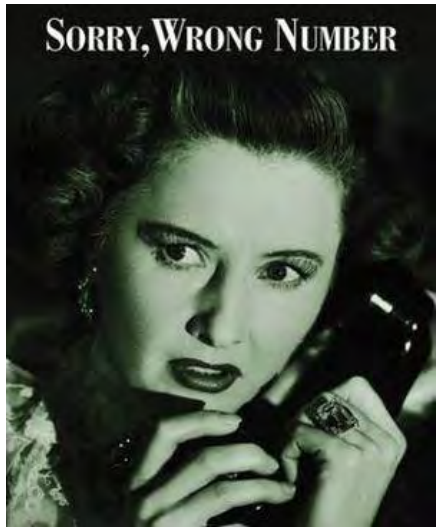
Cancer Screening: Evidence, Opinion and Fact

Dialogue on Cancer April 2018



Ruth Etzioni

Fred Hutchinson Cancer Research Center

FRED HUTCH
40 YEARS OF CURES 1975–2015

Three thoughts to begin

1. Cancer screening is a good idea in principle
   → Detect cancers early while still curable

2. Cancer screening is controversial in practice
   → Evidence about harm/benefit is uncertain

3. Cancer screening is <u>complicated</u>
   → Standard ways of evaluating evidence don't always work and can mislead

Where does evidence about cancer screening come from?

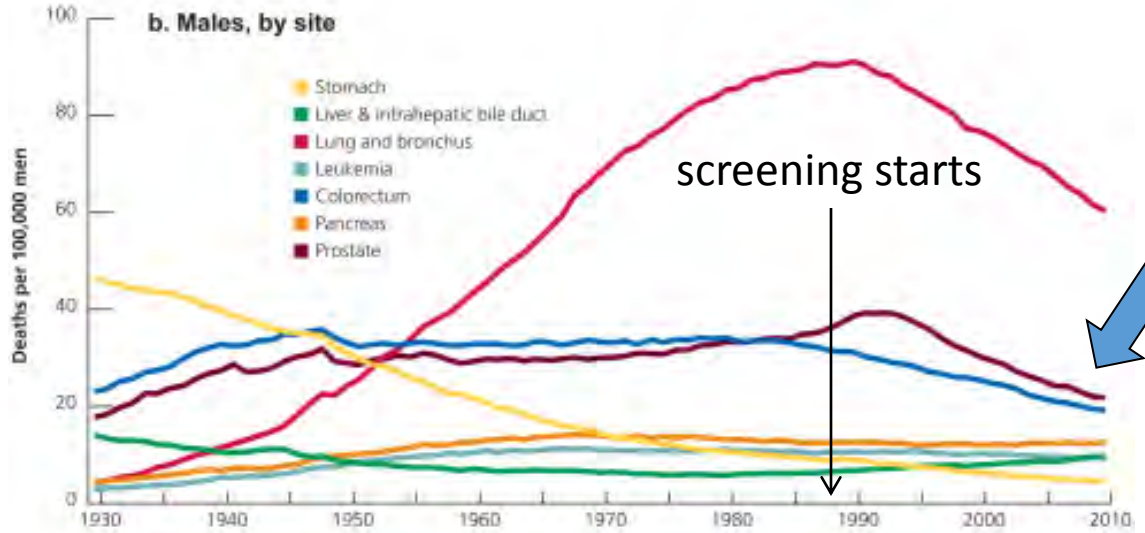
- Clinical trials of cancer screening
- Population trends in cancer cases and deaths before and after screening
- Observational/epidemiologic studies

Why is cancer screening controversial?

1. Population trends reflect other improvements in cancer control

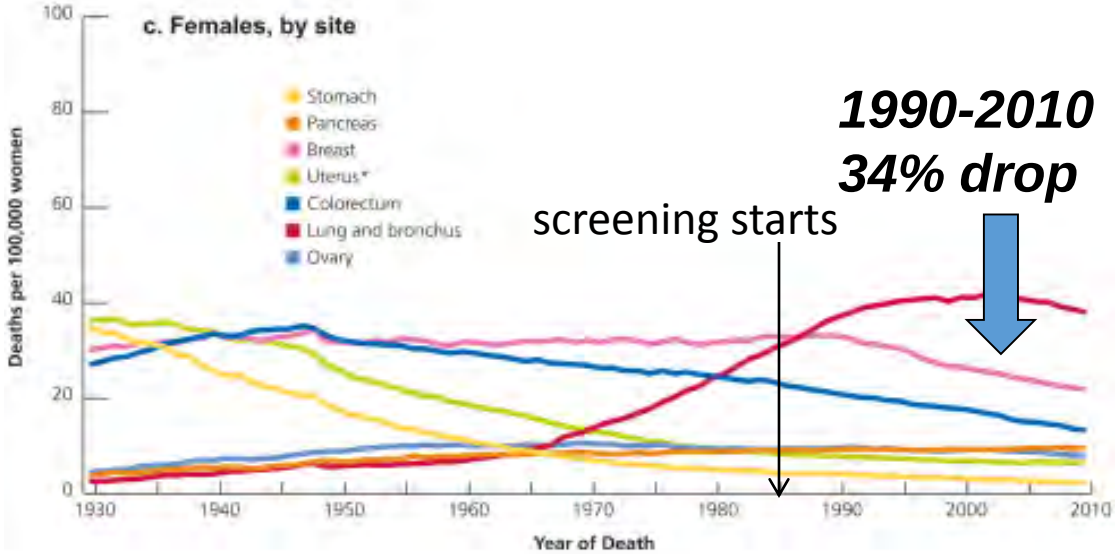
- Primary treatment trends
- Disease monitoring and new treatments for recurrent disease
- Supportive care for cancer patients

Breast and prostate cancer mortality in the US



screening starts

1990-2010
43% drop

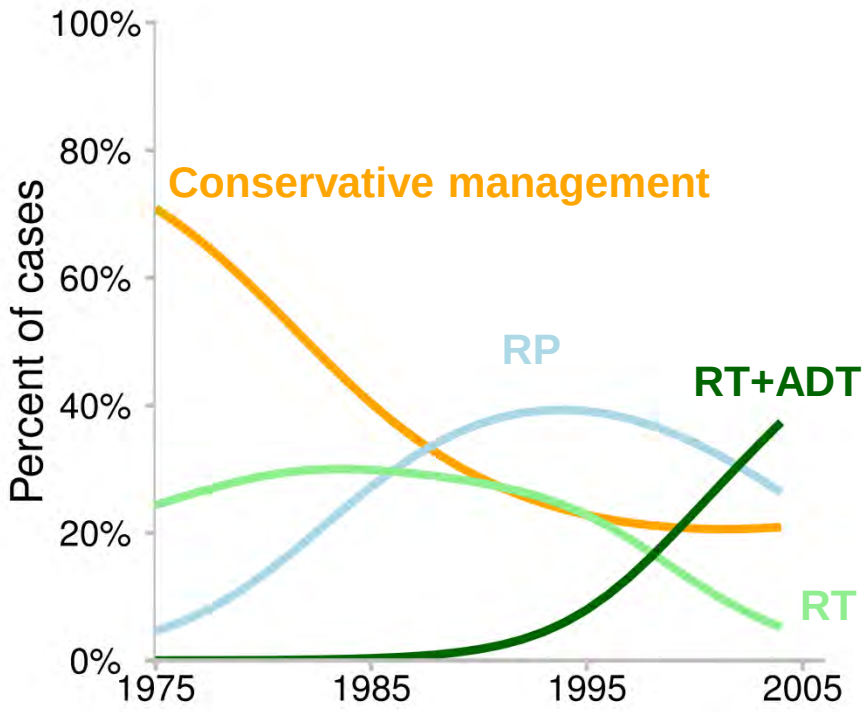


1990-2010
34% drop

screening starts

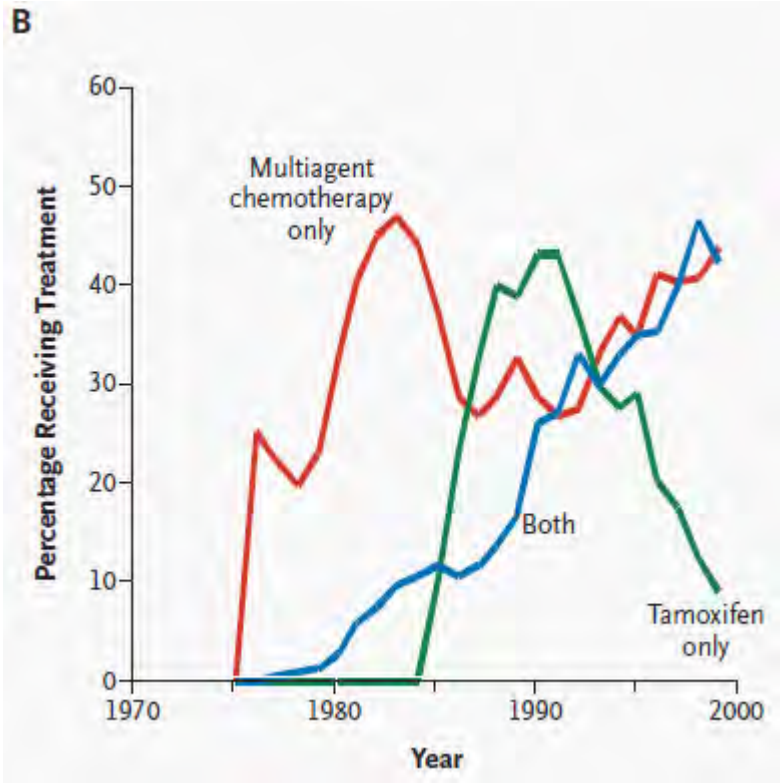
Prostate and breast cancer treatment trends

Prostate Cancer:
Primary treatment



RP: radical prostatectomy
RT: radiation therapy
ADT: hormone therapy

Breast Cancer:
Adjuvant chemotherapy



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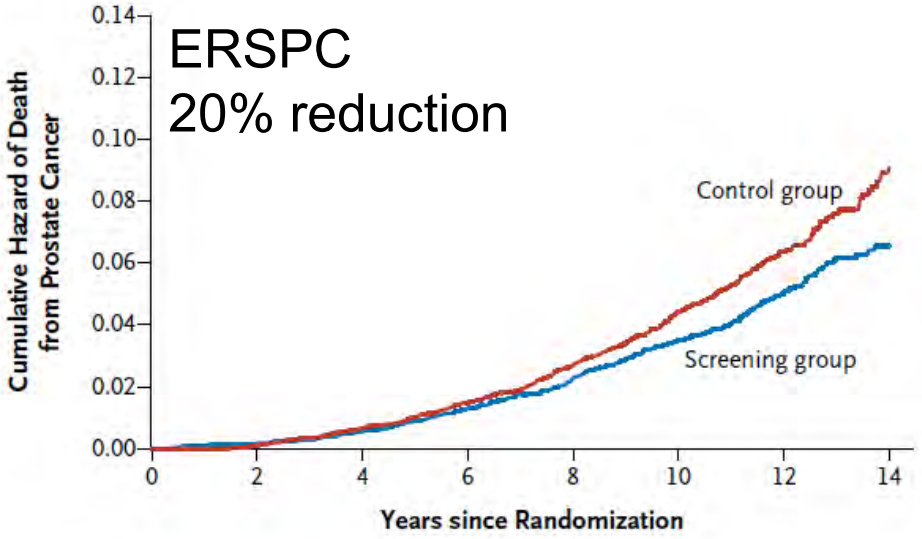
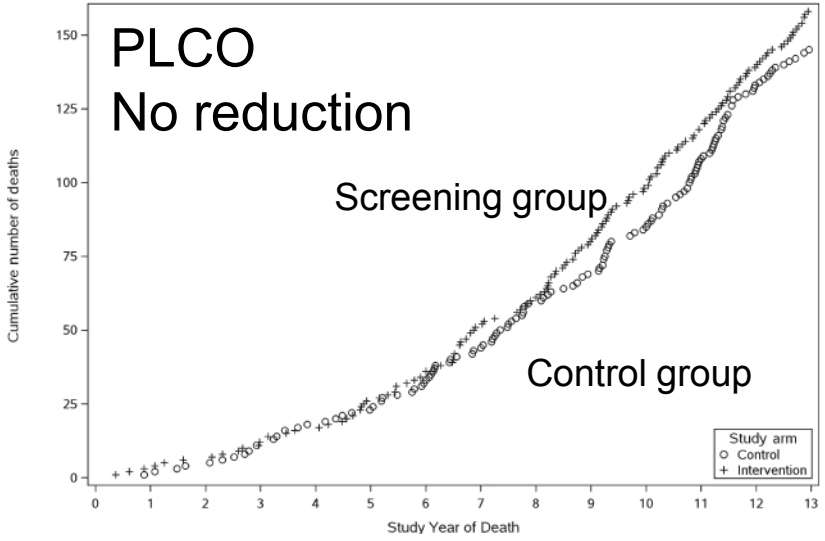
- Many breast screening trials, some with no benefit

Prostate cancer screening trials

Cumulative deaths in screen and control groups



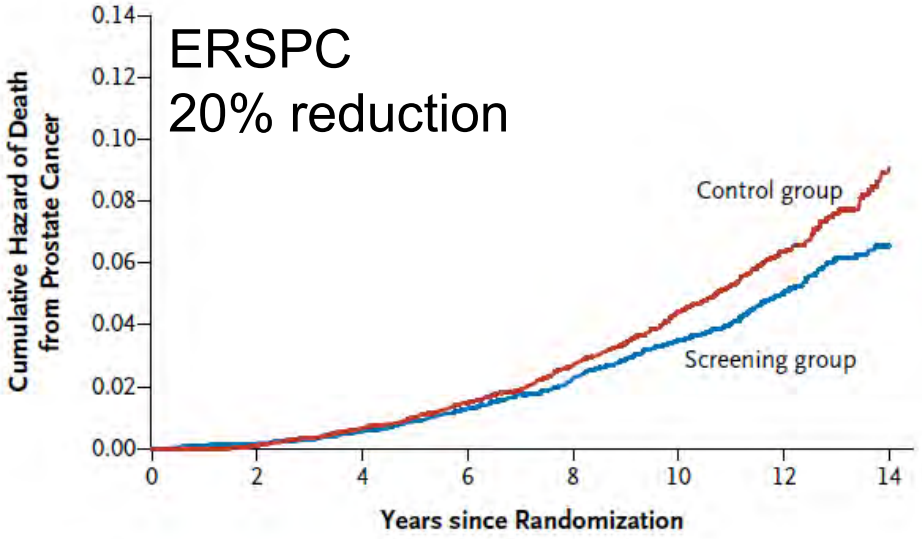
European trial



US trial

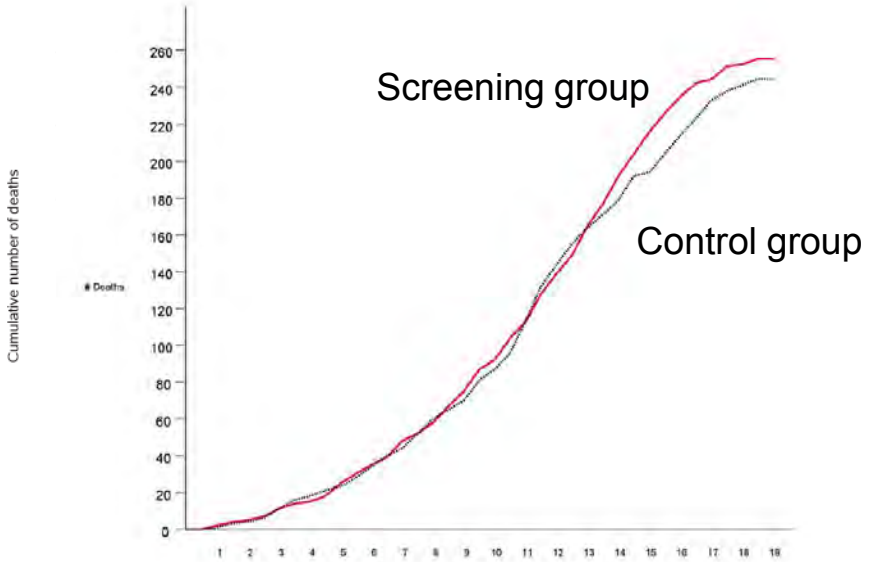
Prostate cancer screening trials

Cumulative deaths in screen and control groups



European trial

Pinsky et al, Cancer 2018



US trial

Breast cancer screening trials

Relative reduction in risk of death in screened group

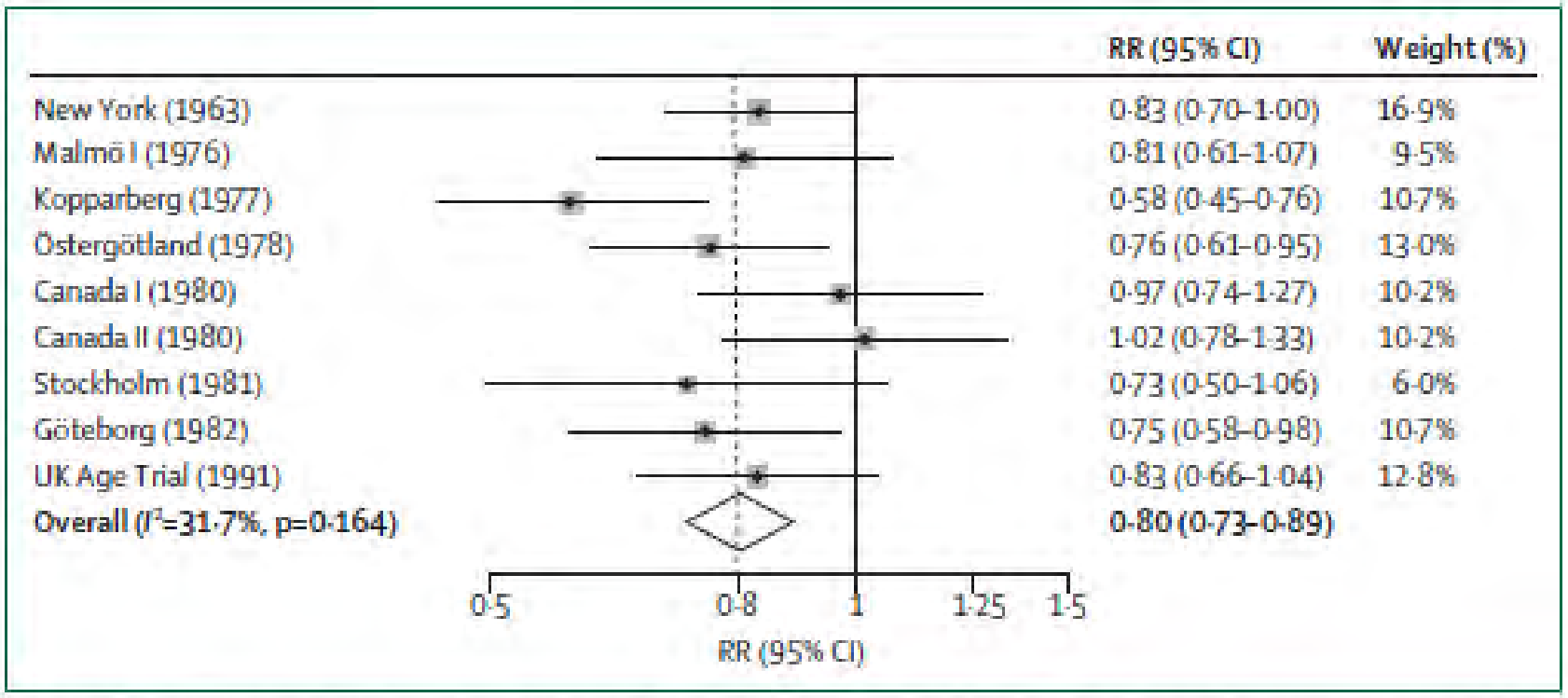


Figure 1: **Meta-analysis of breast cancer mortality after 13 years of follow-up in breast cancer screening trials**
Adapted from the Cochrane Review.[5] RR=relative risk. Malmö II is excluded because follow-up of about 13 years was not available; the Swedish Two County (Kopparberg and Östergötland) and Canada I and II trials are split into their component parts; the Edinburgh trial is excluded because of severe imbalances between randomised groups. Weights are from random-effects analysis.

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3. Observational studies of cancer screening are prone to bias

- Those who choose to get screening may have a different innate risk of disease

4. People are worried about harms of screening like overdiagnosis

- Does cancer screening lead to diagnosis of harmless tumors?

Can the Prostate Test Be Hazardous to Your Health?

By LARRY RATZENSTEIN

FOR millions of American men over age 50, the Prostate Specific Antigen blood test for detecting prostate cancer has become a routine part of their annual check-up. If they don't ask for it, their doctors often recommend it. But there are serious concerns about the test's usefulness and whether the treatment for prostate cancer may be harming more lives than it saves.

Despite a recent barrage of high-profile endorsements for the test by Arnold Palmer and H. Norman Schwarzkopf, among others, and one major medical or public-health group endorses the screening. And in recent years, most of the groups that have evaluated the test either oppose its use for routine screening, or do not recommend it. These include the National Cancer Institute, the American College of Physicians, the American College of Preventive Medicine and the United States Preventive Services Task Force.

The American Cancer Society, which once endorsed the screening, changed its stance in 1997 and now recommends that the Prostate Specific Antigen test, also known as P.S.A., be offered annually to men 50 and older, who should be given information about the risks and benefits of treatment should cancer be found. Even the American Urological Association, whose members are among the most enthusiastic advocates of P.S.A. testing, now endorses the new American Cancer Society policy.

Dr. Gabriel Feldman, the society's national director of prostate and colorectal cancer control, calls the P.S.A. "the most controversial medical test in the country right now."

Some objections to the screening involve errors. The test fails to detect prostate cancer in 1 in 4 men who have the disease (false-negative results), and as many as two-thirds of the men tested receive false-positive results, meaning that biopsies and other follow-ups fail to confirm the cancer finding. A P.S.A. score above four nanograms of antigen per milliliter of serum usually prompts follow-up tests.

But the main reason so many groups oppose P.S.A. screening is the lack of evidence that early detection actually improves a man's chances of surviving prostate cancer. "That's the big secret that nobody likes to talk about," Dr. Feldman said.

A discovery of cancer through P.S.A. testing usually leads to treatment. Dr. Feldman said. "But we don't have any conclusive evidence that surgery or other aggressive treatment make any difference in the long term in helping men live longer or better," he said. "Instead, we are going completely on information." Dr. Feldman contrasts prostate cancer with breast cancer, where clinical studies have proven that regular mammograms result in early detection and treatment that can save lives.

Dr. Feldman added that radical prostatectomy, the principal treatment for prostate cancer, causes 50 percent to 70 percent of all patients to become impotent for at least some period of time. Radiation, the other form of aggressive treatment, can cause similar side effects as well as other complications, he added. There is also some risk: approximately 1 percent of patients who undergo a radical prostatectomy die from it.

The P.S.A. detects prostate cancers 10 to 15 years earlier than was possible with the digital rectal exam. But because of the nature of prostate cancer — it is overwhelmingly a disease that afflicts elderly men and is usually very slow-growing — the early warning is often meaningless.

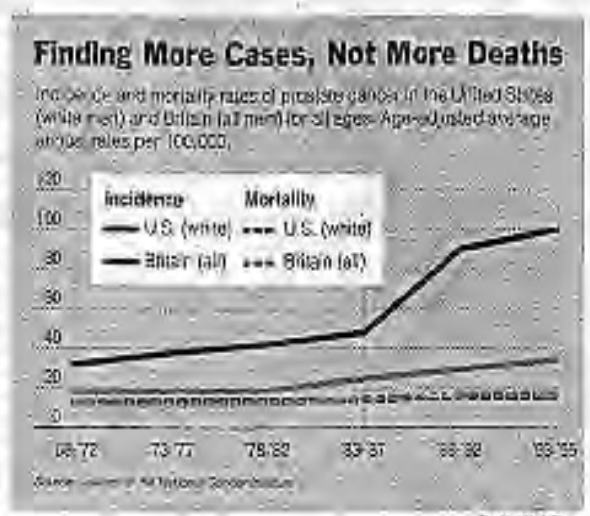
The prostate gland, the size of a walnut, is located in front of the rectum and beneath the bladder. The gland produces the fluid portion of semen and secretes prostate specific antigen, a protein that is pumped into the bloodstream in higher-than-normal amounts by cancerous cells.

While it is not uncommon for a few cancer cells to develop when men are in their 20's or 30's, these cells typically divide so slowly that tumors are rare in men younger than 50. After that, prostate cancer becomes increasingly common: men in their 60's and 70's have a 1-in-6 chance of being diagnosed with prostate cancer; a man living to 100 is almost certain to develop it.

But again, given prostate cancer's longest growth, most older men will die of other causes, like heart disease or stroke. Hence the adage that most prostate cancer patients die with their disease rather than from it. Moreover, the P.S.A. test cannot pinpoint those faster growing tumors for which early treatment might make a difference.

Still, the P.S.A. continues to have strong advocates, not the least of whom are patients who have had surgery and never experienced a recurrence. They are usually convinced that P.S.A. testing has prolonged their lives, if not saved them. Indeed, in some cases the test may have done just that.

And urologists, who in general



The New York Times

MORTALITY rates, however, were basically identical for all nine regions — and actually slightly higher in the Seattle-Puget Sound area. Dr. Brawley cites similar findings from a recent study comparing the United States with Britain. "I believe prostate cancer screening probably does save some lives," Dr. Brawley said, "but I can prove through studies like these that it ruins some lives."

A recent study of men living near the Mayo Clinic has added more fire to the debate. The Journal of Urology this month published a report by researchers who analyzed prostate cancer deaths in Olmsted County, Minn., from 1960 to 1997. They found

treatment doesn't work, why not we using the P.S.A. to look for tumors?"

To underscore their argument, critics of the P.S.A. point to studies showing that prostate cancer screening has little effect on the mortality rates. In a 1997 study in the journal Cancer, Dr. Otis Brawley, a medical oncologist and epidemiologist at the National Cancer Institute, calculated new prostate cancer cases per 100,000 men and prostate cancer deaths per 100,000 men in nine regions of the United States from 1974 through 1994. Not surprisingly, regions screened most intensely for prostate cancer (the Seattle-Puget Sound area, for example) had a much higher incidence of the cancer than regions screening the least (Connecticut, for one).

HEALTH CARE

THE WALL STREET JOURNAL.

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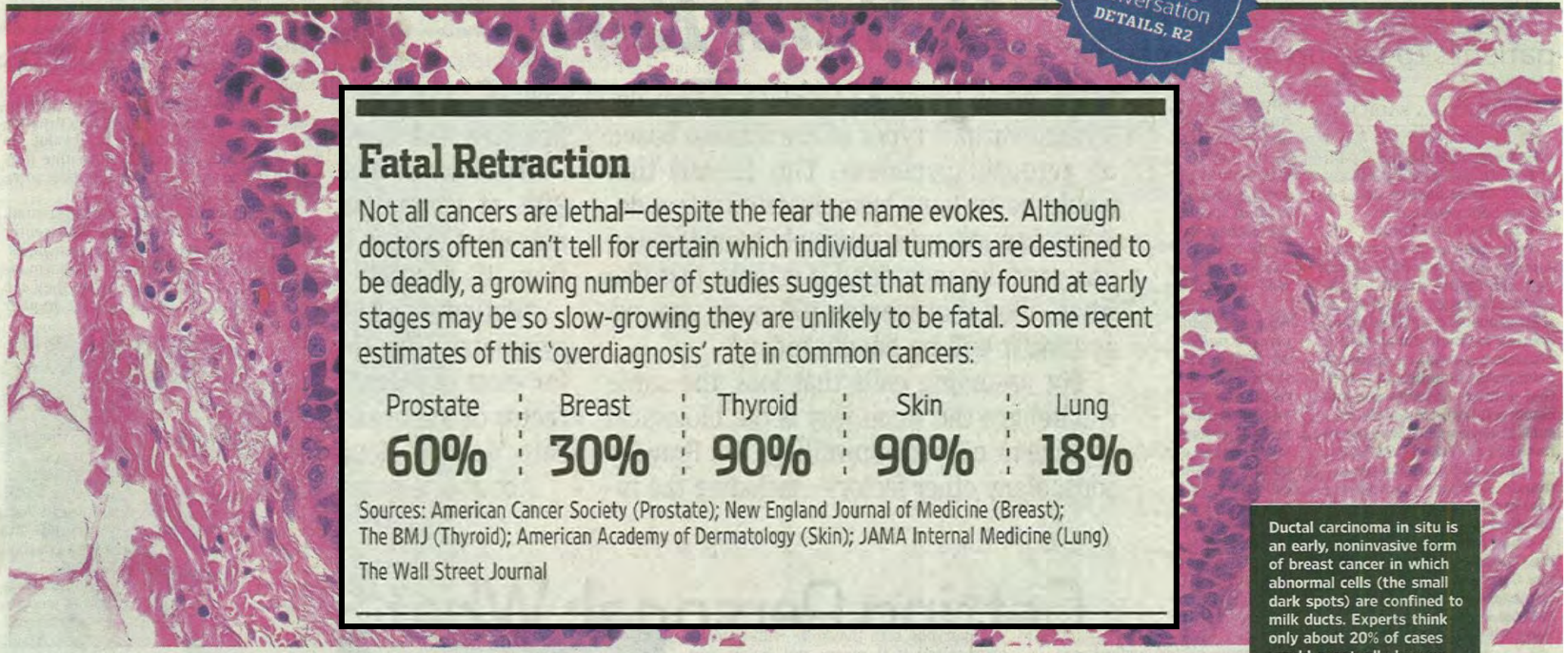
An Online Conversation
DETAILS, R2



Fatal Retraction

Not all cancers are lethal—despite the fear the name evokes. Although doctors often can't tell for certain which individual tumors are destined to be deadly, a growing number of studies suggest that many found at early stages may be so slow-growing they are unlikely to be fatal. Some recent estimates of this 'overdiagnosis' rate in common cancers:

Prostate	Breast	Thyroid	Skin	Lung
60%	30%	90%	90%	18%

Sources: American Cancer Society (Prostate); New England Journal of Medicine (Breast); The BMJ (Thyroid); American Academy of Dermatology (Skin); JAMA Internal Medicine (Lung)

The Wall Street Journal

Ductal carcinoma in situ is an early, noninvasive form of breast cancer in which abnormal cells (the small dark spots) are confined to milk ducts. Experts think only about 20% of cases would eventually become invasive cancer, but virtually all are treated with surgery and radiation.

IT'S TIME TO RETHINK

EARLY CANCER DETECTION

A growing number of experts argue that zealous screening too often leads to overtreatment. They call for changing the way we even talk about the disease.

BY MELINDA BECK

EARLY DETECTION HAS long been seen as a powerful weapon in the battle against cancer. But some experts now see it as double-edged sword.

While it's clear that early-stage cancers are more treatable than late-stage ones, some leading cancer

Gleason score of 6 or below "benign lesions"—although others note that that would mean half of the men treated for prostate cancer in the past 20 years didn't have cancer after all.

Overdiagnosis—the detection of tumors that aren't likely to cause harm—is now a hot topic in other cancers as well. A growing volume of studies estimate that as many as 30% of invasive breast cancers, 18%

Plan for today

- Review some commonly cited “facts and figures” about cancer screening from the abovementioned types of studies

- In each case
  - Explain the basis for the observation
  - Decide whether it is defensible or not

- Objective
  - Learn some of the pitfalls when evaluating screening harms and benefits
  - Come away better equipped to read and critique media reports about screening

Preview

1. Most screen-detected cases are not saved by screening
2. Clinical trials are the most reliable sources of evidence about screening benefit
3. Prostate cancer screening saves very few lives – 0 to 1 lives per 1000 men
4. The Canadian mammography trial shows breast cancer screening is not beneficial
5. Breast cancer screening doesn't work because advanced-stage incidence has not gone down
6. 30% of breast cancers and 60% of prostate cancers are overdiagnosed
7. Ovarian cancer screening doesn't work
8. New blood-based screening tests are going to solve all of our problems

1. Most screen-detected cases are not saved by screening

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

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

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.

"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

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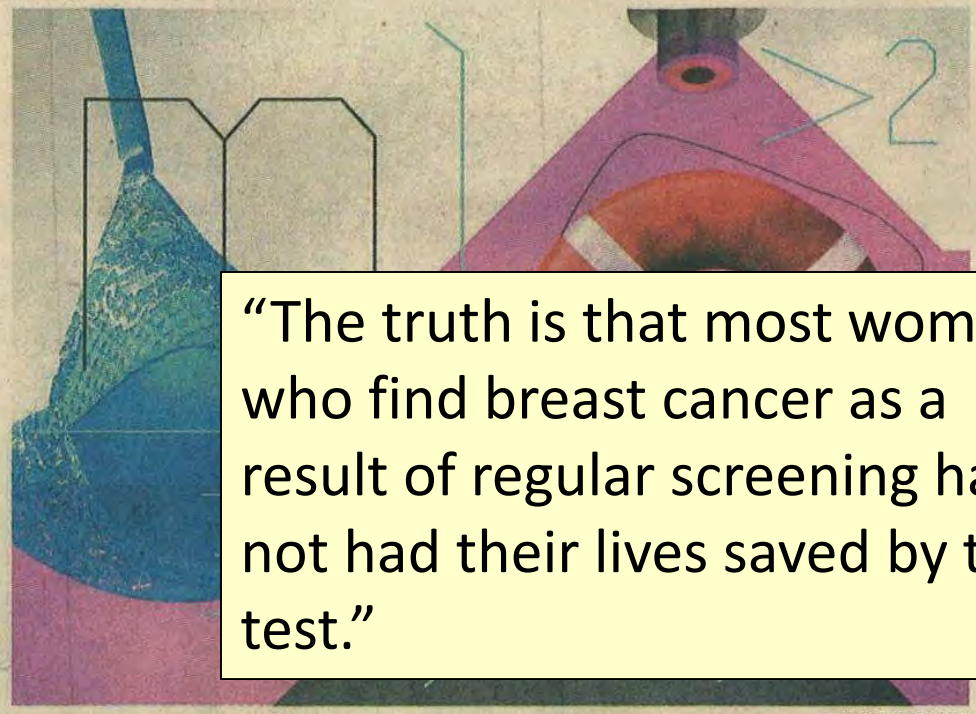


STUART BRADFORD

"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."

Breast cancer screening

Q: How many women would have had a diagnosis of breast cancer without screening?

A: 9% (based on old SEER data)

Q: How many women will die of breast cancer without screening:

A: About 3%

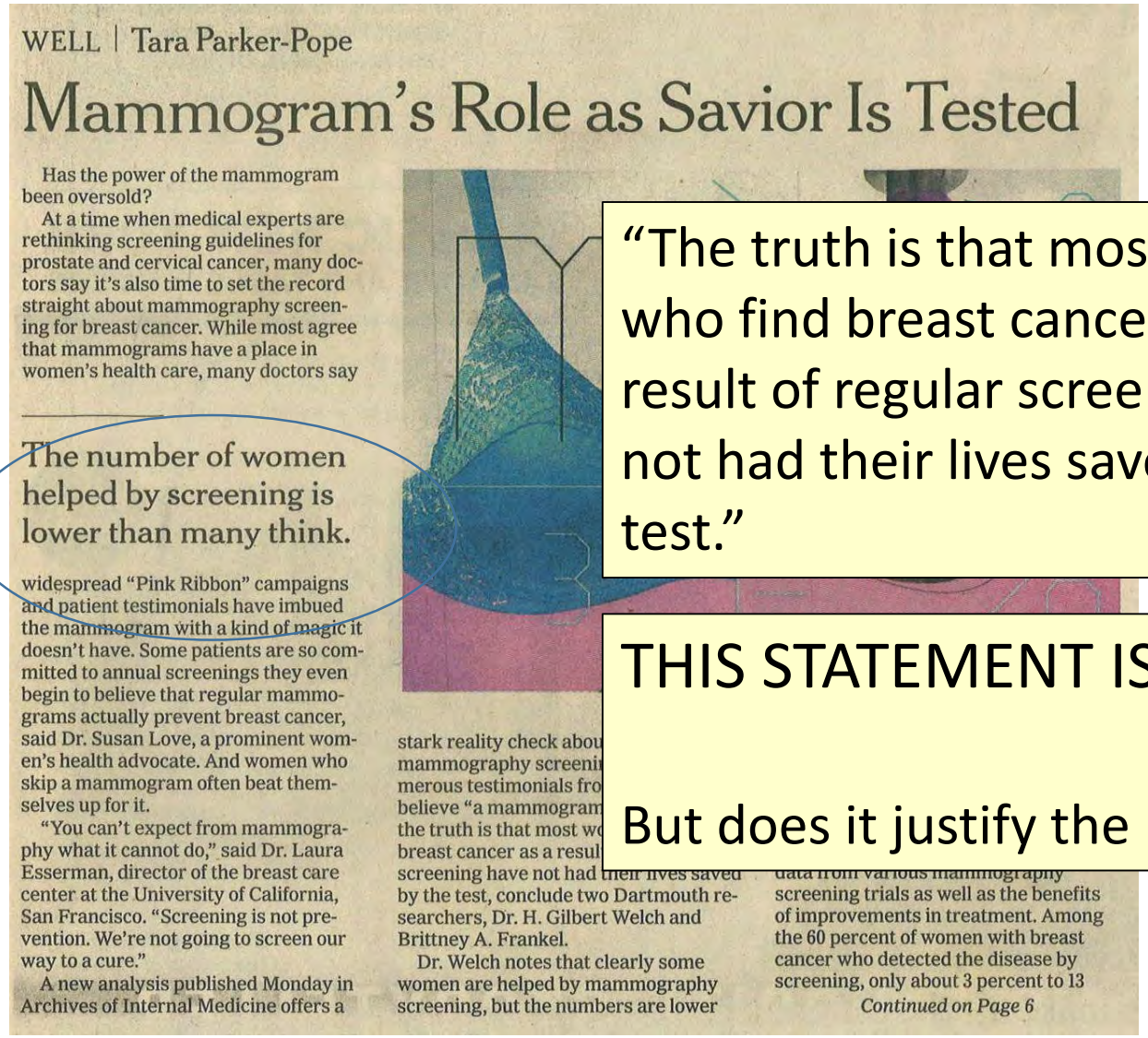
Q: If screening benefit is 20% reduction in breast cancer death, how many women will have their lives saved by screening?

A: About 0.6% (NOTE: this is less than 1%)

Q: How many women will be diagnosed with breast cancer with screening?

A: About 12.5% (based on SEER data from 2011-2013)

A fact of screening



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Continued on Page 6

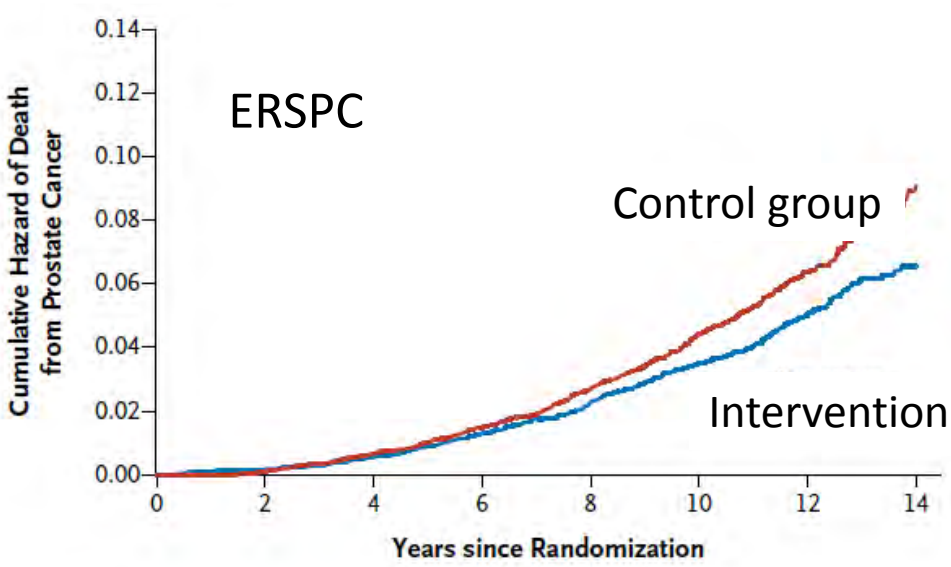
"The truth is that most women who find breast cancer as a result of regular screening have not had their lives saved by the test."

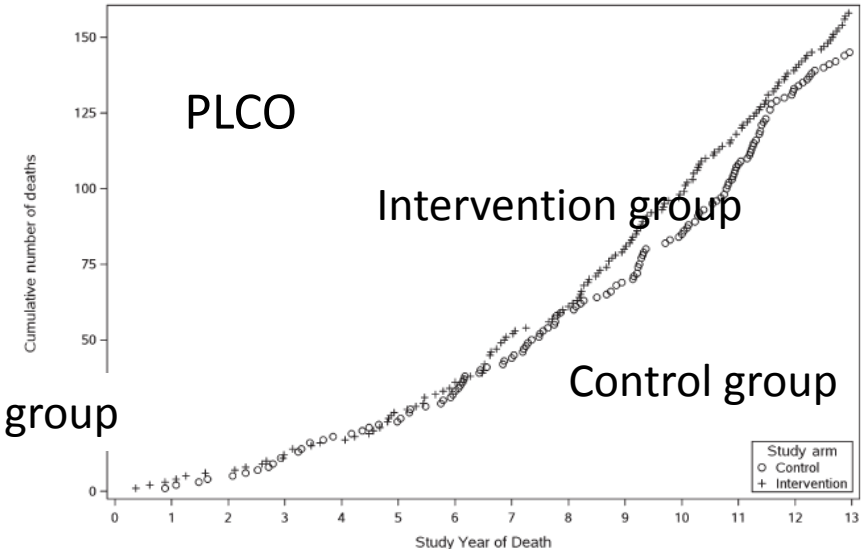
THIS STATEMENT IS TRUE

But does it justify the headline?

2. Clinical trials are reliable sources of evidence about screening benefit

Prostate cancer: Two screening trials

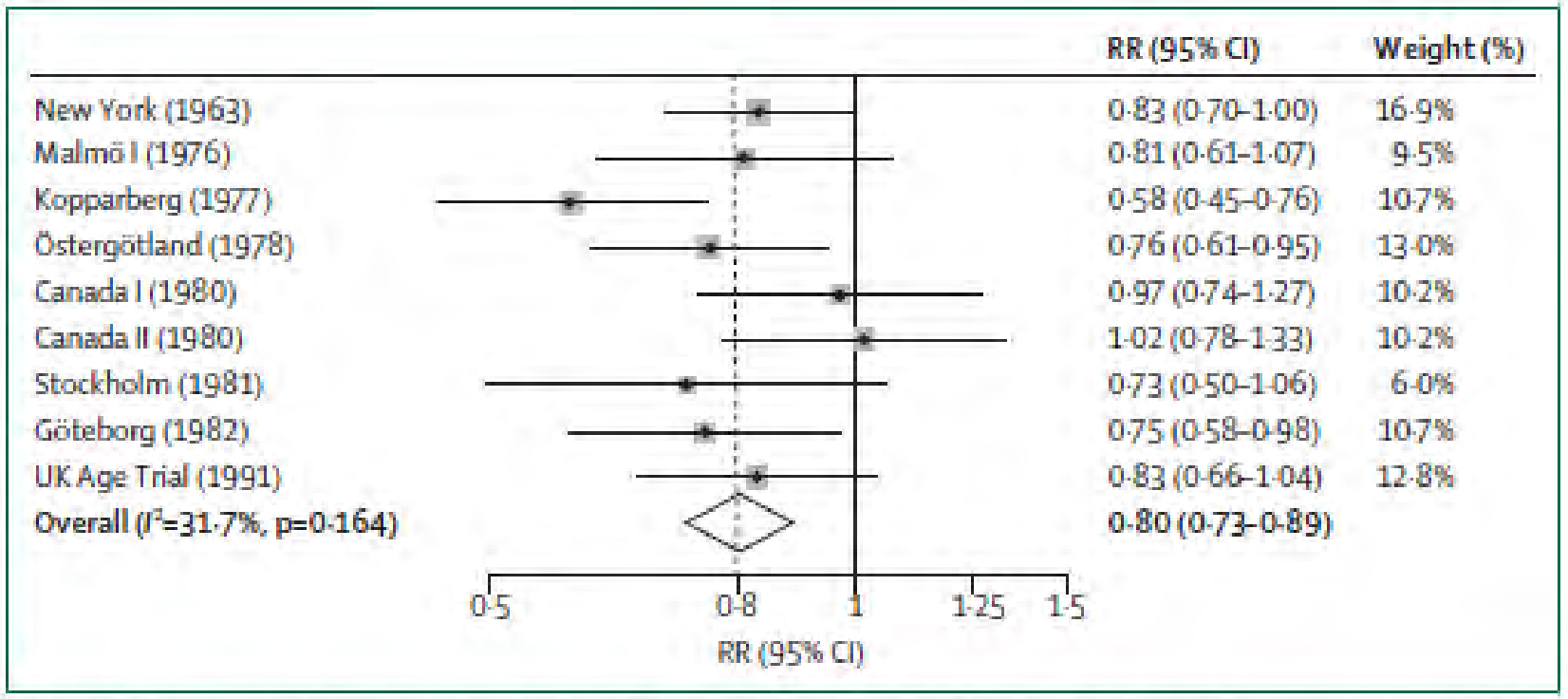




	ERSPC	PLCO
Percent reduction in mortality	21%	0%

Schröder et al., N Engl J Med, 2012; Andriole et al., J Natl Cancer Inst, 2012

Breast cancer: Eight screening trials



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Why so much variability?

Trial design and analysis

- Continuous-screen or stop-screen
- Duration of follow-up

Screening protocol

- Ages, intervals, cutoffs

Compliance, contamination, treatment

- Did screening group attend and comply with biopsy referral?
- Was there screening in the control group?
- What were the treatments available?
- Were the two groups treated similarly?

Timing

- Screening, biopsy and treatment technologies

Trial duration and screening benefit: Prostate cancer

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 15, 2012 VOL. 366 NO. 11

Prostate-Cancer Mortality at 11 Years of Follow-up

Study Years	Screening Group			Control Group			Rate Ratio (95% CI)†	P Value
	Deaths from Prostate Cancer	Person-Yr	Rate per 1000 Person-Yr	Deaths from Prostate Cancer	Person-Yr	Rate per 1000 Person-Yr		
	no.			*no.*				
1–9	189	608,852	0.31	274	745,912	0.37	0.85 (0.71 to 1.03)	
8–9	71	122,867	0.58	118	151,319	0.78	0.74 (0.55 to 0.99)	
10–11	56	97,994	0.57	111	120,900	0.92	0.62 (0.45 to 0.85)	
1–11	245	706,846	0.35	385	866,812	0.44	0.79 (0.67 to 0.92)	
≥12	54	57,387	0.94	77	66,241	1.16	0.80 (0.56 to 1.13)	
Total	299	764,233	0.39	462	933,052	0.50	0.79 (0.68 to 0.91)	

Y 1-9: 15% reduction

Y10-11: 38% reduction

Schroder et al, NEJM 366: 981-990, 2012

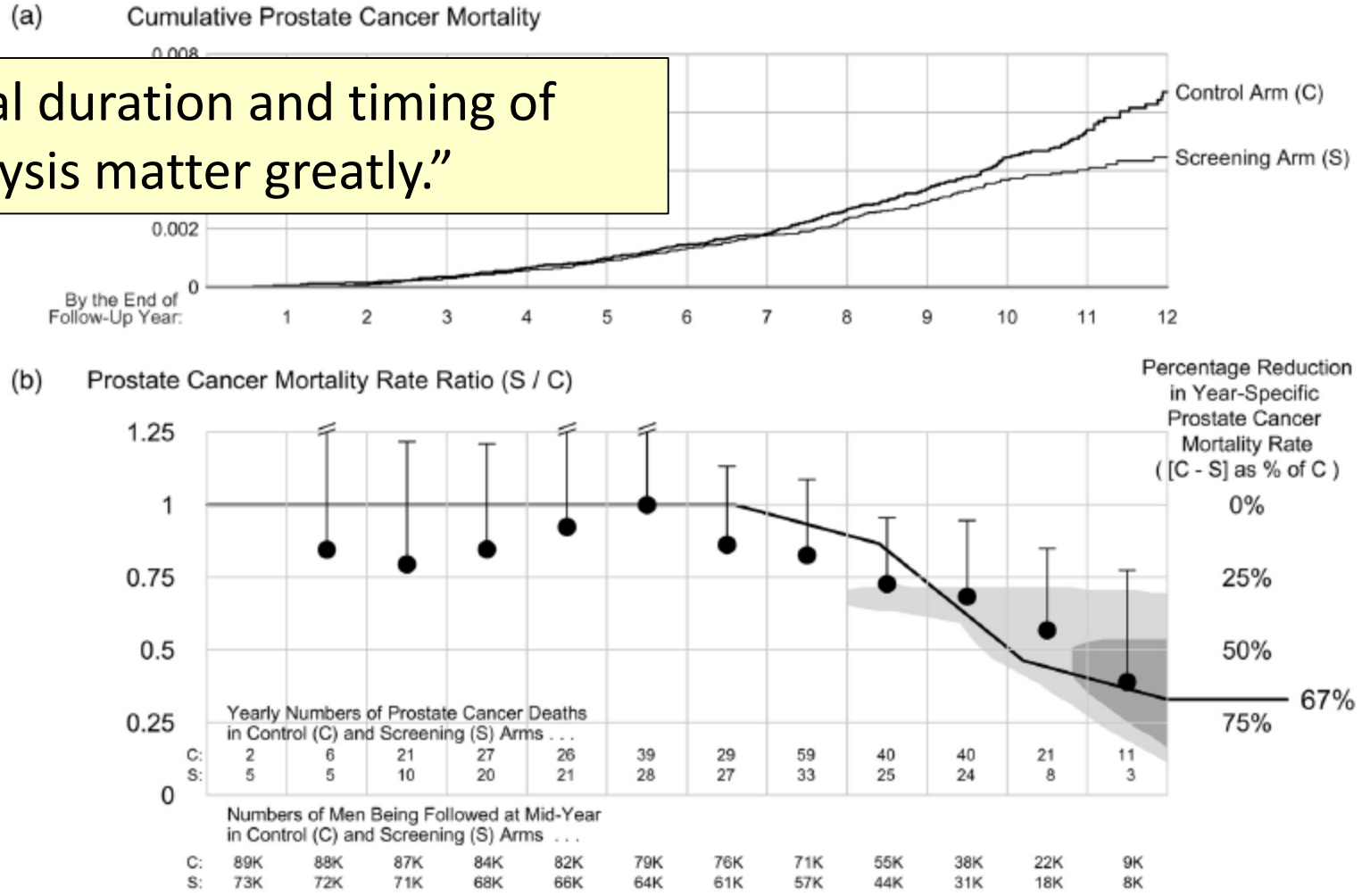
ORIGINAL ARTICLE

Mortality reductions produced by sustained prostate cancer screening have been underestimated

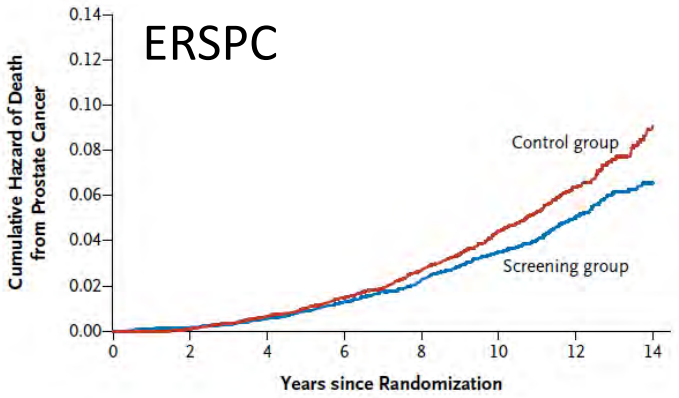
James A Hanley

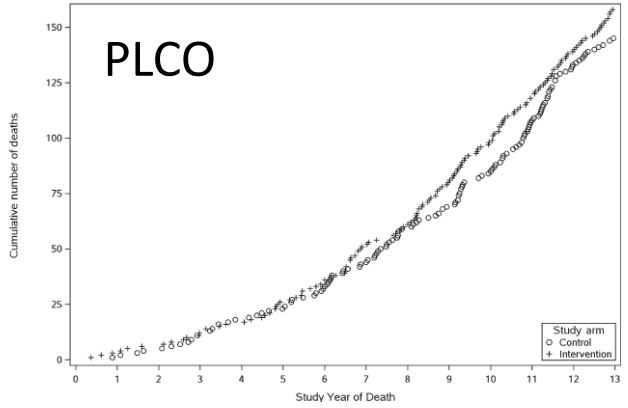
J Med Screen. 2010;17(3):147-51.

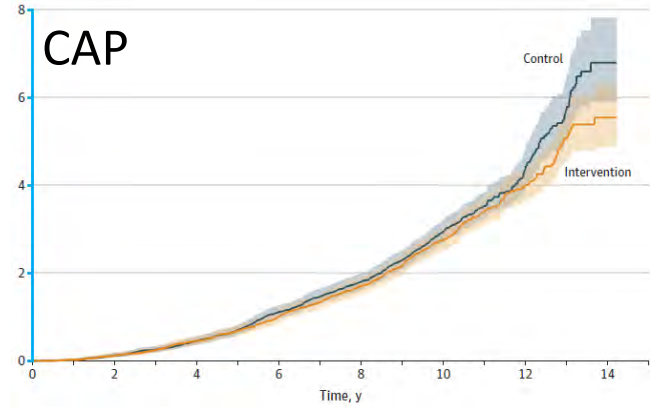
"Trial duration and timing of analysis matter greatly."



Prostate cancer: Three screening trials





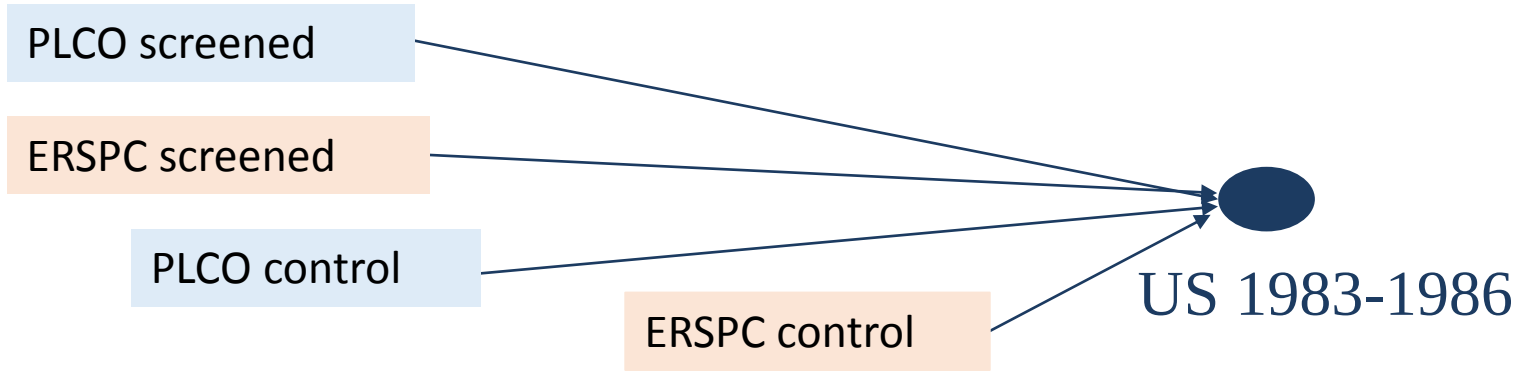


	ERSPC	PLCO	CAP
Screening interval	4 years (most centers) 2 years (Sweden)	Annual	One screen at start of trial
Screening on control arm	Infrequent	74% at least one test 50% tested each year	Infrequent
Compliance with screening	Relatively good	Relatively good	36% of eligible men were screened
Compliance with biopsy	80%	40%	85%

Schröder et al., N Engl J Med, 2012; Andriole et al., J Natl Cancer Inst, 2012; Martin et al, JAMA 2018

ERSPC and PLCO trials are more similar than they seem

- Compare incidence of prostate cancer on each arm of each trial with a common baseline (no screening)



- "Earliness of detection" expressed as a Mean Lead Time
  - Similar for the two PLCO arms, greater for ERSPC screened than ERSPC control arm
  - Lines up exactly with ordering of disease-specific mortality on each arm
- Earliness of detection on screened arms of ERSPC and PLCO trials implies mortality reduction of **25-32%** when compared with ***no screening***

3. Prostate cancer screening saves 0 to 1 lives per 1000 men screened

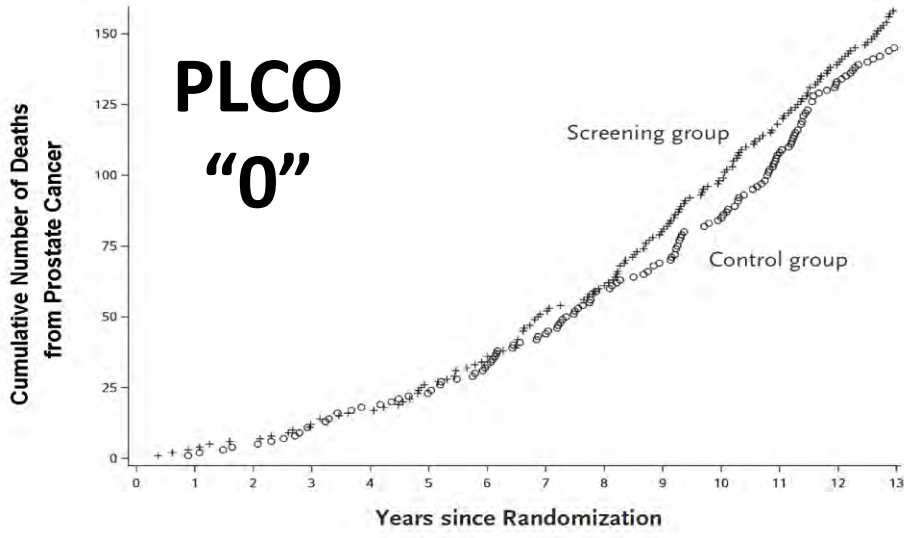
CLINICAL GUIDELINE | Annals of Internal Medicine

Screening for Prostate Cancer: U.S. Preventive Services Task Force Recommendation Statement

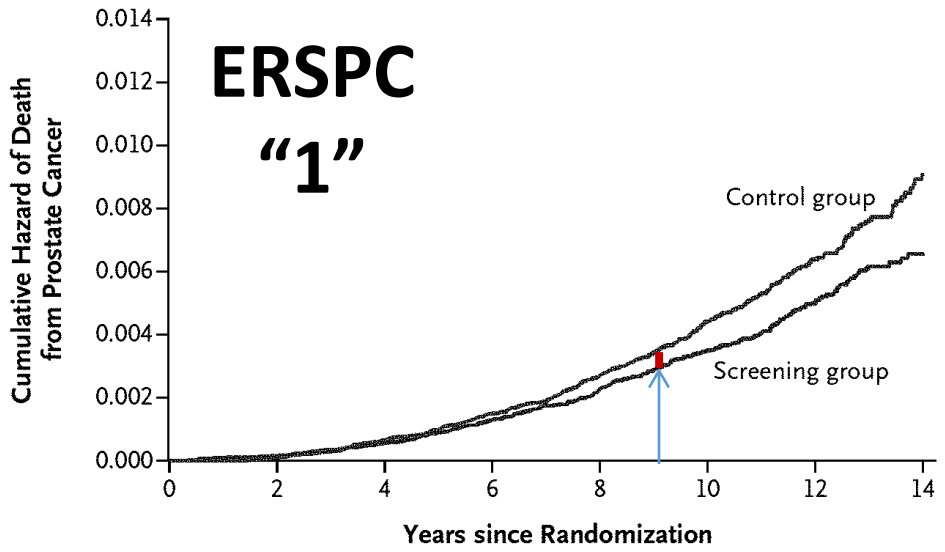
Virginia A. Moyer, MD, PhD, on behalf of the U.S. Preventive Services Task Force*

There is ***adequate evidence*** that the benefit of PSA screening and early treatment ranges from 0 to 1 prostate cancer deaths avoided per 1000 men screened

PLCO
"0"



ERSPC
"1"



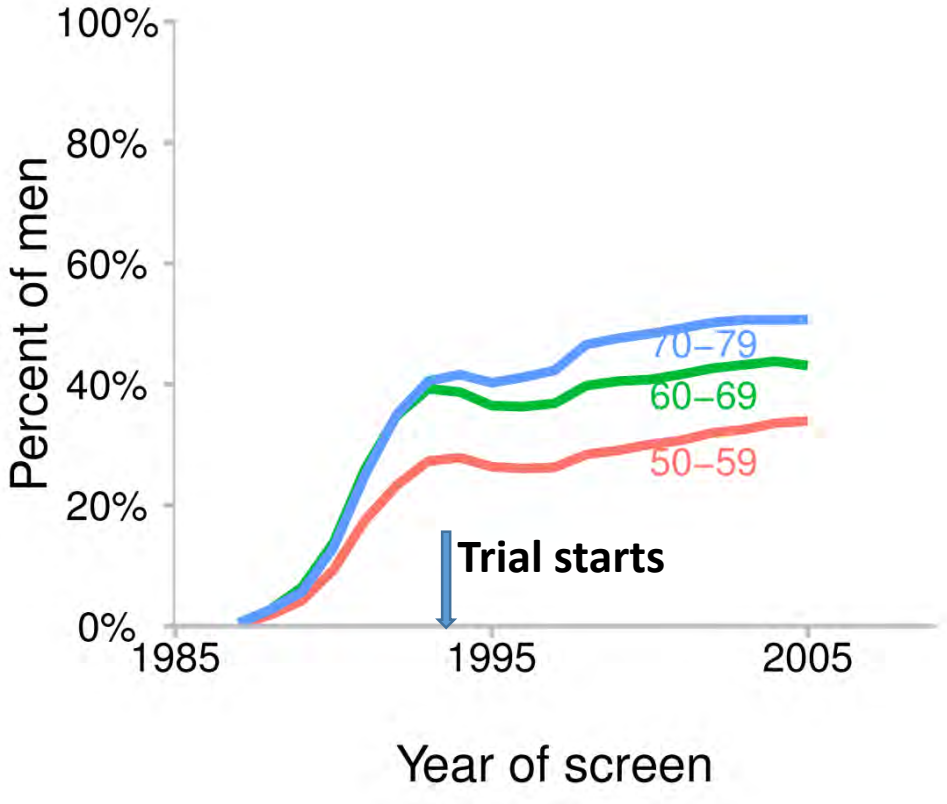
Note: Figures cited are "absolute benefit"

Zero lives saved: The PLCO trial

- PLCO trial began in 1993
- Not a comparison of screening versus no screening
- Many men on control arm screened
  - 74% at least once
  - 50% each year
- Poor compliance with biopsy recommendations
  - Only 40% biopsied within one year of abnormal screen

PSA screening uptake in the US

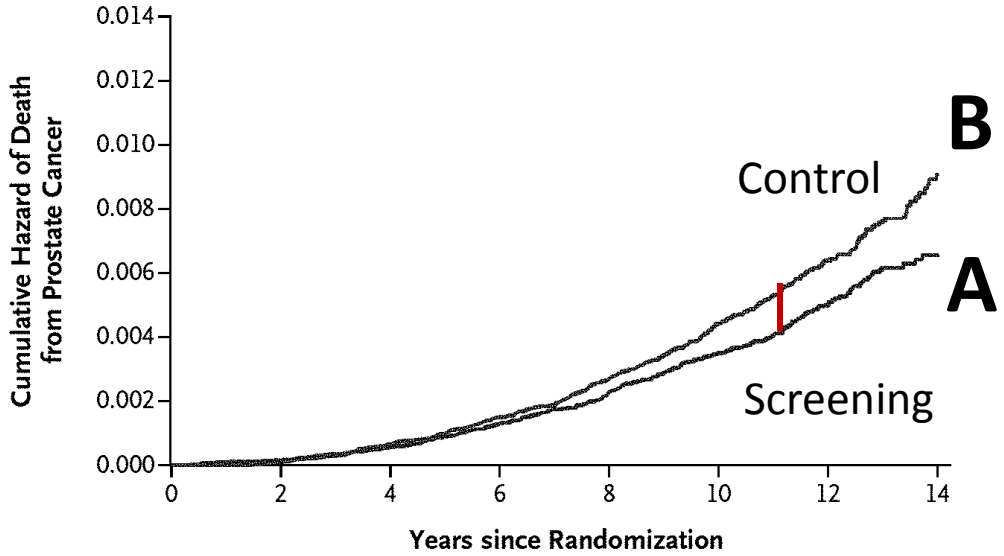
(Source: Mariotto et al, 2007)



One life saved: ERSPC trial

Relative benefit : Deaths in screened group divided by deaths in control group

$$A/B$$



Absolute benefit: Deaths in control group minus deaths in the screened group

$$B - A$$

For a given relative benefit, absolute benefit depends critically on

- Trial duration/timing of analysis
- Baseline mortality without screening – about 5 per 1000 at the time of the analysis

One life saved: ERSPC trial

Relative benefit: 21% = (1 – A/B)

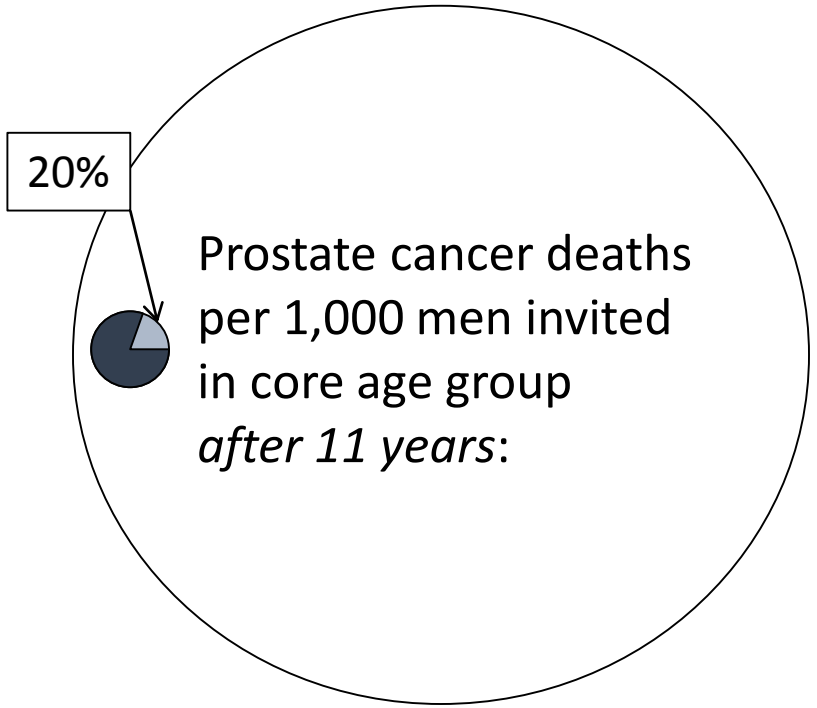
- Among men who would have died of prostate cancer without screening about one fifth were saved by screening
  → **Lives saved among those who would have died without screening**

Absolute benefit: 1 death per 1000 = (B – A) /(size of screened group)

- Because the risk of death without screening was 5 per 1000
- One-fifth reduction means we are saving one person
  → **Lives saved among men entering the screening program**

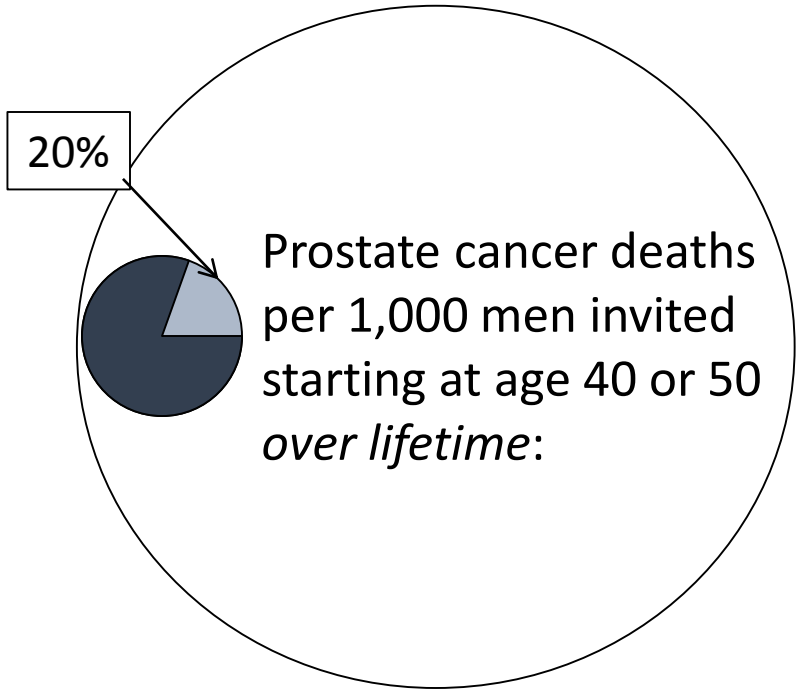
Trial versus population: short vs long term

11 year follow-up



Trial arm	Deaths
Control	**5**
Screening	**4**
Difference	**1**

Long-term follow-up (SEER)



Trial arm	Deaths
Control	**30**
Screening	**24**
Difference	**6**

The latest from USPSTF on prostate cancer screening

Discuss Prostate Screening With Your Doctor, Experts Now Say

By RONI CARYN RABIN APRIL 11, 2017

105

RELATED COVERAGE

THE NEW OLD AGE

Older Men Are Still Being Overtested for Prostate Cancer MAY 23, 2016

WELL

New Diagnostic Tools for Prostate Cancer

DEC. 21, 2015

"For every 1000 men offered screening… **over the course of 10 to 15 years**, three cancers will be prevented from spreading, and one to two deaths of prostate cancer will be prevented"

4. The Canadian trial shows that mammography screening is not beneficial

The New York Times

Vast Study Casts Doubts on Value of Mammograms

By GINA KOLATA FEB. 11, 2014

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MORE

One of the largest and most meticulous studies of mammography ever done, involving 90,000 women and lasting a quarter-century, has added powerful new doubts about the value of the screening test for women of any age.

It found that the death rates from breast cancer and from all causes were the same in women who got mammograms and those who did not. And the screening had harms: One in five cancers found with mammography and treated was not a threat to the woman's health and did

BMJ

BMJ 2014;348:g366 doi: 10.1136/bmj.g366 (Published 11 February 2014)

RESEARCH

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

Anthony B Miller *professor emeritus*[1], Claus Wall *data manager*[1], Cornelia J Baines *professor emerita*[1], Ping Sun *statistician*[2], Teresa To *senior scientist*[3], Steven A Narod *professor*[1 2]

[1]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario M5T 3M7, Canada; [2]Women's College Research Institute, Women's College Hospital, Toronto, Ontario M5G 1N8, Canada; [3]Child Health Evaluative Services, The Hospital for Sick Children, Toronto, Ontario, Canada

Abstract

Objective To compare breast cancer incidence and mortality up to 25 years in women aged 40-59 who did or did not undergo mammography screening.

Design Follow-up of randomised screening trial by centre coordinators, the study's central office, and linkage to cancer registries and vital statistics databases.

Conclusion Annual mammography in women aged 40-59 does not reduce mortality from breast cancer beyond that of physical examination or usual care when adjuvant therapy for breast cancer is freely available. Overall, 22% (106/484) of screen detected invasive breast cancers were over-diagnosed, representing one over-diagnosed breast cancer for every 424 women who received mammography screening in the trial.

Introduction

The Canadian Trial

- A stop-screen trial comparing
  - Mammography+CBE with CBE alone or usual care
  - Screening for 5 years with 25-year follow-up

- Analysis options:
  1. Compare breast cancer deaths in the two groups over the entire follow-up period
  2. Compare breast cancer deaths restricted to cases diagnosed in the two groups during the screening period

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

Analysis options		Screen arm	Control arm
Screening period (5 years)	Cases	666	524
	Deaths (over 25 y)	**180**	**171**
Entire study period (25 years)	Cases	3250	3133
	Deaths (over 25 y)	**500**	**505**

Miller et al BMJ 2014

The Canadian Trial

- A stop-screen trial comparing
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  - Screening for 5 years with 25-year follow-up

- Analysis options:
  1. Compare breast cancer deaths in the two groups over the entire follow-up period
  2. Compare breast cancer deaths restricted to cases diagnosed in the two groups during the screening period

- *Each of these is problematic*
  1. *Dilution of effect from cases diagnosed in both groups after the screening period*
  2. *Non-comparable groups with more cases in the screening group than in the control group*

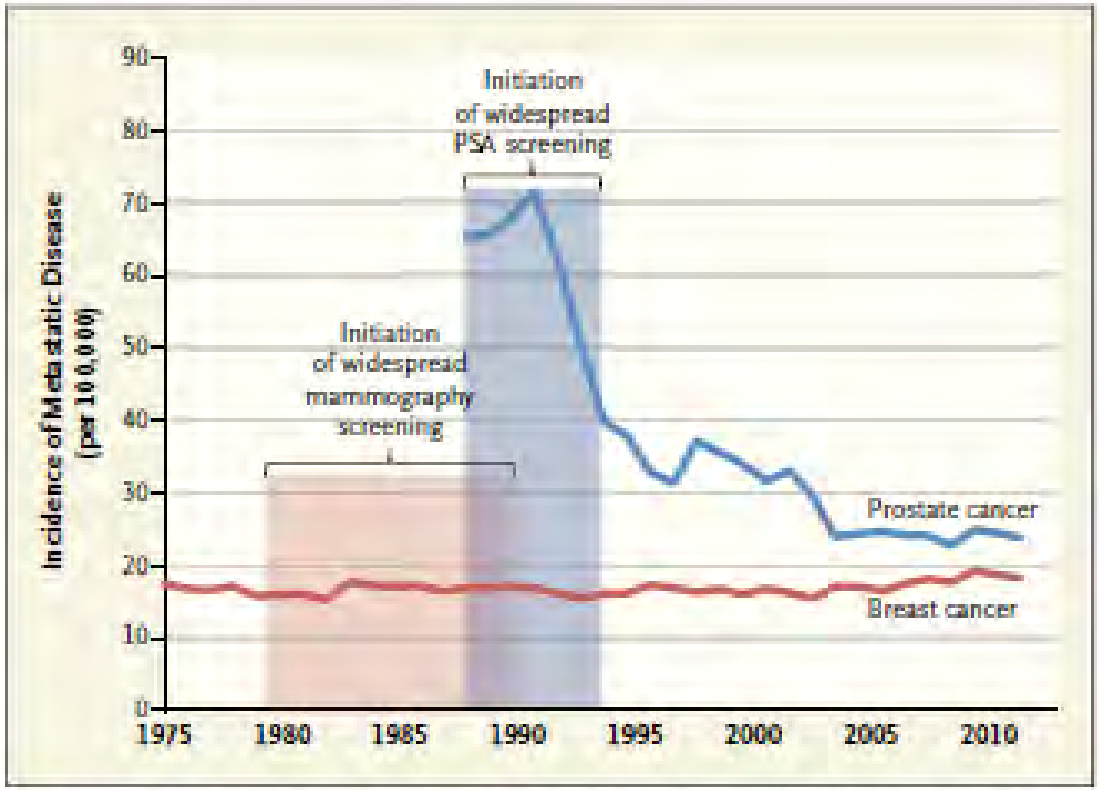
5. Breast cancer screening doesn’t work because advanced-stage incidence has not gone down

The NEW ENGLAND JOURNAL of MEDICINE

Trends in Metastatic Breast and Prostate Cancer — Lessons in Cancer Dynamics

H. Gilbert Welch M.D., M.P.H., David H. Gorski, M.D., Ph.D., and Peter C. Albertsen, M.D.

2015



Incidence of Cancer That Was Metastatic at First Presentation, United States, 1975–2012.

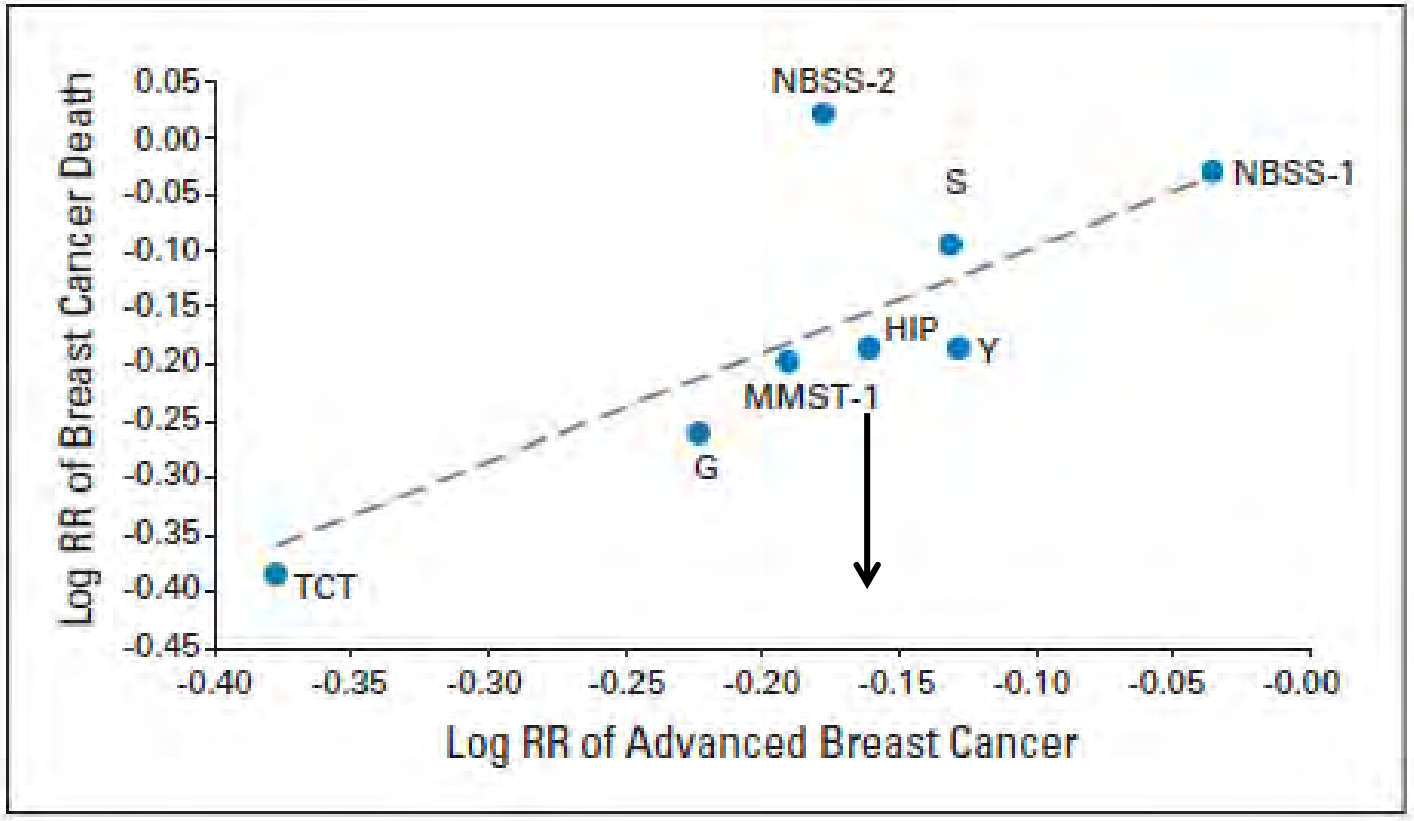
No reduction observed in the population over time

Stage shift under screening: Breast cancer trials

Advanced Breast Cancer and Breast Cancer Mortality in Randomized Controlled Trials on Mammography Screening

Philippe Autier, Clarisse Héry, Jari Haukka, Mathieu Boniol, and Graham Byrnes

Autier P et al,
JCO 2009 Dec 10



Annals of Internal Medicine

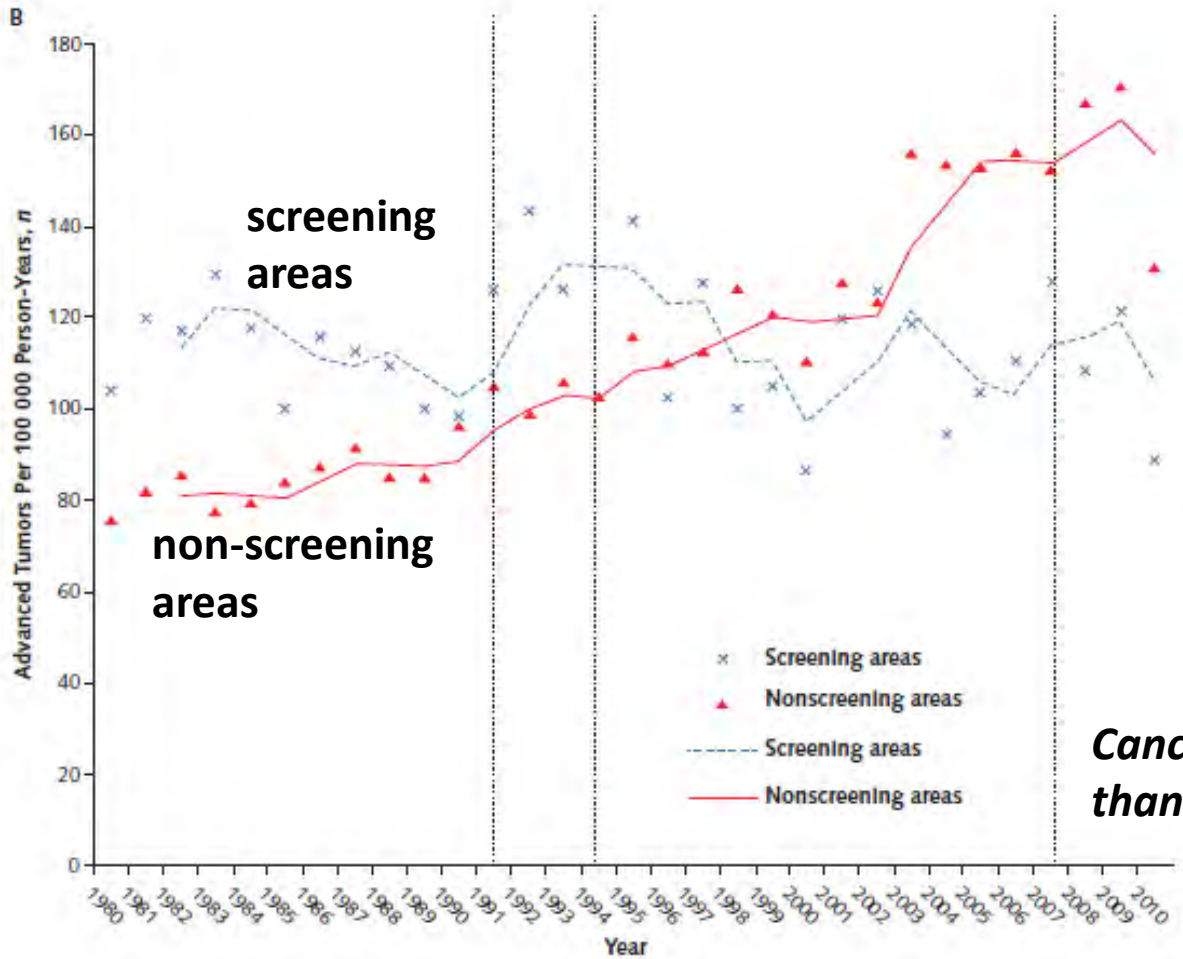
ORIGINAL RESEARCH

Breast Cancer Screening in Denmark

A Cohort Study of Tumor Size and Overdiagnosis

Karsten Juhl Jørgensen, MD, DrMedSci; Peter C. Gøtzsche, MD, MSc; Mette Kalager, MD, PhD*; and Per-Henrik Zahl, MD, DrMedSci*

March 7 2017



Cancers larger than 2cm

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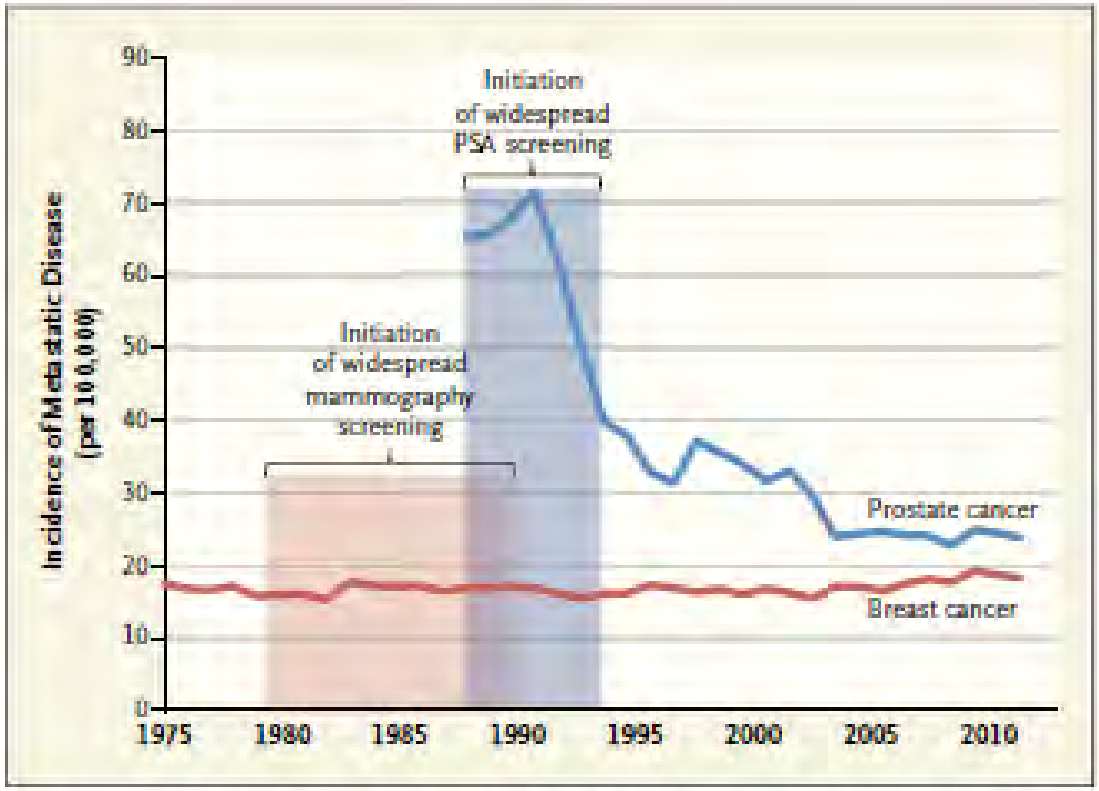

Incidence of Cancer That Was Metastatic at First Presentation, United States, 1975–2012.

No reduction observed in the population over time

- Changes in technology for identifying advanced disease?
- Greater availability of imaging and surgery to stage new cases
- Changes in medical record and registry coding practices?

6. 30 percent of breast cancers and 60 percent of prostate cancers are overdiagnosed

HEALTH CARE

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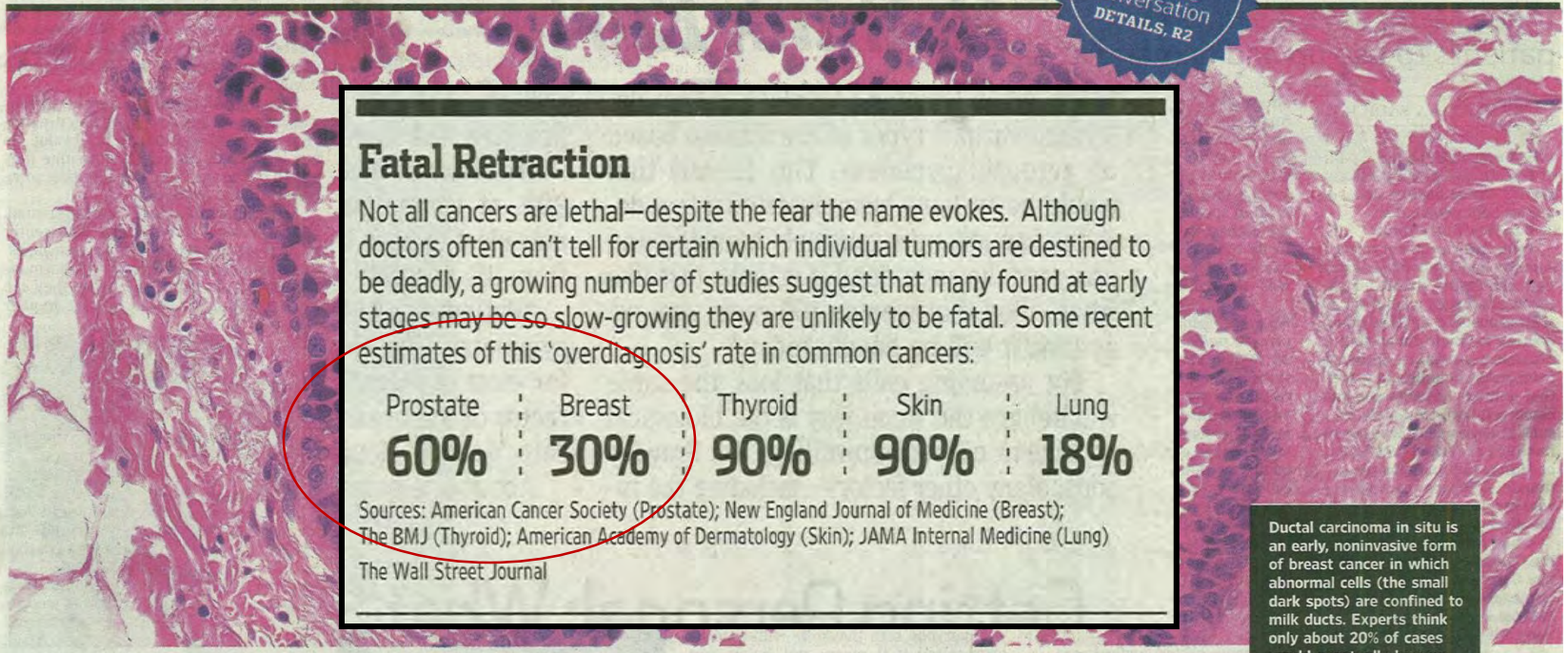


Fatal Retraction

Not all cancers are lethal—despite the fear the name evokes. Although doctors often can't tell for certain which individual tumors are destined to be deadly, a growing number of studies suggest that many found at early stages may be so slow-growing they are unlikely to be fatal. Some recent estimates of this 'overdiagnosis' rate in common cancers:

Prostate	Breast	Thyroid	Skin	Lung
60%	30%	90%	90%	18%

Sources: American Cancer Society (Prostate); New England Journal of Medicine (Breast); The BMJ (Thyroid); American Academy of Dermatology (Skin); JAMA Internal Medicine (Lung)

The Wall Street Journal

Ductal carcinoma in situ is an early, noninvasive form of breast cancer in which abnormal cells (the small dark spots) are confined to milk ducts. Experts think only about 20% of cases would eventually become invasive cancer, but virtually all are treated with surgery and radiation.

IT'S TIME TO RETHINK

EARLY CANCER DETECTION

A growing number of experts argue that zealous screening too often leads to overtreatment. They call for changing the way we even talk about the disease.

BY MELINDA BECK

EARLY DETECTION HAS long been seen as a powerful weapon in the battle against cancer. But some experts now see it as double-edged sword.

While it's clear that early-stage cancers are more treatable than late-stage ones, some leading cancer

Gleason score of 6 or below "benign lesions"—although others note that that would mean half of the men treated for prostate cancer in the past 20 years didn't have cancer after all.

Overdiagnosis—the detection of tumors that aren't likely to cause harm—is now a hot topic in other cancers as well. A growing volume of studies estimate that as many as 30% of invasive breast cancers, 18%

What is overdiagnosis?

Detection of cancers that would never have been diagnosed without screening

- Cancers that are slow growing or non-progressive
- Cancers that arise in individuals with short life expectancy

An overdiagnosed cancer is an excess case of cancer

- Can we estimate overdiagnosis by excess incidence in screened versus unscreened individuals?

Thirty percent of breast cancers overdiagnosed

The NEW ENGLAND JOURNAL of MEDICINE

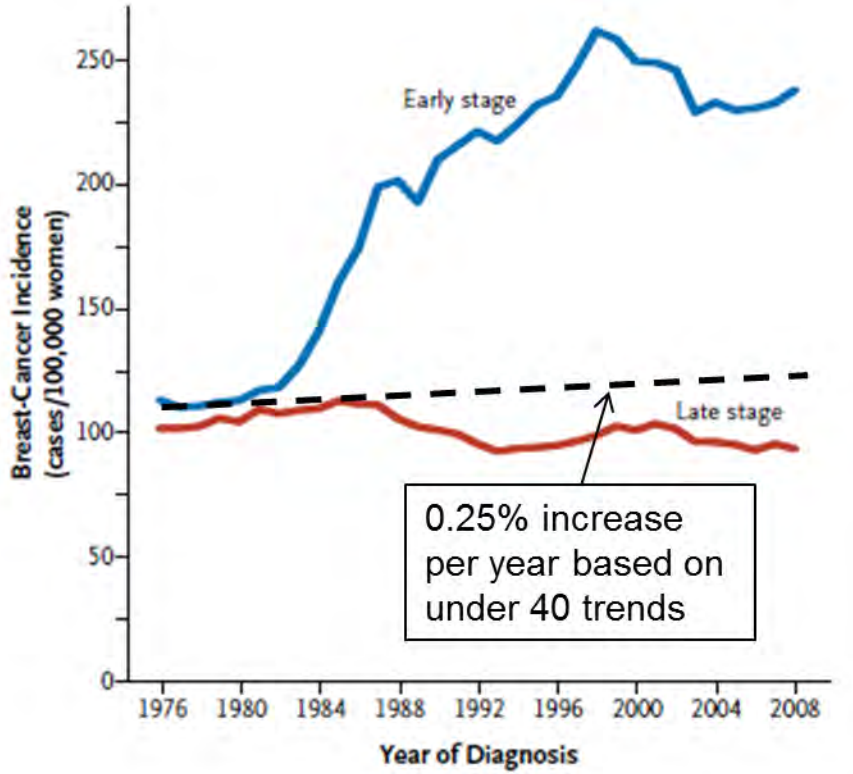
ORIGINAL ARTICLE

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

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

- Compare incidence observed with incidence expected in absence of screening
- Expected incidence based on trend observed in women under 40
- Attribute all excess cases to overdiagnosis

Incidence in women **40 and older**
By calendar year and stage



Bleyer and Welch NEJM 2012

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NEJM 2012

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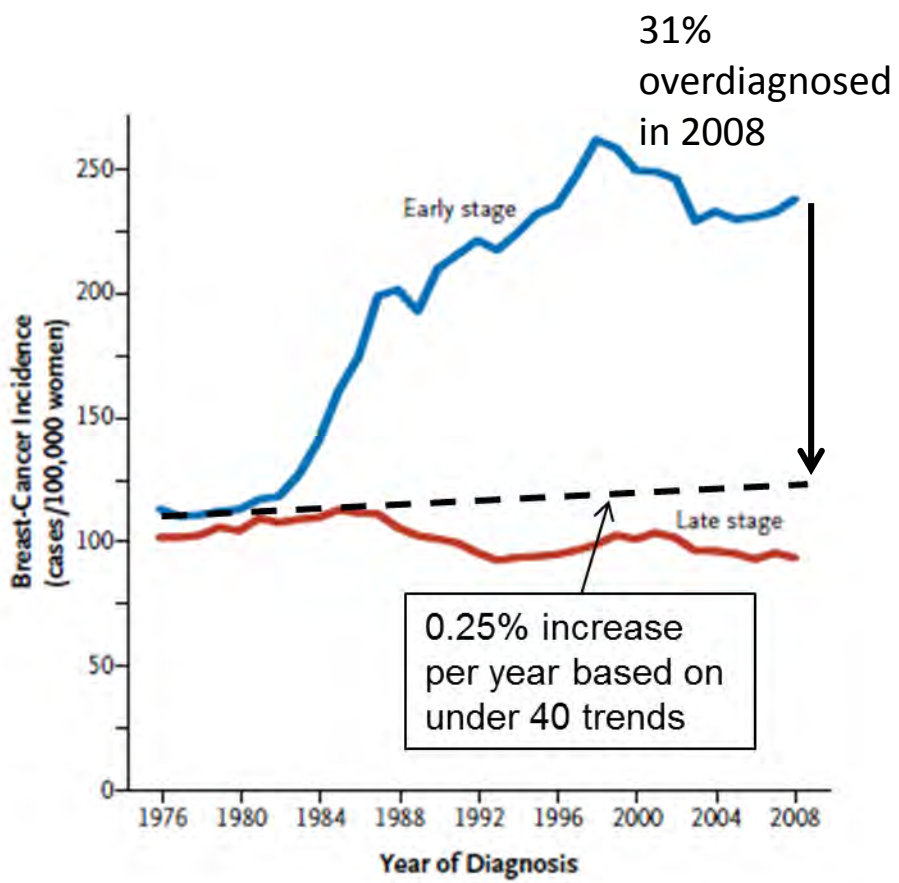
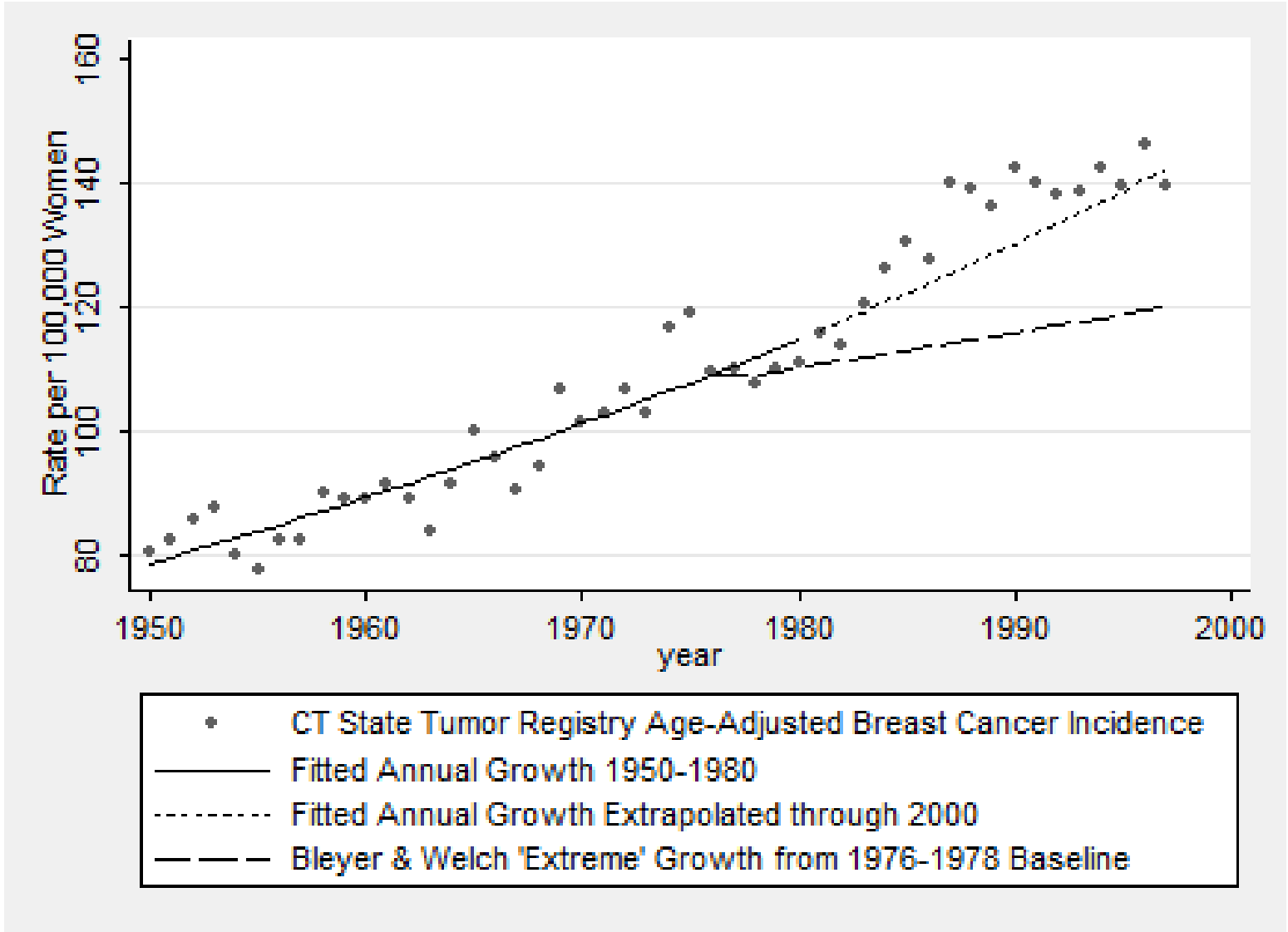
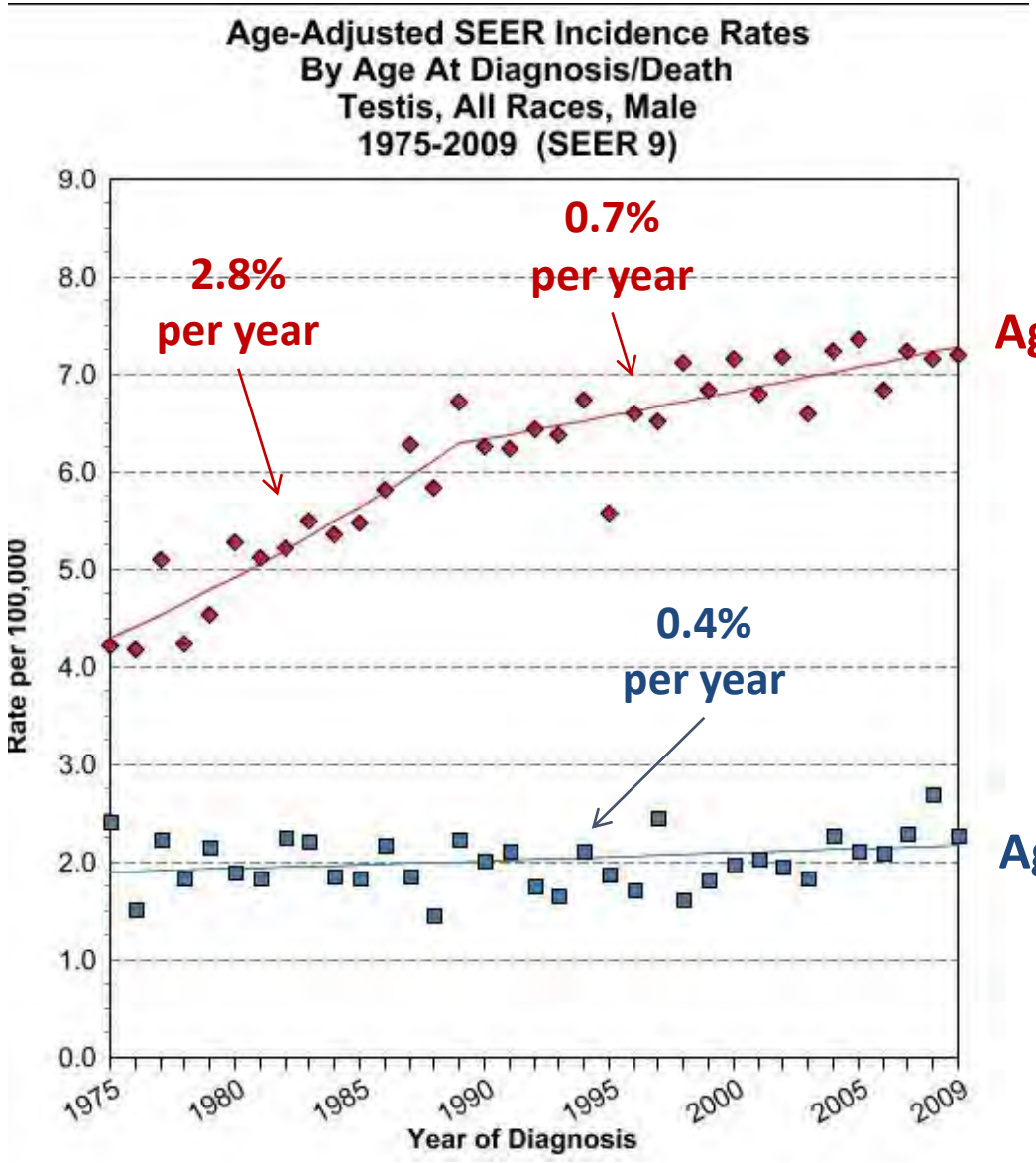
By calendar year and stage



Questioning the background trend



Trends in Testicular Cancer Incidence



Trends in younger men do not match trends in older men

What if we could get a better background trend?

Annals of Internal Medicine

ORIGINAL RESEARCH

Breast Cancer Screening in Denmark

A Cohort Study of Tumor Size and Overdiagnosis

Karsten Juhl Jørgensen, MD, DrMedSci; Peter C. Gøtzsche, MD, MSc; Mette Kalager, MD, PhD*; and Per-Henrik Zahl, MD, DrMedSci*

January 2017

Denmark provides a natural experiment

- Organized screening program (Ages 50-69) began in some areas in 1991-1994
- Study compares incidence trends in screening versus non-screening areas
- Concludes screening not associated with a decline in advanced (> 2cm) cancer
- Different methods of estimating overdiagnosis frequency

Annals of Internal Medicine

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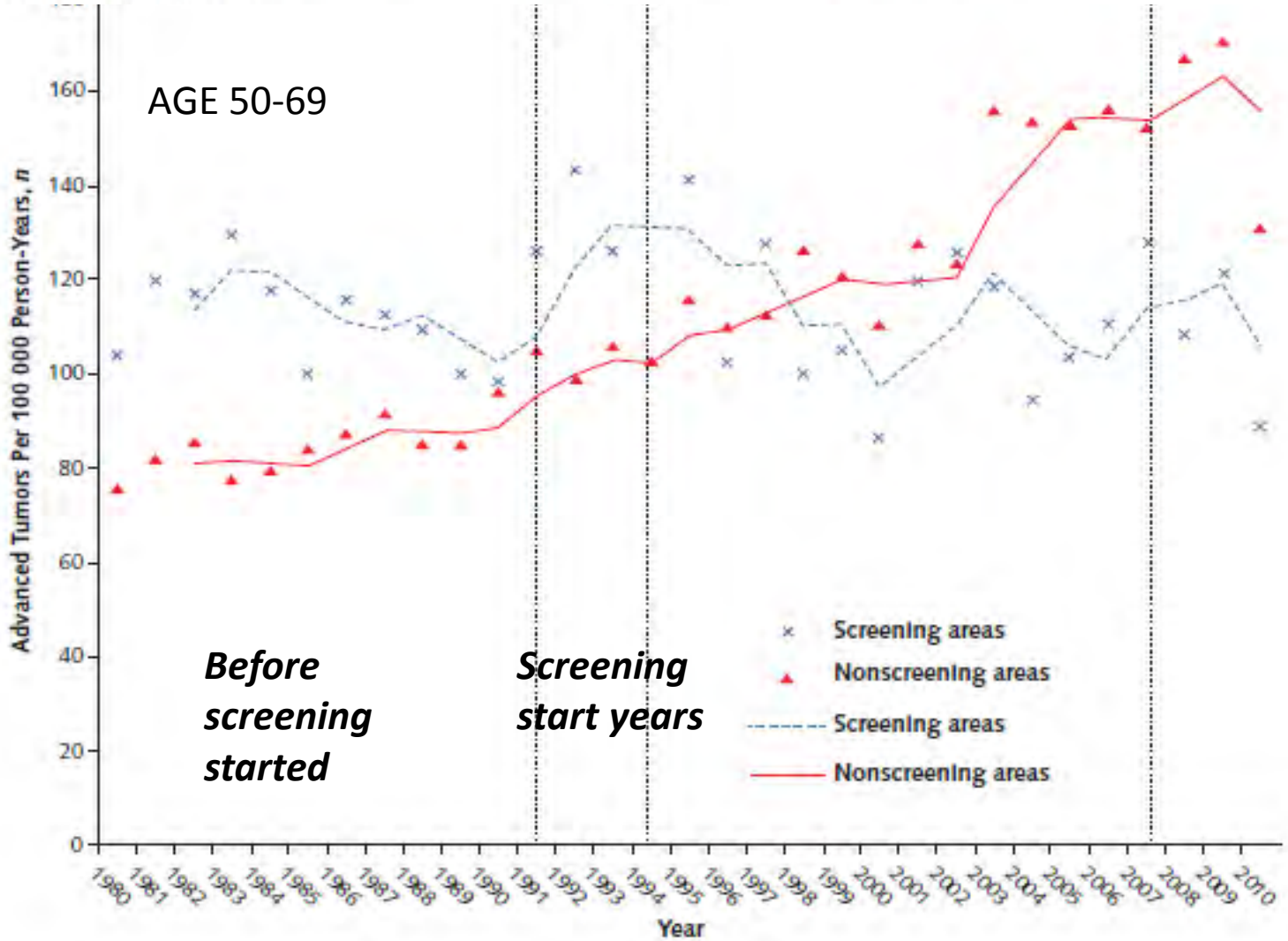


Non-screened areas

Screened areas

Estimates of overdiagnosis from the Danish study

Method 1: tries to account for the relatively lower incidence of advanced cancers in the screening areas and includes older women

- 9.9% invasive
- 16.4% invasive plus DCIS

Method 2: does not account for the relatively lower incidence of advanced cancers in the screening areas

- 38% invasive
- 48% invasive plus DCIS

ABSTRACT CITES ONLY THESE RESULTS SAYING THAT AT LEAST 1 IN 3 ARE OVERDIAGNOSED

Both methods: overdiagnosis is expressed relative to cases that would be detected without screening, not as a fraction of screen-detected cases

EDITORIAL

Annals of Internal Medicine

Accepting the Existence of Breast Cancer Overdiagnosis

HEALTH JAN 10 2017, 7:57 AM ET

Mammograms Aren't Perfect, American Cancer Society Top Doc Says

by MAGGIE FOX

It's time to admit that mammograms are not perfect and that doctors are treating women who don't need treatment for breast cancer, the American Cancer Society's top doctor said Monday after yet another study showed breast cancer screening leads to so-called overdiagnosis.

The new study found that as many as a third of women in Denmark diagnosed with breast cancer through mammograms either didn't have malignant cancer, or had slow-growing tumors that didn't

"The numbers match those found in other studies that cast doubt on whether mammograms actually reduce the risk of dying from breast cancer. A 2012 study published in the New England Journal of Medicine that found that as many as a third of cancers detected through routine mammograms may not be life threatening."

Forbes / Pharma & Healthcare / #PublicHealth

JAN 10, 2017 @ 08:00 AM 3,769

The Latest Study On Breast Cancer Overdiagnosis Fails To Persuade

Elaine Schattner, CONTRIBUTOR

FULL BIO

Opinions expressed by Forbes Contributors are their own.

Yesterday's health news delivered another paper slamming mammography. A report out of Denmark uses statistics to show that overdiagnosis is incredibly frequent. An

"It's simply not valid to cherry-pick findings of non-randomized studies to support one's views."

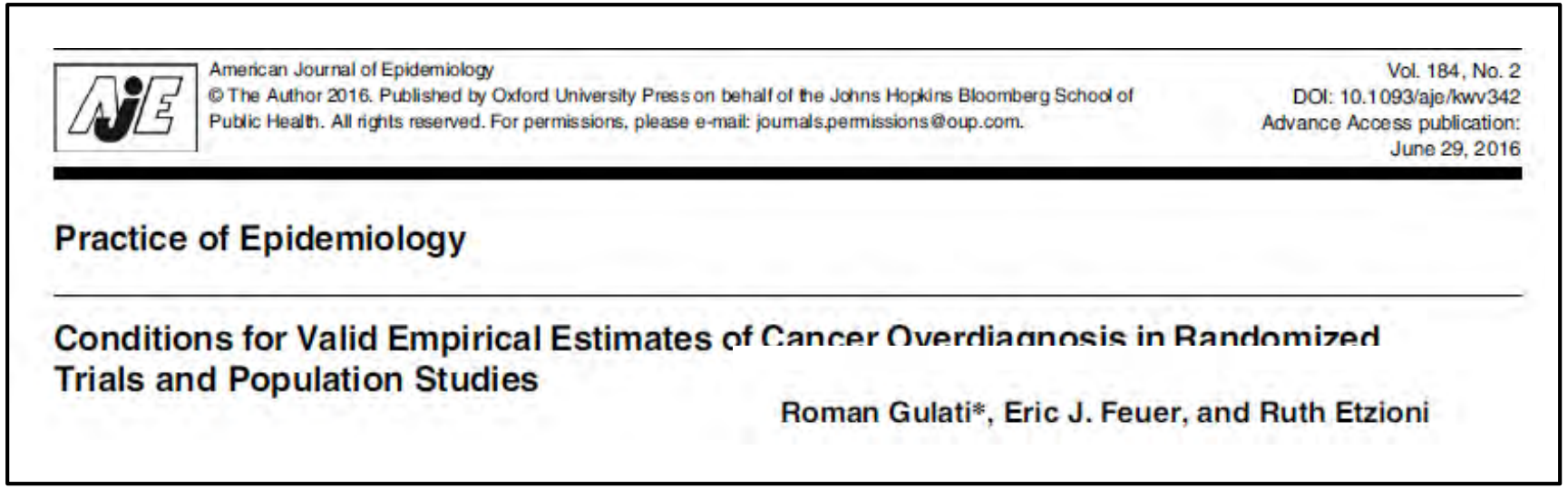
What about clinical trials of screening?

Screening trials should be ideal for estimating overdiagnosis

- Concurrent control group

Most screening trials do not generally produce unbiased estimates

- Depends on design (stop-screen or continuous-screen)
- Depends on measure used (cumulative or annual incidence)
- Depends on timing of the estimation procedure – need to wait



American Journal of Epidemiology

Vol. 184, No. 2
DOI: 10.1093/aje/kwv342
Advance Access publication:
June 29, 2016

Practice of Epidemiology

Conditions for Valid Empirical Estimates of Cancer Overdiagnosis in Randomized Trials and Population Studies

Roman Gulati*, Eric J. Feuer, and Ruth Etzioni

HEALTH CARE

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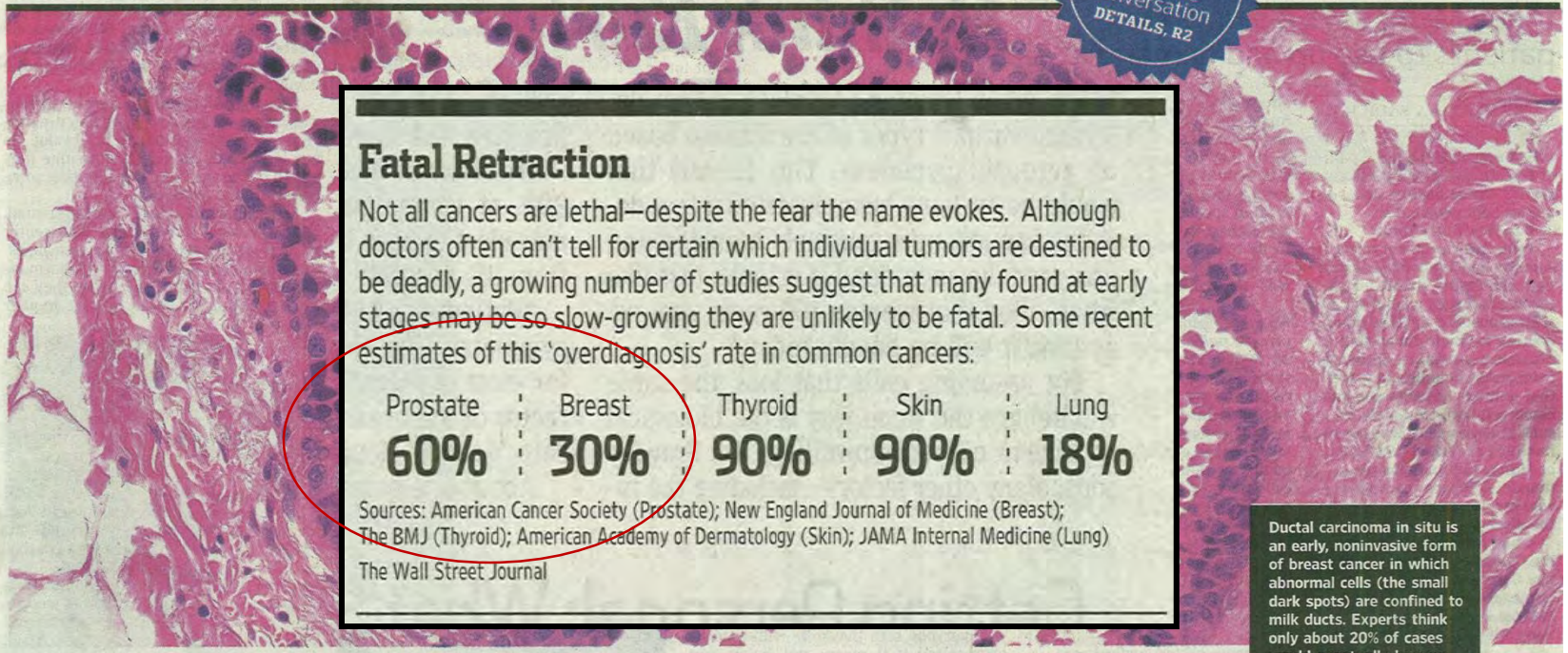

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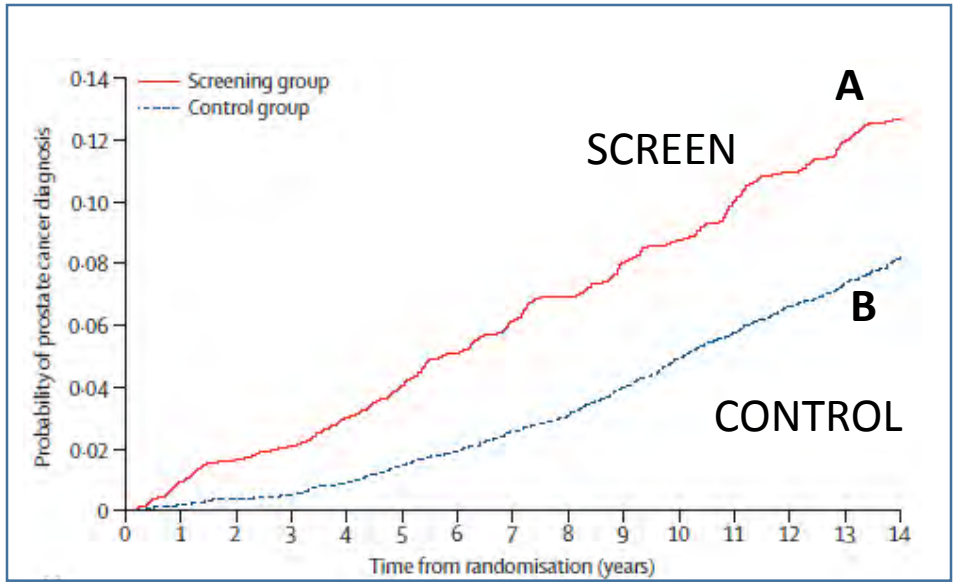
Screening and Prostate-Cancer Mortality in a Randomized European Study

Prostate cancer incidence in ERSPC



"Cumulative Excess incidence; Continued-screen trial"

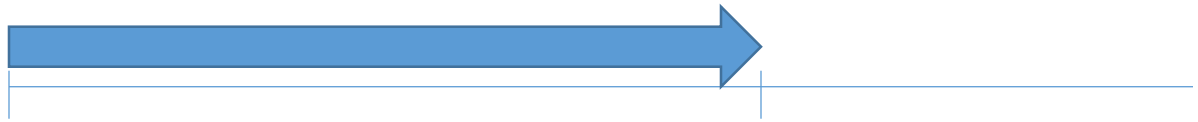
	Cumulative Incidence at 9 years
Screened arm (Screen-detected)	8.2% (**5.8%**)
Control arm	4.8%
Excess	**8.2% - 4.8% = 3.4%**
Excess/screen-detected	**3.4/5.8 = 58%**

Schroder et al
NEJM 2009

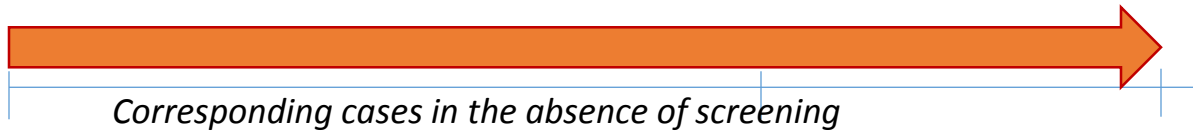
The problem with excess incidence from trials like the ERSPC

- What we know

Cases detected under screening



Represent cases that would have arisen during AND after the trial

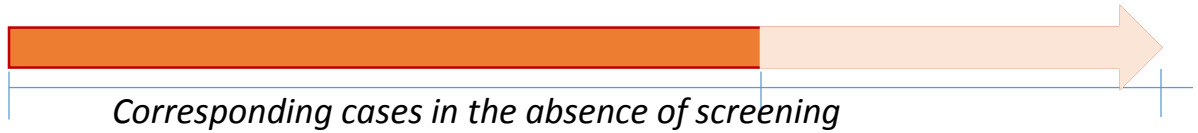


Corresponding cases in the absence of screening

- What we do

Take cases detected under screening

Subtract the cases on the control group that arose during the trial



Corresponding cases in the absence of screening

- If there is no overdiagnosis this approach will still yield a positive result!

So how many prostate cancers are overdiagnosed?

Lead Time and Overdiagnosis in Prostate-Specific Antigen Screening: Importance of Methods and Context

JNCI 2009

Gerrit Draisma, Ruth Etzioni, Alex Tsodikov, Angela Mariotto, Elisabeth Wever, Roman Gulati, Eric Feuer, Harry de Koning

Overdiagnosed cases as percent of	MISCAN	FHCRC	UMICH
All cases detected	18.6	11.9	8.6
Screen-detected cases	42.0	28.0	22.9

So how many breast cancers are overdiagnosed?

- We still don't have a clear answer
  - Estimates based on excess incidence are generally inflated
- Some statistical modeling studies
  - Try to learn about latent preclinical duration and lead time from incidence trends
  - Infer overdiagnosis rates based on lead time
  - Sensitive to modeling assumptions
  - Data inadequate to get sharp estimates

- Our best estimate at this time:
  - About 10-15% of cancers detected
- Likely much higher for DCIS cases

2016

Annals of Internal Medicine ORIGINAL RESEARCH

Collaborative Modeling of the Benefits and Harms Associated With Different U.S. Breast Cancer Screening Strategies

Jeanne S. Mandelblatt, MD, MPH; Natasha K. Stout, PhD; Clyde B. Schechter, MA, MD; Jeroen J. van den Broek, MS; Diana L. Miglioretti, PhD; Martin Krapcho, BS; Amy Trentham-Dietz, PhD, MS; Diego Munoz, PhD, MS; Sandra J. Lee, ScD; Donald A. Berry, PhD; Nicolien T. van Ravesteyn, PhD; Oguzhan Alagoz, PhD; Karla Kerlikowske, MD; Anna N.A. Tosteson, ScD; Aimee M. Near, MPH; Amanda Hoeffken, MPH; Yaojen Chang, DrPH, MS, MPH; Eveline A. Heijnsdijk, PhD; Gary Chisholm, MS; Xuelin Huang, PhD; Hui Huang, MS; Mehmet Ali Ergun, MSc; Ronald Gangnon, PhD; Brian L. Sprague, PhD; Sylvia Plevritis, PhD; Eric Feuer, PhD; Harry J. de Koning, MD, PhD; and Kathleen A. Cronin, PhD, MPH

7. Ovarian cancer screening doesn’t work

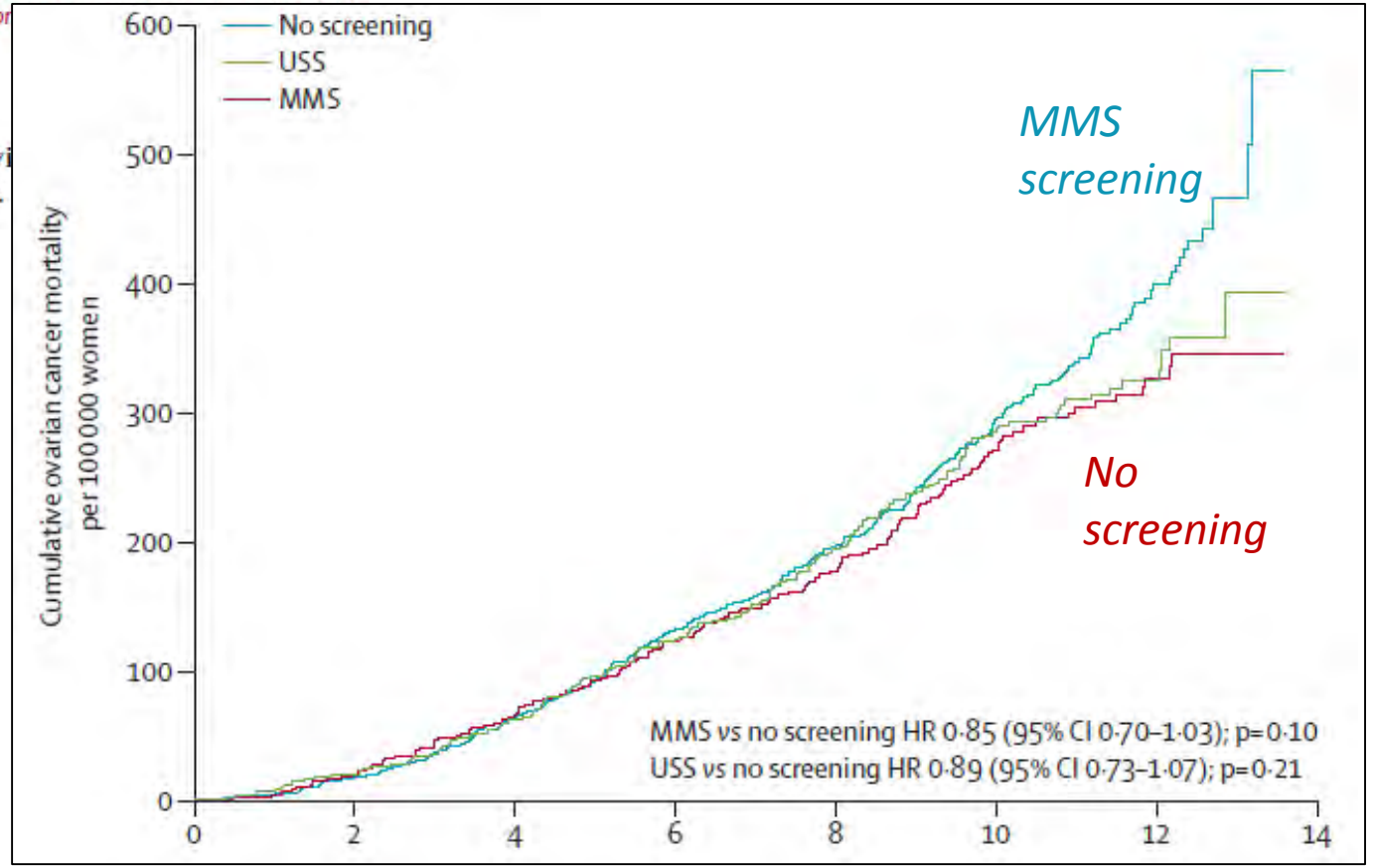
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Ian J Jacobs, Usha Menon*, Andy Ryan, Aleksandra Gentry-Maharaj, Matthew Burnell, Jatinderpal K Kalsi, Nazar N Amso, Sophia Apostolidou, Elizabeth Benjamin, Derek Cruickshank, Danielle N Crump, Susan K Davies, Anne Dawnay, Stephen Dobbs, Gwendolen Fletcher, Jeremy Ford, Keith Godfrey, Richard Gunu, Mariam Habib, Rachel Hallett, Jonathan Herod, Howard Jenkins, Chloe Karpinskyj, Simon Leeson, Sara J Lewis, William R Liston, Alberto Lopes, Tim Mould, John Murdoch, David Oram, Dustin J Rabideau, Karina Reynolds, Ian Scott, Mourad W Seif, Aarti Sharma, Naveena Singh, Julie Taylor, Fiona Warburton, Martin Widschwendter, Karin Williamson, Alistair J McGuire, Stuart Campbell, Mahesh Parmar†, Steven J Skates†*

Lancet, 2017

Summary

Background Ovarian cancer has a poor prognosis, with just 40% of patients survi
to establish the effect of early detection by screening on ovarian cancer mortality.



MMS: Multi-modal screening using CA-125
USS: ultrasound screening

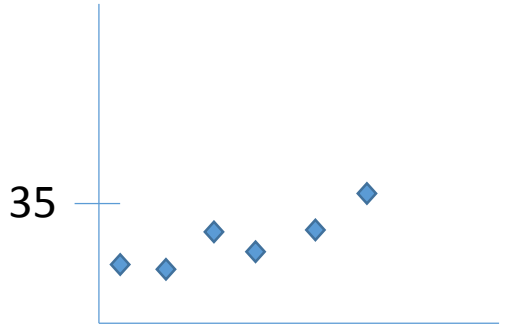
MMS uses ROCA algorithm – learns by observing serial CA125 trajectories over time

15% reduction in risk of ovarian cancer death in MMS arm compared to no screening (p=0.1)

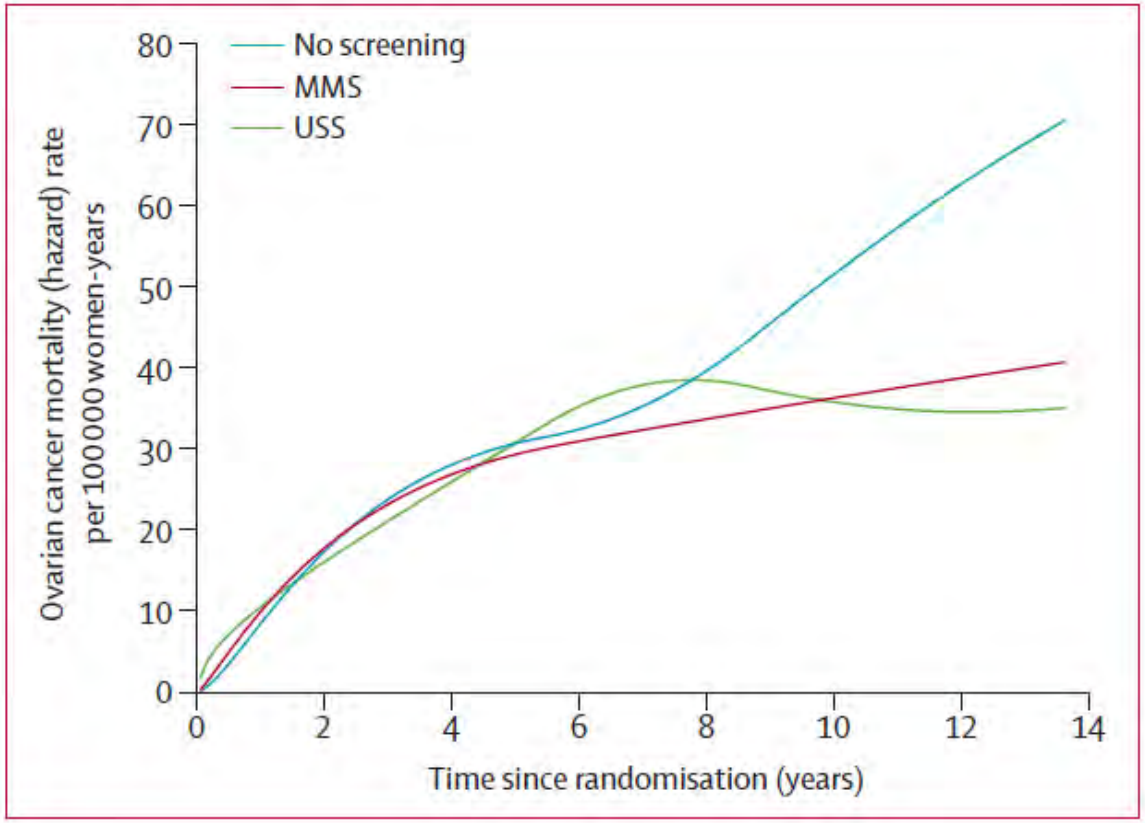
Understanding the UKTOCS trial

ROCA (Risk Of CAncer) algorithm

- Triages women to diagnostic follow-up on the basis of their evolving CA-125 trajectories



- Takes time to classify a woman into high-risk or normal-risk and to refer to biopsy
- Incidence pattern shows that expected excess incidence in screened group only emerges after 7 years



8. New blood-based screening tests are going to solve all of our problems

CANCER

Detection and localization of surgically resectable cancers with a multi-analyte blood test

Joshua D. Cohen,[1,2,3,4,5] Lu Li,[6] Yuxuan Wang,[1,2,3,4] Christopher Thoburn,[3] Bahman Afsari,[7] Ludmila Danilova,[7] Christopher Douville,[1,2,3,4] Ammar A. Javed,[8] Fay Wong,[1,3,4] Austin Mattox,[1,2,3,4] Ralph. H. Hruban,[3,4,9] Christopher L. Wolfgang,[8] Michael G. Goggins,[3,4,9,10,11] Marco Dal Molin,[4] Tian-Li Wang,[3,9] Richard Roden,[3,9] Alison P. Klein,[3,4,12] Janine Ptak,[1,2,3,4] Lisa Dobbyn,[1,3,4] Joy Schaefer,[1,3,4] Natalie Silliman,[1,2,3,4] Maria Popoli,[1,3,4] Joshua T. Vogelstein,[13] James D. Browne,[14] Robert E. Schoen,[15,16] Randall E. Brand,[15] Jeanne Tie,[17,18,19,20] Peter Gibbs,[17,18,19,20] Hui-Li Wong,[17] Aaron S. Mansfield,[21] Jin Jen,[22] Samir M. Hanash,[23] Massimo Falconi,[24] Peter J. Allen,[25] Shibin Zhou,[1,3,4] Chetan Bettegowda,[1,3,4] Luis A. Diaz Jr.,[1,3,4*] Cristian T[illegible] Bert Vogelstein,[1,2,3,4†] Anne M[illegible]

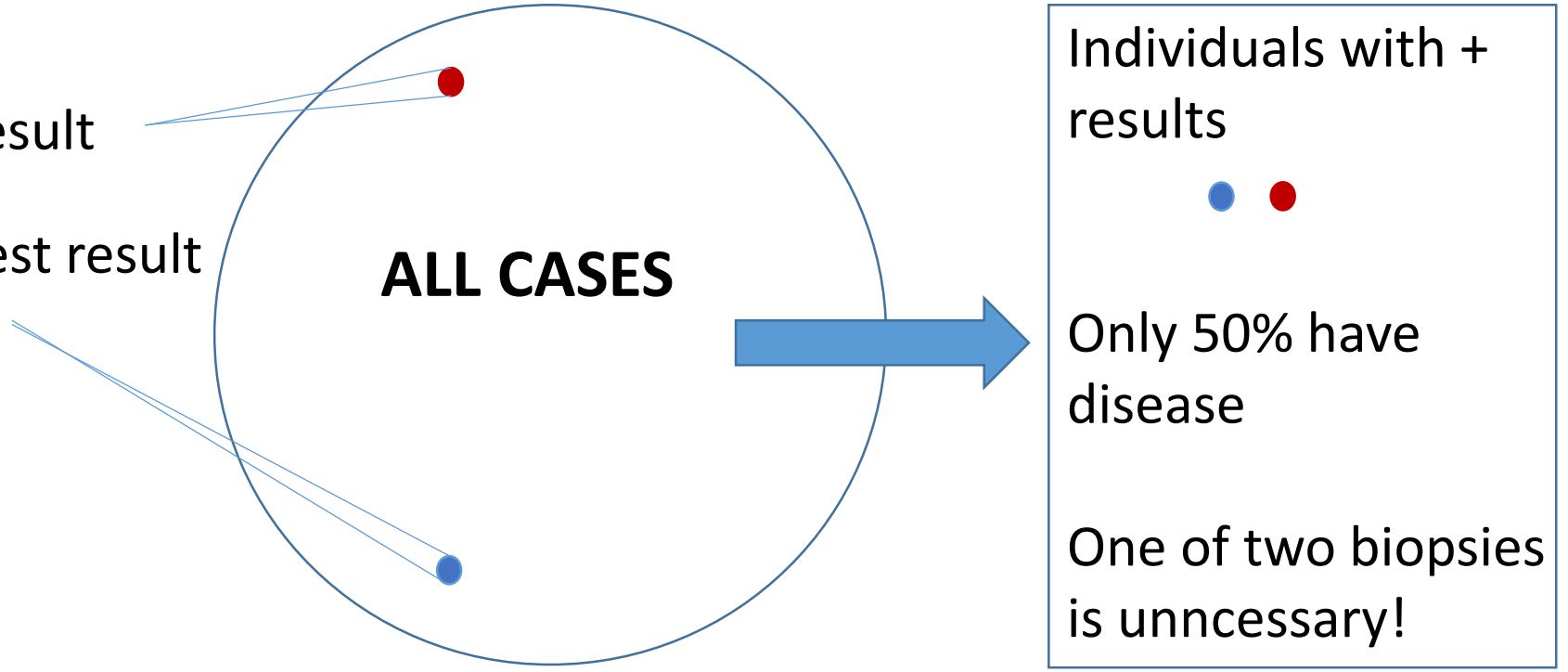
Earlier detection is key to redu[illegible] can detect eight common cancer[illegible] and mutations in cell-free DNA. W[illegible] with nonmetastatic, clinically d[illegible] esophagus, colorectum, lung, o[illegible] 70% of the eight cancer types. [illegible] of five cancer types (ovary, liver, stomach, pancreas, and esophagus) for which there are no screening tests available for average-risk individuals. The specificity of CancerSEEK was greater than 99%: only 7 of 812 healthy controls scored positive. In addition, CancerSEEK localized the cancer to a small number of anatomic sites in a median of 83% of the patients.

"The sensitivities ranged from 69 to 98% for the detection of five cancer types for which there are no screening tests available…
The specificity of CancerSEEK was greater than 99%"

Sensitivity and specificity

- Sensitivity is the ability of the test to pick up a cancer if it is there
- Specificity is the ability of the test to not pick up a cancer if it is not there
- If the condition is rare is it enough to have a pretty **sensitive** and **specific** test?

- Cases with + test result
- Non cases with + test result



Rarest cancers need extremely high specificity e.g. 99.6% for ovarian cancer!

Promise and challenge of liquid biopsies for early detection

- Much excitement about liquid biopsies for early detection of rare cancers
  - Tests need to be extremely specific
  - Even a test that performs reasonably well may not be useful for population screening
  - In early disease setting may not be enough circulating tumor DNA

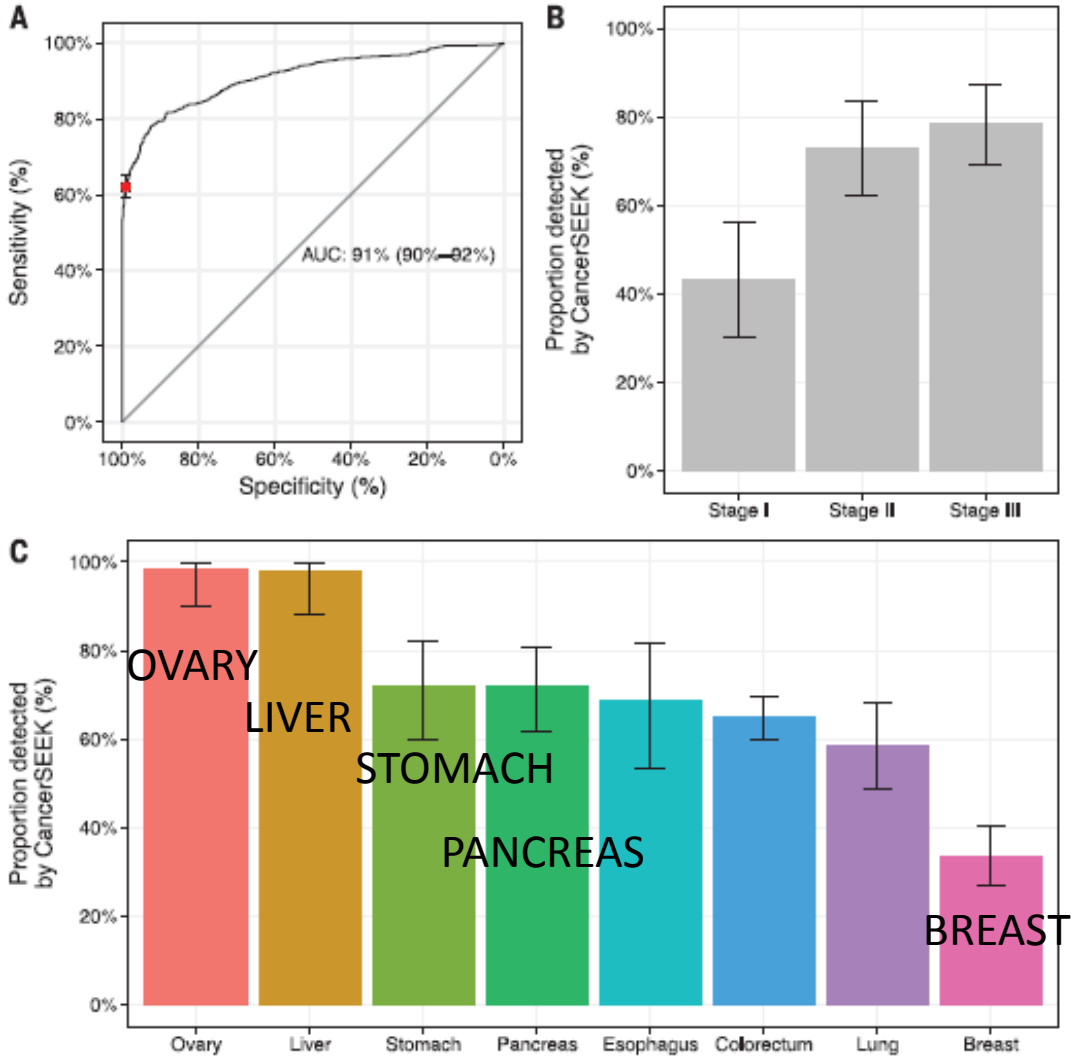
- Same DNA mutations span multiple cancers
  - May be challenging to localize the cancer
  - Pan-cancer test sounds nice but does it make sense?

- Confirmatory diagnostics for very early cancers need to be developed
  - May not be able to visualize the tumor even if can localize it

Critiques of CancerSEEK study

Study not properly designed to address value for early detection

- Cases had already been diagnosed with cancer – not an early detection setting
- Cases stage I-III, only 40% of stage I patients detected by test; report cites overall 70%
- Unclear where control samples were from and whether they had been handled similarly to cases



Review

1. Most screen-detected cases are not saved by screening T F
2. Clinical trials are the most reliable sources of evidence T F
3. Prostate cancer screening saves 0 to 1 lives per 1000 men T F
4. The Canadian trial shows breast cancer screening is not beneficial T F
5. Breast cancer screening doesn't work because advanced-stage incidence has not gone down T F
6. 30% of breast cancers and 60% of prostate cancers are overdiagnosed T F
7. Ovarian cancer screening doesn't work T F
8. New blood-based screening tests are going to solve all of our problems T F

Take home messages

- Evidence about cancer screening harms and benefits can be hard to fathom
  - Trials may not be as unequivocal as we would hope

- Both investigators and reporters have opinions
  - Media tends to oversimplify and impose judgements – beware the byline

- That overdiagnosis exists is a fact
  - Most studies of overdiagnosis are biased and give inflated results
  - Overdiagnosis does not mean a test is not efficacious

- Even the most efficacious test will not save all lives
  - Historic bar for efficacy – 20-30% reduction in disease-specific deaths (not all-cause deaths)
  - The absolute number of lives saved per 1000 screened is limited by the number of deaths without screening