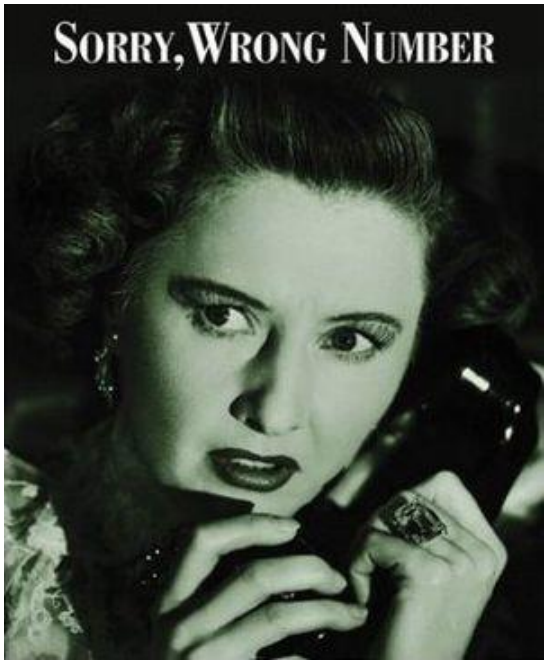
Overdiagnosis in Cancer Screening



Challenges, Problems, Mistakes

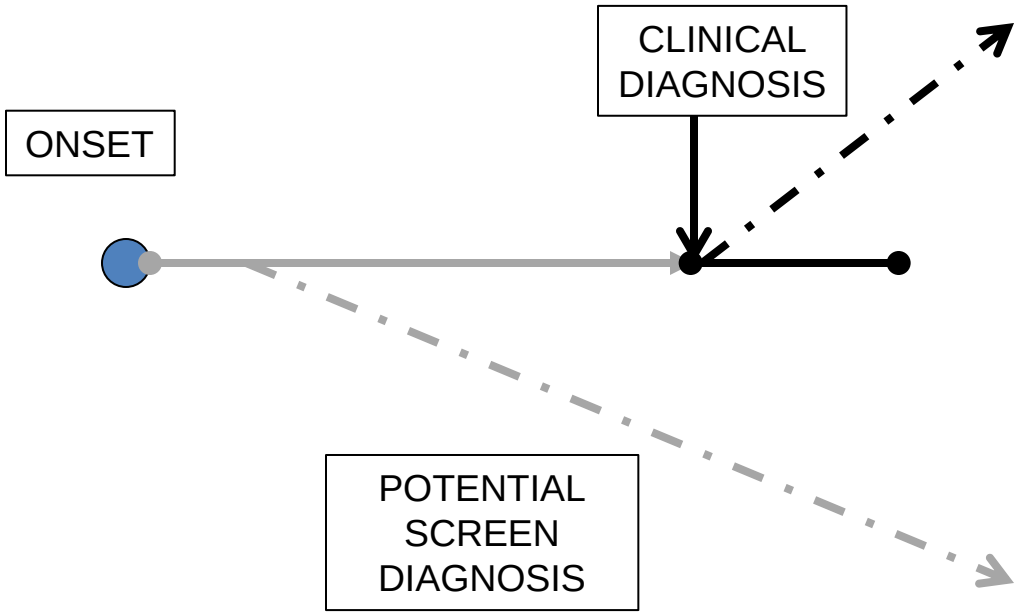
Ruth Etzioni

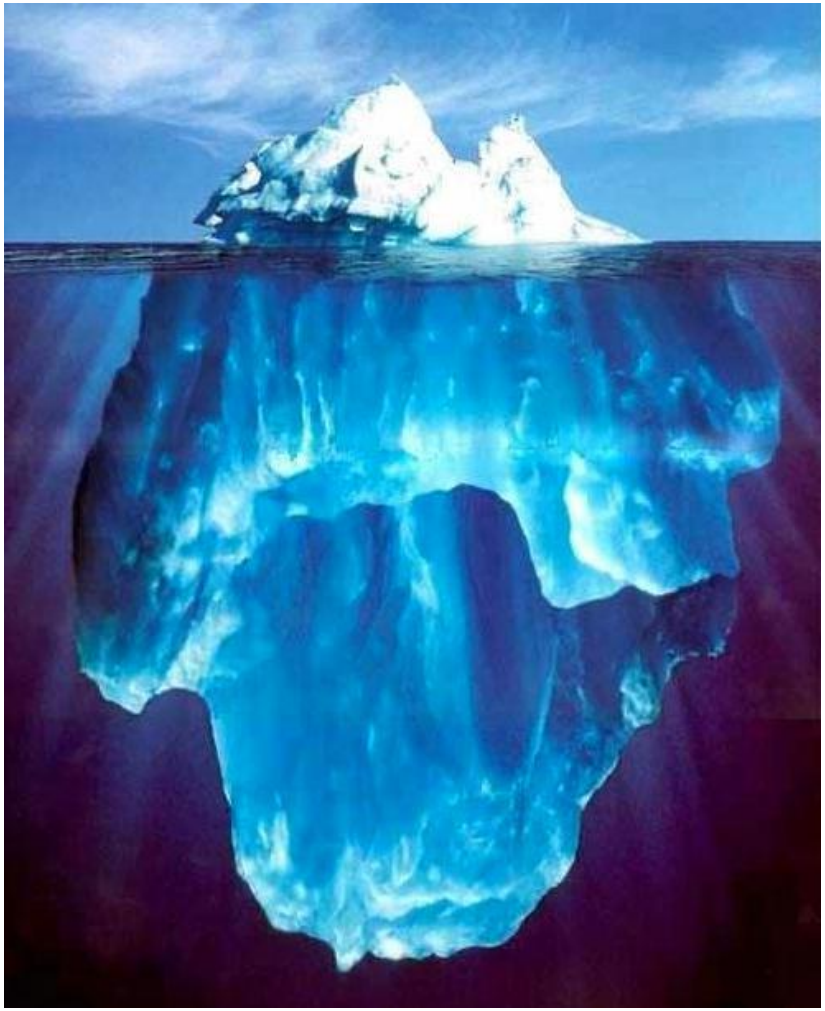
FRED HUTCHINSON CANCER RESEARCH CENTER

A LIFE OF SCIENCE

The Problem of Overdiagnosis

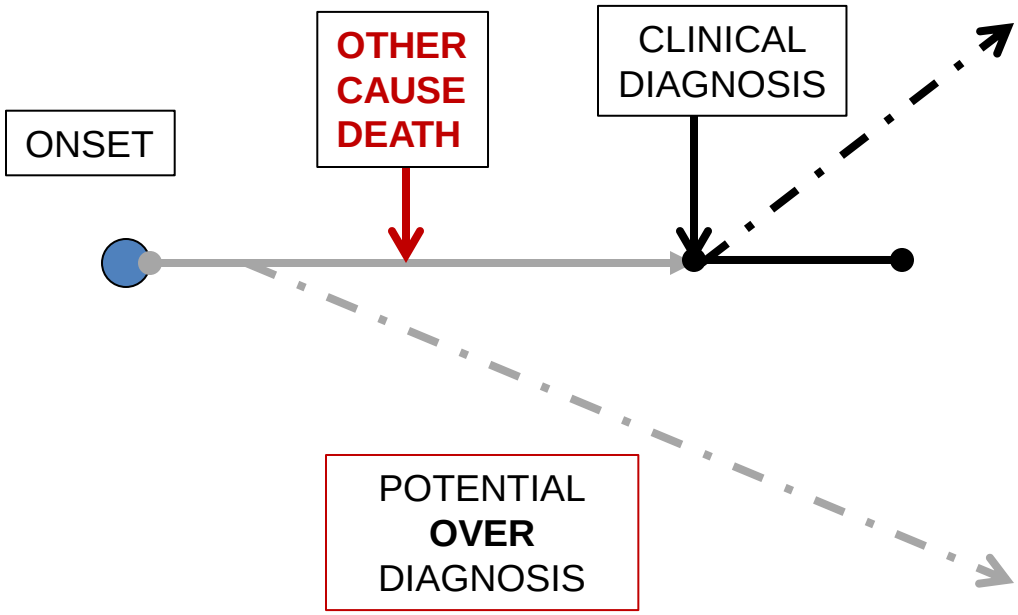
- A lot of cancer lies beneath the surface

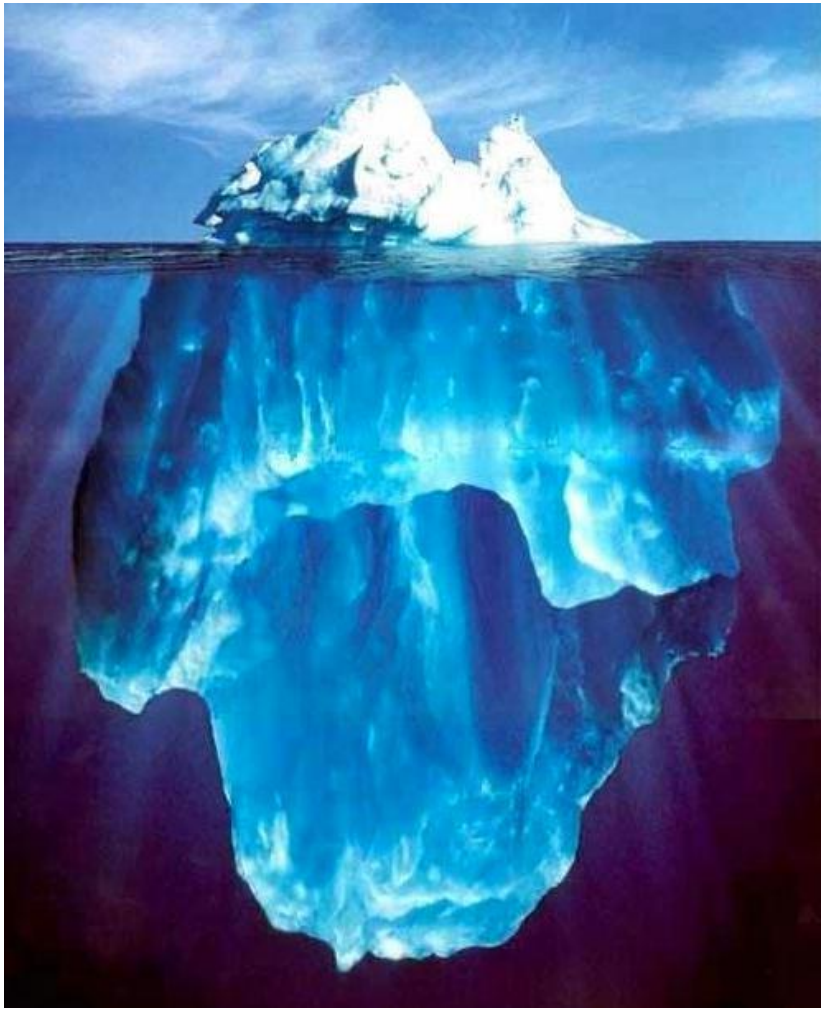




The Problem of Overdiagnosis

- A lot of cancer lies beneath the surface
- Some cancers stay beneath the surface





OVERDIAGNOSIS happens when one of these cancers is detected by screening

How Many Cancers are Overdiagnosed?

Prostate Cancer Diagnosis and Treatment After the Introduction of Prostate-Specific Antigen Screening: 1986–2005

H. Gilbert Welch, Peter C. Albertsen

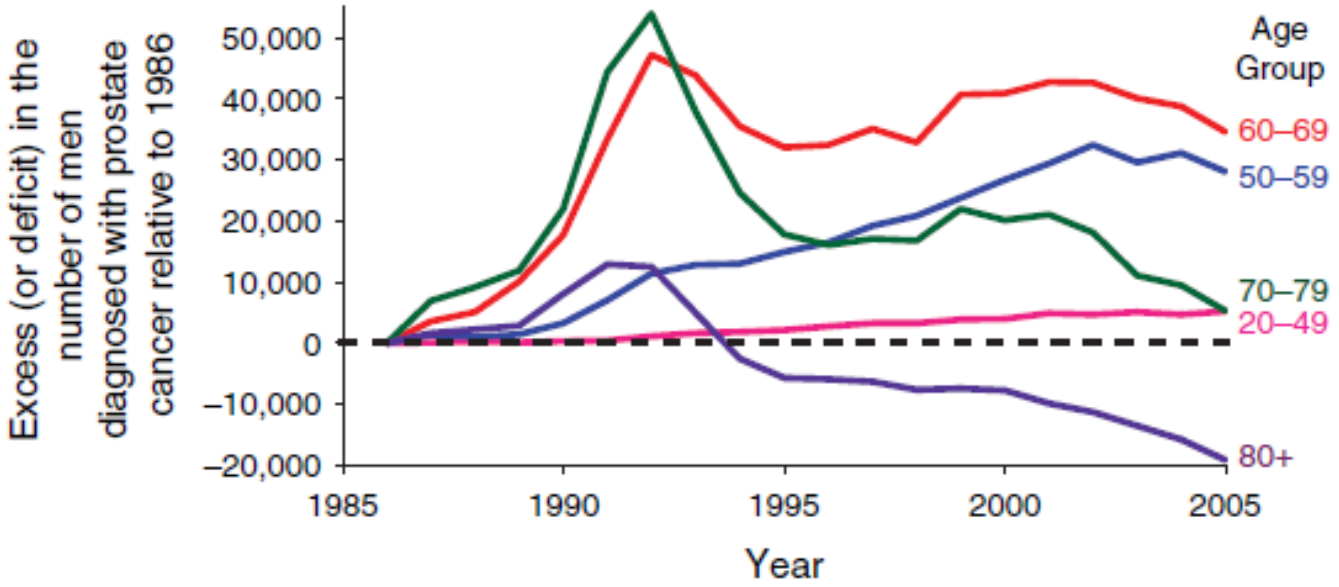


Figure 2. Excess (or deficit) in the number of men diagnosed with prostate cancer relative to 1986.

Since 1986, an estimated additional 1 305 600 men were diagnosed with prostate cancer.

The Great Prostate Mistake

By Richard J. Ablin

TUSCON

EACH year some 30 million American men undergo testing for prostate-specific antigen, an enzyme made by the prostate. Approved by the Food and Drug Administration in 1994, the P.S.A. test is the most commonly used tool for detecting prostate cancer.

The test's popularity has led to a hugely expensive public health disaster. It's an issue I am painfully familiar with — I discovered P.S.A. in 1970. As Congress searches for ways to cut costs in our health care system, a significant savings could come from changing the way the antigen is used to screen for prostate cancer.

Americans spend an enormous amount testing for prostate cancer. The annual bill for P.S.A. screening is at least $3 billion, with much of it paid for by Medicare and the Veterans Administration.

Prostate cancer may get a lot of press, but consider the numbers: American men have a 16 percent lifetime chance of receiving a diagnosis of prostate cancer, but only a 3 percent chance of dying from it. That's because the majority of prostate cancers grow slowly. In other words, men lucky enough to reach old age are much more likely to die with prostate cancer than to die of it.

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Richard J. Ablin is a biology and patholog College of Medicine a Benjamin Ablin Four

that will kill you and the one that won't.

Instead, the test simply reveals how much of the prostate antigen a man has in his blood. Infections, over-the-counter drugs like ibuprofen, and benign swelling of the prostate can all elevate a man's P.S.A. levels, but none of these factors signals cancer. Men with low readings might still harbor dangerous cancers, while those with high readings might be completely healthy.

In approving the procedure, the Food and Drug Administration relied heavily on a study that showed testing could detect 3.8 percent of prostate cancers, which was a better rate than the standard method, a digital rectal

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continue peddling the tests and advocacy groups push "prostate cancer awareness" by encouraging men to get screened. Shamefully, the American Urological Association still recommends screening, while the National Cancer Institute is vague on the issue, stating that the evidence is unclear.

The federal panel empowered to evaluate cancer screening tests, the Preventive Services Task Force, recently recommended against P.S.A. screening for men aged 75 or older. But the group has still not made a recommendation either way for younger men.

Prostate-specific antigen testing does have a place. After treatment for prostate cancer, for instance, a rapidly rising score indicates a return of

A single test has cost billions in unneeded treatment.

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covery four decades driven public health ty must confront re- use of P.S.A. screen- s of dollars and res- cessary, debilitating □

"The European Study showed a small decline in death rates but also found that 48 men would need to be treated to save one life. That's 47 men, who in all likelihood can no longer function sexually or stay out of the bathroom for long …"

48 = NND = Number needed to detect = $\frac{\text{Overdiagnoses}}{\text{lives saved}}$

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Three Decades of Screening Mammography on Breast-Cancer Incidence

Archie Bleyer, M.D., and H. Gilbert Welch, M.D., M.P.H.

"After excluding the transient excess incidence associated with hormone-replacement therapy and adjusting for trends in the incidence of breast cancer among women younger than 40 years of age, we estimated that breast cancer was overdiagnosed in 1.3 million U.S. women in the past 30 years ….. in 2008, breast cancer was overdiagnosed in more than 70,000 women; this accounted for **31%** of all breast cancers diagnosed."

Bleyer and Welch NEJM 2012

WELL | Tara Parker-Pope

Mammogram's Role as Savior Is Tested

Has the power of the mammogram been oversold?

At a time when medical experts are rethinking screening guidelines for prostate and cervical cancer, many doctors say it's also time to set the record straight about mammography screening for breast cancer. While most agree that mammograms have a place in women's health care, many doctors say widespread "Pink Ribbon" campaigns and patient testimonials have imbued the mammogram with a kind of magic it doesn't have. Some patients are so committed to annual screenings they even begin to believe that regular mammograms actually prevent breast cancer, said Dr. Susan Love, a prominent women's health advocate. And women who skip a mammogram often beat themselves up for it.

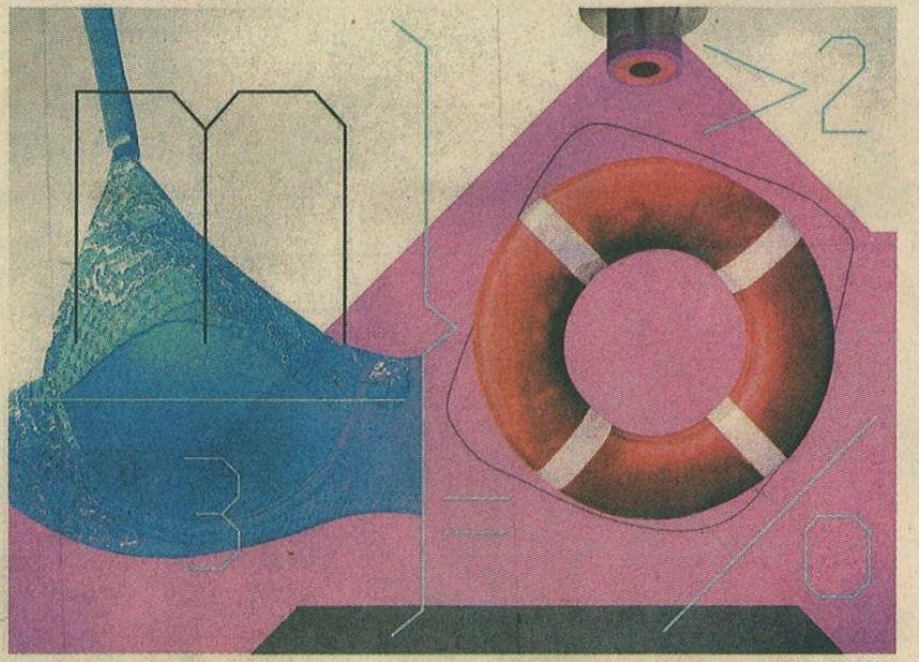
The number of women helped by screening is lower than many think.

"You can't expect from mammography what it cannot do," said Dr. Laura Esserman, director of the breast care center at the University of California, San Francisco. "Screening is not prevention. We're not going to screen our way to a cure."

A new analysis published Monday in Archives of Internal Medicine offers a stark reality check about the value of mammography screening. Despite numerous testimonials from women who believe "a mammogram saved my life," the truth is that most women who find breast cancer as a result of regular screening have not had their lives saved by the test, conclude two Dartmouth researchers, Dr. H. Gilbert Welch and Brittney A. Frankel.

Dr. Welch notes that clearly some women are helped by mammography screening, but the numbers are lower than most people think. The Dartmouth researchers conducted a series of calculations estimating a woman's 10-year risk of developing breast cancer and her 20-year risk of death, factoring in the added value of early detection based on data from various mammography screening trials as well as the benefits of improvements in treatment. Among the 60 percent of women with breast cancer who detected the disease by screening, only about 3 percent to 13

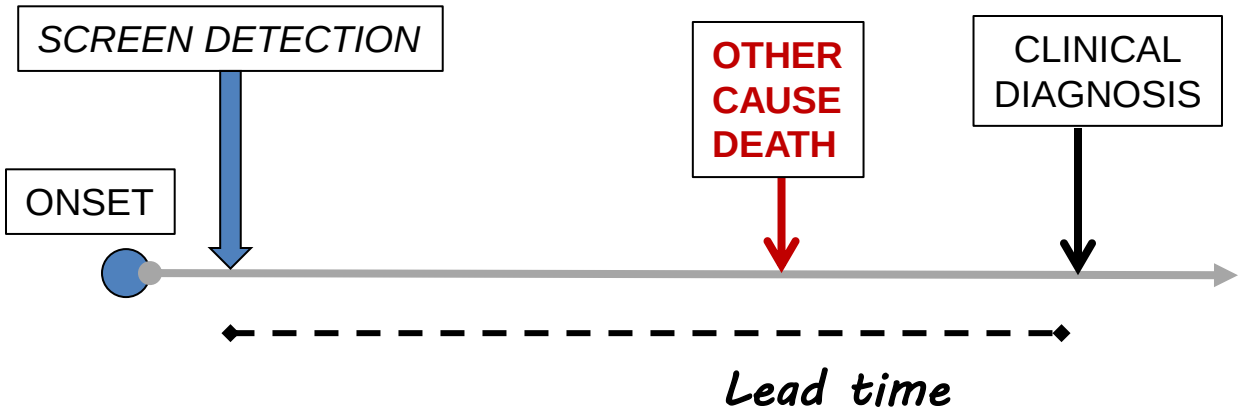
Continued on Page 6



STUART BRADFORD

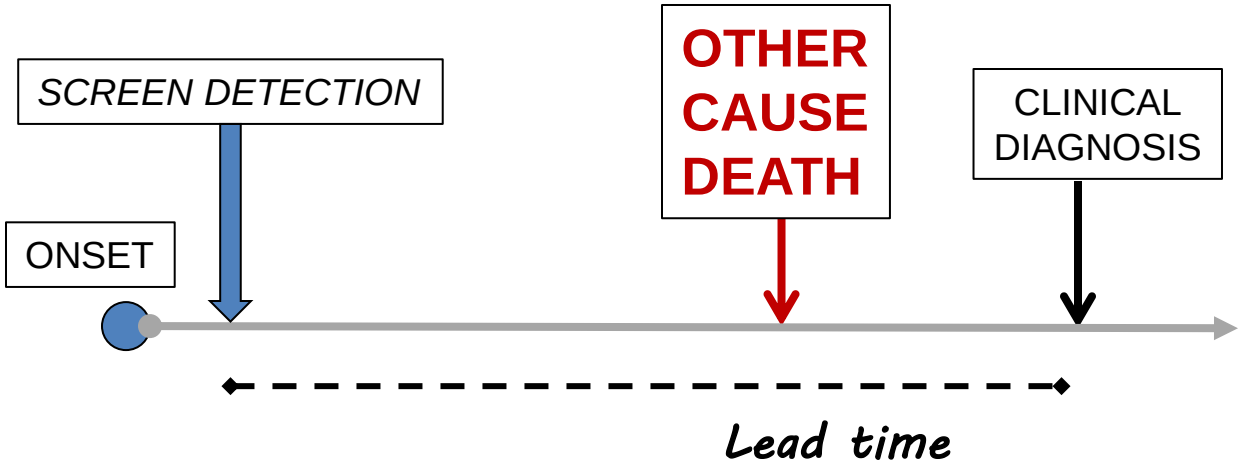
Understanding Overdiagnosis

When Does Overdiagnosis Happen?



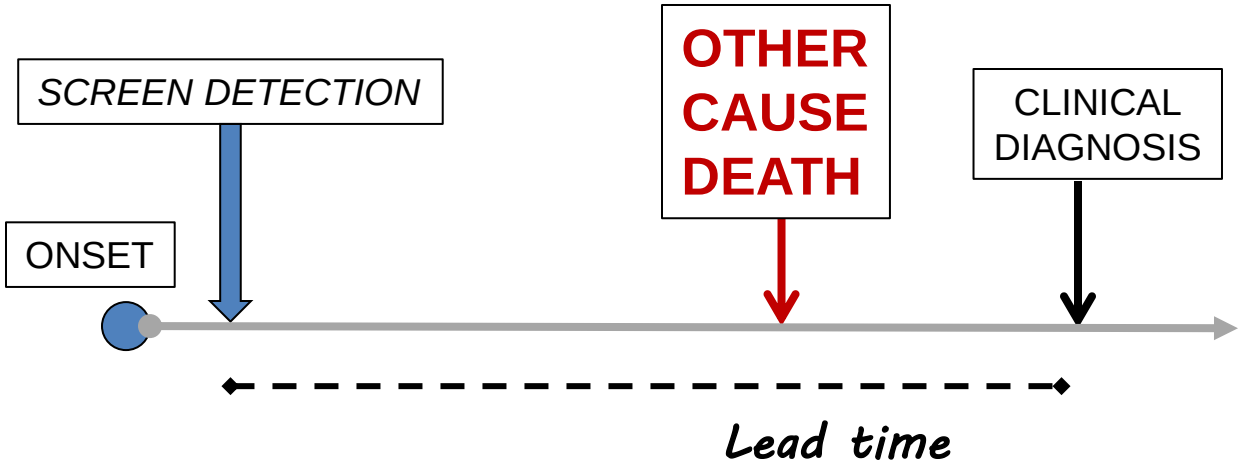
1: LENGTHY LATENT PERIOD or LENGTHY LEAD TIME

When Does Overdiagnosis Happen?



2: HIGH RISK OF DEATH DUE TO AGE OR COMORBIDITY

Overdiagnosis Facts



- An overdiagnosed cancer is a true excess cancer due to screening
- Overdiagnosis is more likely when:
  - Tumors are slow-growing
  - Cases are older or have high comorbidity
- Overdiagnosis occurs when
  - Time from screen detection to OC death is less than the lead time

Estimating Overdiagnosis

Two Ways People Learn About Overdiagnosis

(1) Count excess cases in the presence of screening

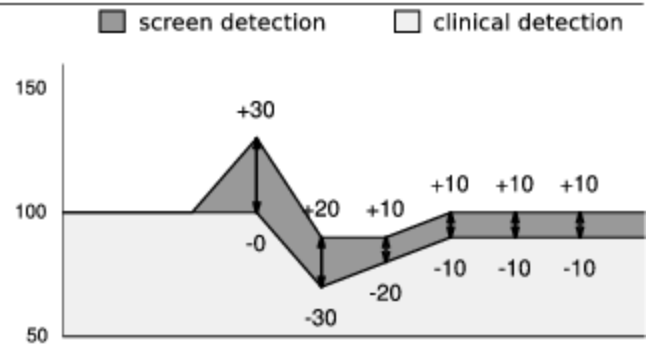
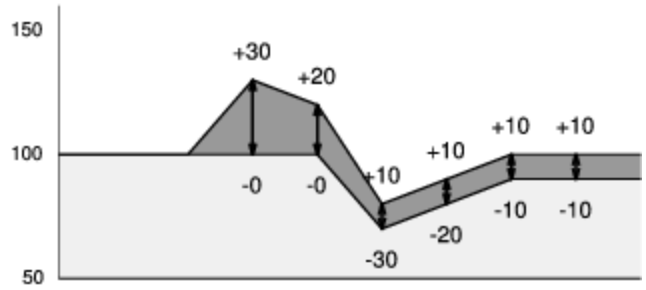
“ ***EXCESS INCIDENCE APPROACH ”***

(2) Learn about the lead time (or underlying natural history)

“ LEAD TIME APPROACH ”

KEY LESSON: APPROACH MATTERS

Excess Incidence Approach

Lead time	Overdiagnosis	Cancer incidence
1 year	0%	
2 years	0%	

Timing

Wait to calculate excess incidence

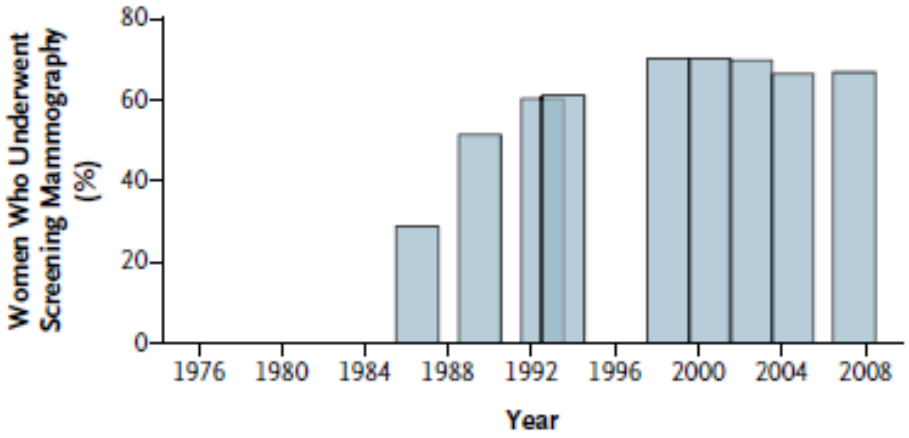
Counterfactual

Impute incidence in absence of screening

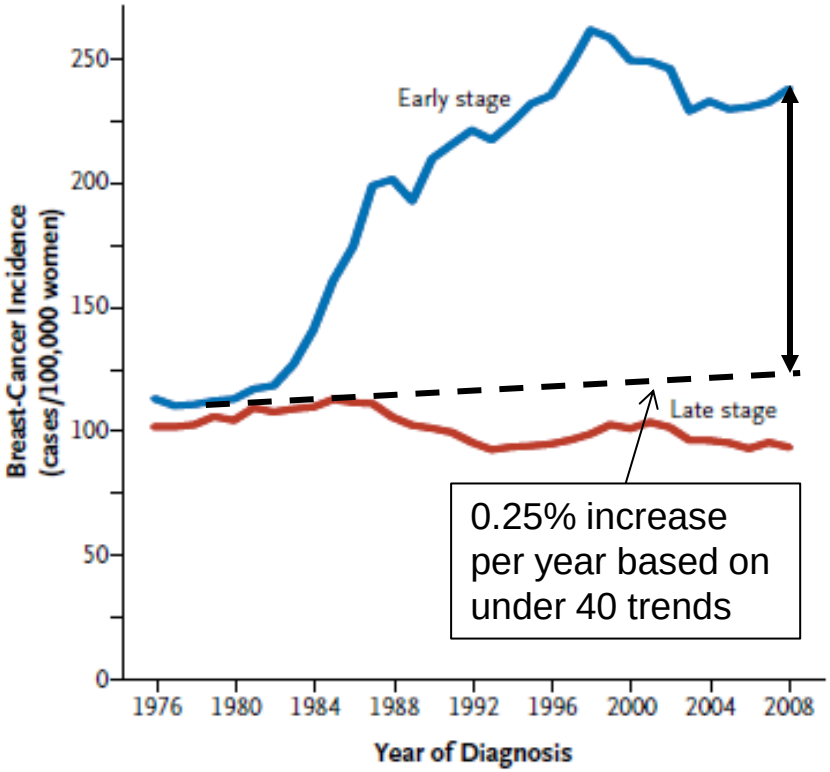
Excess Incidence Approach

Bleyer and Welch

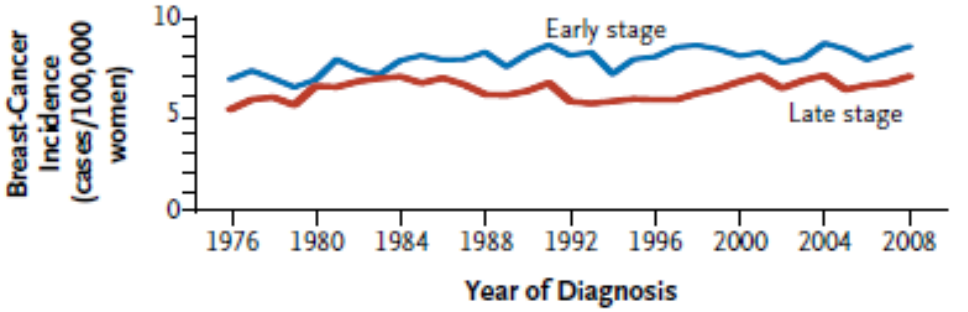
Screening Uptake



Incidence by Stage: Age 50+



Incidence by Stage: Age 40-49



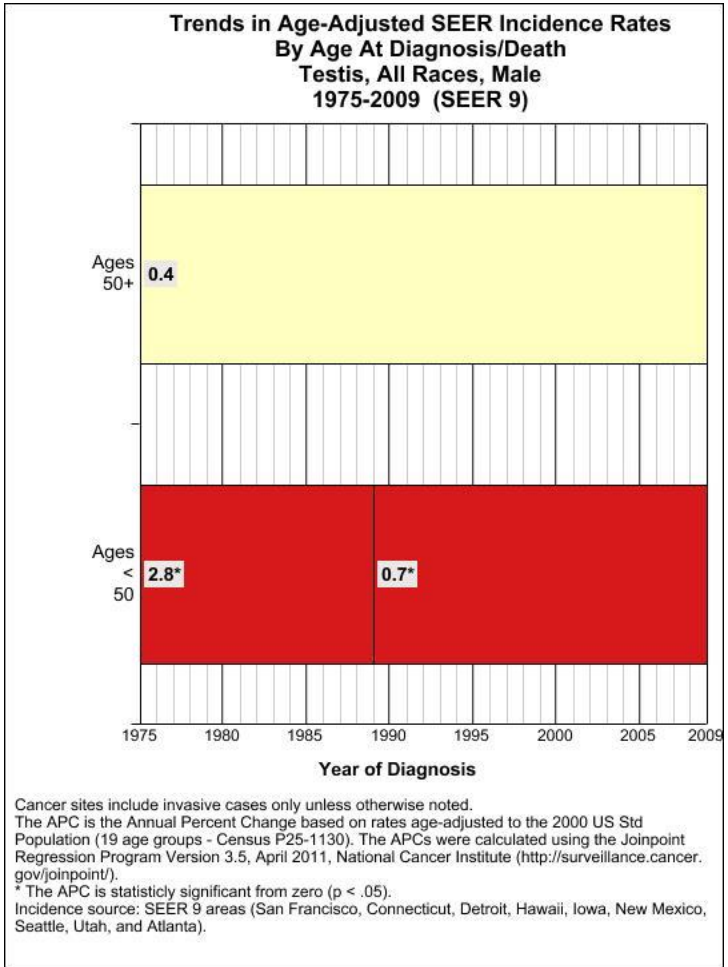
Includes in situ cases

Timing?

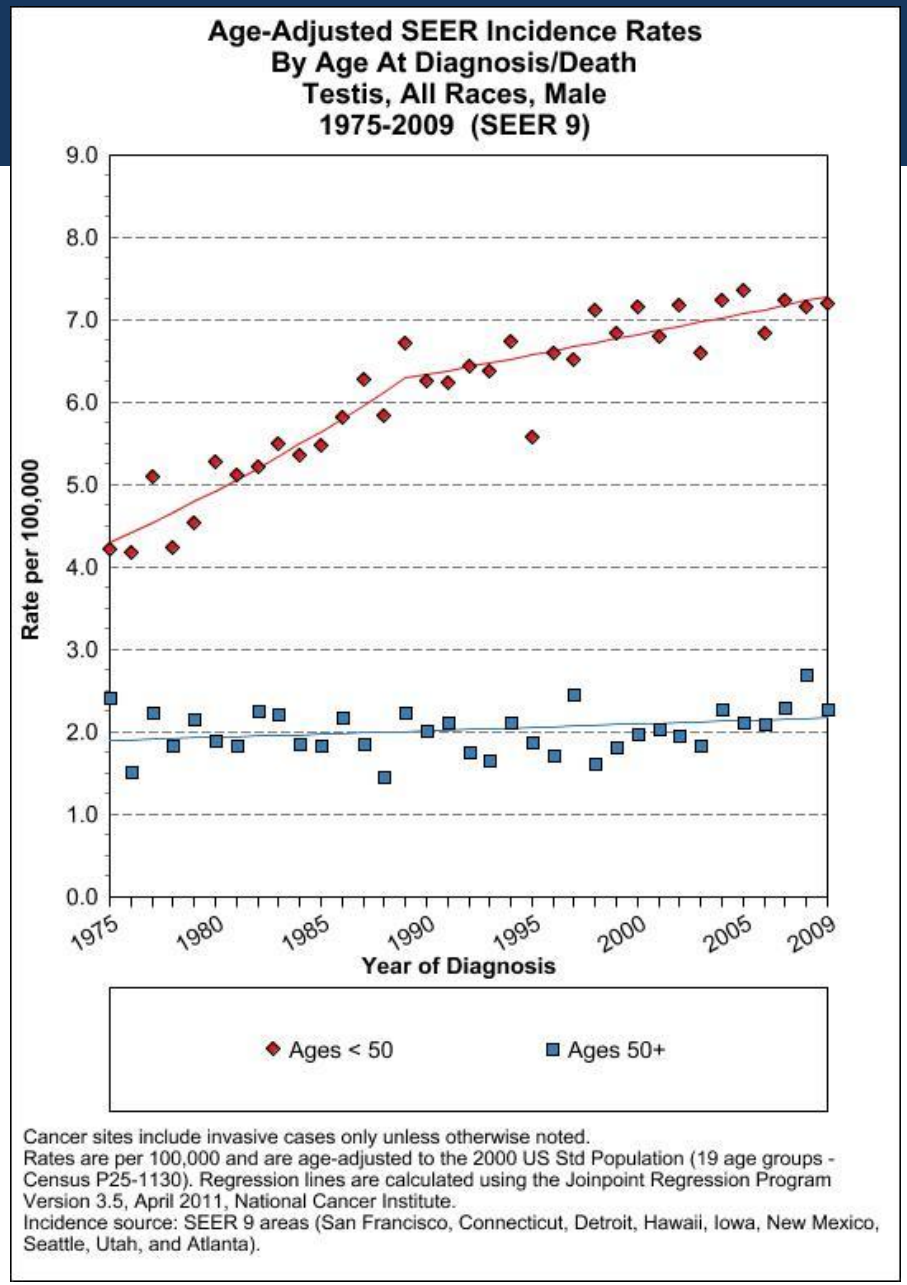
Counterfactual?

Trends in Testicular Cancer Incidence

Trends in younger men do not match those in older men



Cancer sites include invasive cases only unless otherwise noted.
The APC is the Annual Percent Change based on rates age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). The APCs were calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute (http://surveillance.cancer.gov/joinpoint/).
* The APC is statisticly significant from zero ($p < .05$).
Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).



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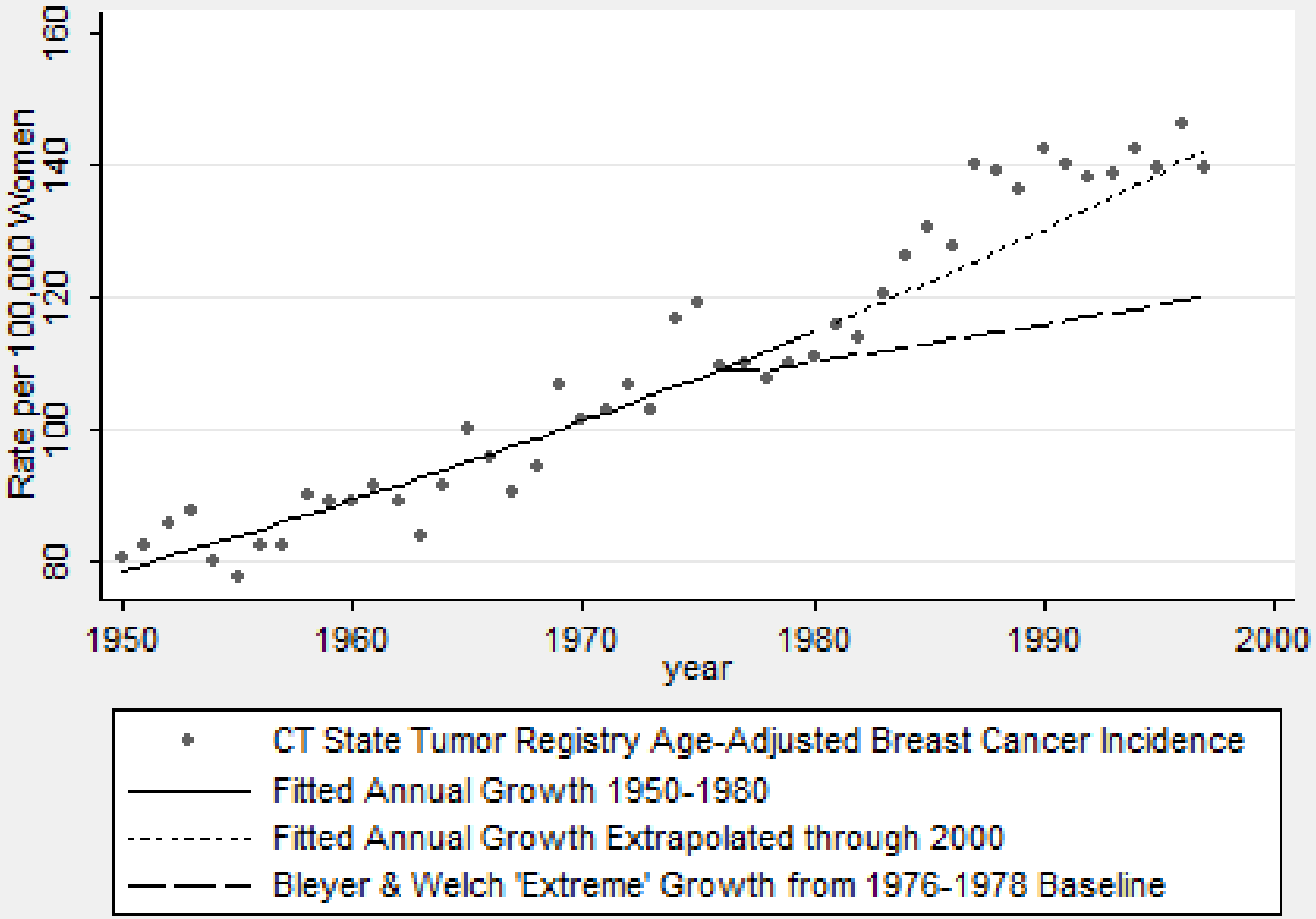
CISNET Counterfactual Incidence



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TUSCON

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The test's popularity has led to a hugely expensive public health disaster. It's an issue I am painfully familiar with — I discovered P.S.A. in 1970. As Congress searches for ways to cut costs in our health care system, a significant savings could come from changing the way the antigen is used to screen for prostate cancer.

Americans spend an enormous amount testing for prostate cancer. The annual bill for P.S.A. screening is at least $3 billion, with much of it paid for by Medicare and the Veterans Administration.

Prostate cancer may get a lot of press, but consider the numbers: American men have a 16 percent lifetime chance of receiving a diagnosis of prostate cancer, but only a 3 percent chance of dying from it. That's because the majority of prostate cancers grow slowly. In other words, men lucky enough to reach old age are much more likely to die with prostate cancer than to die of it.

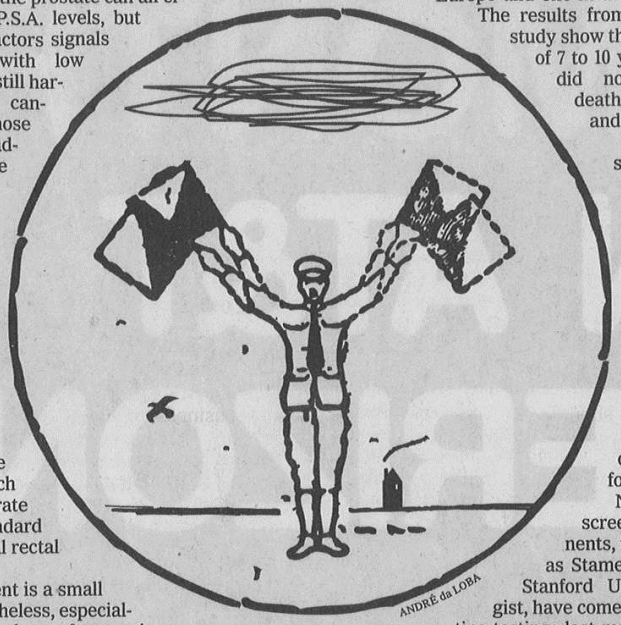
Even then, the test is hardly more effective than a coin toss. As I've been trying to make clear for many years now, P.S.A. testing can't detect prostate cancer and, more important, it can't distinguish between the two types of prostate cancer — the one that will kill you and the one that won't.

Richard J. Ablin is a research professor of immunobiology and pathology at the University of Arizona College of Medicine and the president of the Robert Benjamin Ablin Foundation for Cancer Research.

Instead, the test simply reveals how much of the prostate antigen a man has in his blood. Infections, over-the-counter drugs like ibuprofen, and benign swelling of the prostate can all elevate a man's P.S.A. levels, but none of these factors signals cancer. Men with low readings might still harbor dangerous cancers, while those with high readings might be completely healthy.

In approving the procedure, the Food and Drug Administration relied heavily on a study that showed testing could detect 3.8 percent of prostate cancers, which was a better rate than the standard method, a digital rectal exam.

Still, 3.8 percent is a small number. Nevertheless, especially in the early days of screening, men with a reading over four nanograms per milliliter were sent for painful prostate biopsies. If the biopsy showed any signs of cancer, the patient was almost always pushed into surgery, intensive radiation or other damaging treatments.



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The European study showed a small decline in death rates, but also found that 48 men would need to be treated to save one life. That's 47 men who, in all likelihood, can no longer function sexually or stay out of the bathroom for long.

Numerous early screening proponents, including Thomas Stamey, a well-known Stanford University urologist, have come out against routine testing; last month, the American Cancer Society urged more caution in using the test. The American College of Preventive Medicine also concluded that there was insufficient evidence to recommend routine screening.

So why is it still used? Because drug companies continue peddling the tests and advocacy groups push "prostate cancer awareness" by encouraging men to get screened. Shamefully, the American Urological Association still recommends screening, while the National Cancer Institute is vague on the issue, stating that the evidence is unclear.

The federal panel empowered to evaluate cancer screening tests, the Preventive Services Task Force, recently recommended against P.S.A. screening for men aged 75 or older. But the group has still not made a recommendation either way for younger men.

Prostate-specific antigen testing does have a place. After treatment for prostate cancer, for instance, a rapidly rising score indicates a return of the disease. And men with a family history of prostate cancer should probably get tested regularly. If their score starts skyrocketing, it could mean cancer.

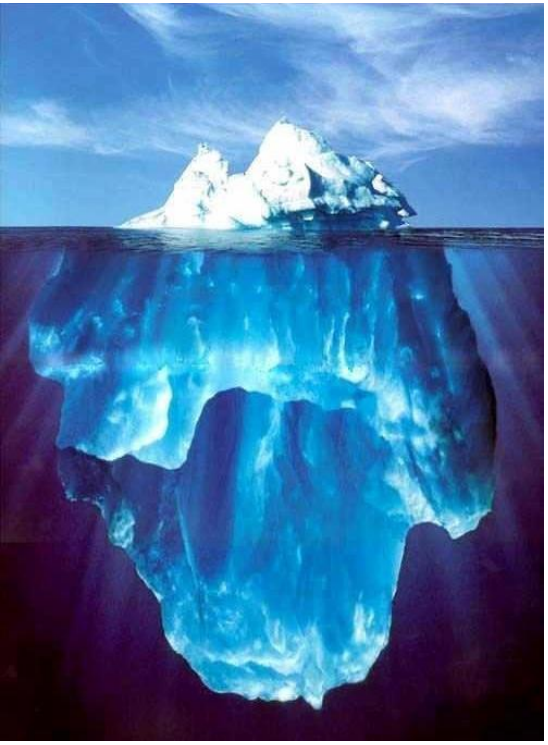
A single test has cost billions in unneeded treatment.

But these uses are limited. Testing should absolutely not be deployed to screen the entire population of men over the age of 50, the outcome pushed by those who stand to profit.

I never dreamed that my discovery four decades ago would lead to such a profit-driven public health disaster. The medical community must confront reality and stop the inappropriate use of P.S.A. screening. Doing so would save billions of dollars and rescue millions of men from unnecessary, debilitating treatments. □

48 = NND = Number needed to detect = <u>EXCESS CASES over 9 years</u>
lives saved over 9 years

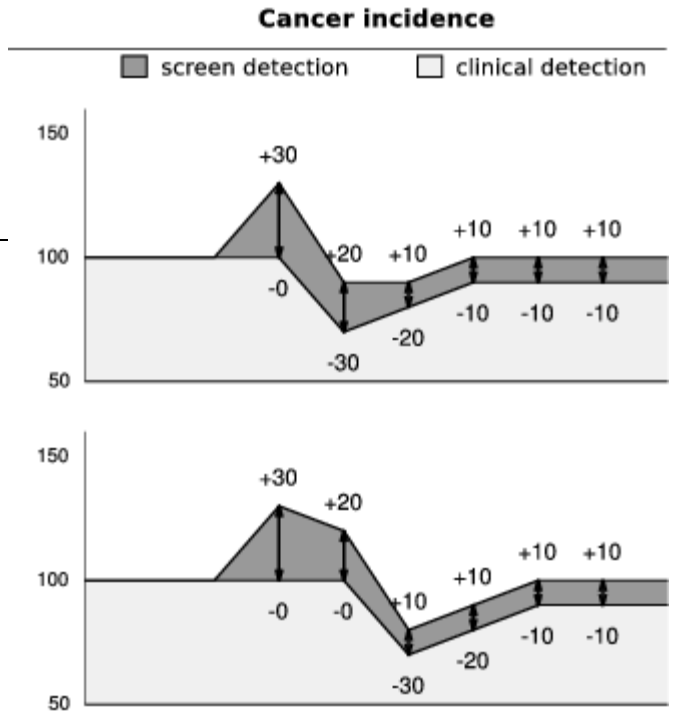
Lead-Time/Modeling Approach



1. Observed data

2. Underlying lead time

3. Overdiagnosis



Excess Incidence vs Lead Time: Breast Cancer

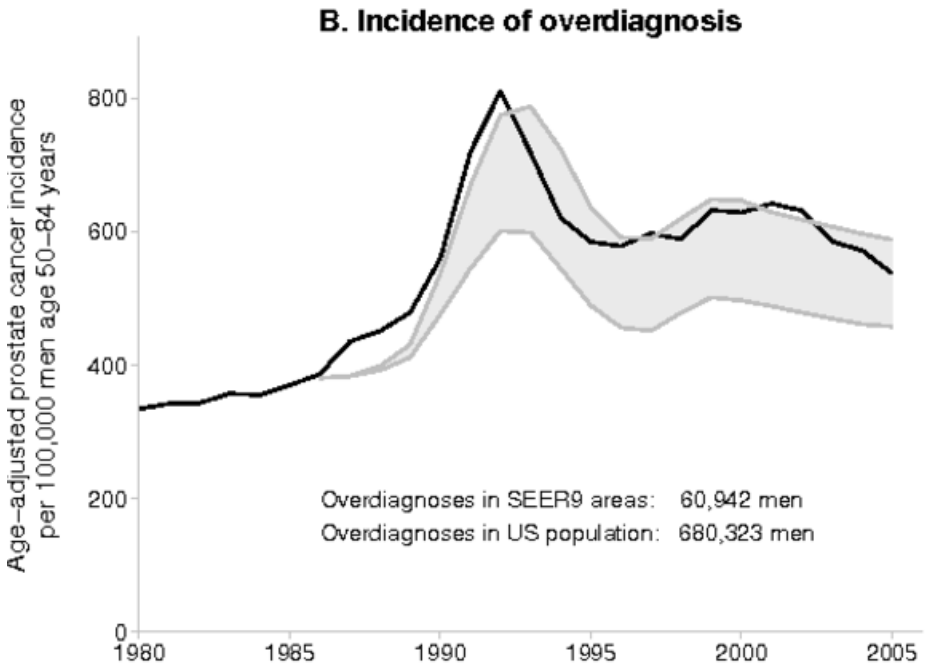
Author	Years of study	In situ cases	Estimate	Measure	Approach
Morrell, 2010	1999–2001	No	**30–42%**	Excess cases/ cases expected without screening	***Excess incidence***
Gotzsche, 2011	Multiple	Yes	**30%**	Excess cases/ cases expected without screening	***Excess incidence***
Kalager, 2012	1996–2005	No	**15–25%**	Excess cases/ cases expected without screening	***Excess incidence***
Bleyer, 2012	1976–2008	Yes	**31%**	Excess cases/ detected cases	***Excess incidence***
Paci, 2006	1986–2001	Yes No	**4.6%** **3.2%**	Cases overdiagnosed/ cases expected without screening	***Lead-time***
Olsen, 2006	1991–1995	No	**4.8%**	Cases overdiagnosed/ detected cases	***Lead-time***
De Gelder 2011	1990–2006	Yes	**8.9%** **4.6%** **5%**	Cases overdiagnosed/ Screen-detected cases Cases overdiagnosed/ detected cases Cases overdiagnosed/ cases expected without screening	***Lead time***

Prostate Cancer Overdiagnosis Two Ways

Disease Modeling vs Excess Incidence

Disease Modeling

Gulati, Gore, Etzioni 2013



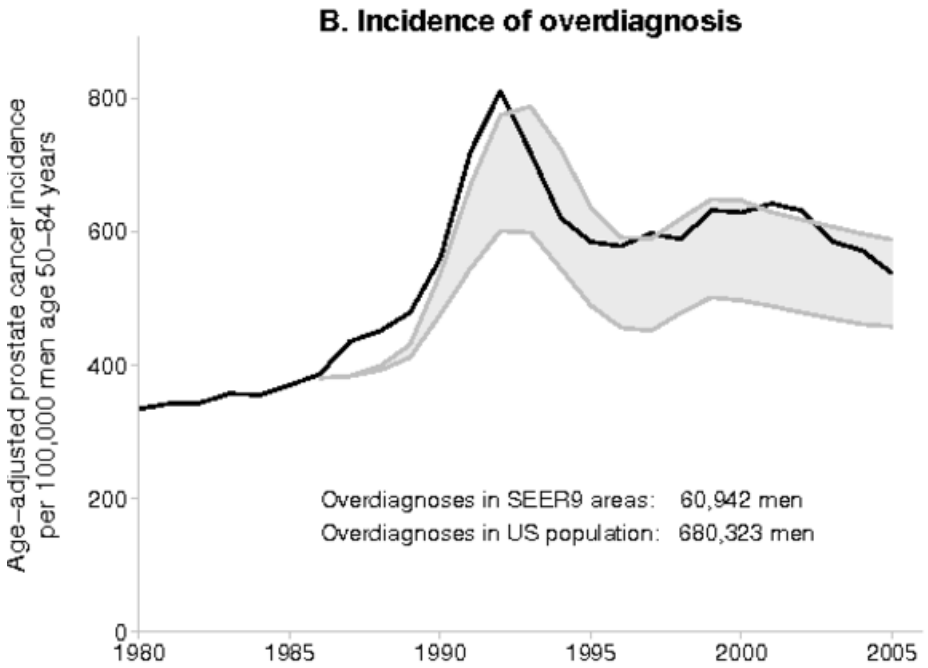
Since 1986, an estimated additional 680,000 men were diagnosed with prostate cancer.

Overdiagnosis Two Ways

Disease Modeling vs Excess Incidence

Disease Modeling

Gulati, Gore, Etzioni Annals of Internal Medicine 2013



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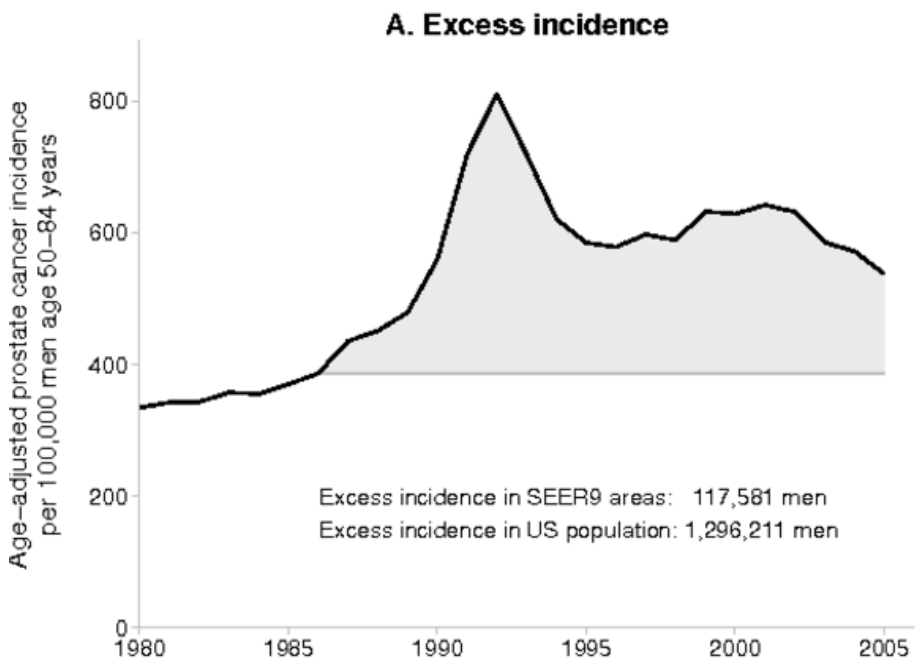
Excess Incidence

Welch, Albertson JNCI 2009



Since 1986, an estimated additional 1.3 million men were diagnosed with prostate cancer.

Model Estimates of NND in Prostate Cancer

JOURNAL OF CLINICAL ONCOLOGY | STATISTICS IN ONCOLOGY

What Is the True Number Needed to Screen and Treat to Save a Life With Prostate-Specific Antigen Testing?

Stacy Loeb, Edward F. Vonesh, E. Jeffrey Metter, H. Ballentine Carter, Peter H. Gann, and William J. Catalona

18

At 12 years

Journal of Clinical Epidemiology

Long-term projections of the harm-benefit trade-off in prostate cancer screening are more favorable than previous short-term estimates

Roman Gulati[a], Angela B. Mariotto[b], Shu Chen[a], John L. Gore[c], Ruth Etzioni[a,*]

9

At 25 years

The NEW ENGLAND JOURNAL of MEDICINE

Quality-of-Life Effects of Prostate-Specific Antigen Screening

Eveline A.M. Heijnsdijk, Ph.D., Elisabeth M. Wever, M.Sc., Anssi Auvinen, M.D., Jonas Hugosson, M.D., Stefano Ciatto, M.D.,* Vera Nelen, M.D., Maciej Kwiatkowski, M.D., Arnauld Villers, M.D., Alvaro Páez, M.D., Sue M. Moss, Ph.D., Marco Zappa, M.D., Teuvo L.J. Tammela, M.D., Tuukka Mäkinen, M.D., Sigrid Carlsson, M.D., Ida J. Korfage, Ph.D., Marie-Louise Essink-Bot, Ph.D., Suzie J. Otto, Ph.D., Gerrit Draisma, Ph.D., Chris H. Bangma, M.D., Monique J. Roobol, Ph.D., Fritz H. Schröder, M.D., and Harry J. de Koning, M.D.

5

Long term

Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial

BMJ

	Cases after 5 years	Excess after 5 years	Excess after 15 years
CBE	524		
Mamm + CBE	666 (212 mamm only)	142	106

Assuming that nearly all over-diagnosed cancers in the Canadian National Breast Screening Study were non-palpable, 50% (106/212) of mammogram detected, non-palpable cancers were over-diagnosed.

Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial

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	Cases after 5 years	Excess after 5 years	Excess after 15 years
CBE	524		
Mamm + CBE	666 (212 mamm only)	142	106

> Assuming that nearly all over-diagnosed cancers in the Canadian National Breast Screening Study were non-palpable, 50% (106/212) of mammogram detected, non-palpable cancers were over-diagnosed.

1. How do we know that screening behavior equalized in the two groups after 5 years?

2. For 50% of non-palpable cancers to be overdiagnosed implies about a ten year lead time but studies of lead time among invasive breast cancers estimate about 3 years average lead time

Right-Sizing Cancer Screening
(and treatment)

Right-sizing cancer screening requires right-sizing our estimates of the risk of overdiagnosis

- ***Risk of overdiagnosis depends on***
  - Individual characteristics (particularly age)
  - Tumor features
- ***For older individuals***
  - More conservative biopsy criteria
  - Stop screening if low life expectancy
  - Stop earlier if PSA consistently low

Addresses Overdiagnosis

- ***For tumors that are clearly low-risk***
  - Establish adequate surveillance procedures
  - Consider re-labeling these lesions

Addresses Overtreatment