td>&lt;1</td>
<td>Recheck in 5+ years</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>Recheck in 6-12 mos vs. early referral based on family history, anxiety, etc + SDM</td>
</tr>
<tr>
<td></td>
<td>&gt;2</td>
<td>Referral</td>
</tr>
<tr>
<td>61-75</td>
<td>&lt;1</td>
<td>Recheck in 5+ years</td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>Recheck in 6-12 months vs. early referral based on family history, anxiety, etc + SDM</td>
</tr>
<tr>
<td></td>
<td>&gt;3</td>
<td>Referral</td>
</tr>
</tbody>
</table>

PSA Screening: Conclusions

- PSA screening may lead to a modest reduction in mortality
- To achieve this mortality reduction, there is a substantial amount of over-diagnosis and over-treatment
- Low risk men are overtreated, High risk men are undertreated
Impact on Practice

• PSA testing may reduce prostate cancer mortality
• There are risks of early detection and treatment
• Shared decision making is key

Overall Screening Recommendations

• Mammograms for women age 50-74 every 2 years; Screening decisions for women 40-49 and > age 75 individualized
• All men and women aged 50-75 should be screened for colorectal cancer
• Screening for lung cancer with low-dose CT reduces mortality in high risk individuals
• A shared decision making approach is recommended for prostate cancer screening
• Stay tuned for risk based screening!