Principles of Cancer Screening

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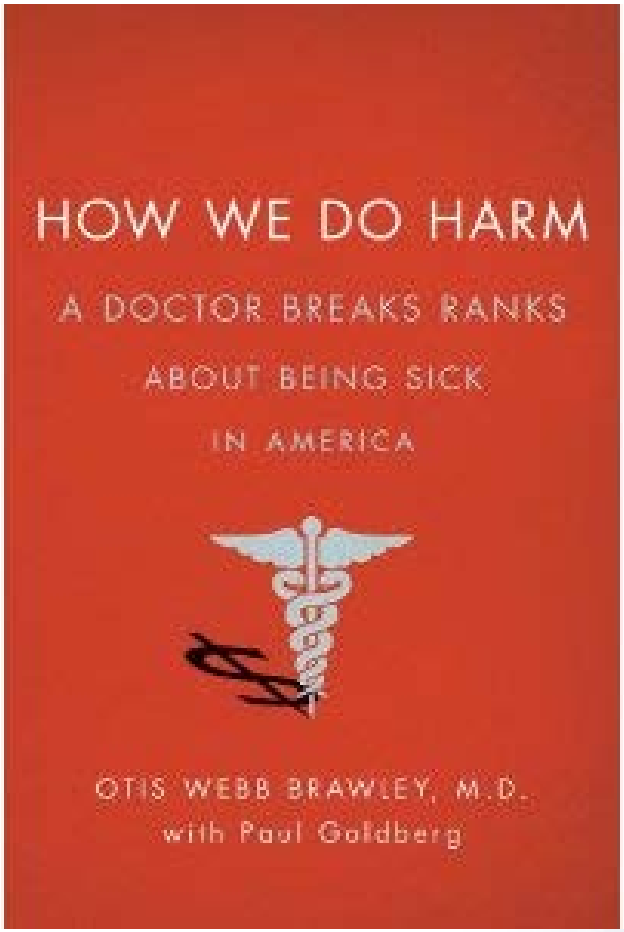
Disclosures

- Employment:
  - Johns Hopkins University
- Consulting
  - National Institutes of Health
  - Centers for Disease Control
  - Department of Defense



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Causes of the Decline in Cancer Death Rates

- Prevention
- Screening
- Treatment

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.

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

Questions to Ask

- How much inconvenience does it cause?
- How much harm does it cause?
- How many lives does it save?

Harm?

- False Positive Findings
  - Undue anxiety
  - Inconvenience of workup
- Morbidity of workup
  - Pain
  - Hospitalizations
  - Death!!!!

To the Screening Epidemiologist

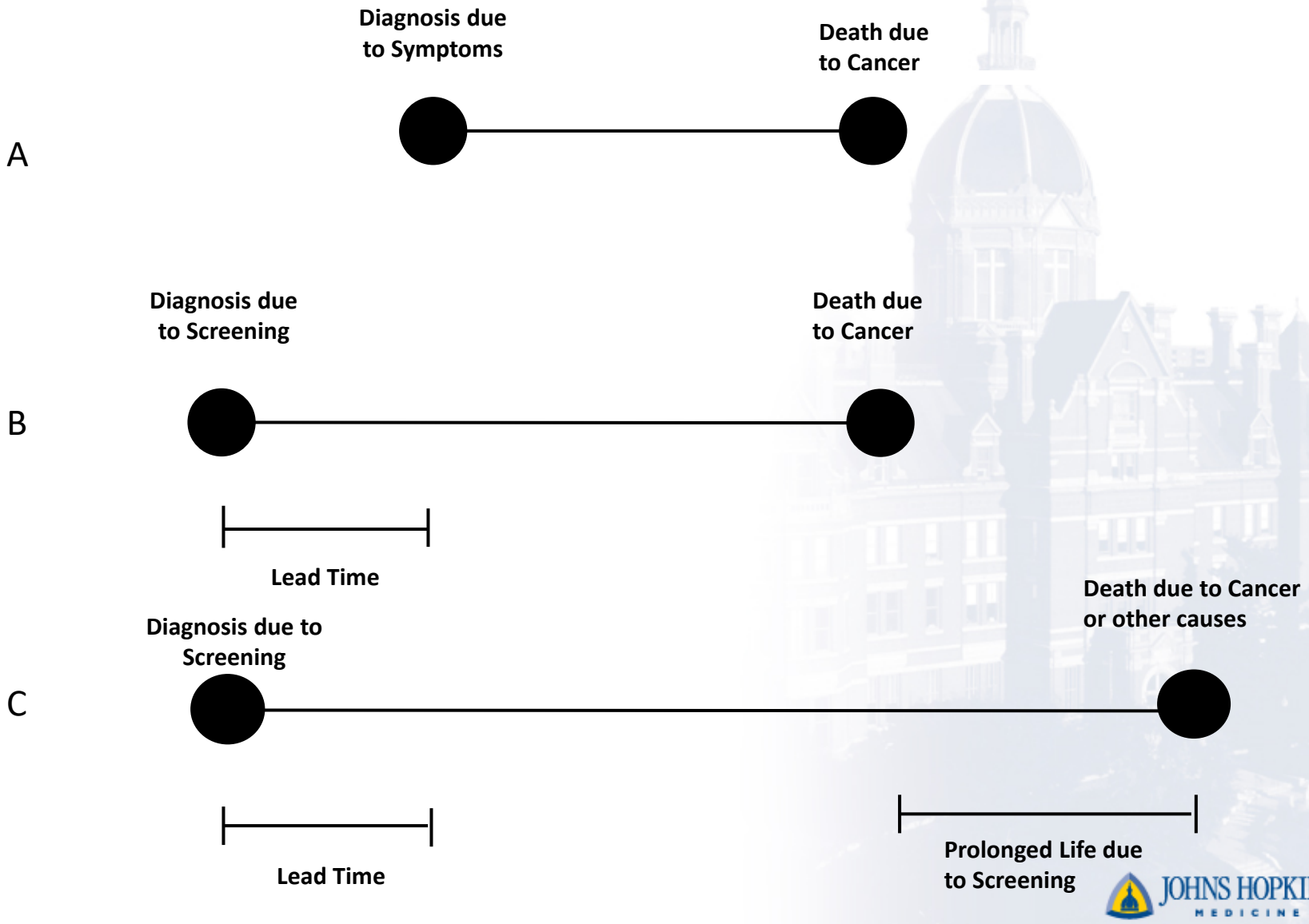
The worth of screening is really measured in a Benefit / Harm Ratio

A look at the forest and not just one tree!

Cancer Screening

- Selection bias
- Lead time bias
- Length bias
- Overdiagnosis

LEAD TIME BIAS



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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.

Rudolph Ludwig Karl Virchow

1821- 1902

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

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.

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Overdiagnosis of Cancer

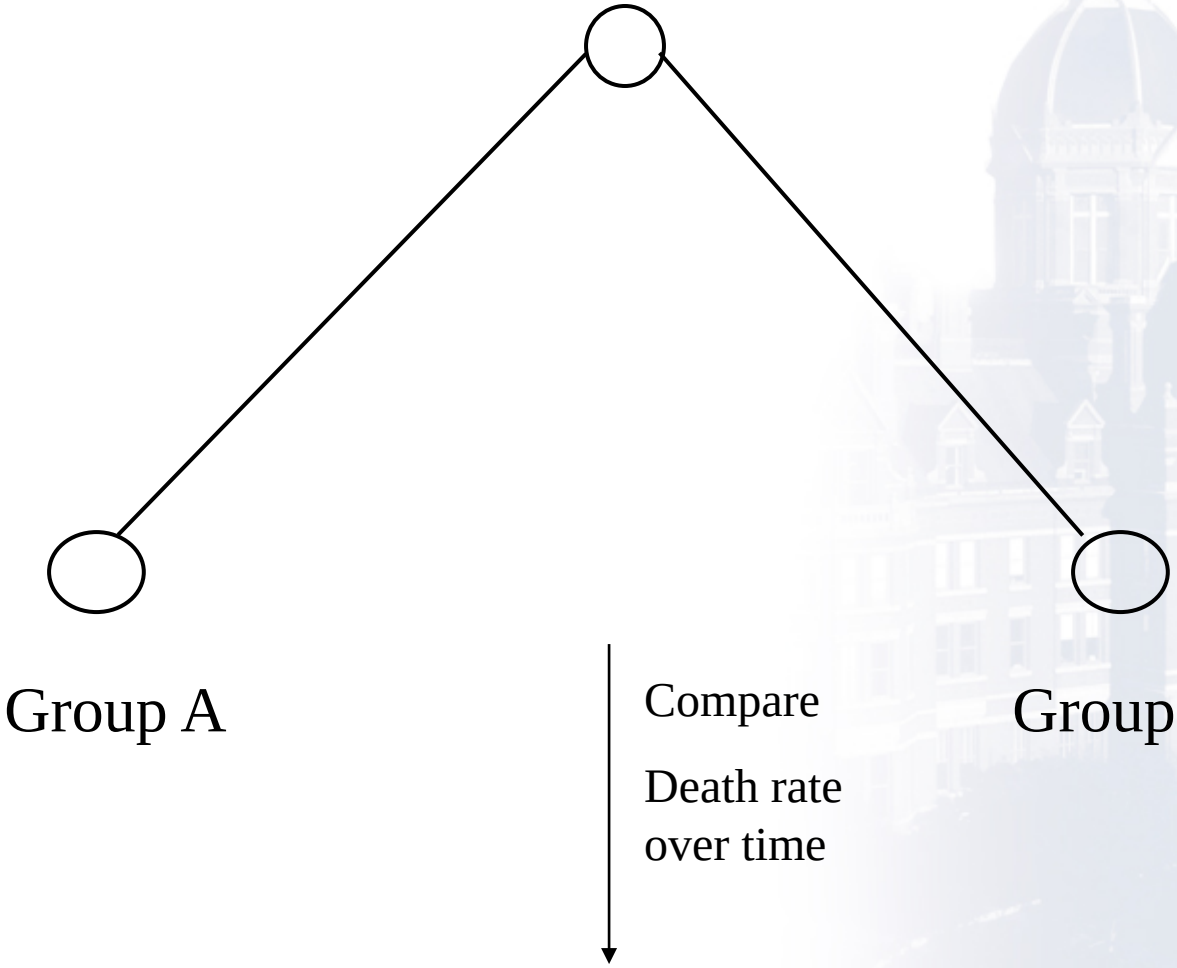
Thyroid Cancer in South Korea,
Widespread thyroid US screening began in 1994!

	1993	2011
Incidence per 100,000	5	75
Mortality per 100,000	4	4

Ahn, Kim, and Welch NEJM 2014

The Gold Standard is a Prospective Randomized Trial

Enrollee Randomization



Principles of Screening

- Efficacy - The result in the group in the clinical trial (trial participants have selection biases especially a “healthy volunteer effect”).

- Effectiveness – The result in the population as a whole (the real world).

Cancer Screening

Well designed clinical studies have demonstrated a mortality reduction through:

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

*no randomized trial of colonoscopy has been completed

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BREAST CANCER

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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 is recommended when mammography is not available.

Smith RA et al, CA Cancer J Clin 2015

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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.

Berry et al NEJM ….

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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

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Colon Cancer Screening

- 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

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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

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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

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CERVICAL CANCER

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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.

Janerich DT, Hadjimichael O, Schwartz PE, Lowell DM, Meigs JW, Merino MJ, Flannery JT, Polednak AP. Am J Public Health. 1995;85(6):791.

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LUNG CANCER

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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 (a bias)
  - Analysis 10 years from start of screening showed LDCT associated with a 20% reduction in relative risk of death

*There is a selection bias, a healthy volunteer effect.

CT: computed tomography

N Engl J Med. 2011 Aug 4;364(22):2148-54.

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

N Engl J Med. 2011 Aug 4;364(22):2148-54.

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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

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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 over detection and overtreatment should be included in this discussion.

AUA PSA Best Practice Statement 2009 and 2013

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Clinical Trials

- Relative risk vs Absolute number
  - Relative risk is good for sales (it can be somewhat deceiving)
  - Absolute is good for perspective
- Relative risk -
  - In the ERSPC (a randomized study of prostate cancer screening in 180,000 men), prostate specific antigen screening over a 12-year period reduces the relative risk of death by 20%
- Absolute value –
  - In the control arm, the PCa specific death rate was 5 per 1000
  - In the screened arm, the PCa specific death rate was 4 per 1000
  - A participant had a 1 in 1000 chance they would benefit
- Statistical significance versus Clinical significance

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.

The Johns Hopkins Medical Institutions