CANCER SCREENING 2009: CURRENT CONTROVERSIES AND EVIDENCE BASED PRIORITIES

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SELECTED CONTROVERSIES

■ What are the public’s expectations about the benefits of cancer screening?
■ Colorectal Cancer
  – What test and how often?
  – Are there new screening options?
■ Breast Cancer Screening
  – Digital Mammography
  – MRI
SELECTED CONTROVERSIES

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

QUESTION

- What percentage of your patients would want to be screened for cancer even if nothing could be done about it?
  - 25%
  - 33%
  - 50%
  - 66%
WHAT ARE THE PUBLIC’S EXPECTATIONS?

- AIM: To determine the public’s enthusiasm for early cancer detection

METHODS

- National telephone survey of adults
  - Dec 2001 through July 2002
- 500 men and women with no history of cancer
RESULTS

- 87% believe that routine cancer screening is almost always good
- Less than 1/3 believe they will ever stop screening
- Two-thirds would be tested even if nothing could be done
- 73% would like a total body CT instead of $1000

QUESTION

- What do you most commonly recommend for colorectal cancer screening?
  - FOBT
  - Sigmoidoscopy
  - Colonoscopy
  - FIT
  - Virtual Colonoscopy
QUESTION

- Which test do you think is best for colorectal cancer screening?
  - FOBT
  - Sigmoidoscopy
  - Colonoscopy
  - FIT
  - Virtual Colonoscopy
  - The test that gets done

COLORECTAL CANCER: EVIDENCE FOR SCREENING

- Second commonest form of cancer in the U.S. and second highest mortality rate
- 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
    • Baxter, 2009 Annals Internal Medicine
SCREENING TESTS

- Fecal occult blood test (FOBT)
- Sigmoidoscopy
- Colonoscopy
- Air contrast barium enema
- Virtual Colonoscopy
- Fecal DNA
- Fecal immunochemical Test (FIT)

NEW JOINT GUIDELINE

- Joint guideline by American Cancer Society, US Multi-society Task Force on CRC and the American College of Radiology
- Guidelines for the early detection of CRC and adenomatous polyps
- Screening tests are grouped into two categories
  - Those that detect cancer early (stool tests)
  - Those that can also detect adenomatous polyps
    » Structural exams
NEW JOINT GUIDELINE

- 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

Computed Tomographic Colonography (Virtual Colonoscopy)

- Non-invasive radiological technique allows visualization of the entire colon
- Bowel preparation similar to conventional colonoscopy
  - Prep-less technique is being evaluated
- Does not require sedation
- Colon distended with carbon dioxide or air
- Breath holding for 20-50 seconds
- Radiation dose similar to barium enema
- 2D and 3D images interpreted by radiologist
- Colonoscopy to remove polyps
**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

**TEST ISSUES**

- **FOBT**
  - Good evidence for reducing mortality
  - Trials repeated FOBT every 1-2 years
  - Positive test requires evaluation of the entire colon
- **Sigmoidoscopy**
  - Fair evidence for reducing mortality
  - Proximal neoplasia can be missed, therefore positive test should be followed by colonoscopy
**FOBT vs IN-OFFICE SINGLE FOBT**

- Sensitivity for advanced neoplasia was 24% for 6 sample FOBT vs 5% for digital FOBT
- Specificity was 94% for 6 sample FOBT and 98% for digital FOBT
- Digital FOBT is a poor screening method
  - Collins, 2005

**SCREENING COLONOSCOPY**

- More sensitive than FOBT/sigmoidoscopy
- More specific than FOBT
- Higher risk
  - (1/2,000 perforation rate for diagnostic colonoscopy)
- More costly
- Presumed to save lives because used in FOBT trials
- Feasibility depends on insurance coverage and gastroenterologist availability
NEWER TESTS

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

VIRTUAL COLONOSCOPY

- Non-invasive colon imaging method using thin section CT
- Recently evaluated in 2531 asymptomatic average risk adults in the multi-center ACRIN Study
- Used more commonly available 2D technology
- Test characteristics
  - Sensitivity
    » 90% for polyps 10 mm or more
    » 78% for polyps ≥6 mm
  - Specificity
    » 86% for polyps 10 mm or more
    » 88% for polyps ≥6 mm
    - Johnson, NEJM 2008
American College of Radiology Imaging Network (ACRIN) Study

- Largest multi-center screening study of 2531 individuals
- Scanners at least 16 slice
- Colonoscopy done according to clinical protocol at each site
- Endoscopy done without knowledge of CTC results
- Radiologists extensively trained
- Pathology centrally reviewed
- Primary outcome; histologically confirmed large adenomas and adenocarcinomas
  » Johnson, 2008

Potential benefits

- Polyps can be detected which can be removed
- Accuracy approaches that of colonoscopy
- Less invasive than colonoscopy
- May be more acceptable than invasive screening tests
  - Studies have been mixed
  - If abnormal, still need colonoscopy
**Potential Harms**

- **Radiation Exposure**
  - Median dose estimate of 8.8 to 10.2 mSv per CT examination
  - 1/1000 could develop solid cancer or leukemia with exposure to 10mSv above background

- **Procedure related harms**
  - Perforation rate low - slightly higher with diagnostic CTC

- **Extra-colonic findings**

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**Extra-colonic findings**

- **Extra-colonic findings are common**
  - 27-69% of individuals

- **“High” clinical significance require surgical or medical treatment or intervention or further investigation**
  - 4.5-11%

- **“Moderate” clinical significance require further investigation or treatment but not immediate medical treatment**
  - 27% of individuals

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

- **Follow-up has been short (maximum of 2 years)**
CT COLONOGRAPHY VS COLONOSCOPY

- Parallel screening programs
  - 3120 got CT colonography
  - 3163 got colonoscopy
- Diagnostic yield of each approach compared
- Similar numbers of advanced neoplasms found
- 7.9% of patients in the CTC group referred for colonoscopy
- Fewer complications in the CTC group
  - Kim et al. NEJM 2007

FECAL DNA TESTING

- DNA alterations in colorectal cancer can be detected in the stool
- Potential advantages
  - Non-invasive
  - No preparation
  - Detection along entire length of the colon
FECAL DNA TESTING

- Evaluated as a screening test in multi-center study
- Fecal DNA test (23 mutations), Hemoccult, Hemoccult Sensa and colonoscopy
- 4482 average risk adults
- Fecal DNA detects more neoplasms than Hemoccult or Hemoccult Sensa, but with more false positive results
  - Ahlquist, 2008

<table>
<thead>
<tr>
<th></th>
<th>Fecal DNA</th>
<th>Hemoccult</th>
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<tbody>
<tr>
<td>Sensitivity for screen relevant neoplasia</td>
<td>20%</td>
<td>11%</td>
</tr>
<tr>
<td>Specificity</td>
<td>96%</td>
<td>98%</td>
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FECAL DNA: REMAINING QUESTIONS

- Are health outcomes improved?
  - Even if we assume benefit based on FOBT trials, how much?
- Do the benefits outweigh the risks?
  - Public expectations about accuracy of DNA testing?
- Frequency of testing?
- Acceptability and availability?
- Cost
  - $400 to $800 vs $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
- Newer FIT can use brush sampling of toilet water rather than spatula scraping of the stool
Fecal Immunochemical Testing

- FIT is more sensitive in detecting CRC and large adenomas (>1 cm) than Hemoccult II
- FIT is a little less specific than Hemoccult II (higher false positive rates)

How are we doing?

- FOBT in past 2 years: 27%
- Ever had a sigmoidoscopy or colonoscopy: 53%

※ BRFSS, 2004
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

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 and MRI
- You perform a clinical breast examination which is normal.
Breast Cancer Screening

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

BREAST CANCER SCREENING

- Breast cancer is the most commonly detected cancer in women and the second leading cause of cancer death
- Several studies have shown that screening mammography can reduce mortality
- Mortality reduction has not been seen in women in their forties
- Increased density of pre-menopausal breast tissue leads to decreased sensitivity
United States Preventive Services Task Force recommends screening mammography with or without clinical breast examination every 1-2 years for women aged 40 and older

- Data are most clear for women aged 50-69
- For women in their forties the evidence is weaker
- Benefit to women aged 70 and older if life expectancy not compromised by co-morbid disease

Evidence insufficient for or against clinical breast examination alone

Evidence insufficient for or against teaching or performing routine breast self-examination
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 should be reviewed, but it is acceptable not to do it
- Women should become informed about benefits, limitations and potential harms of routine screening

ACS RECOMMENDATIONS: OLDER WOMEN

- Screening decisions should be individualized by considering benefits and risks of mammography within the context of current health status and life expectancy
- If a woman is in good health and is a candidate for treatment, she should continue to be screened
ACS RECOMMENDATIONS:
HIGH RISK WOMEN

Women at high risk may benefit from additional screening strategies
- Earlier initiation?
- Shorter screening intervals?
- Adding other screening modalities e.g. ultrasound or MRI

Currently, no evidence to justify recommendations for these approaches

FREQUENCY OF MAMMOGRAPHY

Similar reduction in mortality with screening every one or two years

Many women expect annual screening

If screening is performed for women in their forties, it should be performed annually
BREAST CANCER SCREENING

- Current modalities
  - Mammography
  - Clinical Breast Examination
  - Self breast examination

- Limitations of current screening modalities

- What do we want from a new breast cancer screening test?

NEW TECHNOLOGIES

- Breast MRI
- Digital mammography
- Ultrasound and Mammography
SCREENING HIGH RISK WOMEN

- Women with BRCA1 and BRCA2 mutations or with a family history of breast cancer are often diagnosed at a young age
- Screening is often offered to younger high risk women but efficacy is not known
  - Lower sensitivity of mammography in younger women
  - High tumor growth rate
  - Atypical mammography changes in women with BRCA mutations

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
MRI SCREENING

- Two prospective studies of high risk women
- One included BRCA1 and BRCA2 carriers and one included women with a lifetime risk of breast cancer of 15% or more

SENSITIVITY AND SPECIFICITY OF BREAST CANCER SCREENING TESTS

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<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>
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IMPACT FOR CLINICAL PRACTICE

- All four screening modalities combined had a sensitivity of 95% vs 45% for mammography plus clinical breast exam
- MRI may be useful in screening high risk women, although the effect of MRI screening on mortality is not yet known
- MRI is not currently recommended for screening average risk women

FULL FIELD DIGITAL MAMMOGRAPHY

- Uses detectors similar to those in digital camera
- Overall diagnostic accuracy is similar to film mammography
- Digital mammography was more accurate in some women
  - Women under age 50
  - Women with heterogeneously dense or extremely dense breasts
  - Pre-menopausal or peri-menopausal women
    - Pisano, 2005
- More expensive
- Harder to compare with prior film images
Mammography plus Ultrasound

- Screening ultrasound may detect small cancers not seen on mammography
- 2809 high risk women underwent mammography and ultrasound
- Mammography alone compared to mammography plus ultrasound
- Adding an ultrasound will find 1.1 to 7.2 more cancers per 1,000 but with a significant increase in false positives
  » Berg et al JAMA 2008

QUESTION

- What is your usual practice for PSA screening for men aged 50-70?
  - Usually order PSA
  - Sometimes order PSA
  - Rarely order PSA
  - Never order PSA
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: DIGITAL RECTAL EXAMINATION

- One-third of prostate cancers occur in areas which can be reached
- Higher sensitivity performed by urologists
- An abnormal digital rectal examination increases the likelihood of prostate cancer somewhat
- A negative examination does not change the likelihood of a clinically significant prostate cancer
  - Low sensitivity of the examination
SCREENING TESTS: PSA

- PSA testing has increased dramatically since 1988
- Observational studies have had conflicting findings about the benefits of screening
- One prior RCT suggested a benefit but there was no intention to screen analysis
- Two large randomized controlled trials of PSA screening and mortality recently published

PLCO Cancer Screening Trial

- Prostate, Lung, Colorectal and Ovarian
- 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 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
- Schroder NJM 2009

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
PROSTATE CANCER SCREENING: 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
  - USPSTF 2008

American Cancer Society

- ACS does not recommend routine screening
- Clinicians should discuss the pros and cons of screening
- After discussion, annual screening with DRE and PSA should be offered to men age 50 and over with at least a 10 year life expectancy
- Discussion should occur earlier for men at higher risk
  - American Cancer Society, 2008
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

LUNG CANCER SCREENING

- Does the disease have high prevalence?
  - 213,380 cases in 2007
- Does the disease have serious consequences?
  - Lung cancer is the number one cause of cancer mortality in both men and women
- Is there a detectable preclinical phase????
- Is treatment of preclinical disease more effective than waiting for symptoms to develop?
  - 5 year survival much better in Stage 1 than in more advanced
- Are health outcomes improved as a result of screening?
  - Do any screening tests reduce lung cancer mortality?
LUNG CANCER SCREENING: SYSTEMATIC REVIEW

- Does screening for lung cancer reduce lung cancer mortality
- Included 7 trials of lung cancer screening
  - Only one included women
- 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 vs chest X-ray alone

LOW DOSE SPIRAL COMPUTED TOMOGRAPHY

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

- 8 published studies of LDCT screening for lung cancer
  - 4 were high risk (smokers, former smokers)
  - 4 mixed risk populations (46-86% smokers)
- LDCT can detect lung cancer
  - More early stage cancer
- In high risk populations
  - 1.2% prevalence of lung cancer on LDCT
  - 0.6-2% incidence on annual or follow up screens

LDCT SCREENING

- International Early Lung Cancer Action Project (I-ELCAP)
  - N=31,5567
  - 83% smokers
  - Detailed protocol for follow up of all abnormalities
  - Longitudinal cohort
  - All screened at baseline and most got follow up screening
  - No comparison group
LDCT SCREENING FOR LUNG CANCER

- At baseline, (N=31,567) screened
  - 4,186 positive tests
  - 405 (1.3%) lung cancers
- Annual Screen (N=27,456)
  - 1,460 positive
  - 74 (0.27%) lung cancers
  - 5 interim cancers
- 85% of those detected were stage I cancers

COMPUTED TOMOGRAPHY SCREENING

- Can Spiral CT diagnose early disease?
  - Yes
- Does the ability of spiral CT to detect early lung cancers matter?
  - ??
  - Overdiagnosis?
- Do the benefits outweigh the risks?
  - ??
  - Detection and evaluation of benign nodules
USPSTF RECOMMENDATIONS

- Evidence is insufficient to recommend for or against screening asymptomatic persons for lung cancer with low-dose computerized tomography, chest X-ray, sputum cytology or a combination of these tests
  - Grade “I” recommendation
- Screening with these modalities can detect lung cancer early, but there is no evidence that any screening strategy reduces lung cancer mortality.

PRIMARY PREVENTION OF LUNG CANCER

- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation
- Smoking cessation!!!!!
All men and women aged 50 and older should be screened for colorectal cancer
  - Any screening is better than no screening
Women aged 50 to 69 should undergo mammography every 1-2 years
Digital mammography may be useful for pre-menopausal women or women with denser breasts

MRI screening for breast cancer may be useful in high risk women
Screening for prostate cancer with PSA might result in a small reduction in mortality with a substantial increase in over-diagnosis
There is no evidence that screening for lung cancer reduces mortality