Cancer Screening
Letting Evidence Be Our Guide
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Selected Controversies

• Breast Cancer Screening
  – Who should be screened?
  – Digital Mammography
  – MRI
• Colorectal Cancer
  – What test and how often?
  – Are there new screening options?
• Ovarian Cancer
  – Should we screen?

Selected Controversies

• Lung Cancer
  – Does screening work?
  – What about CT screening?
• Prostate Cancer
  – Should we screen?

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?

1. Add ultrasound
2. Add breast MRI
3. Mammogram alone
4. Add ultrasound and MRI

Breast Cancer Screening

- Breast cancer is the most common cancer in women and the second leading cause of cancer death
- Screening mammography reduces mortality from breast cancer
- Younger women have lower breast cancer risk
- Increased density of pre-menopausal breast tissue leads to decreased sensitivity

The Debate Continues....

June 28, 2011

“ACR urges USPSTF to withdraw mammography screening guidelines”

Swedish Two-County Trial: Impact of Mammographic Screening on Breast Cancer Mortality during 3 Decades

Jorgensen, BMJ, 2009

Harms Of Screening

- False positives
  - Anxiety
  - Additional tests including biopsies
  - One-third of total screening cost
- Over-diagnosis
  - Cancers diagnosed that never would cause symptoms: patients receive all the costs and harms of treatment
  - Estimates: 10% to 26% of invasive breast cancers and 34% of all breast cancers
- Radiation exposure
  - One breast cancer for 3000 women screened annually for 10 years
USPSTF New 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

Age and Mammography


<table>
<thead>
<tr>
<th>Age</th>
<th>Trials Included, n</th>
<th>RR for Breast Cancer Mortality (95% CI)</th>
<th>NNI to Prevent 1 Breast Cancer Death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-49 y</td>
<td>8</td>
<td>0.85 (0.75-0.96)</td>
<td>1904 (329-6278)</td>
</tr>
<tr>
<td>60-69 y</td>
<td>6</td>
<td>0.66 (0.56-0.79)</td>
<td>1339 (122-7466)</td>
</tr>
<tr>
<td>70-74 y</td>
<td>1</td>
<td>1.12 (0.73-1.72)</td>
<td>Not available</td>
</tr>
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</table>

Mammography and Age

“Mammography screening at any age is a tradeoff of a continuum of benefits and harms. The ages at which this tradeoff becomes acceptable to individuals and society are not clearly resolved by the available evidence.”

USPSTF

Frequency of Mammography

- Similar reduction in mortality with screening every one or two years
- Every two years (compared to annually) maximizes benefits of screening & minimizing harms

Mandelblatt, Annals IM, 2009
ACS Recommendations: Average Risk Women

- Begin mammography at age 40
- Clinical breast exam
  - At least every three years for women in their 20s and 30s
  - Annually for women age 40 and over
- Women should be informed about the benefits and limitations of breast self examination (BSE)
  - Prompt reporting of any breast symptoms
  - Technique may reviewed, but it is acceptable not to do it
- Women should become informed about benefits, limitations and potential harms of routine screening

The Debate Continues....

June 28, 2011: 133,000 women followed for 29 years.
27% decrease in BC mortality. Total mortality not reported.

New Technologies

- Digital Mammography
- Breast MRI
- Ultrasound and Mammography

Digital mammography

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

- Does MRI have a role for screening in high risk women?
  - MRI is a very sensitive method of breast imaging and has been used as a diagnostic tool in women with breast cancer
  - Not influenced by breast density
  - Specificity is variable
  - Expensive

Impact For Clinical Practice

- MRI may be useful in screening high risk women
- The effect of MRI screening on mortality is not known
- MRI is not currently recommended for screening average risk women
- Ultrasound adds little to mammography

Sensitivity And Specificity Of Breast Cancer Screening Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>77%</td>
<td>95%</td>
</tr>
<tr>
<td>Mammography</td>
<td>36%</td>
<td>99.8%</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>33%</td>
<td>96%</td>
</tr>
<tr>
<td>Clinical Breast Exam</td>
<td>9%</td>
<td>99%</td>
</tr>
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</table>

Bottom line

- 40-49 informed consent
- 50-74 screen every 2 years
- 75+ informed consent - don’t if life expectancy less than 10 years
- Don’t promote SBE
- Digital mammography for women < 50
- BRCA equivalent: MRI
Ovarian Cancer

Question

• Ms. O. is a 52 year old woman whose best friend was recently diagnosed with ovarian cancer. She is concerned about ovarian cancer and wants “whatever test you can give her” for it. What do you recommend?

Ovarian Cancer: What Test?

1. CA-125
2. Transvaginal ultrasound
3. CA-125 and transvaginal ultrasound
4. None of these tests

Ovarian Cancer: Should We Screen?

• Lifetime risk of ovarian cancer
  – No affected relatives 1%
  – One affected relative 5%
  – 2 affected relatives 7%
  – Hereditary syndrome 40%

• Ovarian cancer limited to the ovaries is associated with a much higher survival rate
Ovarian Cancer: Screening Techniques

- Serum CA-125 assay
- Trans-vaginal ultrasound
- Serum CA-125 plus ultrasound

Prostate, Lung, Colorectal and Ovarian (PLCO) Trial 2011

- AIM: To determine whether annual screening with CA-125 and transvaginal sonography can reduce ovarian cancer mortality


PLCO

- 78,216 women aged 55-74 randomized to screening or usual care
- Annual CA 125 plus ultrasound
  - CA 125 >35 or abnormal sono was positive
- Follow-up of positive screens by patients’ physicians
- 12.4 years follow-up

PLCO Results

<table>
<thead>
<tr>
<th>Group</th>
<th>Screen</th>
<th>Control</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>39,105</td>
<td>39,111</td>
<td>--</td>
</tr>
<tr>
<td>OC diagnosis</td>
<td>212 (5.7)</td>
<td>176 (4.7)</td>
<td>1.2 (1.0-1.5)</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>

Ovarian Cancer (rate/10,000)
PLCO Results

- 3285 women with false positive screens
  - 1080 surgical follow-up
  - 163 serious surgical complications

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."

Primary Prevention of OC

- Oral contraceptives
  - 37% risk reduction
- Pregnancy
- Breast feeding

Lung Cancer Screening

Question?

Mr. Nico Teen 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?

1. Chest X ray
2. Sputum cytology
3. Spiral CT
4. None of these tests
**Lung Cancer Screening:**
*Systematic Review of Chest X-rays*

- 7 trials of lung cancer screening
- Frequent screening with chest x-rays was associated with an increase in mortality
  - RR 1.11 (95% C.I. 1.00-1.23)
- No difference in chest X-ray plus cytology versus chest X-ray alone

(Manser, Thorax, 2003)

**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): Published in NEJM June 29, 2011**

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 RR (95% CI)</th>
<th>CXR</th>
</tr>
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<tbody>
<tr>
<td>Lung Cancer Deaths</td>
<td>247 (.80-.93)</td>
<td>309</td>
</tr>
<tr>
<td>Any death</td>
<td>1877 (.93-.98)</td>
<td>2000</td>
</tr>
</tbody>
</table>

Balanced by...

- 75,000 CT scans
- 18,146 positive tests
- 17,066 false positive tests
- 673 thoracotomy / mediastinoscopy
- 303 broncoscopies
- 99 needle biopsies
- To prevent 62 deaths from lung cancer
Health Policy not yet established

- ~ 94 million current or former smokers in the U.S.
- ~ 7 million meet NLST criteria
- The only cancer screening trial with a statistically significant decrease in total mortality
- Expensive... $ $$

Primary Prevention Of Lung Cancer

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

Colorectal Cancer

Question?

What do you most commonly recommend for colorectal cancer screening?

1. Fecal occult blood test (FOBT)
2. Sigmoidoscopy
3. Colonoscopy
4. Air contrast barium enema
5. Virtual Colonoscopy
6. Fecal DNA
7. Fecal immunochemical Test (FIT)
Colorectal Cancer: Evidence For Screening

- U.S. Men and Women: 3rd most common cancer and cause of death from cancer
- Screening with fecal occult blood test (FOBT) or sigmoidoscopy is associated with a reduction in CRC mortality
- Recent case-control study showed that colonoscopy was associated with fewer CRC deaths
  - Left sided CRC

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)

Joint Guideline Recommendation

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

Joint Guideline Recommendation

- Providers and patients should understand the limitations and requirements of noninvasive tests
  - Less likely to prevent cancer than the invasive tests
  - Must be repeated at regular intervals to be effective
  - If test is abnormal, invasive test (colonoscopy) will be needed
**USPSTF Recommendation**

- Screen with FOBT, sigmoidoscopy or colonoscopy in individuals aged 50-75
  - Risks and benefits of each method vary
- No routine screening for individuals age 76-85
- Do not screen individuals aged 85 and over
- Evidence is insufficient for CT colonography or fecal DNA

**Newer Tests**

- Virtual Colonoscopy
- Stool-based molecular testing
  - Fecal DNA
- Fecal immunochemical tests

**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%
- “High” clinical significance require surgical or medical treatment or intervention or further investigation
  - 5 - 11%
- 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

**Fecal DNA Testing**
- Screening test in multi-center study
- Fecal DNA test (23 mutations), FOBT, and colonoscopy
- 4482 average risk adults
- Fecal DNA detects more neoplasms than FOBT, but with more false positive results
- Expensive: $400 to $800 versus $3 to $40 for FOBT

**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)

Ahquist, 2008
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

How Are We Doing?

- FOBT in past year or lower endoscopy in the past 10 years
  - 62.9% of adults aged 50-75
- Rates are increasing but very slowly

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 new joint guidelines but not in USPSTF guidelines

QUESTIONS

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

1. Usually order PSA
2. Sometimes order PSA
3. Rarely order PSA
4. Never order PSA

BRFSS, 2008
Prostate Cancer: Should We Screen?

- Disease has high prevalence
  - 10% lifetime risk
  - 30% of men have prostate cancer at autopsy
- Disease has serious consequences
  - Sometimes but may be a benign disease for many men
- Detectable preclinical phase - PSA
- Treatment for preclinical disease is more effective?
  - Complications of prostate cancer treatment
    - 8.4% incontinence
    - 60% impotence
  - Prostate Cancer Outcomes Study 24 month follow up Screening
- Screening reduces cancer mortality?

SCREENING TESTS: PSA

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

PLCO 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

European Randomized Study of Screening for Prostate Cancer (ERSPC)

- 182,000 men aged 50-74 in seven European countries
- PSA screening at least once every four years vs no screening
  - Protocols differed in the 7 countries
- During 9 year follow up, incidence of prostate cancer was higher in the screening group
  - 8.2% vs 4.8%
- Mortality lower in the screened group
  - 7 fewer prostate cancers per 10,000 screened men
- To prevent one death
  - 1,410 men needed to be screened
  - 48 additional prostate cancers treated
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

USPSTF RECOMMENDATIONS

• The evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA or DRE in men younger than 75.
  – PSA can detect early prostate cancer, but inconclusive evidence about whether early detection improves health outcomes.
  – Harms include frequent false positives and unnecessary anxiety, biopsies and potential complications of treatment of some cases of cancer that may never have affected a patient’s health.
  – Grade “I” recommendation

• USPSTF recommends against screening men aged 75 and older

American Cancer Society

• Men with at least a 10 year life expectancy should have an opportunity to make an informed decision with their health care provider about whether to be screened

• Screening should not occur without an informed decision making process

• Men at average risk should receive the information beginning at age 50

• Information should be provided at age 45 for men at higher risk
  – Age 40 for very high risk
    * American Cancer Society, 2010

• For men unable to decide, the decision can be left to the discretion of the health care provider

• Men with less than a 10 year life expectancy should not be offered screening
  – At age 75, only half of men have a life expectancy of 10 years or more

• Men without access to regular care should be tested only if high quality informed decision making is available through community based programs
  – Follow-up and counseling
    * ACS 2010
American Cancer Society

• For those who choose to be screened
  – PSA with or without DRE
  – Screening yearly for men whose PSA is 2.5 ng/ml or greater
  – If PSA < 2.5 ng/ml, screening can be extended to every 2 years
  – PSA of 4.0 ng/ml or greater referral
  – PSA of 2.5-4.0 ng/ml individualized risk assessment
    • Age, African American, family history, previous negative biopsy
      • ACS, 2010

New American Urological Association Guidelines

• Men who choose to be screened should have both DRE and PSA
• The decision to use PSA testing should be individualized
  – Inform men of the potential benefits and risks
• Early detection and risk assessment for prostate cancer should be offered to all men aged 40 and older who wish to be screened and who have an estimated life expectancy of more than 10 years
  – American Urological Association, 2009

Prostate Cancer Screening: Summary

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

Summary Of Recommendations

• Women aged 50 to 74 should undergo mammography every 2 years
• Screening decisions for women in their forties and for women and for women aged 75 and older should be individualized
• MRI screening for breast cancer may be useful in high risk women
• All men and women aged 50-75 should be screened for colorectal cancer
  – Any screening is better than no screening
Summary Of Recommendations

- Screening for ovarian cancer is harmful
  - No reduction in ovarian cancer mortality
  - False positives with surgery and complications
- Screening for lung cancer with low-dose CT reduces mortality
  - Policy recommendations are still pending
- Screening for prostate cancer may reduce mortality but there are significant risks and harms to early detection and treatment

Thank you!

Questions?