Screening in Oncology

*Practice and Controversy*

Ravi D. Rao
Hematology - Oncology
Outline

• What is screening?
• Issues with application of screening in Oncology
• Updates & issues regarding screening in 4 specific cancers:
  ▪ Breast cancer
  ▪ Colon cancer
  ▪ Lung cancer
  ▪ Prostate cancer
WHAT IS SCREENING

......... strategy used in a population to identify the possible presence of an as-yet-undiagnosed disease in individuals without signs or symptoms.
Screening

............ strategy used in a population to identify the possible presence of an as-yet-undiagnosed disease in individuals without signs or symptoms.

- Strategy: blood test/invasive procedure/questionnaire
- A population: specific group
- Possible presence: no test is perfect
- As-yet-undiagnosed (if symptoms present, not “screening”)
- Disease (goal is to reduce suffering)
- Individuals
- Without symptoms: i.e., early detection
Problems with screening in Oncology

Ideally, cancer screening should target common cancers, and that should lead to cures and improved overall survival, or reduced suffering or at least reduced cancer-specific death.

• Early detection may not change outcomes in many cancers
• “Overdiagnosis”
• Mis-diagnosis
• False sense of security
• Expense
• Emotionality vs logic in analyzing data
Cancer screening is controversial

- Breast cancer
- Colon cancer
- Lung cancer
- Prostate cancer
- Cervical cancer
- Thyroid cancer
- High risk screening in BRCA patients
Breast Cancer Screening

Mammograms

What to Expect During a Mammogram

1. Fill out pre-test questionnaire
2. Each breast is compressed horizontally between two plates for imaging
3. Each breast is compressed diagonally between two plates for imaging
Breast cancer screening

- Current recommendations
- Controversy: *Does mammogram screening help at all?*
- Issue of over diagnosis
- Dense breast verbiage in reports: what to do?
- BRCA positive patients
Breast cancer screening guidelines

• Current screening guidelines
  ▪ 40-49: patients’ choice – annual mammogram
  ▪ 50-74: mammogram q 2 years
  ▪ Stop at 75 (or if life expectancy is <10 years)
  ▪ Dense breasts: *may need more than a regular mammogram*

• *None of these are “A” recommendations, btw.*

• Higher risk patients: start at 40
  ▪ Family history, BRCA positive, Chest radiation

• Risk prediction tools exist that you should become familiar with…. (Gail model, eg).
Mammograms’ benefit: unclear

- **Cochrane analysis of best RCTs**: no overall benefit in breast cancer mortality
- Only 2 randomized studies showed a benefit
- Several other randomized studies: no benefit
- More cancers found in screened group (vs control)...
  - 31% increase in need for breast surgery in intervention arm
  - 24% increase in use of radiation
- And yet, no corresponding reduction in death rates.....
  
  *(so is the identification of these patients futile?)*
The final meta-analysis...benefits of mammograms are very minimal

- No decrease in all-cause mortality
- A lot of work done on many patients to achieve very minimal (or no) benefit

Nelson, et al, Annals of Internal Medicine
How a good screening test should work..

Screened

Year 1: Cancer diagnosis

Year 2: Cancer diagnosis

Year 3: Cancer diagnosis

Control

More advanced cases
More deaths
This does **NOT** happen with breast cancer and mammogram screening

Screening group always has more cancer diagnoses than unscreened group
Over-Screening: Breast Cancer
Women Aged 40-49
(average risk; screened every 2 yrs for 11 yrs)

2,100 women screened:
- 700 have false +ve result requiring further imaging
- 75 have biopsy
- 10 have part or all of a breast unnecessarily removed
- 1 escapes death from breast cancer

http://canadiantaskforce.ca/
Summary

- Increase detection with minimal drop in death rate
- Indolent and self-limited tumors identified and treated
  - Well documented cases of self regressing breast cancers
- Higher intervention rates with screening: up to 60% more
- Screening has become a political issue
Dense breasts

Dense breasts

- Ductal elements (white) > fat (black)
- Single case of a woman who blamed her missed diagnosis of breast cancer because of dense breast...led to laws about dense breast verbiage

- Definition of dense breasts – changed over time

- Next step – MRI (no), Ultrasound (maybe).

- Unclear if ultrasound screening actually will be cost effective

- What to do about this if patients ask you is...unclear

- The verbiage therefore is quite meaningless.

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Are you DENSE?

exposing the best-kept secret®

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WARNING:
The Disneyland Resort contains chemicals known to the state of California to cause cancer and birth defects or other reproductive harm.

Proposition 65,
California Health & Safety Code
BRCA positive patients: MRI + mammogram

- 18+: self-breast exams performed periodically
- 25+: clinical exams q6-12m
- 25+: MRI yearly
- 30+ : Mammography yearly
- Stagger MRI and mammograms by 6m
  - Sensitivity with mammo, MRI, combo: 32, 75, 84%
  - Specificity mammo, MRI, combo : 99, 96, 99%
- Prophylactic mastectomies are still preferred
Colon Cancer Screening

- Current guidelines
- Different modalities that are approved
- New techniques: colonography and DNA testing
- Effectiveness of colon cancer screening
Colon Cancer Screening

- 4% of all people in the US will get colon cancer dx
  - 1/3 of these will die of disease
- Current guidelines are based on the polyp → dysplasia→ cancer continuum
  - Takes 7-10 years
  - 90% of all cancers arise 50+
- Only 2/3rds of patients are screened (goal is 80%)
- Baseline risk assessment first: Family history and symptoms
- Various modalities tested/approved
- Less controversial, less harm/cost
FOBT (and now FIT)

- Fecal blood detection (guaiac, immunohistochemistry - FIT)
  - Guaiac: Dietary restrictions, 3 consecutive samples
    - 2 samples each time
    - Temperature, time to analysis (return sample within 1 day)
  - Fecal immunohistochemistry (FIT): more sensitive
  - Do not use stool obtained during DRE [have patient turn in sample]
  - Positive predictive value for cancer – 7%, [cancer + polyps – 27%]
- Less sensitive for polyps...this means that this test has to be done continuously year after year..
- 32% reduction in death rates vs unscreened
- Women have less benefit than men..(25% vs 41% reduction) in risk of death
Other modalities & recommendations..

- Double contrast barium enema q 5 years (1+ cm polyps)
- Sigmoidoscopy: every 5 years
  - Only the last 60 cm is evaluated (captures half of tumors)
  - Women and older patients have more proximal tumors (rightward migration)
- Colonoscopy: gold standard every 10 years
- Capsule endoscopy: every 5 years
CT enterography or virtual colonoscopy, q5 years

- Stool tagged with an oral contrast agent; spiral CT scan done to capture images
- Do not do if: high risk patient, symptoms+
  - Recent colonic surgery
  - Inflammation (colitis, diverticulitis)
- Polyp detection sensitivity is 66% (less if <8mm polyp)
- May be useful if high index of suspicion and if patient had an incomplete colonoscopy
  - If large distal cancer present, and suspicion of proximal synchronous cancer…this may be useful
- Other considerations: will need a preparation diet, discomfort due to insufflation of colon, radiation exposure, incidental findings
Colonoscopy (gold standard) q 10 years

- No randomized study of colonoscopy vs observation has ever been done
- Cost, preparation is not popular
- All estimates of efficacy are based on comparisons with historical controls or with use of other modalities
  - 35-80% reduction in cancer incidence
  - 50-70% reduction in death from colon cancer in population
- Benefit is less (maybe absent) in those with proximal cancers
- Cancers diagnosed via screening are smaller, earlier stage, and had better outcomes even after controlling for stage
Colon cancer: Stool DNA testing
Cologard

- Multi-gene assay: 4 genes tested
  - Tumor cells are sloughed off into stool.
- Entire stool sample collected and shipped off for analysis
- Done every 3 years
- Sensitivity: 92% for cancer; 42% for polyps
  - Better for larger tumors, more distal tumors
- A good alternative to doing colonoscopy directly
- Take up rate of non invasive tests for colon cancer is usually double that of colonoscopy – so overall effectiveness may be higher in a population
Most methods are equally efficacious

• Approximately saves 20 lives from CRC-deaths per 1000 (baseline 25)

• Compliance with process >> the exact process chosen
  ▪ Non compliance is highest with colonoscopy
  ▪ Having options is good

• Interval cancers: 12% of all cancers in screened patients
  ▪ Disease biology (rapidly growing tumors)
  ▪ These patients do worse..
  ▪ Improper preparation
  ▪ Technique, experience of person doing procedure
Compliance is key

- No randomized study done to compare screening colonoscopy vs observation (for obvious reasons)
  - Computer models used
  - Tremendous benefit in reduction in CRC death calculated

- With proper compliance the following can be expected in terms of reduction of mortality caused by colon ca..
  - 81% with annual fecal blood IHC (FIT)
  - 82% with CT colonography every 5 years
  - 85% with SIG every 10 years with annual FIT
  - 87% with colonoscopy every 10 years
Lung cancer: new kid on the block

- Background to low dose CT screening
- Current recommendations
- Issues with screening program implementation
- Programmatic approach to lung cancer screening – help or hinderance?
CIGARETTES
TILL DEATH DOES US APART
Reasons to screen for lung cancer

- 175K new cases a year. Almost all die.
- Early stage is curable:
  - 5 YS for stage IA: 70%
  - 5 YS of IIIA or above: <5%
- Most cancers arise in high risk groups
  - Easy to identify - smokers, COPD
- 94 million – current and ex-smokers in US
- Early detection is possible
  - CT scans
  - Chest X rays
  - Other new modalities
Downsides to screening

- Pseudo-disease phenomenon – *screen diagnosed disease always has a better prognosis than disease diagnosed clinically*
- Death rate from lung cancer surgery: ~2%
- Serious complications: 20% to 44%.
- Up to 12% of people who are screened for lung cancer with CT end up getting surgery/biopsy
- Anxiety
- Cost
Low dose helical Chest CT may be the answer

- Chest X-ray screening studies were negative
  - Chest X ray threshold for diagnosis is higher – so most patients are diagnosed too late
- “Regular” Chest CT: radiation dose too high
- CT chest for nodule detection could be done more quickly
  - Single-breath hold Helical CT
  - 80% reduction in dose of RT
  - Technique adequate to identify lung cancer related nodules
- Randomized clinical trials showed a benefit to using low dose CT for screening
High Risk groups

- Current Smokers with >30 pack years
  - Even if quit <15 years ago
- Exposure to Asbestos, beryllium
- Family history of lung cancer
- Age (>50)
- COPD
Lung cancer screening: things to know

• High risk group: approximately 4% incidence of cancer at initial screen
• 25% of all scans will show an abnormality
  ▪ 90% will undergo additional imaging
• 10-15% of these will undergo a procedure for diagnosis
• Half of these will have a moderate + severe complication
• 1% will die within 60 days of procedure
• One in 6 of those with suspicious findings will end up actually being cancer
• Number needed to screen to save one life: 320
Screening recommendations

- Annual low-dose CT scan screening for high-risk individuals
- Need a consultation before the scan (shared decision making)
  - This makes it different from all other screening modalities
- Post scan multidisciplinary approach to manage findings
- Pathways to deal with
  - Lesions definitive for cancer
  - Lesions that are suspicious
  - Small nodules/GGO (ground glass opacities)
  - Incidental findings
  - Smoking cessation
- Lung cancer screening has to be a ‘program’... not an isolated process
Prostate cancer & screening

- Common, not very fatal
- PSA is not a good test
- Therapy is expensive and toxic
- Current recommendations
- Future
Prostate cancer and PSA screening

- 12% of all men will develop prostate cancer
  - 2.4% of all men will die of this
- 161,000 new cases in 2017
- 45% drop in death rates after initiation of screening
- PSA: specificity is 6% and 95% sensitive
- Many negative biopsies as a result of this problem
- Painful and expensive way to find out that you do not have cancer
Current guidelines

• Start at
  ▪ Average-risk men – 50
  ▪ BRCA carriers – 40 years
  ▪ African American and those with a family history of early onset Prostate cancer: 40 years

• Do PSA only. No need to do concurrent DRE

• Every 2 years

• Stop at 70 (or 75) or if life expectancy is <10 years

• Other variables: can do q 4 years. Also consider stopping if PSA is <1 at age 60, etc..
PSA-alone for screening is problematic

• PSA screening works
  ▪ Increased diagnoses in early stages (68% in 1990 to 91% in 2009). Death rate dropped (2/3rds due to screening)
  ▪ Presentation in stage IV dropped from 21% to 4%
  ▪ Early diagnosis leads to more cures

• So, what is the controversy about?
  ▪ 20 million PSA tests
  ▪ 5 million elevated values
  ▪ Almost a million biopsies
  ▪ 0.18 million new prostate ca diagnoses
  ▪ Up to 40% of them are candidates for active surveillance
Prostate cancer incidence has dropped after adoption of PSA testing...
PSA not a good screening tool

- PSA screening leads to too many biopsies, does not tell us high vs low risk disease
- PSA modifications have been tried with little benefit:
  - PSA density
  - PSA velocity
  - Free vs total PSA ratio
  - Age adjusted PSA
  - Race adjusted PSA
  - “Genetically adjusted PSA”
    - Some people normally make more PSA than others....
    - Interpret PSA based on genetic markers (and adjust numbers up or down)
Beyond PSA testing.... These are expensive and not well validated

- Prostate Health Index (phi)
- 4K score
- PCA3 (urine protein) and TMPRSS2:ERG (urine RNA)
- SELECT MDx
PHI score

- Approved in 2012 by the FDA
- Uses a formula incorporating total PSA, free PSA and p2PSA isoform
- Special algorithm used to calculate PHI = p2PSA/fPSA x √tPSA
- Valid when PSA is between 4-10
- Can avoid 30% of biopsies; makes PSA more cost effective
- Higher PHI score: more chance of getting a positive biopsy and also higher Gleason Score cancer

<table>
<thead>
<tr>
<th>PHI Score</th>
<th>Probability of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-26.9</td>
<td>9.8%</td>
</tr>
<tr>
<td>27.0-35.9</td>
<td>16.8%</td>
</tr>
<tr>
<td>36.0-54.9</td>
<td>33.3%</td>
</tr>
<tr>
<td>&gt; or =55.0</td>
<td>50.1%</td>
</tr>
</tbody>
</table>
Thank you.

QUESTIONS ?
4K score

- Blood test incorporates 4 biomarkers
  - human kallikrein2 and total, free and intact PSA, plus clinical variables (age, DRE findings, h/o prior negative biopsy)
- Predicts probability of high grade disease
- Algorithm incorporates physical exam findings (nodule), and prior biopsy findings
- Reduces number of biopsies by **30-58%**
- Delayed diagnosis in only 1.3-4.7% of Gleason≥7 cancers
Urine tests..

- **Prostate cancer antigen 3**: Protein expressed only in prostate cancer
  - Found in urine; after a prostate massage.
  - Protein found in urine which ends up carrying prostate cells
  - PCA3 predicts low-volume disease and pathologically insignificant Pca
  - Limited in the prediction of aggressive cancer.

- **TMPRSS2:ERG**
  - A protein that is found only in prostate cancer cells
  - Found in urine.
  - Positive test predicts prostate cancer
    - 8.3% of the BPH, 15.6% of the NP, and 50% of the PCa samples

- **SELECT MDx**
  - mRNA levels of the DLX1 and HOXC6 in urine
  - Happens to have the best discriminatory capacity for high risk disease
We will see more Prostate cancer cases starting soon...

• Screening rates are already down by >20%. *Number of newly diagnosed early stage cancers is now dropping*!

• However, in a few more years....prostate cancer diagnosis will start becoming more common
  ▪ Increase in deaths to become apparent in 2020

• Older men have a higher rate of metastatic disease at dx
  ▪ >75 year population is growing fast

• Trend of increased newly diagnosed stage IV patients has already started
Only 2 positive studies have problems: New York, Two-County study in Norway

- Problems in these 2 positive studies...
  - Randomization not done appropriately
  - Cause of death – not ascertained
  - Some women enrolled in their 30s in error (not target population)
  - Mammograms not standardized

- Death rate may have been increased by use of Radiation Tx
- Data collection was dodgy
- Norwegian study: One county had a case rate that was vastly different than the other.
<table>
<thead>
<tr>
<th>Author, Year (Reference)</th>
<th>Trial Name</th>
<th>Mean Follow-up, y</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Women aged 39–49 y</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nyström et al., 2002 (30)*</td>
<td>MMST II</td>
<td>11.2</td>
<td>0.64 (0.39–1.06)</td>
</tr>
<tr>
<td>Tabár et al., 1995 (26)</td>
<td>Kopparberg</td>
<td>12.5</td>
<td>0.73 (0.37–1.41)</td>
</tr>
<tr>
<td>Tabár et al., 1995 (26)</td>
<td>Östergötland</td>
<td>12.5</td>
<td>1.02 (0.52–1.99)</td>
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<tr>
<td>Moss et al., 2015 (27)</td>
<td>Age</td>
<td>17.5</td>
<td>0.93 (0.80–1.09)</td>
</tr>
<tr>
<td>Bjurstam et al., 2003 (25)</td>
<td>Gothenburg</td>
<td>13.8</td>
<td>0.69 (0.45–1.05)</td>
</tr>
<tr>
<td>Habbema et al., 1986 (29)</td>
<td>HIP</td>
<td>14.0</td>
<td>0.75 (0.53–1.05)</td>
</tr>
<tr>
<td>Nyström et al., 2002 (30)*</td>
<td>Stockholm</td>
<td>14.3</td>
<td>1.52 (0.80–2.88)</td>
</tr>
<tr>
<td>Nyström et al., 2002 (30)*</td>
<td>MMST I</td>
<td>18.2</td>
<td>0.74 (0.42–1.29)</td>
</tr>
<tr>
<td>Miller et al., 2014 (15)</td>
<td>CNBSS-1</td>
<td>21.9</td>
<td>1.04 (0.87–1.24)</td>
</tr>
<tr>
<td><strong>Overall (I² = 25%; P = 0.230)</strong></td>
<td></td>
<td></td>
<td>0.92 (0.75–1.02)</td>
</tr>
</tbody>
</table>

| **Women aged 50–59 y**   |            |                   |                        |
| Tabár et al., 1995 (26)  | Östergötland | 12.5              | 0.85 (0.52–1.38)       |
| Tabár et al., 1995 (26)  | Kopparberg | 12.5              | 0.48 (0.29–0.77)       |
| Nyström et al., 2002 (30)* | Stockholm | 13.7              | 0.56 (0.32–0.97)       |
| Bjurstam et al., 2003 (25)| Gothenburg | 13.8              | 0.83 (0.60–1.15)       |
| Habbema et al., 1986 (29)| HIP        | 14.0              | 0.83 (0.61–1.13)       |
| Nyström et al., 2002 (30)* | MMST I    | 18.1              | 0.98 (0.75–1.29)       |
| Miller et al., 2014 (15) | CNBSS-2    | 21.9              | 0.94 (0.78–1.13)       |
| **Overall (I² = 38.0%; P = 0.139)** |  |                   | 0.86 (0.68–0.97)       |

| **Women aged 60–69 y**   |            |                   |                        |
| Tabár et al., 1995 (26)  | Kopparberg | 12.5              | 0.58 (0.35–0.96)       |
| Tabár et al., 1995 (26)  | Östergötland | 12.5            | 0.62 (0.43–0.91)       |
| Nyström et al., 2002 (30)* | Stockholm | 13.1              | 0.94 (0.46–2.02)       |
| Habbema et al., 1986 (29)| HIP        | 14.0              | 0.85 (0.48–1.47)       |
| Nyström et al., 2002 (30)* | MMST I    | 15.5              | 0.64 (0.45–0.92)       |
| **Overall (I² = 0.0%; P = 0.739)** |  |                   | 0.67 (0.54–0.83)       |

| **Women aged 70–74 y**   |            |                   |                        |
| Tabár et al., 1995 (26)  | Östergötland | 12.5              | 0.82 (0.43–1.58)       |
| Tabár et al., 1995 (26)  | Kopparberg | 12.5              | 0.76 (0.42–1.36)       |
| Nyström et al., 2002 (30)* | MMST I    | 13.6              | 0.98 (0.15–6.60)       |
| **Overall (I² = 0.0%; P = 0.962)** |  |                   | 0.80 (0.51–1.28)       |