Cancer Screening 2015
Using Best Evidence to Guide Practice

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Disclosures

• I have no conflicts of interest
Outline

• Lung Cancer
  – Should we screen?
  – If so, who should we screen?

• Cervical Cancer Screening
  – New Recommendations

• Colorectal Cancer
  – What test and how often?
  – Are there new screening options?

Lung Cancer Screening
Case

• Ms. Nica Teen is a 69 year old woman with a 50 pack-year history of smoking and COPD. You have previously been unsuccessful in encouraging her to quit smoking. She comes in for a check-up, is worried about developing lung cancer and wants to know what test you think she should have. What do you recommend?
  – Chest X ray
  – Sputum cytology
  – Spiral CT
  – None of these tests

PLCO: Lung Cancer Screening

• PLCO randomly assigned 154,901 adults aged 55 through 74 to annual CXR for 4 years vs. usual care
• Followed for 13 years
• Cumulative lung cancer mortality
  – 14.0/10,000 py screening group vs. 14.2/10,000 py control group
  – Rate ratio: 0.99 (95% CI 0.87-1.22)

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

<table>
<thead>
<tr>
<th></th>
<th>LDCT</th>
<th>CXR</th>
<th>Δ</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Deaths</td>
<td>356</td>
<td>443</td>
<td>87</td>
<td>.80 (.73-.93)</td>
</tr>
<tr>
<td>Any death</td>
<td>1877</td>
<td>2000</td>
<td>121</td>
<td>.93 (.86-.98)</td>
</tr>
</tbody>
</table>

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

Absolute risk reduced from 1.7% in CXR to 1.4% in LDCT group
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

Balanced by...

- 75,000 CT scans
- 18,146 positive tests
- 17,066 false positive tests
- 673 thoracotomy / mediastinoscopy
- 303 bronchoscopies
- 99 needle biopsies
- To prevent 87 deaths from lung cancer
**NLST Harms**

- **False positives**
  - At least 1 positive test in 39% CT
    - 96% of the positive results were false positives
- **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**

**Concern: Control = Chest x-ray**

- Screening with CXR was ineffective in 30,341 subjects in the PLCO meeting NLST criteria
  - 30+ pack year, smoked within past 15 years
  - Cumulative lung cancer mortality was 36.1/10,000 py screening group vs. 38.3/10,000 py controls
    - Rate ratio: 0.94 (0.81-1.10)
- Reasonable to conclude that CT screening is more effective than usual care
Guidelines and recommendations

• Recommend for those meeting NLST entry criteria at specialized centers
  – ACCP / ASCP / ATS
  – ACS
  – ALA
  – NCCN
  – AATS

The NLST Setting

• 76% of sites were NCI designated cancer centers
• 82% were large academic medical centers
• All likely to have specialized thoracic radiologists and board certified thoracic surgeons on site
• CT scanners extensive quality control
• Nodule management algorithm but not mandated
Guidelines and recommendations

- USPSTF prior recommendations
  - Smoking cessation counseling: “A” (2009)
    - 85% of cancers among smokers attributed to smoking

USPSTF Recommendation

- Annual screening for lung cancer with low-dose computed tomography (LDCT) in
  - adults aged 55 to 80 years
  - 30 pack-year smoking history
  - 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
Published December 31, 2013
USPSTF Recommendation

- The moderate net benefit of screening depends on
  - limiting screening to persons who are at high risk,
  - the accuracy of image interpretation being similar to that found in the NLST (National Lung Screening Trial), and
  - the resolution of most false-positive results without invasive procedures

Medicare Coverage Decision

- Annual lung cancer screening with LDCT for 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 written during lung cancer screening shared decision making visit furnished by physician or certified non-physician practitioner

  – February, 2015
Primary Prevention Of Lung Cancer

- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation!!!!!
Implications

• Smoking cessation
• Strict adherence to guidelines
  – 55-79 years, 30+ pack years, quit <15 yrs
• Use experienced centers to ensure quality and effectiveness

Cervical Cancer Screening
Case

- Ms. Pamela (Papa) Niclau, a 48 yo woman with no vaginal or abdominal complaints, history of normal pap smears every 3 years whose last pap was at age 45, comes to see you to follow-up on her blood pressure, she asks if she is due for her pap smear, and does she really need to keep getting these?

You answer:

1. You should continue to get paps every three years until you die of old age
2. You should continue to get paps every three years until age 65
3. We could do a pap with HPV co-testing and if all is normal, not test again for another 5 years

Cervical Cancer Screening

- Dramatic reduction in incidence and mortality with routine cervical cancer screening
  - 1950: 25-30/100,000
    2011: 7.5-11/100,000
  - 2011 in US:
    - 12,109 diagnosed;
    - 4,092 died of cervical CA
    - 14th cause of cancer death

www.cdc.gov
Cervical Cancer Screening

• In U.S. mortality remains highest for African American women

• Worldwide where access to screening and treatment of pre-cancerous lesions is low, incidence and mortality remain high
  – Africa
  – Latin America
  – Caribbean

Cervical Cancer Screening

• HPV is the causative agent in the majority of cases of cervical cancer

• Long latency period for development of cervical cancer

• Many lesions will regress on their own
HPV Co-testing

• 5-year cumulative incidence CIN 3 or worse
• 331,818 women ≥ 30 years old; KPNC
• Screening visits: HPV and pap smear
• Biopsy visit: colposcopically directed biopsies

Katki et al., The Lancet Vol 12 July 2011

HPV Co-testing

• 94% of women had concordant tests
  – 92.5% HPV negative/Pap negative
  – 1.4% HPV positive/Pap positive
• Among discordant tests HPV positive/Pap negative accounted for more abnormal biopsy findings (including cancers)
• Women HPV negative/Pap negative had low risk of cervical ca at 5-years: 3.2 per 100,000 women
HPV Primary Screening?

- ATHENA trial evaluated HPV test as primary screen for cervical cancer in women ≥25 years old
- HPV alone detected more cases of CIN 3+ but required more colposcopies
- Promising but not currently recommended as a primary screening test

Monsonego, Gynecologic Oncology 137 (2015) 47–54

Cervical Cancer Screening Guidelines

<table>
<thead>
<tr>
<th>USPSTF 2012</th>
<th>ACS/American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology Joint Guidelines 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pap smear every 3 years in women aged 21-65</td>
<td>Pap every 3 years in women aged 21-29</td>
</tr>
<tr>
<td>For women aged 30-65 who want to lengthen the screening interval, screen with a combination of cervical cytology and HPV testing every 5 years (optional)</td>
<td>For women aged 30-65 Pap plus HPV testing is the preferred method. Pap every 3 years is acceptable</td>
</tr>
<tr>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal</td>
<td>Discontinue in women over the age of 65 in whom smears have been consistently normal. Continue to screen women diagnosed with cervical pre-cancer</td>
</tr>
<tr>
<td>No HPV screening in women younger than 30</td>
<td>No HPV testing in women less than age 30 unless needed after an abnormal test result.</td>
</tr>
<tr>
<td>No screening in women who have had a hysterectomy (removal of the cervix)</td>
<td>No screening in women who have had a hysterectomy (removal of the cervix).</td>
</tr>
</tbody>
</table>
Routine Pelvic Examination?

• Diagnostic accuracy for detecting ovarian cancer
  – 5,633 women in 3 cohort studies
    • 4 cases over 1 year;
    • PPV from 0%-3.6%;
    96.7-100% of abnormal pelvic exams did not identify ovarian CA

• PLCO: no reduction in ovarian CA mortality with screening pelvic exam (or with combo of pelvic/ultrasound/CA-125 screening) over 5 years

• ACP recommends against performing screening pelvic examination in asymptomatic, non-pregnant adult women

Colorectal Cancer
Question

- How many of you offer.....
  - Fecal occult blood test (FOBT)
  - Fecal immunochemical Test (FIT)
  - Sigmoidoscopy
  - Colonoscopy
  - Air contrast barium enema
  - Virtual Colonoscopy
  - Fecal DNA

1. Just 1 of these?
2. Two?
3. Three?
4. Four or more?

Joint Guideline: ACS, ACR,...

- 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
**Joint Guideline Recommendation**

- Clinicians should make patients aware of the full range of screening options
- Offer patients a choice between a test that is
  - effective at both early cancer detection and cancer prevention through the detection and removal of polyps and
  - primarily effective at cancer detection
- CRC prevention should be the primary goal of screening

**USPSTF**

  - Routine screening from age 50 until 75
    - Individualized decisions from 76 to 85
    - No screening after 85
USPSTF (continued)

  - Acceptable modalities
    - Colonoscopy
    - Fecal blood test
      - Fecal immunochemical test, high-sensitivity hemoccult
    - Flexible sigmoidoscopy
  - Insufficient evidence for CT colonography, fecal DNA

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)
- More sensitive in detecting CRC and large adenomas (>1 cm) than FOBT
- FIT is a little less specific than FOBT
Colonoscopy

- American College of Gastroenterology guidelines for colorectal cancer screening
  (Rex DK. Am J Gastroenterol 2009;104:739)
  - Colonoscopy... remains the preferred CRC screening strategy

Colonoscopy: RCTs in progress

- VA
  - Colonoscopy versus fecal immunochemical test in reducing mortality from colorectal cancer
- Spain
  - Colorectal cancer screening in average-risk population: immunochemical fecal occult blood testing versus colonoscopy
- Netherlands
  - Colonoscopy or colonography for screening
Sigmoidoscopy: PLCO

• 154,890 average risk men and women aged 55-74 assigned to screening with Flex Sig with repeat at 3-5 years vs usual care
  – 11.9 year follow up

• Reduced CRC incidence
  – Relative risk: 0.79 (95% CI 0.72-0.85)
  – Absolute risk reduction: 3.3/10,000 person years

  • Number needed to invite to screening (NNI): 285
    (95% CI 210-427)
  » Schoen et al NEJM 2012

One Time Flexible Sigmoidoscopy

• RCT where 100,210 individuals in Norway aged 50-64 underwent one time sigmoidoscopy with or without FOBT vs usual care

• CRC Incidence and mortality reduced in both sigmoidoscopy and sigmoidoscopy/FOBT groups
  – HR mortality 0.74
  – HR incidence 0.80

• Adding FOBT did not make a difference
  » Holme et al JAMA 2014
Flexible Sigmoidoscopy

• United Kingdom study showed one-time flex sig reduced CRC incidence by 23% and mortality by 31% (Atkin WS. Lancet 2010;375:1624)

• Fewer primary care physicians now recommend flex sig (Klabunde CN. Am J Prev Med 2009;37:8)
  – 78% (2000) to 26% (2007)
  – Colonoscopy recommendations increased from 38% to 95%

Other Tests

• Virtual Colonoscopy
• Stool based molecular testing
  – Fecal DNA
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
- Breath holding for 20-50 seconds
- 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
Extra-colonic Findings

- Extra-colonic findings common: 27 – 69%

- 7-16% of individuals need additional evaluation for extra-colonic findings, but very few abnormalities ultimately required definitive treatment

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
- 9989 average risk adults in multiple centers
- Fecal 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%
- Problems with sample collection or assay application greater with DNA test
  - 6.3% vs 0.3%

Imperiale, 2014

Colorectal Cancer Screening

- Randomized screening trial in Spain of biennial FIT vs. one-time colonoscopy
- 53,302 participants ages 50 to 69
- Primary outcome is CRC mortality after 10 years
- Interim report on participation rates and diagnostic findings
  - (Quintero E. NEJM 2012;366:697)
Colorectal Cancer Screening: Choices

- Randomized trial offering colonoscopy, FOBT, or choice of colonoscopy/FOBT
- 997 participants ages 50 to 79
- 12-month follow up
  - (Inadomi JM. Arch Intern Med 2012;172:575)
- Recommending only colonoscopy led to lower adherence
Screening Completion

How Are We Doing?

<table>
<thead>
<tr>
<th>Year</th>
<th>FOBT in past year or ever scope in 10?</th>
</tr>
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<tbody>
<tr>
<td>2002</td>
<td>54%</td>
</tr>
<tr>
<td>2004</td>
<td>57%</td>
</tr>
<tr>
<td>2006</td>
<td>61%</td>
</tr>
<tr>
<td>2008</td>
<td>64%</td>
</tr>
<tr>
<td>2010</td>
<td>65%</td>
</tr>
<tr>
<td>2012</td>
<td>65%</td>
</tr>
</tbody>
</table>

Inadomi JM. Arch Intern Med 2012;172:575

MMWR, 2013
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

• Virtual colonoscopy and fecal DNA testing are included as options in the joint guidelines but not in USPSTF guidelines

Implications for Practice

▪ Offer screening

▪ Testing modalities
  ▫ Fecal immunochemical tests more acceptable and accurate than Hemoccult II
  ▫ Flex sig if good option in your practice setting
  ▫ Colonoscopy vs. FIT RCTs ongoing
  ▫ CT colonography not reimbursed by Medicare
Implications for Practice

- Recognize importance of patient preferences
  - “The best test is the one that gets done”
- Positive fecal blood tests must be evaluated with diagnostic colonoscopy

Summary Of Recommendations

- Screening for lung cancer with low-dose CT reduces mortality
  - USPSTF Recommends screening high risk individuals
- HPV Co-testing every 5 years option/recommended after age 30 (stop after 65)
- ACP recommends against screening pelvic examination in asymptomatic, non-pregnant adult women
- All women and men aged 50 -75 should be screened for colorectal cancer
  - Any screening is better than no screening