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

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

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
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


<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 (329-6375)</td>
</tr>
<tr>
<td>50-59 y</td>
<td>6†</td>
<td>0.86 (0.76-0.96)</td>
<td>1339 (322-7456)</td>
</tr>
<tr>
<td>60-69 y</td>
<td>2‡</td>
<td>0.68 (0.54-0.82)</td>
<td>377 (220-1050)</td>
</tr>
<tr>
<td>70-74 y</td>
<td>1§</td>
<td>1.12 (0.73-1.72)</td>
<td>Not available</td>
</tr>
</tbody>
</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
Probability of False Positives

- Cohort study of 169,456 women who underwent first screening at age 40-59 and 4,492 women with incident invasive breast cancer
- After 10 years, over half of women will have at least one false positive recall and 7-9% will have false positive biopsy recommendation
  - Biennial screening decreases cumulative probability of false positives but may be associated with a small absolute increase in probability of late stage cancer diagnosis
  - Hubbard, Annals Int Med, 2011

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.

Newer Technologies

- Digital Mammography
- Breast MRI
- Ultrasound and Mammography
### Digital mammography

- Higher sensitivity, same specificity in women < 50 years old
  - Sensitivity 82% versus 76% film
  - Specificity 88%
- Cancer detection rates overall similar between film and digital mammography
- Test characteristics better for women aged 40-49, dense breasts and estrogen receptor negative tumors

Kerlikowske, Ann Intern Med, 2011

### 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

### 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>
</tbody>
</table>

### 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
Mammography plus Annual Ultrasound or Single MRI

- 2,809 high risk women with dense breasts
  - Annual ultrasound and mammography for 3 years
  - 612 of 703 women who had MRI had complete data
- Adding MRI will find 14.7 more cancers per 1,000 but with many false positives
- Number of screens to detect one cancer
  - Mammography 127
  - Supplemental U/S 234
  - Adding MRI* 68
  - *After mammogram and ultrasound negative

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

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)

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 Ovarian Cancer

- 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):

- 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>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer Deaths</td>
<td>247</td>
<td>309</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.73-0.93)</td>
</tr>
<tr>
<td>Any death</td>
<td>1877</td>
<td>2000</td>
<td>0.93</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.86-0.98)</td>
</tr>
</tbody>
</table>

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

NLST, NEJM 2011

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 in Transition

- ~ 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… $$ $$
Health Policy

- California Technology Assessment Forum assessed LDCT for lung cancer screening
- Panel voted that LDCT met criteria for screening high risk individuals (like those in NLST) at specialized centers
  
  » CTAF, October, 2011

Health Policy: ACCP and ASCO 2012

- For smokers and former smokers aged 55-75 who have smoked for 30 pack-years or more and either continue to smoke or have quit within the past 15 years, annual screening with LDCT should be offered
  - Only in settings that can deliver the comprehensive care provided to NLST participants

Health Policy: ACCP and ASCO 2012

- For those who have accumulated fewer than 30 pack years of smoking or are younger than 55 or older than 74 or who quit smoking more than 15 years ago or who have severe comorbidities that would preclude potentially curative treatment, CT screening should not be performed

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
Other organizations

• Stay tuned
• New recommendations will be forthcoming

Primary Prevention Of Lung Cancer

• Smoking cessation
• 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
• Case-control study showed that colonoscopy was associated with fewer CRC deaths
  – Left sided CRC

Baxter, Annals IM, 2009

Sigmoidoscopy: New Evidence

• PLCO Trial
  • 154,900 men and women aged 55-74 assigned to screening with FS with repeat at 3-5 years vs usual care
  • 11.9 year follow up
  • Reduced incidence of both proximal and distal CRC
  • Reduced mortality in distal CRC (RR 0.50 (0.38-0.64) but not proximal CRC

  – Bilsbo et al NEJM 2012

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 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
**Laxative-Free CT Colonography**

- Low fiber diet, orally ingested contrast material and specialized processing software “electronic cleansing”
- 605 adults underwent CTC and OC
- CTC was more accurate in detecting adenomas 10 mm or larger and less so for smaller lesions
  - 91% sensitivity vs 70% for adenoma 8 mm or larger
- Patients preferred it

**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

Ahlquist, 2008

**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

**How Are We Doing?**

- National Health Interview Survey
  - 62.9% of adults aged 50-75 up to date based on USPSTF recommendations
- Rates are increasing but very slowly

NHIS, 2010
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

QUESTION

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

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

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 NEJM 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

USPSTF RECOMMENDATIONS 2012

- Recommends against PSA based screening for prostate cancer
  - 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 "D" recommendation

USPSTF 2012
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 Urological Association Guidelines

- May, 2012 News Release “AUA outraged at USPSTF’s failure to amend 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 but is not recommended by USPSTF
• 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

• 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