Global Deaths (millions per annum)

WHO (2003)
CANCER – WORLDWIDE BURDEN (2005)

11 million New Cases

7 million Deaths

25 million Living with Cancer
CANCER – WORLDWIDE BURDEN (2030)

27 million New Cases

17 million Deaths

75 million Living with Cancer
Cancer
The Global Challenge

• Application of new knowledge from
  – Basic research
  – Clinical research
  – Cancer control research

• This is a challenge for all cancer clinicians be they physicians or behavioral scientists
How can we provide adequate high quality care (to include preventive care) to a population that has so often not received it?
Cancer Screening

• A series of tests with some uncertainties:
  – some known proven harms
  – some possible benefits
  – some proven benefits
• Finding disease is not a measure of success in screening

Increased survival is not a legitimate measure of success outside of a randomized clinical trial

Reduction of mortality is the proof of effective screening
Lead Time Bias

Diagnosis due to symptoms

Diagnosis due to screening

Death due to Cancer

Lead Time
Length Bias

Cancer diagnosed in between scheduled screens is more aggressive than those diagnosed at scheduled screenings. Those diagnosed at initial screening are least aggressive of all.
Over-diagnosis

A form of length bias

Cancer Develops

Diagnosed
Treated
Cured

Cancer Develops

Never Diagnosed
Never Treated

Death from other than cancer
Enrollee Randomization

Group A

compare over time

Group B
Cancer Screening

• Well designed clinical studies have demonstrated the utility of:
  – Mammography and CBE for Breast Cancer
  – Stool Blood Testing, Sigmoidoscopy and Colonoscopy for Colorectal Cancer
  – Pap and HPV testing for Cervical Cancer
ACS Breast Cancer Screening Guidelines

- Clinical breast exam (at time of a checkup):
  - 20-39: Every 3 years
  - 40+: Annually
- **Mammography**: Annually beginning at age 40
- **No specific age to stop screening**—screening should continue as long as women are in good health
- **Monthly breast self exam** (de-emphasized in favor of awareness)
- We do say women should be told of the **limitations** of mammography
Comparing the major differences between the ACS and USPSTF breast cancer screening guidelines

- ACS recommends annual mammography screening beginning at age 40

- The USPSTF recommends against routine screening in women ages 40-49

- The USPSTF recommends biennial screening between ages 50-74
What the Taskforce Said!

- There is evidence that screening women in their forties decreases relative risk of death by 15%

- **Routine** screening of women in their forties is not recommended
What the Taskforce Said!

- The number needed to screen to save one life in a decade:
  - Age 40 to 49, 1900
  - Age 50 to 59, 1340
  - Age 60 to 69, 340
What the Public Heard!

- There is evidence that screening women in their forties decreases relative risk of death by 15%.

- Screening of women in their forties is **not recommended**.
What the Taskforce was trying to say!
A decade of screening 1900 women

- 1330 call backs for reassessment
- 665 breast biopsies
- 8 cancers diagnosed
- 1 life saved
- Some unquantified overdiagnosis
What the Taskforce was trying to say!
A decade of screening 1900 women

• Given these numbers a 40 year old woman screened annually has:
  
  – a 0.0042% chance of diagnosis

  – a 0.00005% chance of her life being saved

• Mammography screening is so lousy that it may scare young women away from it. Decreasing usage in the 50’s and 60’s when it is a better more useful test.
## Breast Cancer Screening in the U.S. The Potential

<table>
<thead>
<tr>
<th>Age</th>
<th>Number in Population</th>
<th>USPSTF Estimate of Number Needed to Screen</th>
<th>Avertable Deaths</th>
<th>Lives Lost due to Non-Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>40's</td>
<td>22,327,592</td>
<td>1,900</td>
<td>11,751</td>
<td>4,113</td>
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<tr>
<td>50's</td>
<td>20,542,363</td>
<td>1,340</td>
<td>15,330</td>
<td>5,366</td>
</tr>
<tr>
<td>60's</td>
<td>13,909,277</td>
<td>340</td>
<td>40,910</td>
<td>14,318</td>
</tr>
</tbody>
</table>
A Decade of Screening
The Potentials and the Sacrifices

• 100% screening and 100% good treatment of women in their 40’s has the potential to save 11,751 lives

• Ignoring the 35% of women in their 50’s and 60’s who do not get screened sacrifices 19,684 lives.
Otis W. Brawley, M.D.

Chief Medical Officer
Executive Vice President
American Cancer Society

Professor of Hematology, Oncology, Medicine and Epidemiology
Emory University
Prostate Cancer and the U.S. Food and Drug Administration (FDA)

- PSA has never been FDA approved for screening (use in asymptomatic men)
- PSA is FDA approved for detection and diagnosis in symptomatic men
- PSA is also FDA approved for following diagnosed disease
Prostate Cancer

• We need to approach this issue logically and rationally

• We must realize:
  – What we know.
  – What we do not know.
  – What we believe.
Faith Based versus Evidence Based Medicine

- We in medicine have a tendency to adopt things before fully accessing their benefit or harm.
- We also criticize those who question the benefit and some even praise/worship advocates with a monetary interest.
  - Bone marrow transplant for breast cancer
  - Lung cancer screening with Chest Xray
  - Neuroblastoma Screening with urine VMA
  - The Halsted Mastectomy
  - Postmenopausal hormone replacement
  - Prostate cancer screening???
Pretend you are a 50 year old male and a preventive pill exists:

- If you take the pill it will definitely double your risk of prostate cancer diagnosis from 10% lifetime to 20% lifetime.
- It you take it, it may decrease your lifetime risk of prostate cancer death by 20% from 3% to 2.4%

Would you take this pill?
Principles of Screening

- Finding disease is not a measure of success in screening

  Increased survival is not a legitimate measure of success outside of a randomized clinical trial

  Reduction of mortality in a randomized trial is the only true proof of effective screening
The Lessons of Lung Cancer Screening

- Chest X-ray Screening found disease:
  - at more favorable stage
  - increased survival
  - increased the incidence of lung cancer
    (found more disease)
The Lessons of Lung Cancer Screening

- In randomized trials the death rate from lung cancer and lung cancer diagnostic procedures was:
  - 3.4 per 1000 per year among those screened annually for ten or more years
  - 2.8 per 1000 per year in the control group

- The Mayo Clinic Experience 1960-1975
Prostate Cancer Screening
The Four Randomized Studies

Deaths in the Screened Arm (when analyzed by intention)

- Norrkoping (Sweden) study 4% excess
- Quebec (Canadian) study 16% excess
- PLCO (American) study 13% excess
- ERSPC (European) study 20% decrease
The PLCO

- 73,000 men aged 55 to 74 randomized to screening annually vs routine follow-up
- Began in 1993, ten U.S. Centers
- Median follow-up about ten years
- Death rates not statistically significant
  - Prostate cancer and
  - Overall death rate (higher in screened)
B Prostate-Cancer Deaths

Cumulative No. of Deaths

Year

Screening

Control
The ERSPC

- 162,000 men aged 55 to 69 randomized to screening vs routine follow-up (there was no standardized protocol)
- Began in 1991, seven countries
- Median follow-up about nine years
- Death rate 20% difference favoring screening
  - $P=.04$ (minimally statistically significant)
  - NNT 48 to 1 (overtreatment)
  - Overall death rate not reported
  - Treatment differences did exist
The ERSPC

Positive finding – 20% risk reduction of prostate cancer death (pooled data).

Those in the screened arms likely had different treatment patterns than those in the control arms.

To prevent one prostate cancer death:
- Screen 1410 men
- Treat 48 men

Is the group of studies positive or negative? A meta-analysis of the studies would be helpful.
Overdiagnosis and Screening
The Prostate Cancer Prevention Trial (the placebo arm)

- Median age 62 with PSA less than 3.0 and screened annually for seven years.
- 14% diagnosed with cancer due to screening during the seven years.
- 14% diagnosed with cancer on terminal biopsy done per protocol among those with a “normal screen” for seven years.

- Thomspoon et al, NEJM, 2003
PCPT (the placebo arm)

- A total of 28% of men median age 69 diagnosed with prostate cancer.
- PSA screening missed as much disease as it found.
- There was overdiagnosis as it is estimated that 3% of this population will die of the disease.
Unanswered Questions in Prostate Cancer Medicine

- In quiescent metastatic disease, does early use of hormonal therapy increase survival more so than use of hormonal disease at the time of symptoms?
  - In the U.S. there is increasing use of hormonal therapy for a PSA rise after prostatectomy with uncertain efficacy
  - Increasing use of hormonal therapy for asymptomatic metastatic disease to bone with uncertain efficacy
  - In the U.S., one in three prostate cancer patients eventually is treated with hormones
True FACT

- Androgen Deprivation Therapy for prostate cancer has significant side effects

HR
- Diabetes Mellitus 1.4*
- Coronary Heart Disease 1.16*
- Myocardial Infarction 1.11*
- Sudden Cardiac Death 1.16*

* Statistically Significant Hazard Ratio
Keating et al., JCO 2006
• In the CAPCURE database Androgen deprivation therapy post prostatectomy or post radiation therapy increases risk of cardiac death  HR 2.6 (95% CI 1.4 to 4.7) More than 5% versus 2% in five years
  – Tsai JNCI, 2007

• Some of the RTOG studies have not confirmed this finding.
Unanswered Questions in Prostate Cancer Medicine

- Can the decline in prostate cancer mortality be seen without screening and its inherent overdiagnosis?

- Is the decline in prostate mortality actually due to an increase in the number of men dying of cardiovascular disease due to anti-androgen therapy for prostate cancer?

- While overdiagnosis clearly exists, a small advantage to screening cannot be excluded!!!
2010 ACS Guideline for the Early Detection of Prostate Cancer

• The American Cancer Society recommends that asymptomatic men who have at least a ten-year life expectancy have an opportunity to make an informed decision with their health care provider about whether to be screened for prostate cancer, after receiving information about **the uncertainties, risks, and potential benefits** associated with prostate cancer screening.
American Urological Association

Given the uncertainty that PSA testing results in more benefit than harm, a thoughtful and broad approach to PSA is critical.

Patients need to be informed of the risks and benefits of testing before it is undertaken. The risks of overdetection and overtreatment should be included in this discussion.

PSA Best Practice Statement 2009
European Association of Urology

- Recommends against mass screening.
- Recommends for informed decision making within the physician-patient relationship.

“Men should obtain information on the risks and potential benefits of screening and make an individual decision”

European Urology 56(2), 2009
Recommending Against Screening

- U.S. Preventive Services Taskforce
- Canadian Taskforce on the Periodic Health Examination
- American College of Preventive Medicine
- American College of Physicians
Prostate Cancer

• We need to approach this issue ethically, logically and rationally

• We must explain to patients:
  – What we know.
  – What we do not know.
  – What we believe.
The Challenge for Prostate Cancer Scientists

- We currently use a histologic definition of cancer that was developed by German pathologists in 1845.

- We need to be able to distinguish between the localized cancers that are destined to kill and the localized cancers that are destined to stay localized.
The Kinds of Prostate Cancer

- Cure is possible, but not necessary
  - Proven to exist
- Cure is necessary, but not possible
  - Proven to exist
- Cure is necessary and possible
  - Hopefully exists (subject of study)
    - Schellhammer modification of Whitmore
Take Home Message

- Prostate cancer screening (within the doctor-patient relationship) can be a reasonable practice.
- Men should be told that its benefits are unclear:
  - Some men will be diagnosed and receive unnecessary treatment.
  - Some men will be diagnosed and may receive lifesaving treatment.
Prostate Cancer and Chemoprevention

• Pretend you are a 50 year old male and a pill exists:
  – If you take the pill it will definitely double your risk of prostate cancer diagnosis from 10% lifetime to 20% lifetime.
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