Current Controversies in Cancer Screening: Letting Evidence Be Our Guide

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Principles of Cancer Screening

• Screening for cancers associated with a decrease in cancer-specific mortality
• Disease is prevalent, serious and has a detectable preclinical phase
• Treatment of pre-symptomatic disease is more effective than treatment after symptoms develop
• Benefits of the test should outweigh potential harms

Enthusiasm for Cancer Screening in the United States: National Survey

• 87% — “Good Idea Almost Always”
• 74% — “Most or All the Time Finding Cancer Early Saves Lives”
• 56% — “Want to be tested for cancers which would never cause problems during the persons lifetime”
• 73% — “Would prefer to receive a total-body CT scan instead of receiving $1000”

Do Primary Care Physicians Understand Cancer Screening Statistics?

• 412 physicians surveyed in 2010 -11
• 2 screening test Scenarios: a) Improved 5-year survival and increase early detection vs. b) reduce mortality and increase incidence
• 69% recommended test a vs. 23% for b
• Majority of physicians showed poor understanding of screening statistics
• Poor numeracy skills all around?

JAMA. 2004; 291:71-78
Colon Cancer Screening

Primary Prevention and Early Detection

50 y woman with no Family History of Colon CA for routine visit

What do you usually recommend about CRC screening in patients like this?
A) Ignore the topic unless she brings it up
B) Routinely order annual FOBT or FIT and evaluate further only if positive
C) Discuss all screening options and select modality based on patient preference
D) Refer directly to the GI consultant for discussion of colonoscopy
E) Recommend CT colonography

60 year old man, no FHx and found to have one 0.5 cm adenoma

How should a patient like this be followed?
A) Repeat colonoscopy in 1 to 2 years
B) Repeat colonoscopy in 3 years
C) Repeat colonoscopy in 5 years
D) Routine screening by whatever modality
E) Recommend CT colonography at 3 to 5 years

Screening for Colon Cancer

- 3 large randomized trials have shown that screening with fecal occult blood test or sigmoidoscopy is associated with a 15% to 33% reduction in colon cancer mortality
- U.S. Preventive Services Task Force recommends screening at age 50 y and re-evaluating at age 75 y; stop at 85 y in all
- 50% of CRC diagnosed at late stage
National Polyp Study Removing Polyps Reduces Colon Cancer Risk

- Transition of polyp to invasive cancer is from 6 to 10 years
- Hyperplastic polyps + adenomas indistinguishable on colonoscopy
- Hyperplastic polyps do not progress and do not need more intensive follow-up
- Adenomas vary by size and those < 1 cm are much less likely to progress
- 1 cm or more needs closer follow-up
- advanced neoplasia: villous histology, dysplasia, or adenomas > 1 cm

Colon Cancer Screening 2012
ACP Recommendations
For Average risk patients starting at age 50:
- Annual stool test — FIT, FOBT, stool DNA
- Flexible sigmoidoscopy – 5 years (DCBE, CT colonography)
- Colonoscopy every 10 years
For higher risk patients start at age 40y or 10y younger than age at which youngest affected relative was diagnosed:
- Colonoscopy every 10 years (no FOBT x 5 y)
- Select test based on benefits, harms, availability and patient preference
- STOP at age 75 y or < 10 y life expectancy

Fecal Immunochemical Tests
- Similar specificity to guaiac FOBT
- Uses labeled antibodies that attach to antigens of any human globin in stool
- No upper GI source
- Sensitivity of 61% to 91% for cancer, and advanced adenomas—better
- 97% specificity—less false positives
- One sample sufficient
- No special diet needed
- More expensive

**Is Colonoscopy Better?**

- Colonoscopy covers the entire colon
- Distal polyps are not always predictive of proximal neoplasia – 80% of high risk lesions would have been detected
- Colonoscopy may also miss more advanced left-sided lesions
- Up to 2.8 per 1000 screening colonoscopies result in serious harm
- Effectiveness of colonoscopy may be overrated

**Efficacy Studies of Colonoscopy**

- National Polyp Study: patients had polyps removed between 1980-90; follow-up National Death Index
- 2602 had polyps removed, 12 died from CRC, mortality reduction of 53% (Zauber AG, et al, NEJM 2012; 366: 687-96)
- German study of 1688 cases/1932 controls
- Colonoscopy in preceding 10 y protective: OR = 0.23 for all; OR = 0.44 right-sided; OR= 0.16 left sided (Brenner H, et al. Annals Intern Med 2011; 154: 22-30)

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**Colonoscopy vs. FIT for CRC Screening RCT in Spain**

- 26,703 offered colonoscopy vs. 26,599 offered screening with FIT q 2y
- Rate of participation higher with FIT strategy (34.2% vs. 24.6%)
- CRC initial detection similar (0.1%)
- More advanced adenomas with colonoscopy (1.9% vs. 0.9%)
- More small adenomas (4.2% vs. 0.4%)

Quintero E, et al, NEJM 2012; 366: 697-706

**60 year old man, FHx CRC in father at 60, found to have 3 adenomas (1 cm)**

How should a patient like this be followed?

A) Repeat colonoscopy in 1 to 2 years
B) Repeat colonoscopy in 3 years
C) Repeat colonoscopy in 5 years
D) Routine screening by whatever modality
E) Recommend CT colonography at 3 to 5 years
Colon Cancer Family History and High-Risk Patients

- If single first-degree relative under age 60 years has a history of colon cancer or a ≥ 1 cm adenomatous polyp begin screening at age 40 or 10 y before the diagnosis of relative with CRC
- African Americans have highest incidence and should start at age 40 y
- Inflammatory bowel disease
- Advanced adenomas
- Screen every 5 years?
- Estrogen decreases incidence (WHI)

Screening in High Risk Individuals

- People who have a polyp >1 cm, 3 or more adenomatous polyps, dysplasia, or any villous adenoma should repeat colonoscopy at 3 years
- Subsequent follow-up depends on the type of polyps detected
- Tubular adenomas less than 1 cm: may repeat colonoscopy in 5 years
- Interval for surveillance debated
- Medicare pays for repeat in 2 years

Strategies to Increase CRC Screening

- Patient navigator increased screening at 1 y in RCT in LEP patients (40% vs. 19%) and Blacks (40% vs. 17%)
  Laser K, Arch Intern Med 2011; 171: 905-912
- Electronic messages via personal health record increased initially but not sustained (Sequist TD et al, Arch Intern Med 2011; 171: 636-41)
- Patient outreach with mailings, digital video, telephone increased at 6 months (18% vs. 12%)
  Cameron KA, Arch Intern Med 2011; 171: 642-6

Results – RCT in 6 SFDPH Clinics

<table>
<thead>
<tr>
<th>Data for flu shot recipients in 6 SFDPH clinics</th>
<th>FLU Only Arm N=677</th>
<th>FLU-FOBT Arm N=695</th>
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</thead>
<tbody>
<tr>
<td>CRCS Up-to-Date before (Oct 2009)</td>
<td>31.3%</td>
<td>32.5%</td>
</tr>
<tr>
<td>CRCS Up-to-Date After (Mar 2010)</td>
<td>35.6%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Change (p=0.02)</td>
<td>+4.3 points</td>
<td>+13.0 points</td>
</tr>
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Odds Ratio for Unscreened Becoming Screened in Multivariate Analysis: 2.22 (1.24-3.95)
Breast Cancer Screening

Is there any controversy for Mammography at 40?

45 y woman with no Family History of BC with one previous normal mammogram

What do you usually do about breast cancer screening in patients like this?

A) Routinely order and recommend annual mammography
B) Recommend against screening until age 50
C) Discuss other screening modalities with MRI and ultrasound
D) Initiate discussion about screening controversy and present risk of false positive as well as benefits
E) Recommend routine screening every 2 y

Breast Cancer Incidence Declines

- SEER Registries for 2003
- 8.6% decrease in annual incidence
- Only in women 50 years and older and most evident in estrogen receptor positive tumors
- Overall 13% decline since 2001
- Mortality has declined 30% since 1990—partially from screening

Incidence by age in the US 2000 - 2006

NEJM 2007; 356: 1670-74
Breast Cancer Screening

- 1 in 8 women will develop breast cancer over lifetime
- Benefit of early detection and 25% decrease in mortality
- For every 2000 women screened in 10 years, one cancer death is prevented and 10 women are over-treated
- Screening leads to more aggressive treatment—DCIS may never progress
- Co-pay of $10 led to 8.3% lower rate of biennial screening (Trivedi, NEJM 2008;358:375)

US Preventive Services Task Force
Breast Cancer Screening Guidelines

- Recommends mammography every 2 years for women aged 50 to 74 years
- Insufficient evidence of benefit for clinical breast exam in asymptomatic women
- Breast Self-Exam shows no reduction in mortality—Grade D or not recommended
- Women 40 to 49 y should discuss risk and benefits of screening taking into account patient’s values—individualize decision
- Insufficient evidence of benefit in women over 75 y if life expectancy not limited by co-morbidity

USPTF, Ann Intern Med 2009; 151: 716

Relative Risk of Breast Cancer Mortality in Screened Women

<table>
<thead>
<tr>
<th>Ages</th>
<th>RR death</th>
<th>NNS</th>
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<tbody>
<tr>
<td>39 - 49</td>
<td>0.85 (0.75 - 0.96)</td>
<td>1904</td>
</tr>
<tr>
<td>50 - 59</td>
<td>0.86 (0.75 - 0.99)</td>
<td>1339</td>
</tr>
<tr>
<td>60 - 69</td>
<td>0.68 (0.54 - 0.87)</td>
<td>377</td>
</tr>
</tbody>
</table>

- Women aged 50-69: 20-30% reduction in breast cancer mortality
- For women in their 40s the mortality reduction comes at a cost of many false positives: PPV = 4% vs. 13%

Screening Mammography in Older Women

Almost 50% of new cases of breast cancer and 67% of deaths > 65 y
- Lowers risk of stage 4 cancer if screened in Medicare analyses
- 10 yr risk at age 70 is high at 6.5%
- Wealthier ($100k+ net worth) women are more likely to get screened independent of 5 year survival
- Should individual 10 year survival be estimated and screening decisions made with shared decision making?

Ann Int Med 2003;139:835-842; Arch Intern Med 2008; 168: 514-520
Modeling of 6 Screening Strategies Developed in NCI Network

- DCIS included or proportion assumed to not progress; Use stages or tumor size
- 6 models come to similar qualitative estimates of contributions of screening and treatment
- Evaluate starting age 40-50 and end at 69-84
- 8 strategies ranked as “efficient” — all but 2 start at age 50 y and 7/8 are biennial
- Biennial screening maintains 81% of benefit and reduces false positives by 50%


Potential Benefits and Harms

<table>
<thead>
<tr>
<th>% Mortality reduction</th>
<th>Screen q2 yr 50-69 yrs (9)</th>
<th>Screen q yr 40-69 yrs (27)</th>
<th>Screen q2 yr 50-79 yrs (12-13)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>16%</td>
<td>19%</td>
<td>25%</td>
</tr>
<tr>
<td>Life-yrs gained/1000</td>
<td>99</td>
<td>164</td>
<td>130</td>
</tr>
<tr>
<td>False positive/1000</td>
<td>780</td>
<td>2250</td>
<td>1020</td>
</tr>
<tr>
<td>Extra biopsy/1000</td>
<td>55</td>
<td>158</td>
<td>71</td>
</tr>
</tbody>
</table>

Strongest risk factor: breast density

- BI-RADS
  - Almost entirely fat RR 1.0
  - Scattered densities RR 2.0
  - Heterogeneous RR 2.8
  - Extremely dense RR 4.1

- Percent density
  - ≥ 75% versus < 10% RR 5.3
- Change in density BI-RADS increases risk 5-10 fold

JNCI 2007; 99:386-95

Percent fibroglandular volume

8% 16% 26% 30% 41%

32% 62% 70% 84% 92%

Courtesy J. Shepherd, UCSF
**Screening Mammography Differences May Explain Breast Cancer Disparities**

- Mammography Registry Cohort: 1,010,555 women, 40+ y, from 1996-2002, 17,558 diagnosed with breast cancer
- Non-white women were 20%-40% more likely to receive inadequate mammography screening
- African American women had higher rates of high-grade tumors regardless of screening
- Lower rates of cancer among Asian, American Indian, Latinas

*Smith-Bindman, AJM 2006; 144: 541-53*

**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 y, >50% women will have at least one false positive recall and 7-9% will have false positive biopsy
- Biennial screening decreases cumulative probability of false positives

*Hubbard, Annals Int Med, 2011*

**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 for Breast Cancer**

- 969 Women with unilateral breast cancer diagnosed, mean age of 53 y
- MRI Screen of contra lateral breast after normal mammogram and clinical exam
- 30 occult breast cancers found (3.1%)
  - 121 biopsies done (12.5%)
  - 18 invasive cancers; 12 DCIS
- MRI is not influenced by breast density, specificity is variable, expensive
- May be most useful in highest risk women

*NEJM 2007; 356: 1295-1303*
Mammography plus Ultrasound for Women at Elevated Risk

- 2809 women with dense breast tissue examined with mammography plus ultrasound in random order
- Yield additional 1 to 7 cancers per 1000 women
- Three times more biopsies recommended with lower PPV of 8.9% vs. 22.6%

JAMA 2008; 299: 2151-2163

Clinical Interventions to Improve Cancer Screening

- Randomized Trial evidence supports use of telephone management with 10% increase in mammography
- RCT of Web based reminder system with 2 letters, 3 months before due date and telephone call to non-responders showed 9% increase (Chaudry R. Arch Intern Med 2007; 167: 606-11)
- Risk-tailored messages on breast CA in 899 diverse women had no effect on screening at 18 m except in Worriers (85% vs 64%) Bodurtha J. J Women's Health 2009; 18: 41

Reducing Risk of Breast Cancer

1. Early childbirth, breast feed
2. Exercise 3 - 7 hours / week
3. Maintain normal body weight
4. Minimize alcohol
5. Avoid long term hormones, especially progestins
6. Low fat diet?
7. Family history–genetic test?
Estimated 30 - 80% reduction in risk

Prostate Cancer Screening

Is There Benefit?
65 y man with no Family History or previous testing for prostate CA in routine visit

What do you usually do about prostate cancer screening in patients like this?
A) Ignore the topic unless he brings it up
B) Routinely order annual PSA as allowed by Medicare
C) Discuss PSA and DRE screening with interval frequency of 3-4 years
D) Initiate discussion about controversy and present risk of false positive as well as benefits
E) Recommend against routine screening

Prostate Cancer Risks
- 15% lifetime risk; 30% of men have prostate cancer at autopsy; 3% risk of dying
- Risk factors of Age and First degree Family history
- Race: African American men have highest incidence rates of prostate cancer in the world and twice as likely to die from it than are other Americans (screen at age 45?)
- Asian/PI and American Indian low rates

The Changing Face of Prostate Cancer

PSA Screening
- 15% men age > 50 have elevated PSA
- Higher PSA, predicts more prostate cancer
  - PSA 2.6-4 ng/dl: 12%
  - PSA 4-10 ng/dl: 22%
  - PSA >10 ng/dl: 66%
- Other tests: PSA density, PSA velocity, % free PSA (decrease with CA), are no better than PSA alone
- Single PSA at age 60 y of < 1 results in < 1% risk of prostate cancer death in 25 y
Prostate Cancer Screening?

- Prostate cancer benign in many
  - Similar survival of observation vs. initial treatment (surgery or radiation) in cohort
  - Similar risk of prostate cancer deaths in U.S and U.K.
  - Prostate cancer mortality declined following use of PSA and TURP
- Complications of surgery significant: 8% incontinent, 60% with ED and 0.5-1% perioperative death

Prostate Cancer Screening Trial: PLCO

- 76,693 men randomized to annual screening (PSA for 6 y and DRE for 4 y) vs. usual care from 1993-2001
- PSA done in 85% screened and 40% to 52% of usual care men
- More cancers found: 116 vs 95 per 10,000 person-years
- No mortality difference: 50 vs 44
- Rate ratio = 1.13 (95% CI = 0.75 - 1.70)
- Similar results at 10 years F/U

European Prostate Cancer Screening Trial

- 182,000 men randomized to screening PSA once every 4 y vs. no screening
- PSA done in 82% screened and 40% to 52% of usual care men
- 85% adhered to biopsy referral
- More cancers found with cumulative incidence 8.2% vs. 4.8% at 9 years
- Prevent one death: number needed to screen = 1410; 48 new cases would need treatment
- Rate ratio = 0.80 (95% CI = 0.65 - 0.98)
Systematic Review of Six Trials

- PSA with or without DRE
- 387,286 participants
- Increased probability of prostate cancer diagnosis (RR=1.46) and of stage 1 cancer (RR=1.95)
- No effect of screening on death from prostate cancer RR = 0.88, 95% CI = 0.71-1.09
- Methodological flaws in all trials
- Limited data on quality of life and potential harm

PSA Screening Trial in Sweden

- DRE initially, then PSA, up to age 69
- 1494 men randomized, followed for 20 years
- Increased probability of prostate cancer diagnosis (RR=1.46) and of stage 1 cancer (RR=1.95)
- No effect of screening on death from prostate cancer RR = 1.16; 95% CI = 0.78-1.73
- No benefit of screening

Radical Prostatectomy vs. Watchful Waiting RCT

- 15 year follow-up of 695 men with early prostate cancer
- 14.6% vs. 20.7% death from prostate cancer at 15 years
- All levels of risk benefit, <65 years old
- NNT to avert 1 death = 15 overall and NNT = 7 for men <65 y
- Extra-capsular tumor — RR 6.9 of death from prostate cancer

U.S. Preventive Services Task Force 2011 Recommendations

- Moderate high-quality evidence that routine screening for prostate cancer has no net benefit
- Harm outweighs benefit and Discourage routine PSA test in anyone
- Assessment of public comment ongoing

**Prostate Cancer Screening Options**

- Screen all men as routine - if yes, every 4 years; DRE at the same time
- Discuss potential benefits and harms of screening and individualize decision to screen - “shared decision”
- ACS/AUA: Discouraging testing not appropriate and not offering testing inappropriate; start at age 40 or 50
- Screen once at age 50, if PSA <1, repeat at age 60 and if < 1, stop
- No deaths from PC if PSA <1 at age 60

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**Lung Cancer Screening**

**Lung Cancer Screening**

**LDCT Scan Screening for High-Risk Patients**

- Chest radiographs with or without sputum cytology showed no lung cancer mortality benefit in RCT
- Low Dose Spiral Computed Tomography scans lung in 20 seconds (single breath)
- No IV contrast, less radiation than conventional CT, detects smaller lesions

**CT-Based Lung Cancer Screening Trial**

- NELSON trial—first two rounds of screening
- Initial nodule volume > 0.5 cm
- 0.3% (20/7361) of high risk patients with initially negative CT scans had lung cancer detected
- Defining criteria for follow-up of CT findings will help limit invasive tests for false positives

The National Lung Screening Trial
NEJM June 29, 2011

- 53,454 randomized to LDCT or CXR
- Smokers of ≥30 pack-years
- Former smokers quit < 15 years ago
- 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>
</thead>
<tbody>
<tr>
<td>Lung CA Deaths</td>
<td>247</td>
<td>309</td>
</tr>
<tr>
<td>Any death</td>
<td>1877</td>
<td>2000</td>
</tr>
</tbody>
</table>

20% reduction in lung cancer death:

The National Lung Screening Trial: Other Results

- 75,000 LDCT scans done
- 18,146 positive tests
- 17,066 false positive tests
- 673 thoracotomy or mediastinoscopy
- 303 bronchoscopies
- 99 needle biopsies
- To prevent 62 deaths from lung cancer in 6.5 years

Conclusions and Recommendations

- Screening for lung cancer with LDCT decreases mortality in high-risk patients
- 7 million smokers/ex-smokes meet eligibility criteria of 30 pack-years, current smoker or quit <15 years
- Coverage not yet decided by CMS

Screen for Ovarian Cancer?

Not Recommended
Ovarian Cancer: Should We Screen?

- Lifetime risk of ovarian cancer
  - No affected relatives: 1.2%
  - One affected relative: 5%
  - 2 affected relatives: 7%
  - Hereditary syndrome: 40%

- Other risk factors: Older Age, nulliparity, Whites, History of breast, colon or uterus cancer

- Protective factors: breast feeding, pregnancy >1, OCP (37% reduction)

Ovarian Cancer: Screening Techniques

- No evidence for pelvic exam
- Serum CA-125 assay
- Trans-vaginal ultrasound
- Serum CA-125 plus ultrasound

Ovarian cancer limited to the ovaries is associated with a much higher survival rate

- Non-specific symptoms

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

- 78,216 women age 55-74: randomized to screening with annual CA 125 + ultrasound vs. usual care with 12.4 y follow-up
- CA 125 >35 or abnormal U/S was positive
- F/U of positive screens by patients' physicians
- Cancer diagnosis: 5.7% vs. 4.7% (RR = 1.2)
- Ovarian cancer death: 3.1% vs. 2.6% (RR = 1.2, 95% CI 0.8-1.7)
- False positives 8.4% leading to 2.8% with surgical procedures (Buys, et al, JAMA 2011; 305: 2295-2303)

Ovarian Cancer Screening: Recommendations

- NIH Consensus Conference and USPSTF: no evidence for widespread screening
- High risk women (≥ 2 1st degree relatives) referred and screened
Is there an Age Limit to Screening?

- Recommendations stop at 65-70 for cervical, 75 for breast and CRC
- Discuss at 76 to 85 if life expectancy expected to be 10 y
  NHIS: screening in persons ≥80 y 50% breast, 38% cervical, 47% CRC, 42% prostate
- MD recommendation drives

Sources for Information

- Center to Reduce Cancer Health Disparities: http://crchd.nci.nih.gov/