Cancer Screening: Controversial Topics

10/27/17

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Outline

- Case review
- Introduction
- Why this matters
- Breast Cancer
- Prostate Cancer
- Conclusion
Case

- 75 year old female w/ O2 dependent COPD
- Symptoms of constipation, weight loss, decreased appetite, “hemorrhoid flare”
- Empiric cortisone with no improvement
- Referred for 1st colonoscopy (refused in past)
  - Found to have a frieable anal and distal rectal mass
  - Biopsy proven squamous cell carcinoma
Case

- Further history in my office – patient had rectal bleeding for > 1 year, fecal incontinence, and severe pain on BM.
- Exam showed a > 5 cm circumferential anal canal mass extending into the distal rectum, + left inguinal node
Case

- Locally advanced anal canal cancer
- Treatment was planned for definitive chemoradiation – curative intent
- Patient passed away within days of my initial evaluation
Case

- If your patient has symptoms, you are not screening – you need prompt diagnostic test.
- If you don't ask the question (or do the exam) you will not know.
- Properly performed rectal, Gyn breast exams take time but can save lives.
- Screening has implications for the population and also for your individual patient.
Introduction

• Cancer screening seeks to detect cancer before a person has any symptoms.

• Screening can mean:
  • History and Physical Exam
  • Laboratory Test
  • Imaging
  • Invasive Procedure
  • Genetic Screening
Introduction

• Screening tests have risks.
  • Some screening tests can cause serious problems.
  • False-positive test results are possible.
  • False-negative test results are possible.
  • Finding the cancer may not improve the person's health or help the person live longer.
Introduction

Certain factors may cause disease-specific outcomes to look like they are getting disproportionately better with screening when they are not.

- Lead Time bias
- Length time bias
- Overdiagnosis
Introduction

Ideal Cancer Screening Tests:

- Screen for a cancer that is easier to treat and cure when found early.
- Has few false negative results
- Has few false positive results.
- Decreases the chance of dying from cancer.
- Is cost effective for the healthcare delivery system
Why is this important?

<table>
<thead>
<tr>
<th>Common Types of Cancer</th>
<th>Estimated New Cases 2015</th>
<th>Estimated Deaths 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Breast Cancer (Female)</td>
<td>231,840</td>
<td>40,290</td>
</tr>
<tr>
<td>2. Lung and Bronchus Cancer</td>
<td>221,200</td>
<td>158,040</td>
</tr>
<tr>
<td>3. Prostate Cancer</td>
<td>220,800</td>
<td>27,540</td>
</tr>
<tr>
<td>4. Colon and Rectum Cancer</td>
<td>132,700</td>
<td>49,700</td>
</tr>
<tr>
<td>5. Bladder Cancer</td>
<td>74,000</td>
<td>16,000</td>
</tr>
<tr>
<td>6. Melanoma of the Skin</td>
<td>73,870</td>
<td>9,940</td>
</tr>
<tr>
<td>7. Non-Hodgkin Lymphoma</td>
<td>71,850</td>
<td>19,790</td>
</tr>
<tr>
<td>8. Thyroid Cancer</td>
<td>62,450</td>
<td>1,950</td>
</tr>
<tr>
<td>9. Kidney and Renal Pelvis</td>
<td>61,560</td>
<td>14,080</td>
</tr>
<tr>
<td>10. Endometrial Cancer</td>
<td>54,870</td>
<td>10,170</td>
</tr>
</tbody>
</table>
A Brief word

“The Tyranny of Randomized Controlled Trials”

- **Equipoise** – feasible in principle but difficult in practice – leads to crossover
- Careful patient selection may mean results are not generalizable to population
- Participating centers may not represent hospitals nationally – experience
- Systematic bias of study design (funding source)
Breast Cancer
Why screen for Breast Cancer?

Breast cancer is easier to treat when found early

• Pillars of breast cancer treatment are surgery, systemic therapy, and radiotherapy

• Surgery: Lumpectomy vs Mastectomy, ALND vs SLN bx

• Systemic therapy: need for chemotherapy vs not

• Radiotherapy: breast only radiation vs RT regional lymphatics

• Detecting breast cancer earlier can and does lead to decreased physical and psychosocial side effects for the patient.

- Source: NCCN guidelines
Is breast cancer easier to treat when found early?
Is breast cancer easier to treat when found early?

LOCOREGIONAL TREATMENT OF CLINICAL STAGE I, IIA, OR IIB DISEASE OR T3, N1, M0

- ≥4 positive\(^q\) axillary nodes
  - Radiation therapy to whole breast with or without boost\(^t\) to tumor bed (category 1), infracavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk (category 1). It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.

- 1–3 positive axillary nodes
  - Radiation therapy to whole breast with or without boost\(^t\) to tumor bed (category 1). Strongly consider radiation therapy to infracavicular region, supraclavicular area, internal mammary nodes, and any part of the axillary bed at risk. It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.

- Negative axillary nodes
  - Radiation therapy to whole breast with or without boost\(^t\) to tumor bed, and consider regional nodal radiation in patients with central/medial tumors or tumors >2 cm with other high-risk features (young age or extensive lymphovascular invasion [LVI]).

  - Consideration of accelerated partial breast irradiation (APBI) in selected low-risk patients.\(^r,^s\)
  - It is common for radiation therapy to follow chemotherapy when chemotherapy is indicated.\(^t\)
Is breast cancer easier to treat when found early?

<table>
<thead>
<tr>
<th>T2</th>
<th>Tumor &gt;20 mm but ≤50 mm in greatest dimension</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>Tumor &gt;50 mm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules).</td>
</tr>
</tbody>
</table>

*Note: Invasion of the dermis alone does not qualify as T4*

<table>
<thead>
<tr>
<th>T4a</th>
<th>Extension to the chest wall, not including only pectoralis muscle adherence/invasion</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4b</td>
<td>Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d’orange) of the skin, which do not meet the criteria for inflammatory carcinoma</td>
</tr>
<tr>
<td>T4c</td>
<td>Both T4a and T4b</td>
</tr>
<tr>
<td>T4d</td>
<td>Inflammatory carcinoma</td>
</tr>
</tbody>
</table>

**Table 1**

American Joint Committee on Cancer (AJCC)
TNM Staging System For Breast Cancer

**Primary Tumor (T)** The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.

TX  Primary tumor cannot be assessed
T0  No evidence of primary tumor
Tis Carcinoma in situ
Tis (DCIS) Ductal carcinoma in situ
Tis (LCIS) Lobular carcinoma in situ
Tis (Paget’s) Paget’s disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget’s disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted
T1  Tumor ≤20 mm or less in greatest dimension
T1mi Tumor ≤1 mm in greatest dimension
T1a Tumor >1 mm but ≤5 mm in greatest dimension
T1b Tumor >5 mm but ≤10 mm in greatest dimension
T1c Tumor >10 mm but ≤20 mm in greatest dimension
<table>
<thead>
<tr>
<th>pN1</th>
<th>Micrometastases; or metastases in 1–3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected***</th>
</tr>
</thead>
<tbody>
<tr>
<td>pN1mi</td>
<td>Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN1a</td>
<td>Metastases in 1–3 axillary lymph nodes, at least one metastasis greater than 2.0 mm</td>
</tr>
<tr>
<td>pN1b</td>
<td>Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***</td>
</tr>
<tr>
<td>pN1c</td>
<td>Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastases in 4–9 axillary lymph nodes; or in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases</td>
</tr>
<tr>
<td>pN2a</td>
<td>Metastases in 4–9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)</td>
</tr>
<tr>
<td>pN2b</td>
<td>Metastases in clinically detected**** internal mammary lymph nodes in the absence of axillary lymph node metastases</td>
</tr>
<tr>
<td>pN3</td>
<td>Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected***; or in ipsilateral supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

**pN3a** | Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes |
**pN3b** | Metastases in clinically detected**** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected*** |
**pN3c** | Metastasis in ipsilateral supraclavicular lymph nodes |

*** “Not clinically detected” is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.

**** “Clinically detected” is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle aspiration biopsy with cytologic examination.

**Distant Metastasis (M)**

**M0** | No clinical or radiographic evidence of distant metastases

**cM0(I+)** | No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases

**M1** | Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

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**Kettering Cancer Care**

**Kettering Health Network**
**Table 1 (continued)**

<table>
<thead>
<tr>
<th>ANATOMIC STAGE/PROGNOSTIC GROUPS</th>
<th>Stage 0</th>
<th>Stage IA</th>
<th>Stage IB</th>
<th>Stage IIA</th>
<th>Stage IIB</th>
<th>Stage IIIB</th>
<th>Stage IIIC</th>
<th>Stage IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>Tis</td>
<td>N0</td>
<td>M0</td>
<td>T0</td>
<td>N2</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>T1*</td>
<td>N0</td>
<td>M0</td>
<td>T1*</td>
<td>N2</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1*</td>
<td>T1*</td>
<td>N1mi</td>
<td>M0</td>
<td>N1mi</td>
<td>N1</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>N1**</td>
<td>T2</td>
<td>N0</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>T4</td>
<td>N1</td>
<td>T4</td>
<td>N1</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M0</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* T1 includes T1mi
** T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.

- M0 includes M0(i+).
- The designation pM0 is not valid: any M0 should be clinical.
- If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
- Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
- Postneoadjuvant therapy is designated with “yc” or “yp” prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

**HISTOLOGIC GRADE (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)**

- GX: Grade cannot be assessed
- G1: Low combined histologic grade (favorable)
- G2: Intermediate combined histologic grade (moderately favorable)
- G3: High combined histologic grade (unfavorable)

**HISTOPATHOLOGIC TYPE**
The histopathologic types are the following:

- **In situ Carcinomas**
  - NOS (not otherwise specified)
  - Papillary (predominantly micropapillary pattern)
  - Intraductal
  - Tubular
  - Paget's disease and intraductal
  - Lobular

- **Invasive Carcinomas**
  - NOS
  - Paget's disease and infiltrating
  - Undifferentiated
  - Ductal
  - Squamous cell
  - Inflammatory
  - Medullary, NOS
  - Adenoid cystic
  - Medullary with lymphoid stroma
  - Secretory
  - Cribriform

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Breast Cancer

• Screening Guideline first introduced in 1976
• Dissemination of screening at a population level has had an unprecedented impact on breast cancer detection
• Since the mid 1980s, as breast cancer screening has gained traction, breast cancer related death has dropped > 30% in the USA.
• Guidelines are basis for quality metrics, pay-for-performance, and other healthcare delivery policies
• Controversies remain regarding relative benefit and harm
Guidelines

Remember, these guidelines are for average risk women.

• No symptoms
• No history of breast cancer / DCIS/LCIS/atypia
• No family history of breast cancer
• No suggestion of a hereditary syndrome
• No history of childhood malignancy / previous radiation
<table>
<thead>
<tr>
<th>Before 1980</th>
<th>Today</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast self-exam (BSE)</td>
<td><strong>Pre 1980</strong></td>
</tr>
<tr>
<td>Start during high school years</td>
<td><strong>Monthly</strong></td>
</tr>
<tr>
<td>Clinical breast exam (CBE)</td>
<td>20 and over</td>
</tr>
<tr>
<td><strong>&quot;Periodically&quot;</strong></td>
<td><strong>Women, Age 50-74 Years</strong></td>
</tr>
<tr>
<td>Mammogram (starting in 1976)</td>
<td>35 - 39</td>
</tr>
<tr>
<td>Only if personal history of breast cancer</td>
<td><strong>Women, Before the Age of 50 Years</strong></td>
</tr>
<tr>
<td>40 - 49</td>
<td>May have mammogram if they or their mother or sisters had breast cancer</td>
</tr>
<tr>
<td></td>
<td><strong>Women, 75 Years and Older</strong></td>
</tr>
<tr>
<td>50 and over</td>
<td>May have mammograms yearly</td>
</tr>
<tr>
<td></td>
<td><strong>All Women</strong></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Women, 40 Years and Older</strong></td>
</tr>
</tbody>
</table>

**KETTERING Cancer Care**
Self Breast Exam

Very little research has been done

• Huge numbers of patients needed – funding issue
• Crossover issue
• Long time interval may be needed to detect mortality difference
Self Breast Exam – Shanghai JNCI

- > 130,000 patients taught BSE with medically supervised refresher every 6 months vs 130,000 patients not taught

- No overall survival or mortality benefit

- # of patients **diagnosed** with breast cancer ~3% (in both groups) was detected by **self exam – crossover**

- slight (2%) increase in mastectomy rate in pts not taught BSE

- Ratio of biopsy to cancer diagnosis 1:3 for control and 1:4 for BSE (difference highest in first 6 months of trial, down with time)

Clinical Breast Exam - CNBSS2 JNCI

- Canadian trial randomizing CBE ± mammography (40k patients)
- Trial was planned with a fixed sample to evaluate whether CBE led to a 40% reduction in breast cancer mortality!
- The trial was designed to test if mammography added benefit to breast exam
- This is behind the USPSTF “insufficient evidence” statement

Mammography
# Mammography Guidelines

<table>
<thead>
<tr>
<th>Age</th>
<th>USPSTF</th>
<th>ACS</th>
<th>ACOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-44</td>
<td>Personal Decision</td>
<td>Personal Decision</td>
<td>Yearly</td>
</tr>
<tr>
<td>45-49</td>
<td>Personal Decision</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
<tr>
<td>50-55</td>
<td>Biennial</td>
<td>Yearly</td>
<td>Yearly</td>
</tr>
<tr>
<td>55-74</td>
<td>Biennial</td>
<td>Biennial</td>
<td>Yearly</td>
</tr>
<tr>
<td>&gt;75</td>
<td></td>
<td></td>
<td>Yearly</td>
</tr>
</tbody>
</table>
Areas of disagreement

• Screening for women 40-49
• Time interval for screening mammography
• Screening >75
<table>
<thead>
<tr>
<th>Table 12. Age-Specific Screening Outcomes per Screening Round</th>
<th>Age, yr</th>
<th>40-49</th>
<th>50-59</th>
<th>60-69</th>
<th>70-79</th>
<th>80-89</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women screened, n</td>
<td></td>
<td>113,770</td>
<td>127,958</td>
<td>94,507</td>
<td>50,204</td>
<td>18,752</td>
</tr>
<tr>
<td>Invasive breast cancer cases, n</td>
<td></td>
<td>349</td>
<td>574</td>
<td>651</td>
<td>427</td>
<td>154</td>
</tr>
<tr>
<td>DCIS cases, n</td>
<td></td>
<td>191</td>
<td>246</td>
<td>208</td>
<td>120</td>
<td>43</td>
</tr>
<tr>
<td><strong>Outcomes, n per 1,000 women screened</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>False-positive mammography result</td>
<td></td>
<td>121.2</td>
<td>93.2</td>
<td>80.8</td>
<td>69.6</td>
<td>65.2</td>
</tr>
<tr>
<td>False-negative mammography result</td>
<td></td>
<td>1.0</td>
<td>1.1</td>
<td>1.2</td>
<td>1.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Additional imaging recommended†</td>
<td></td>
<td>124.9</td>
<td>98.5</td>
<td>88.7</td>
<td>79.0</td>
<td>74.5</td>
</tr>
<tr>
<td>Biopsy recommended†</td>
<td></td>
<td>16.4</td>
<td>15.9</td>
<td>16.5</td>
<td>17.5</td>
<td>15.6</td>
</tr>
<tr>
<td>Screen-detected invasive cancer</td>
<td></td>
<td>2.2</td>
<td>3.5</td>
<td>5.8</td>
<td>7.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Screen-detected DCIS</td>
<td></td>
<td>1.6</td>
<td>1.8</td>
<td>2.1</td>
<td>2.3</td>
<td>2.1</td>
</tr>
<tr>
<td><strong>Number Needed to Screen, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women undergoing mammography to diagnose 1 case of invasive breast cancer</td>
<td></td>
<td>464</td>
<td>285</td>
<td>172</td>
<td>139</td>
<td>141</td>
</tr>
<tr>
<td>Women recommended for additional imaging to diagnose 1 case of invasive breast cancer</td>
<td></td>
<td>58</td>
<td>28</td>
<td>15</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Women recommended for biopsy to diagnose 1 case of invasive breast cancer</td>
<td></td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>
### Pooled Relative Risk for Breast Cancer Mortality from Mammography

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Trials Included, $n^*$</th>
<th>RR for Breast Cancer Mortality (95% Crl)</th>
<th>NNI to Prevent 1 Breast Cancer Death (95% Crl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-49</td>
<td>8</td>
<td>0.85 (0.75-0.96)</td>
<td>1,904 (929-6,378)</td>
</tr>
<tr>
<td>50-59</td>
<td>6</td>
<td>0.86 (0.75-0.99)</td>
<td>1,339 (322-7,455)</td>
</tr>
<tr>
<td>60-69</td>
<td>2</td>
<td>0.68 (0.54-0.87)</td>
<td>377 (230-1,050)</td>
</tr>
<tr>
<td>70-74</td>
<td>1</td>
<td>1.12 (0.73-1.72)</td>
<td>Not available</td>
</tr>
</tbody>
</table>
NNS to diagnose 1 Breast cancer

<table>
<thead>
<tr>
<th>Source</th>
<th>No. needed to screen</th>
<th>Follow-up period (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK review (2012)</td>
<td>180*</td>
<td>25</td>
</tr>
<tr>
<td>USPSTF, depending on age (2009)</td>
<td>377-1904†</td>
<td>~ 15</td>
</tr>
<tr>
<td>EUROSCREEN (2012)</td>
<td>111*</td>
<td>30</td>
</tr>
</tbody>
</table>
Mammography

USPSTF may be overestimating risks of mammography relative to benefits in comparison to our European colleagues
Mammography – what are the risks?

• Risk of False Positive
• Overtreatment?
• Radiation Exposure
Risk of False Positive - Recall

• False Positive probability: ~15% at first mammogram, ~10% subsequently

• False Positive leading to biopsy recommendation: 2.5% first mammogram, ~1% subsequently (cumulative ~ 7% @ 10 yrs)

• Availability of comparison mammograms halved the odds of a false-positive recall

• A non–statistically significant increase in the proportion of late-stage cancers was observed with biennial compared with annual screening

Risk of False Positive - Recall

Cumulative incidence of recall

Risk of False Positive - Recall

A significant increase in the proportion of late-stage cancers was observed with biennial compared with annual screening.

Risk of False Positive - Psychosocial

- Survey of > 1000 patients who participated in a screening trial
- Increased short-term anxiety
- No change in long-term anxiety
- No measurable health utility decrement.
- False-positive mammograms increased women’s intention to undergo future cancer screening

Risk of Overdiagnosis

Source: Puliti, et al. JMS 2012;19(1)
Risk of Radiation exposure

Mammography exposes people to 0.4 mSv of additional radiation above background

- A flight from Los Angeles to New York is 0.04 mSv
- Average annual dose from food is 0.3 mSv
- Average yearly background dose is 3.1 mSv
## Risk of Radiation exposure

<table>
<thead>
<tr>
<th>Adult X-ray Exam</th>
<th>Average Effective Dose (mSv)</th>
<th>Lifetime Risk of Cancer Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral Mammography*</td>
<td>0.48</td>
<td>age 70: 1 in 500,000*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>age 60: 1 in 250,000*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>age 50: 1 in 125,000*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>age 40: 1 in 70,000*</td>
</tr>
</tbody>
</table>
Shared Decision Making
Breast Screening Decisions
A mammogram decision aid for women ages 40-49
Your risk in the next 5 years

Based on your responses, your chance of developing breast cancer in the next 5 years is 0.9%. That means that out of 1000 women like you, 9 of them will develop breast cancer in the next 5 years.

Of 1,000 women like you:

In the next 5 years, 991 will not get breast cancer

In the next 5 years, 9 will get breast cancer

Other things to know

There are other factors such as breast feeding, alcohol intake, body weight, and physical activity that may affect your breast cancer risk. Just how much they affect that risk is not certain. To learn more about strategies for reducing your breast cancer risk, click here.

Now that you know your breast cancer risk, let's talk about mammograms.
You are at low to average risk of developing breast cancer.

Your chance of developing breast cancer in the next 5 years is about 0.9%. This means that out of 1,000 women like you, 9 of them will develop breast cancer in the next 5 years and 991 will not.

Of 1000 women like you at low to average risk who have screening mammograms, over their lifetime:

<table>
<thead>
<tr>
<th>Number of Deaths Due to</th>
<th>Breast Cancer</th>
<th>Other causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammograms EVERY YEAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting at age 40</td>
<td>22</td>
<td>978</td>
</tr>
<tr>
<td>Starting at age 50</td>
<td>23</td>
<td>977</td>
</tr>
<tr>
<td>Mammograms EVERY OTHER YEAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starting at age 40</td>
<td>24</td>
<td>976</td>
</tr>
<tr>
<td>Starting at age 50</td>
<td>25</td>
<td>975</td>
</tr>
</tbody>
</table>

But your decision about having a screening mammogram is not just about the numbers. In the next section, we'll explore your personal values and concerns about breast cancer and screening mammograms.
Gaps in the evidence

Evidence Gaps in Population-Based Personalized Breast Cancer Screening

- Benefits and harms of screening in women aged ≥75 y.
- Optimal approaches for risk assessment, risk communication, and shared decision-making.
- Performance of breast MRI for subgroups of women, over time, and by indication.
- Appropriate performance measures to optimize the screening process.
- Comparative assessment of tomosynthesis.
- Understanding risk of DCIS progression to invasive cancer.
- Methods for measuring overdiagnosis.
- Process measures validated for efficient, high-quality screening.
- Refined breast cancer risk models including factors such as breast density, genetic markers, and prior imaging results.
Conclusions - Breast

- Breast cancer screening is a highly charged topic
- There is very little evidence regarding self exam and clinical breast exam – 3% of patients are diagnosed by self exam regardless of if they are taught or not
- Mammography decreases breast cancer mortality
- The risks of mammography decline with age and with ability to compare to previous mammograms
- The risk /benefit ratio for mammography in women 40-50 is slightly less favorable – this must be weighed against the aggressive nature of breast cancers in young patients on an individual basis
Prostate Cancer
Why screen for prostate cancer?

Prostate cancer is easier to treat when found early.

- Surgery – Need to LND, need for adjuvant RT/ADT
- Systemic therapy: need for ADT and/or chemotherapy
- Radiotherapy: prostate alone vs prostate + pelvic nodes, one time radiation implant vs 40 external treatments.

Source: NCCN guidelines
Is prostate cancer easier to treat when found early?

RISK GROUP

EXPECTED PATIENT SURVIVAL

INITIAL THERAPY

Active surveillance

- PSA no more often than every 6 mo unless clinically indicated
- DRE no more often than every 12 mo unless clinically indicated
- Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
- Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative

ADJUVANT THERAPY

≥20 y

EBRT or brachytherapy

See Monitoring (PROS-7)

Adverse feature(s) and no lymph node metastases:

- EBRT
- Observation

<10 y

Observation

10–20 y

Radical prostatectomy (RP)

± pelvic lymph node dissection (PLND) if predicted probability of lymph node metastasis ≥2%

Active surveillance

- PSA no more often than every 6 mo unless clinically indicated
- DRE no more often than every 12 mo unless clinically indicated
- Repeat prostate biopsy no more often than every 12 mo unless clinically indicated
- Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative

Very low:

- T1c
- Gleason score ≤ 6/Gleason grade group 1
- PSA < 10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core
- PSA density < 0.15 ng/mL/g
Is prostate cancer easier to treat when found early?

**Risk Group**
- T3a or Gleason score 8/ Gleason grade group 4 or Gleason score 9–10/ Gleason grade group 5 or PSA >20 ng/mL

**Initial Therapy**
- **High:**
  - EBRT\textsuperscript{i} + ADT\textsuperscript{m} (2–3 y; category 1)\textsuperscript{\textregistered}
  - or
  - EBRT\textsuperscript{i} + brachytherapy ± ADT\textsuperscript{m} (2–3 y)
  - or
  - RP\textsuperscript{j} + PLND

**Adjuvant Therapy**
- See Monitoring (PROS-7)
  - Adverse feature(s) and no lymph node metastases: K
    - EBRT\textsuperscript{i}
    - or
    - Observation\textsuperscript{l}
  - No adverse features or lymph node metastases
    - Lymph node metastasis: ADT\textsuperscript{m} (category 1) ± EBRT\textsuperscript{i}
      - (category 2B)
      - or
      - Observation\textsuperscript{l}
    - PSA failure
      - See Radical Prostatectomy Biochemical Failure (PROS-8)
      - or
      - See Radiation Therapy Recurrence (PROS-9)
  - Undetectable PSA after RP or PSA nadir after RT
    - See Monitoring (PROS-7)
Prostate Cancer

- Prostate cancer is a clinically heterogenous disease, affecting > 200,000 men per year, > 30,000 of whom die from disease.
- 40% low risk, ~ 40% intermediate risk, ~ 20% high risk.
- Associated with high fat diet, # sexual partners, tobacco use, insulin resistance.
- Risk for prostate cancer significantly higher in AA vs Caucasian M.
- In the 1970s-1980s, prostate cancer mortality rates were approximately 30/100k and steadily increasing.
Prostate Cancer

- PSA screening became available in the early 1990s and widespread screening was available by the late 1990s.
- Based on SEER analysis, since the early 1990s, prostate cancer related mortality has decreased 40%.
- The incidence of metastatic disease at presentation has declined by approximately three-fourths in the US since the advent of PSA screening.
Prostate Screening: Guidelines

- Concern for overdiagnosis of clinically irrelevant cancers
- At the same time, the risk factors for development of the disease are increasing
- The long term effect of reduced screening on a population basis is not known
Prostate Screening: Guidelines

Modeling studies show:

• PSA screening yields survival benefits that have contributed, to some extent, to the dramatic and sustained drop in prostate cancer death rates in this country.

• Second, PSA screening advances prostate cancer diagnosis by five to six years on average.

• Approximately one in four screen-detected cases reflects overdiagnosis.
Prostate Screening: Guidelines

What risk groups do the guidelines not address?

• Family History
  • consider number of relatives and age at diagnosis
  • Family history of breast/ovarian (potential BRCA carrier) or colorectal, endometrial, gastric pancreatic (possible Lynch)
• African American ethnicity
Prostate Screening: Guidelines

• USPSTF
  • recommends against PSA screening

• AUA
  • men 40-55 at high risk should be offered screening
  • Screening men > 55 should be offered screening if life expectancy > 15 years
  • Interval of screening should be individualized based on baseline PSA
# Prostate Screening: Basis of guidelines

<table>
<thead>
<tr>
<th></th>
<th>PLCO (&quot;US&quot;)</th>
<th>ERSPC (&quot;European&quot;)</th>
<th>Goteberg (&quot;Swedish&quot;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. Men</strong></td>
<td>76,693</td>
<td>162,388</td>
<td>20,000</td>
</tr>
<tr>
<td><strong>Age Range</strong></td>
<td>55-74</td>
<td>55-69</td>
<td>50-64</td>
</tr>
<tr>
<td><strong>Screening group</strong></td>
<td>PSA q1yr x6, DRE qyr x4</td>
<td>PSA q4yr</td>
<td>invitation to PSA q2 yrs</td>
</tr>
<tr>
<td><strong>Control group</strong></td>
<td>'usual' care</td>
<td>no screening</td>
<td>no screening</td>
</tr>
<tr>
<td><strong>Med f/u (years)</strong></td>
<td>13</td>
<td>13</td>
<td>14 yrs</td>
</tr>
<tr>
<td><strong>Indication for biopsy</strong></td>
<td>PSA&gt;4 or abnormal DRE</td>
<td>PSA&gt;3</td>
<td>PSA&gt;2.5-3.4 (dep on yr)</td>
</tr>
<tr>
<td><strong>Intervention arm compliance</strong></td>
<td>85% PSA, 86% DRE</td>
<td>82% screened ≥ once Avg. 2.27 per subject</td>
<td>76% of invited had ≥1 PSA</td>
</tr>
<tr>
<td><strong>PrCa detection (scr/cont)</strong></td>
<td>11.1% vs 9.9%</td>
<td>9.6% vs 6.0%</td>
<td>12.7% vs 8.2%</td>
</tr>
<tr>
<td><strong>PrCa deaths (scr/cont)</strong></td>
<td>158 vs 145</td>
<td>299 vs 462</td>
<td>44 vs 78</td>
</tr>
<tr>
<td><strong>RR of PrCa death</strong></td>
<td>1.09 (0.87-1.36)</td>
<td>0.79 (0.69-0.91)</td>
<td>0.56 (0.39-0.82)</td>
</tr>
<tr>
<td><strong>NNI (Invite)/ NND (Diagnose)</strong></td>
<td>na</td>
<td>781/27</td>
<td>293/12</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>44% prescreened in both arms</td>
<td>Up to 52% of cont. arm screened</td>
<td>PPV 24.1%</td>
</tr>
<tr>
<td></td>
<td>Low/Int risk: 84.8% (scr) vs 68.4% (cont)</td>
<td>Younger men, less prescreening</td>
<td>lower PSA threshold</td>
</tr>
</tbody>
</table>

Andriole et al., JNCI 2012; Schroder et al., Lancet 2014; Hugosson et al., Lancet 2010
Prostate Screening: Risks of screening

Biopsy related side effects

Overtreatment
Prostate Screening: Risks of screening

Biopsy related side effects: hematuria, hematochezia, hematospermia, dysuria and retention, pain and infection.

- Hematuria 14% to 50% of the time
- Hematospermia 10% to 70% of patients
Prostate Screening: Reducing Risk

- Strategies that screen less frequently than every year, and even less frequently for men with low PSA levels, are likely to be of value in reducing costs and harms while preserving most of the potential benefit of PSA-based screening
- Risk stratification
- Novel biomarkers?
Prostate Screening: Reducing Risk

• Rotterdam Prostate Cancer Risk Calculator
  • ERSPC data-based on a population aged 55-74 yr. The analyses are based on the biopsy outcomes of 3616 men screened for the first time, 24.5% of whom had prostate cancer detected.
  • Has not specifically been validated in the US population
  • Risk < 12.5% - no biopsy recommended
  • 12.5-20% - consider biopsy based on comorbidity
  • 20% or more – biopsy recommended
Future Risk Calculator

Time = 0 (Now)

Age (years) 50
PSA (ng/ml) 5
DRE Abnormal Normal
Family history * Yes No
DRE volume class (cc) 25
Previous neg. biopsy Yes No

Calculate

Time = 4 (4 years later)

Probability of NO Prostate Cancer: 89.5%
Probability of potential LOW RISK Prostate Cancer: 5.3%
Probability of potential AGGRESSIVE Prostate Cancer\(^2\): 5.2%

Select Risk Calculator:
Your Risk Calculators (for non-medical people)

Risk Calculator 6

Predicting cancer in the future

This prototype looks at a man’s future risk over a four year period - a promising tool in reducing uncertainty, unnecessary testing, and overdiagnosis with regard to prostate cancer. This individualized multivariate model includes age, prostate-specific antigen, digital rectal examination, family history, prostate volume, and previous biopsy status.

* Has your father or brother has prostate cancer?

* Future risk implies 4 years after assessment of predictors and is based on a screening algorithm using a lateral sextant biopsy indication based on a PSA >= 3.0 ng/ml cut-off

\(^2\) A prostate cancer with a clinical stage > T2b or Gleason score >= 7 or PSA > 10.0 ng/ml

Kettering Cancer Care
Kettering Health Network
# Prostate Cancer: New Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type</th>
<th>Test Description</th>
<th>Clinical Utility</th>
<th>Cost/Insurance Coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Kscore (OPKO Laboratory, Nashville, TN, USA)</td>
<td>Blood</td>
<td>Panel of 4 kallikrein proteins: total PSA, free PSA, intact (single-chain PSA) and human kallikrein 2</td>
<td>Likelihood that a patient will have high-grade pathology (Gleason ≥7) on needle biopsy</td>
<td>CLIA-certified. Not covered by insurance. $395</td>
</tr>
<tr>
<td>Prostate Health Index (Beckman Coulter, Brea, CA, USA)</td>
<td>Blood</td>
<td>Combines PSA, free PSA and p2PSA via a formula</td>
<td>Likelihood of finding prostate cancer on a repeat biopsy</td>
<td>FDA-cleared for use in men &gt;50 years who have a PSA of 4–10 ng/mL and a negative DRE. Covered by Medicare and most insurance. $80–100</td>
</tr>
<tr>
<td>PCA3/Progensa (Hologic, Bedford, MA, USA)</td>
<td>Urine</td>
<td>Nucleic acid amplification test measuring the concentration of PCA3 and PSA RNA in post-DRE specimens</td>
<td>Scores &lt;25 are associated with lower likelihood of positive biopsy; those ≥25 are associated with a higher likelihood of positive biopsy</td>
<td>FDA-cleared for use in men ≥50 years considering repeat biopsy after ≥1 previous negative biopsies. $385, covered by most insurance</td>
</tr>
<tr>
<td>ConfirmMDx (MDxHealth, Irvine, CA, USA)</td>
<td>Biopsy tissue</td>
<td>Quantifies DNA hypermethylation of three genes associated with prostate cancer; methylation of these genes is believed to occur even in non-malignant cells that are contiguous with cancerous tissue, leading to a field effect</td>
<td>When performed on a patient’s previous negative prostate biopsy, DNA changes can suggest the presence of cancer nearby that may have been missed, thus warranting a repeat biopsy</td>
<td>CLIA-certified. $3300, with limited Medicare coverage</td>
</tr>
</tbody>
</table>
Prostate Screening: Reducing Risk

• Prostate Health Index
  • It predicts the likelihood of finding prostate cancer on a subsequent biopsy.
  • The basis of the PHI lies in the identification of the free PSA precursor isoform [-2]proPSA, which forms 25–95% of the fPSA fraction in men with prostate cancer, compared with just 6–19% in biopsy-negative men
  • Higher PHI values were associated with a higher percentage of positive biopsies, as well as with a higher percentage of high-grade cancer (Gleason score of ≥7).
Prostate Screening: Risks of screening

Overtreatment

• Estimates of overdiagnosis vary widely
• Less than 5% to more than 75%
• Lead times of 5 to 15 years
• Overdiagnosis estimates are not portable across geographic settings because they depend not only on the screening and biopsy protocol, and compliance with biopsy referral under screening, but also on practice patterns and disease incidence in the absence of screening.
Prostate Screening: Overtreatment?

Overtreatment

• Our best estimates for the fraction of screen-detected cases overdiagnosed in the US in the 1990's is approximately one in four, but the likelihood of overdiagnosis is highly age dependent.
Prostate Screening: Observation

**Risk Group**

<table>
<thead>
<tr>
<th>Expected Patient Survival</th>
<th>Initial Therapy</th>
<th>Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥20 y[^a]</td>
<td>Active surveillance[^h]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• PSA no more often than every 6 mo unless clinically indicated</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• DRE no more often than every 12 mo unless clinically indicated</td>
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<td></td>
<td>• Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative</td>
<td></td>
</tr>
<tr>
<td></td>
<td>EBRT[^h, i] or brachytherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>See Monitoring (PROS-7)</td>
<td></td>
</tr>
<tr>
<td>Very low:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- T1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Gleason score ≤6/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gleason grade group 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PSA &lt;10 ng/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- PSA density &lt;0.15 ng/mL/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10–20 y[^a]</td>
<td>Radical prostatectomy (RP)[^j]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>± pelvic lymph node dissection (PLND) if predicted probability of lymph node metastasis ≥22%</td>
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<tr>
<td></td>
<td>Adverse feature(s) and no lymph node metastases:[^k]</td>
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</tr>
<tr>
<td></td>
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<td>See Monitoring (PROS-7)</td>
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<tr>
<td>&lt;10 y</td>
<td>Active surveillance[^h]</td>
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<tr>
<td></td>
<td>Observation[^l]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>See Initial Clinical Assessment (PROS-1)</td>
<td></td>
</tr>
</tbody>
</table>

[^a]: ≥20 y
[^h]: Active surveillance
[^i]: or brachytherapy
[^j]: Radical prostatectomy
[^k]: EBRT
[^l]: or Observation
[^m]: See Monitoring
[^n]: Progressive disease
[^o]: See Initial Clinical Assessment
[^p]: Kettering Cancer Care
[^q]: Kettering Health Network
Prostate Screening: Conclusions

• Prostate cancer mortality has significantly decreased since initiation of PSA screening

• PSA screening for African American men, or men with family history of prostate cancer / genetic syndrome, should be strongly considered

• Screening average risk men with long life expectancies is reasonable

• Predictive tools and novel biomarkers may aid in shared decision making
Thank you!

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