Cancer Screening
Harms and Benefits

Otis W. Brawley, MD, MACP, FASCO, FACE
Bloomberg Distinguished Professor of
Oncology and Epidemiology
Disclosures

• Employment:
  – Johns Hopkins University

• Consulting
  – National Institutes of Health
  – Centers for Disease Control
  – Department of Defense
US Cancer Death Rate
1900 to 2016

Age Adjusted to 2000 Standard
Causes of the Decline in Cancer Death Rates

- Prevention
- Screening
- Treatment
Why the Decline?

- Prevention (especially tobacco control)
- Wise early detection (especially colorectal, breast, cervix)
- Improvements in cancer treatment
<table>
<thead>
<tr>
<th>Cause</th>
<th>% cancer caused</th>
<th>Deaths in United States</th>
<th>Magnitude of possible reduction (%)</th>
<th>Period of time (years)</th>
<th>Evidence example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>33%</td>
<td>188,744</td>
<td>75%</td>
<td>10–20</td>
<td>Utah vs Kentucky</td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>20%</td>
<td>114,390</td>
<td>50%</td>
<td>2–20</td>
<td>Bariatric surgery</td>
</tr>
<tr>
<td>Hereditary factors (*)</td>
<td>16%</td>
<td>91,520</td>
<td>50%</td>
<td>2–10</td>
<td>Oophorectomy; MRI; Tamoxifen; Colonoscopy</td>
</tr>
<tr>
<td>Diet</td>
<td>5%</td>
<td>28,600</td>
<td>50%</td>
<td>5–20</td>
<td>Folate, colorectal cancer</td>
</tr>
<tr>
<td>Lack of exercise</td>
<td>5%</td>
<td>28,600</td>
<td>85%</td>
<td>5–20</td>
<td>Adolescent activity</td>
</tr>
<tr>
<td>Occupation</td>
<td>5%</td>
<td>28,600</td>
<td>50%</td>
<td>20–40</td>
<td>Asbestos</td>
</tr>
<tr>
<td>Viruses</td>
<td>5%</td>
<td>28,600</td>
<td>100%</td>
<td>20–40</td>
<td>Liver cancer, HPV vaccine</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3%</td>
<td>17,200</td>
<td>50%</td>
<td>5–20</td>
<td>Regulation</td>
</tr>
<tr>
<td>UV and ionizing radiation</td>
<td>2%</td>
<td>11,400</td>
<td>50%</td>
<td>5–40</td>
<td>Medical exposures</td>
</tr>
<tr>
<td>Prescription drugs</td>
<td>1%</td>
<td>5,720</td>
<td>50%</td>
<td>2–10</td>
<td>Hormone therapy</td>
</tr>
<tr>
<td>Reproductive factors</td>
<td>3%</td>
<td>17,200</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Pollution</td>
<td>2%</td>
<td>11,400</td>
<td>0</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

We could reduce cancer deaths 60% by paying attention to known risk factors


(*) JNCI 89:287,1997
JAMA 2016 315:68-76
CANCER SCREENING
BE CAUTIOUS!!!!
Cancer Screening

• Screening is doing a test to determine if cancer might be present in an asymptomatic individual.

• Most distinguish mass screening versus screening within physician-patient relationship.

• Diagnostic tests are used when there are symptoms to cause a clinical suspicion of disease.
Principles of Screening

Finding disease is not a measure of success in cancer screening.

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

Reduction in mortality is the only true proof of effective screening. (Requires a randomized trial)
Principles of Screening

• There are several examples of cancer screening tests that have:
  – found localized disease,
  – increased the amount of disease found,
  – increased the proportion surviving five years and
  – Possibly increased risk of death.

• Some without changing the risk of death:
  – urine vanillylmandelic acid (VMA) screening for neuroblastoma.
    -Wood et al, NEJM, 2002
  – chest x-ray screening for lung cancer.
    -Marcus et al, JNCI, 2006
Cancer Screening

- A series of tests with some uncertainties and some risk.
- Many do not appreciate the harms of screening.
- Often the harms are better proven than the benefits.
Questions to Ask

• How much inconvenience does it cause?
• How much harm does it cause?
• How many lives does it save?
Inconvenience?

• How many people need to get screened to save a life?

• How difficult is it to get screened?
  – Preparation
  – Equipment
Harm?

• False Positive Findings
  – Anxiety
  – Negative diagnostic workup

• Morbidity
  – Pain
  – Hospitalizations
  – Death!!!!
To the Screening Epidemiologist

The worth of screening is really measured in a Benefit / Harm Ratio

A look at the forest and not just one tree!
Cancer Screening

• Lead time bias
• Length bias
• Overdiagnosis
LEAD TIME BIAS

A

Diagnosis due to Symptoms

Death due to Cancer

B

Diagnosis due to Screening

Death due to Cancer

Lead Time

C

Diagnosis due to Screening

Prolonged Life due to Screening

Lead Time

Death due to Cancer or other causes
Lead Time Bias

- Because of lead time bias, survival can increase without a decrease in mortality rate.

- Indeed, both survival and mortality increased in randomized trials of CXR and sputum cytology screening in the 1970’s.

Marcus et al., JNCI, 2006
Length Bias

Biologic behavior of a cancer is key to its screenability.

Slower growing, less deadly tumors are actually easier to find, treat, and cure.

Fast growing cancers do not benefit from screening.
Overdiagnosis of Cancer
a form of length bias

There are some small screen detected cancers that are not a clinical threat to the patient.

- We cure some cancers that do not need to be cured!!!!
- How to determine that these tissues are non-threatening is a major area of research.
Overdiagnosis of Cancer

Thyroid Cancer in South Korea

<table>
<thead>
<tr>
<th></th>
<th>1993</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence per 100,000</td>
<td>5</td>
<td>75</td>
</tr>
<tr>
<td>Mortality per 100,000</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Ahn, Kim, and Welch NEJM 2014

November 18, 2019
Overdiagnosis of Cancer
(A Difficult Concept to Comprehend)

Estimates:
- 10 to 20% of radiologically detected lung cancers
- 10 to 50% of mammographically detected invasive breast cancers
- Up to 80% of Ductal Carcinoma In Situ of the breast
- 40 to 60% of ultrasound detected thyroid cancers
- 60% of PSA detected prostate cancers
Rudolph Ludwig Karl Virchow

1821-1902
Adenocarcinoma
Advances in cancer diagnosis:

- X-ray – 1890’s
- Mammogram - 1950’s
- Ultrasound – 1960’s
- Computerized Tomography (CT) - 1970’s
- Magnetic Resonance Imaging (MRI) - 1980’s
- Stereotactic biopsy – 2000’s to present
Mammogram with a Ductal Carcinoma
Adenocarcinoma
Overdiagnosis is the pathologic equivalent of racial profiling.

It looks like something that has killed in the past, therefore we assume it is something that kills.
What is the Real Diagnosis?
Cancer is a subjective diagnosis!

When 49 pathologists look at 2940 biopsies, inter-observer agreement rates were:

- 89% (95% CI 84-92) for invasive cancer,
- 79% (95% CI 76-81) for ductal carcinoma-in-situ,
- 43% (95% CI 41-45) for atypia, and
- 77% (95% CI 74-79) for benign without atypia.

What is Cancer?
The Evolution of Our Concept of the Disease

• Moving from a 19th Century definition to a 21st Century definition

• Moving to the biopsy and genomics
  – Oncotype Dx
  – Mammoprint
The Gold Standard is a Prospective Randomized Trial

Enrollee Randomization

Group A  Group B

Compare Death rate over time
Cancer Screening

Well designed clinical studies have demonstrated a mortality reduction through:

- Mammography for Breast Cancer
- Stool Blood Testing and Sigmoidoscopy for Colorectal Cancer
- Pap and Visual Screening for Cervical Cancer
- Low Dose Spiral CT screening in those at high risk for lung cancer
BREAST CANCER
Breast Cancer Screening

• Routine Mammography is recommended for normal risk women

• Controversies
  – Starting at age 40, 45, or 50 and over
  – Every year vs every two years
  – Quality of image and quality of radiologist
  – Importance of a program of routine screening and image comparison

• Clinical Breast Examination when mammography is not available.

Smith RA et al, CA Cancer J Clin 2015
Breast Cancer Screening

- Screening will miss some disease that we wish we could find especially among younger women with dense breasts.

- Screening will find some disease that does not need treatment (overdiagnosis).

- Overdiagnosis is a special question for 3D Mammography (The TMIST Trial)

Smith RA et al, CA Cancer J Clin 2015
Breast Cancer

• Death rates have declined by 40 percent in past thirty years.

• Assessment suggests 40 to 50 percent of the decline is due to screening programs.
Breast Cancer
Strategies to Reduce Cancer Mortality

CISNET Modeling of outcomes from 2013 to 2025

- With current breast cancer screening and treatment patterns, there will be 50,100 to 57,400 deaths in 2025
- With guideline appropriate screening of all women 40 and above and current treatment patterns there will be 5100 to 6100 fewer deaths
- With all women receiving appropriate therapy and no change in screening rates there would be 11,400 to 14,500 fewer deaths
- If all women received appropriate screening and treatment there would be 18,100 to 20,400 fewer deaths

Mandelblatt et al, Cancer, 2013
COLON CANCER
Colon Cancer Screening Saves Lives

- Stool blood testing (three samples per year analyzed in a lab) – results of randomized trials and is really underappreciated
- Sigmoidoscopy (every three to five years) – results of randomized trials
- Colonoscopy (every ten years) – to date no randomized trials

Smith RA et al, CA Cancer J Clin 2019
Colon Cancer Screening

• A positive stool test or polyps on sigmoidoscopy requires a colonoscopy

• Colon screening is thought to reduce risk of death by at least 35% and risk of cancer (through polypectomy) by 20%

• Colon screening is the least controversial of all screening tests.

Smith RA et al, CA Cancer J Clin 2019
Colon Cancer Screening

- Stool DNA testing has become widely available in the past five years.

- The currently available test has some specificity issues and results in a high number of colonoscopies.

Smith RA et al, CA Cancer J Clin 2019
CERVIX CANCER
Cervical Cancer Screening

• Pap smear,
• HPV testing,
• Visual inspection of cervix

• The first randomized trial was completed this century!!!!

Smith RA et al, CA Cancer J Clin 2019
Cervical Cancer Screening

- Pap test every year X 3 beginning at age 21 or within 3 years of starting sexual activity

- After 3 normal yearly smears, a smear every 3 years

Smith RA et al, CA Cancer J Clin 2015
Cervical Cancer Screening

• An abnormal screen can be followed up with HPV testing.

• Women age 30 and over might consider HPV testing in lieu of pap tests.

• Abnormal pap smear or positive HPV test should be followed by colposcopy and biopsy.

Smith RA et al, CA Cancer J Clin 2015
Cervical Cancer

- Approximately 4,100 Americans die of cervical cancer each year.

- A survey of medical histories show the overwhelming majority have not had a cervical screening test in ten years prior to diagnosis.

LUNG CANCER
The National Lung Screening Trial

- Nearly 54,000 at high risk enrolled in the trial
  - age 55 and above
  - 30 pack year or greater history of smoking; if quit, did so less than 15 years prior to trial entry
  - Reasonable health

- Subjects prospectively randomized to chest X-ray (sham) or low dose spiral CT (LDCT) yearly for three years
  - Done at 30 sites with lung cancer expertise
  - Analysis 10 years from start of screening showed LDCT associated with a 20% reduction in relative risk of death

CT: computed tomography
The National Lung Screening Trial: A Closer Look

- In this high risk group, the benefit/risk ratio of 5.4 lives saved for:
  - Every 2 people with a complication due to an invasive procedure
  - Every 1 life lost prematurely due to diagnostic procedures

- This study was done in 30 of the best hospitals in the country
  - Results may differ as LDCT screening is adopted at other facilities.
  - The benefit-risk ratio may decrease

LDCT: low dose spiral CT
Lung Cancer Screening Recommendations

Six Respected Groups Recommend the Doctor “Consider” spiral CT for those:

– Healthy aged 55 years and above,
– H/0 30 pack years of smoking or more,
– If quit smoking did so less than 15 years ago,
– Who understand that there are risks of unnecessary diagnostic procedures and even death associated with screening.

Wender et al, CA Cancer J Clin 2013
An Efficient Screening Program

• Approximately 160,000 Americans currently die of lung cancer every year.

• A screening program has potential of preventing 8,000 to 10,000 deaths per year!!!

• If done well screening would lead to 1,500 to 1,850 deaths secondary to diagnostic interventions (bronchoscopy, biopsy, etc.).
PROSTATE CANCER
Prostate Cancer Screening

• There are positive and negative trials, all with significant biases tainting their results.

• It is likely that screening saves some lives but causes significant harm.

• The harms are better proven than the benefits.

Brawley OW, Annals of Internal Medicine, 2012
Prostate Cancer Screening

• 11 of 11 prospective randomized trials have shown the harms of prostate cancer screening
  – Considerable overdiagnosis.
  – Overtreatment.
  – Harms of treatment:
    • Fever and sepsis associated with diagnostic biopsies.
    • Mental anguish.
    • Poor quality of life after diagnosis and treatment.

• 2 of 11 prospective randomized trials have claimed a small mortality reduction.

• All 11 trials have flaws.
Applying ERSPC to the Population fourteen years of follow-up

Of 1000 men aged 55 to 69 screened regularly over a twelve year period

- 100 will be diagnosed with prostate cancer
- The number treated is declining in recent years
- 4 will die of the disease

ASCO Patient Consent, 2019
Applying ERSPC to the Population fourteen years of follow-up

Of 1000 men aged 55 to 69 who choose not to be screened over a twelve year period:

- 60 will be diagnosed with prostate cancer
- 5 will die of the disease
Applying ERSPC to the Population
fourteen years of follow-up

5 per 1000 dying going to 4 per 1000 is the 20% reduction in relative risk of death

Screening saves 1 life in 1000 men screened regularly for 12 years, but at what cost?

Of the 100 diagnosed through screening 96 think they are the 1 in 1000 whose life was saved.
Recommending Against Routine Prostate Cancer Screening

- U.S. Preventive Services Taskforce
- Canadian Taskforce on the Periodic Health Examination
- American College of Preventive Medicine
- American College of Physicians
- American Academy of Family Physicians
Recommending for **Informed Decision Making**

- American Cancer Society
- National Comprehensive Cancer Network
- American Society for Clinical Oncology
- European Urology Association
- American Urology 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 over detection and overtreatment should be included in this discussion.

AUA PSA Best Practice Statement 2009 and 2013
Prostate Cancer Screening

Quality of Treatment is very important in outcome.
- Surgery
- Radiation therapy
- Observation for low grade lesions

Increasing volumes due to screening can tax and diminish the quality of a treatment program.
Prostate Cancer Screening
A Complex Message

This is ripe for confusion and distrust
  – Many (who mean well) promote screening and do not understand the nuances.
  – Many promote screening because it is money making.

Confusion and distrust can cause disparities in receipt of care
“It is difficult to get a man to understand something, when his salary depends on his not understanding it.”

Upton Sinclair, 1935
Cancer Screening

• Can be beneficial! Can be harmful!

• Often both and only a good randomized clinical trial can disclose the net benefit to the population (risk/benefit ratio).

• Need to follow good science.
How Can We Provide Adequate High Quality Care (to Include Preventive Services) to Populations That So Often Do Not Receive It?

- Unnecessary care interferes with institutional abilities to provide necessary care.

- Complex resource intensive care (such as lung cancer screening) can divert or take away from other vital care.

- State by state disparities are increasing with the Affordable Care Act!!
State Medicaid Expansion Plans as of mid 2019

- **Dark Blue**: Adopted and Implemented
- **Light Blue**: Adopted but Not Implemented
- **Orange**: Not Adopted
Fact:
College educated Americans have a much lower risk of cancer death compared to non college educated. This is true among all races and ethnicities.

Siegel, et al. CA
2018;68:329-339
Applying Known Science (Prevention and Treatment)

- It is estimated that 607,000 Americans will die of cancer this year.
- If all Americans had the cancer death rate of college educated Americans, the number would be 455,000.
- Nearly one-fourth of cancer deaths (152,000 Americans) would not occur!

Siegel, et al. CA
2018;68:329-339
Applying Known Science (Prevention and Treatment)

- At least 152,000 deaths per year are preventable if all Americans received known medical prevention and treatment.

- The majority of those preventable deaths are in white Americans.

- The issue of disparities in health are not just a racial minority health issue.

The Most Important Question in Cancer Control

How Can We Provide Adequate High Quality Care (to Include Preventive Services) to Populations That So Often Do Not Receive It?
EQUALITY

EQUITY
The Johns Hopkins Medical Institutions