Evidence, opinion and fact in cancer screening and prevention

Ruth Etzioni PhD

Fred Hutchinson Cancer Research Center

Cancer screening and prevention

RESEARCH
OBSERVATION
DATA

EVIDENCE
DECISIONS
POLICIES

OPINION

Where does evidence about cancer screening and prevention come from?

1. Clinical trials
2. Cancer trends
3. Observational studies

Where does evidence about cancer screening and prevention come from?

1. Clinical trials

   DO NOT ALWAYS AGREE

2. Cancer trends

3. Observational studies

Ten breast cancer screening trials

Relative reduction in risk of death in screened group

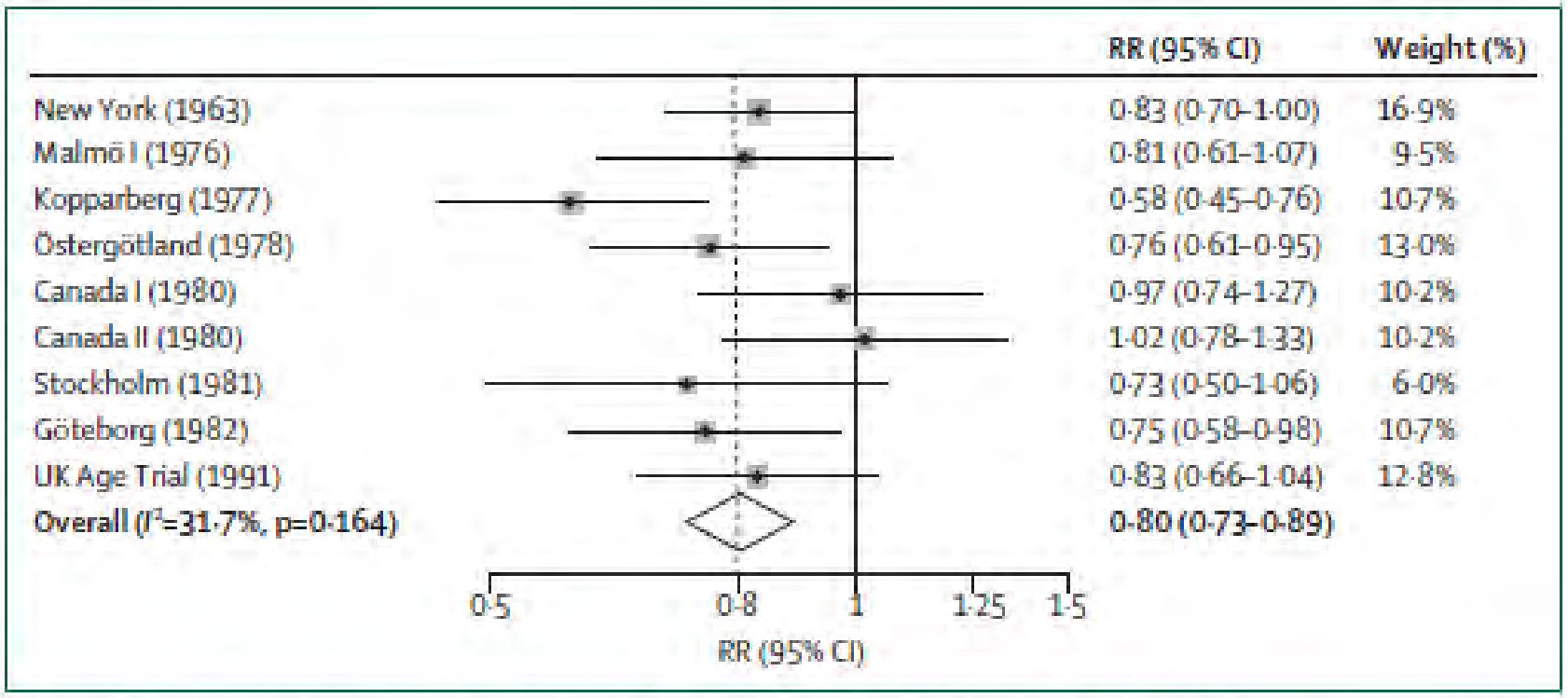
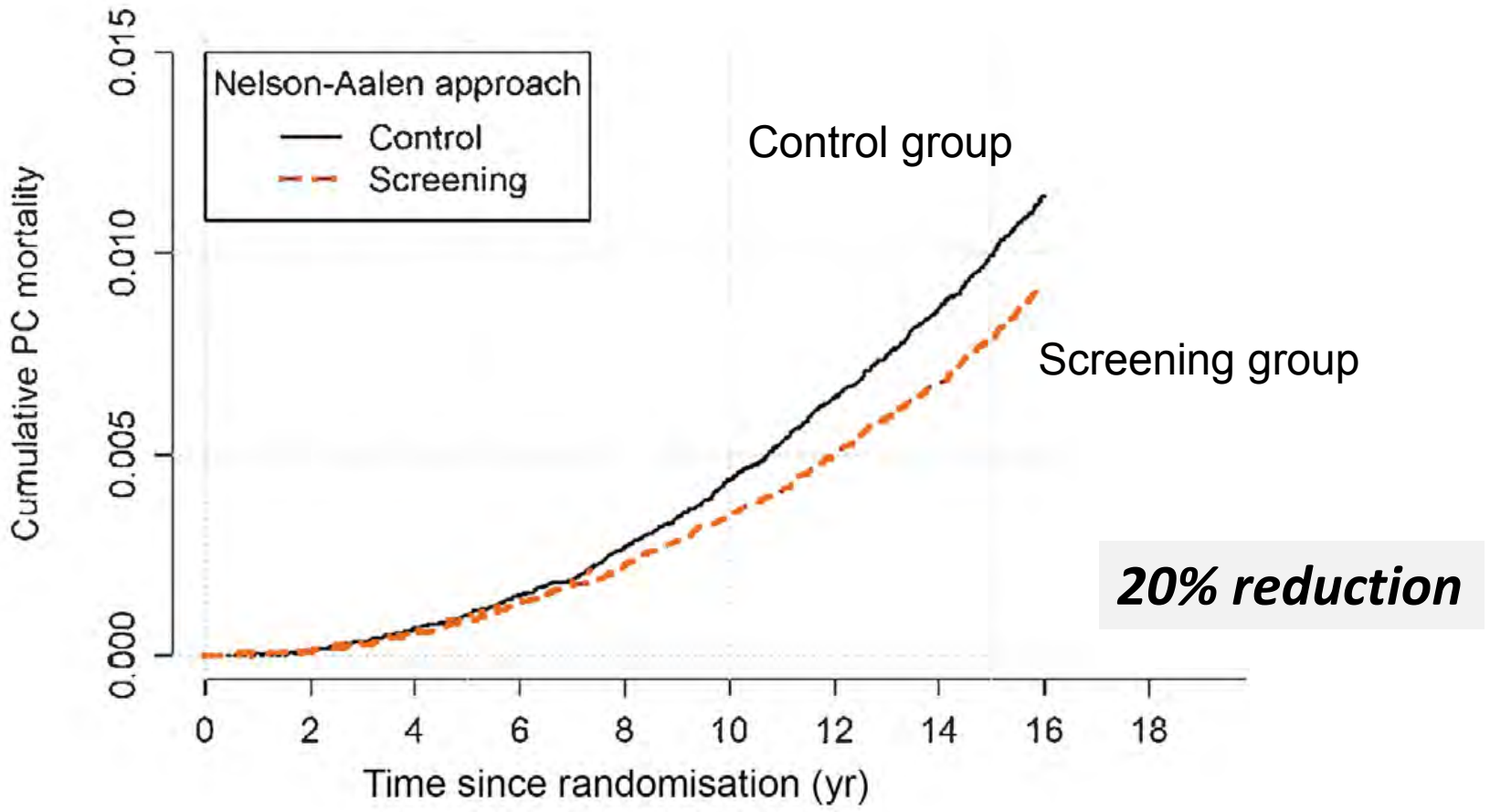


Figure 1: **Meta-analysis of breast cancer mortality after 13 years of follow-up in breast cancer screening trials**
Adapted from the Cochrane Review.[5] RR=relative risk. Malmö II is excluded because follow-up of about 13 years was not available; the Swedish Two County (Kopparberg and Östergötland) 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.

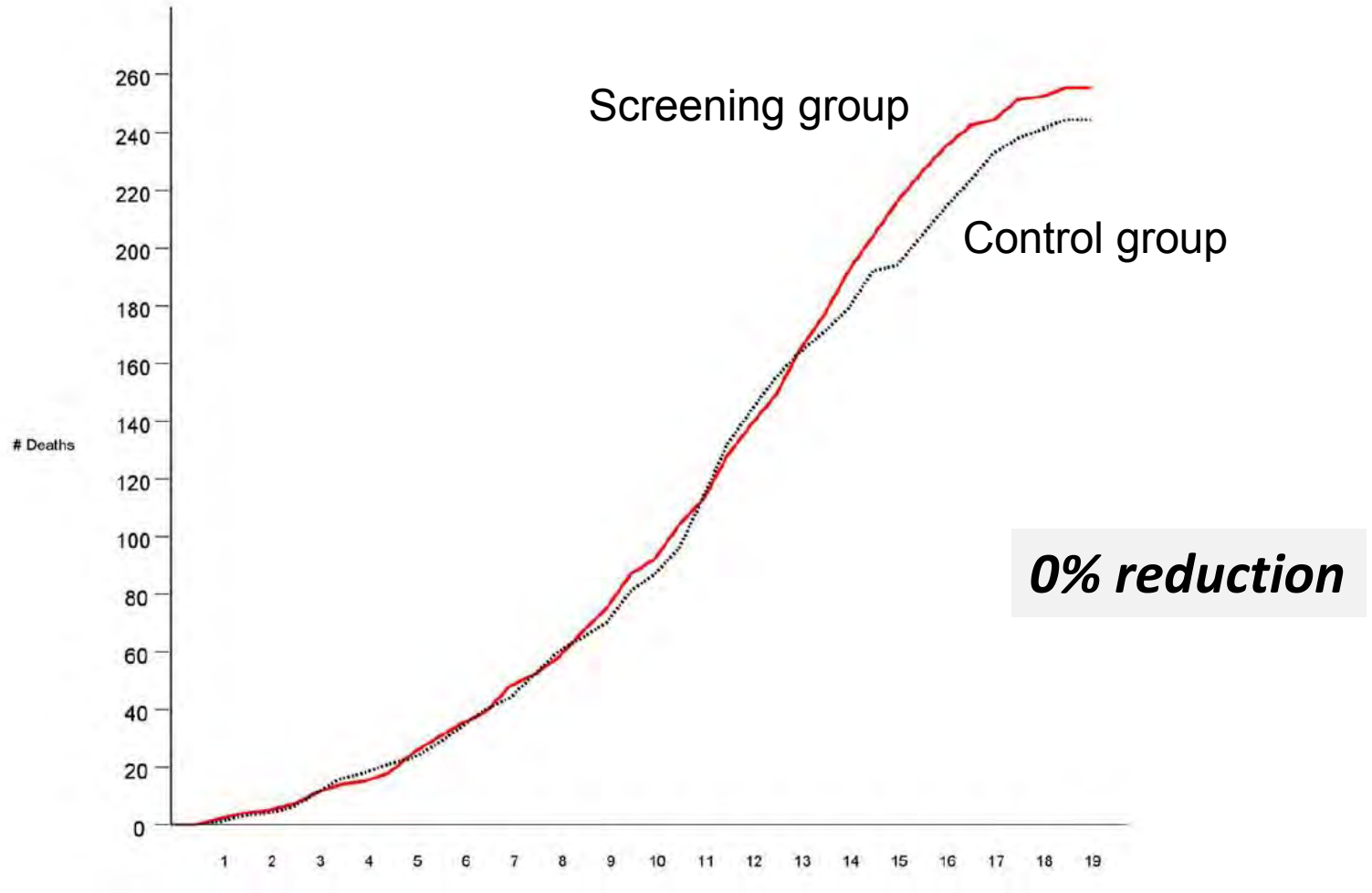
European prostate cancer screening trial

Cumulative deaths in screen and control groups



US prostate cancer screening trial

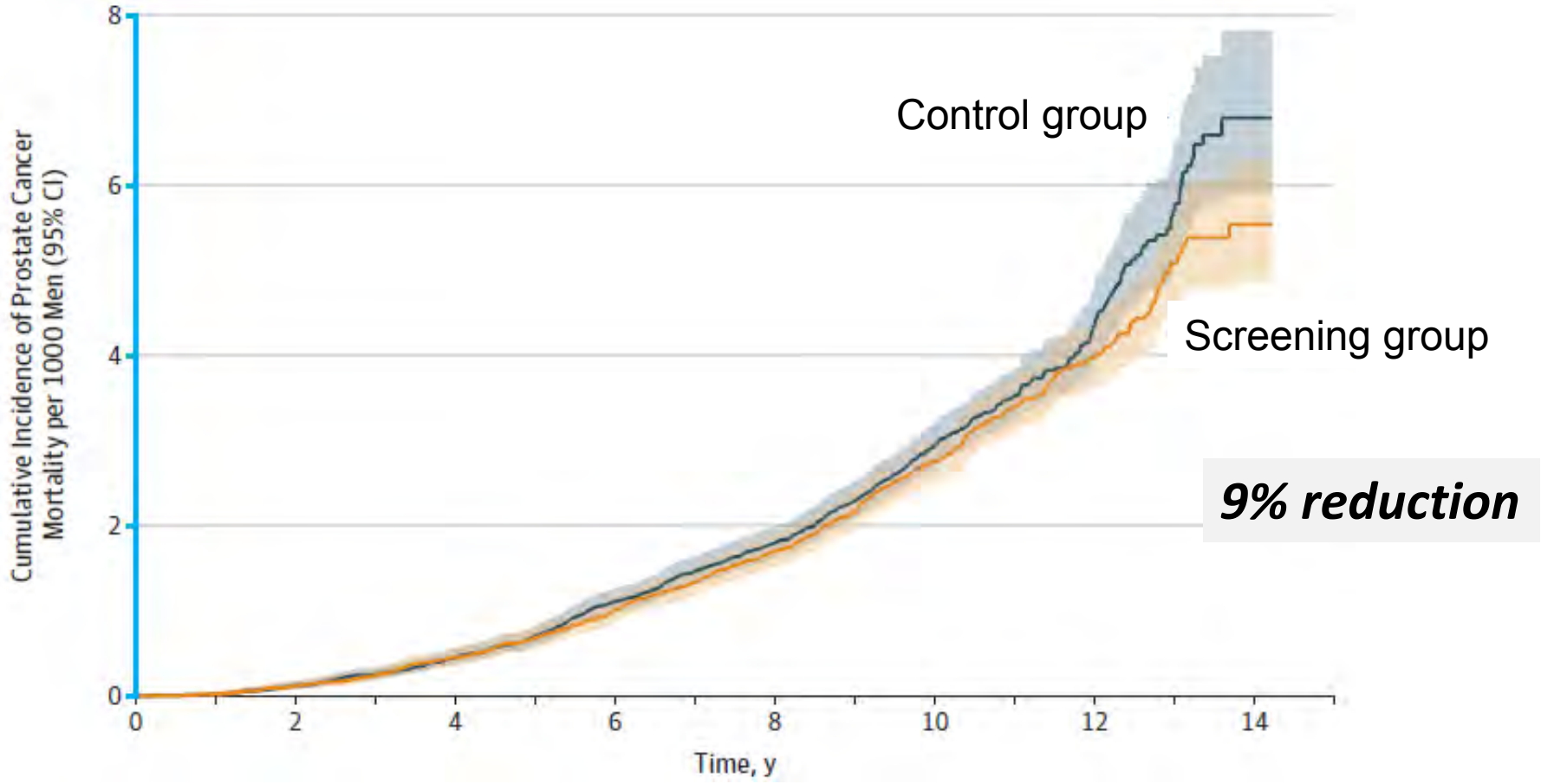
Cumulative deaths in screen and control groups



0% reduction

UK prostate cancer screening trial

Cumulative deaths in screen and control groups



Where does evidence about cancer screening and prevention come from?

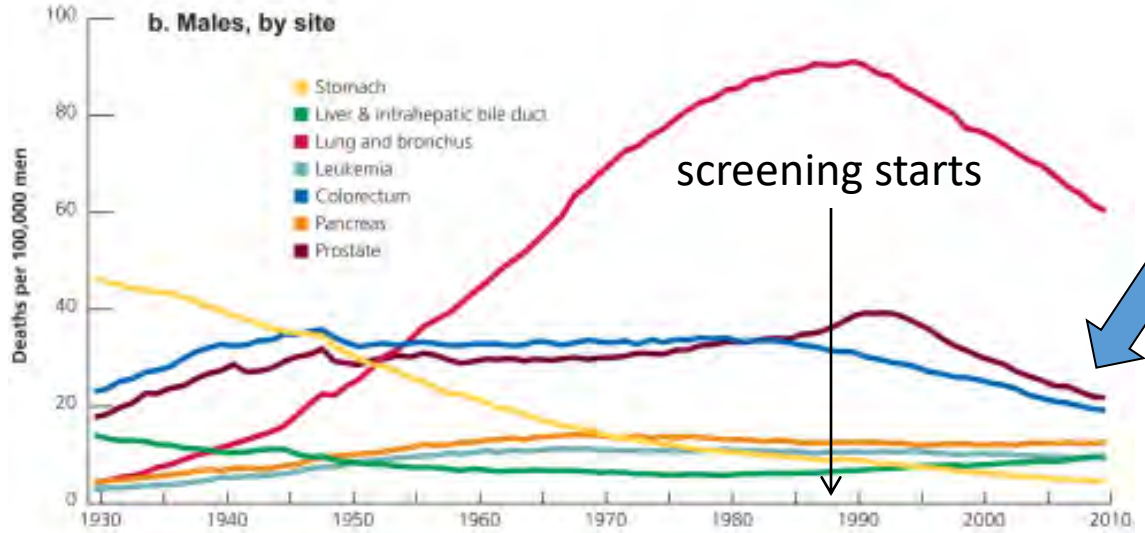
1. Clinical trials

2. Cancer trends

   HAVE MULTIPLE EXPLANATIONS

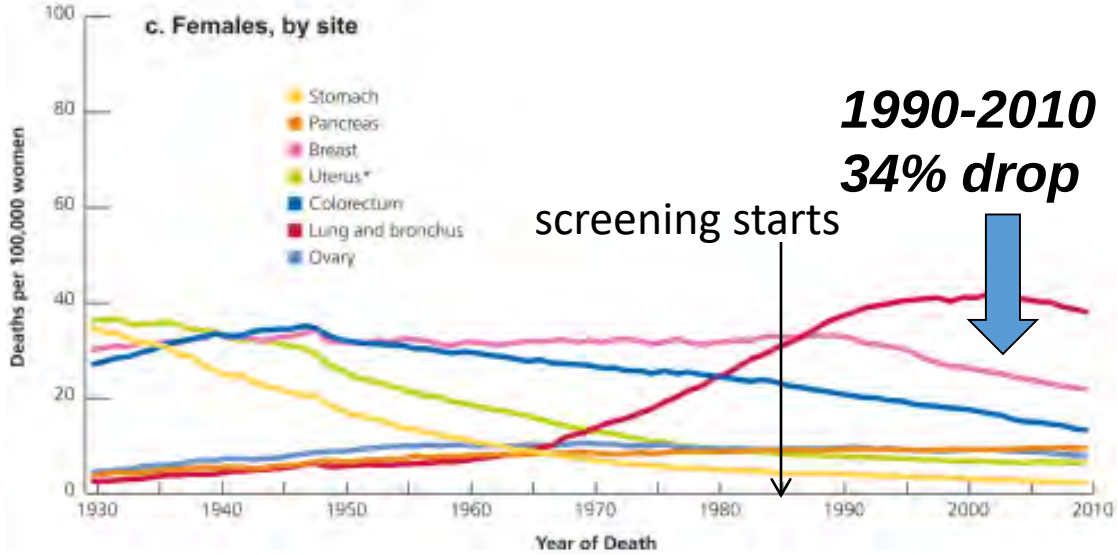
3. Observational studies

Breast and prostate cancer mortality in the US



screening starts

1990-2010
43% drop

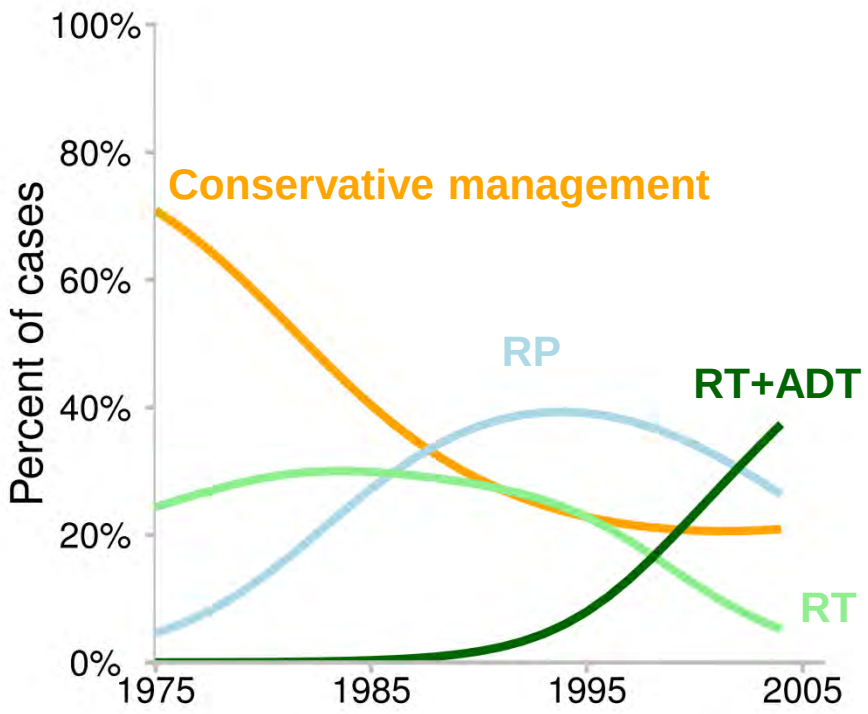


1990-2010
34% drop

screening starts

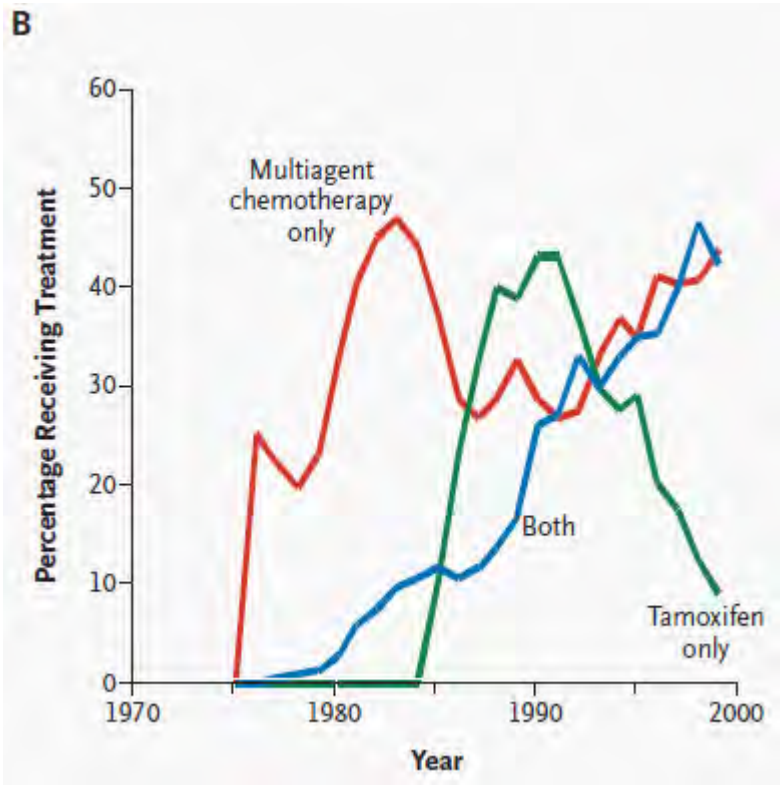
Prostate and breast cancer treatment trends

Prostate Cancer
Increase in curative treatment

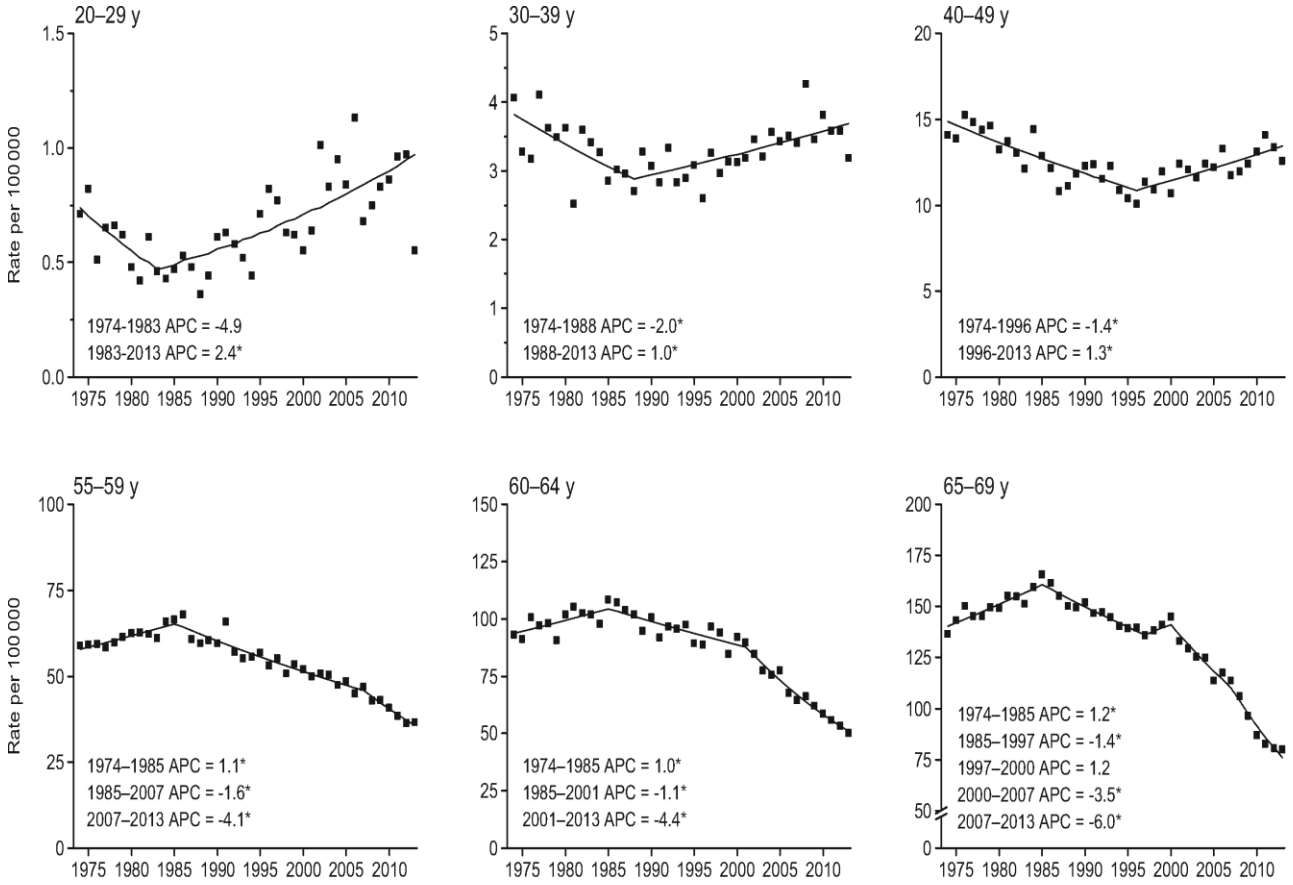


RP: radical prostatectomy
RT: radiation therapy
ADT: hormone therapy

Breast Cancer
Increase in adjuvant chemotherapy



Colorectal cancer incidence in young people



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1. Clinical trials
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FACTORS OTHER THAN THE ONES STUDIED MAY ACTUALLY EXPLAIN THE RESULTS

Plan for today

- Review some opinions and facts about cancer screening and prevention
- In each case
  - Explain the basis for the observation
  - Decide whether it is defensible or not
- Objectives
  - Learn about pitfalls when evaluating cancer screening and prevention
  - Come away better equipped to read about screening and prevention

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 doesn’t save lives
4. Breast cancer screening doesn’t work because advanced-stage incidence is flat
5. 30% of breast cancers and 60% of prostate cancers are overdiagnosed
6. Ovarian cancer screening doesn’t work
7. New blood-based screening tests are going to solve all of our problems
8. Excess body weight causes cancer
9. Alcohol consumption increases your chance of getting breast and some other cancers
10. Women with dense breasts have a greater risk of getting breast cancer

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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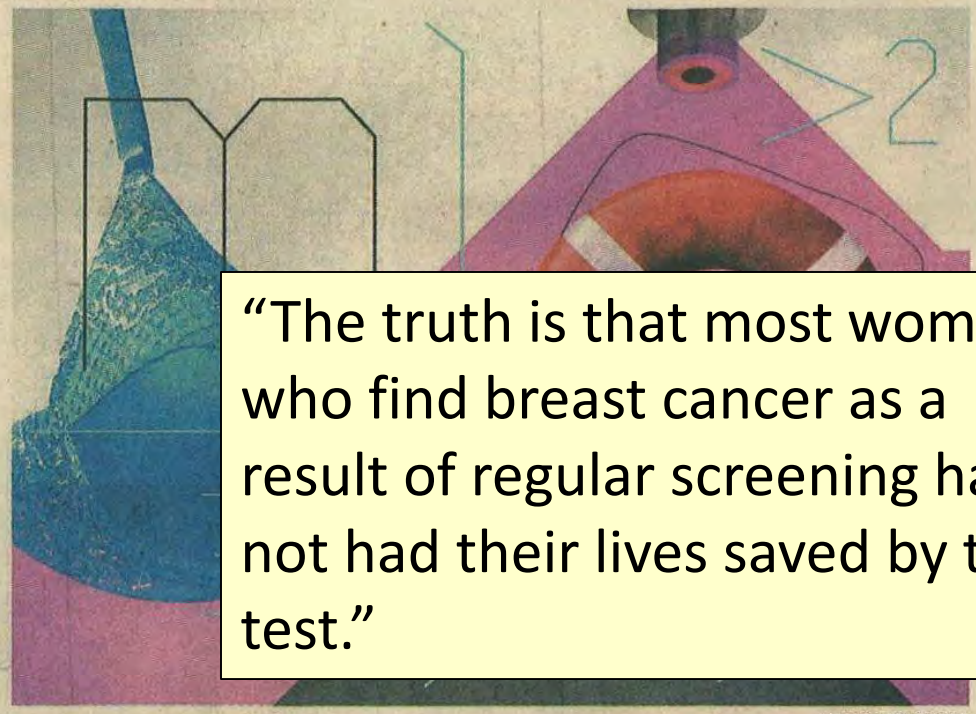


STUART BRADFORD

"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 without screening?

A: 9% (based on old SEER data)

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

A: About 3%

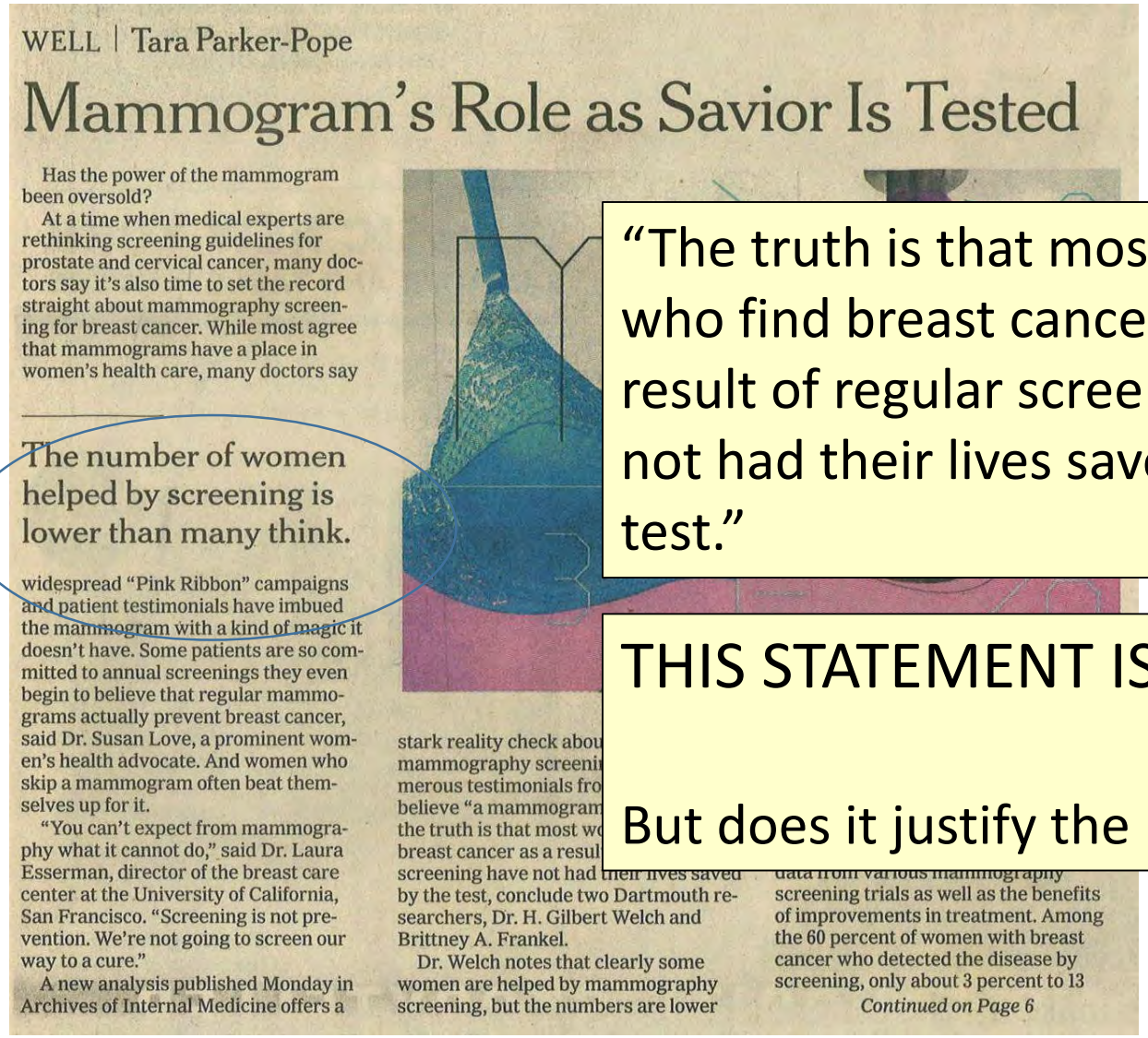
Q: If screening benefit is 20% reduction in breast cancer death, how many women will have their lives saved by screening?

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

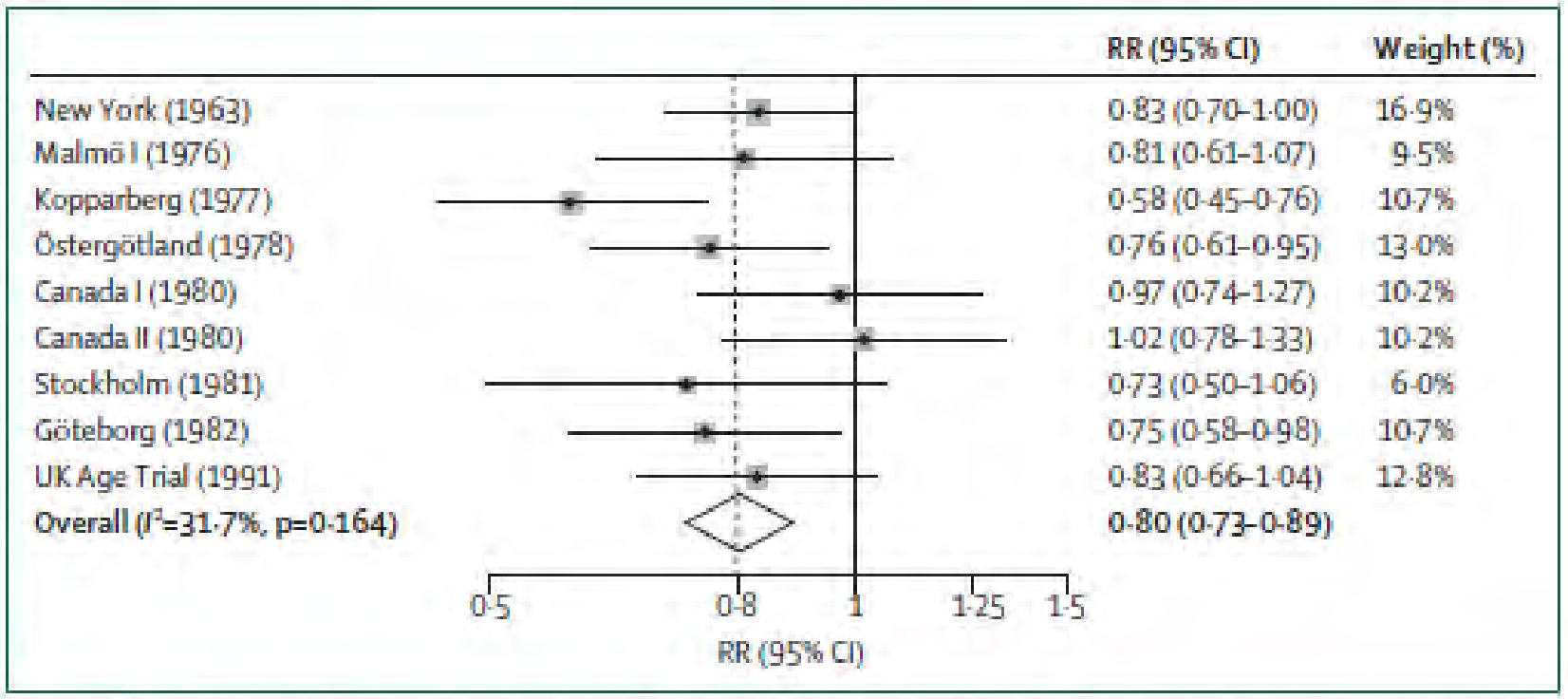
"The truth is that most women who find breast cancer as a result of regular screening have not had their lives saved by the test."

THIS STATEMENT IS TRUE

But does it justify the headline?

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

Breast cancer: Eight screening trials



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Why so much variability?

Trial design and analysis

- Continuous-screen or stop-screen

Screening protocol

- Ages, intervals, cutoffs

Compliance, contamination, treatment

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

Timing of the trial

- Screening, biopsy and treatment technologies available
- Follow-up duration

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

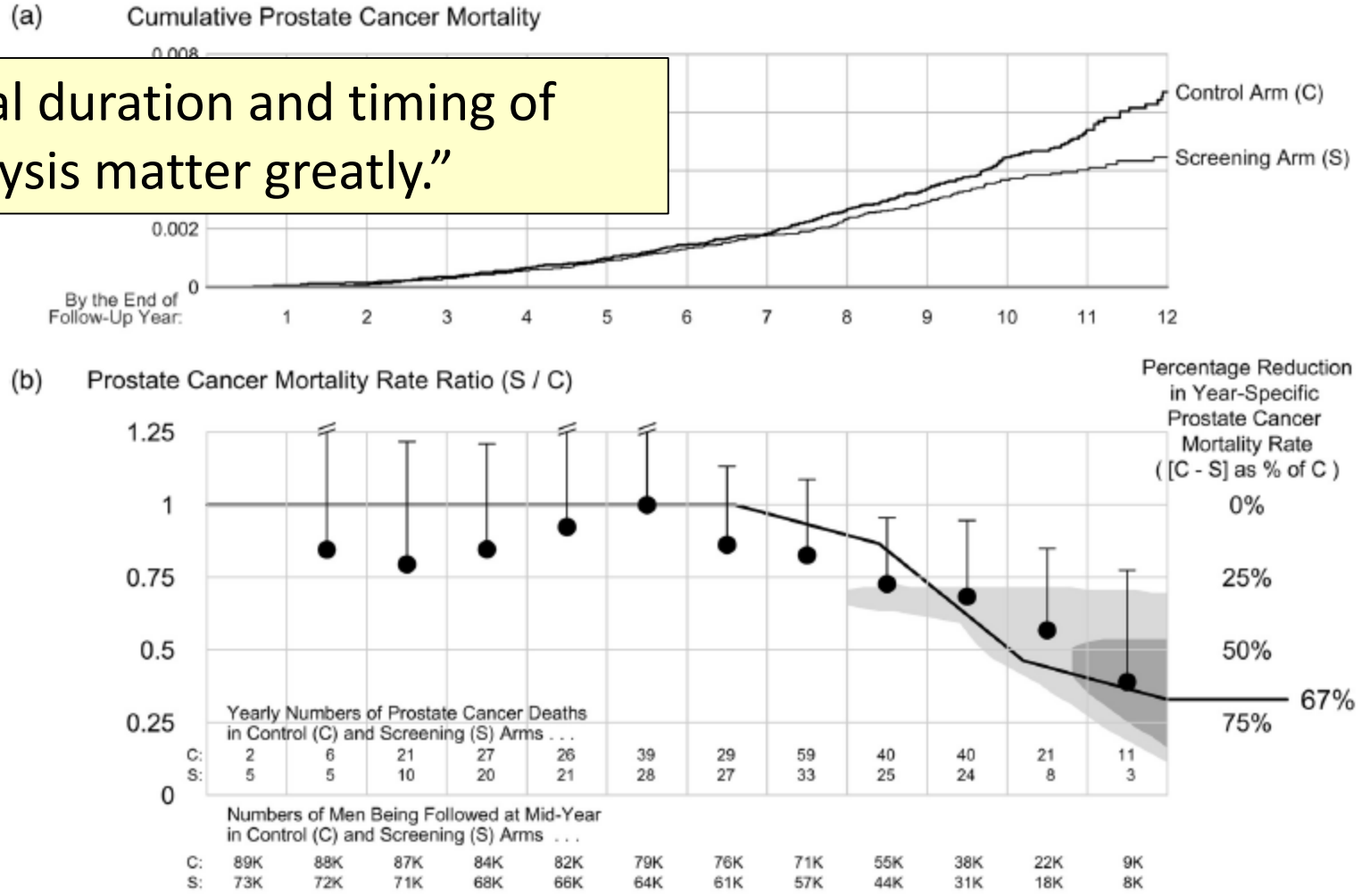
ORIGINAL ARTICLE

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."



An ovarian cancer screening trial

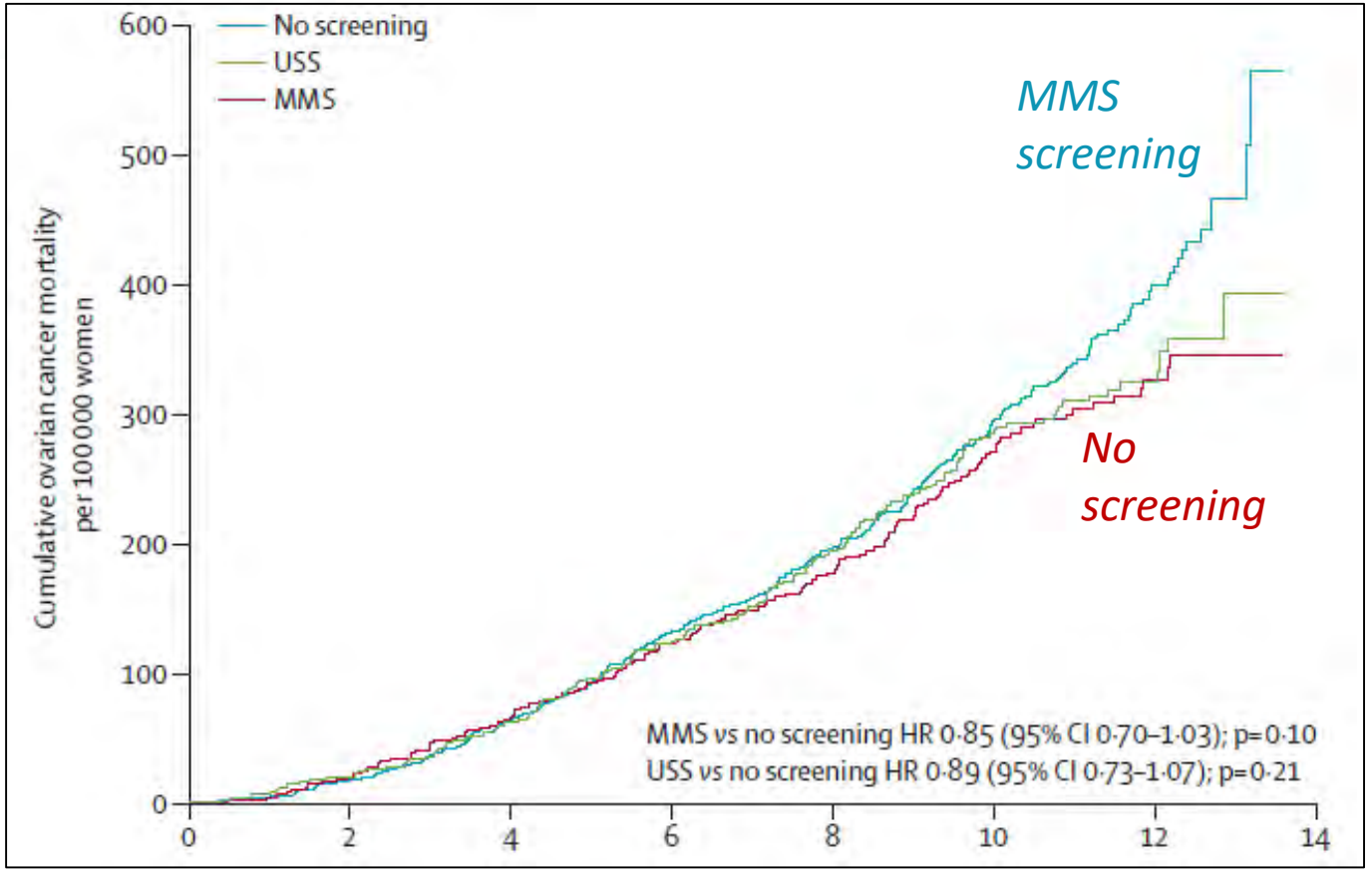
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

Lancet, 2017

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

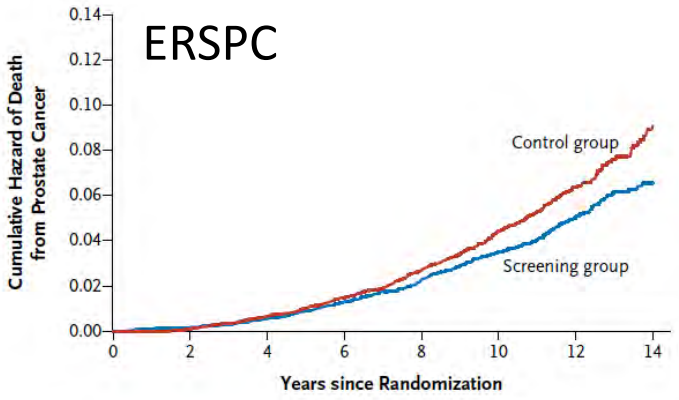
MMS uses ROCA algorithm – learns by observing serial CA125 trajectories over time

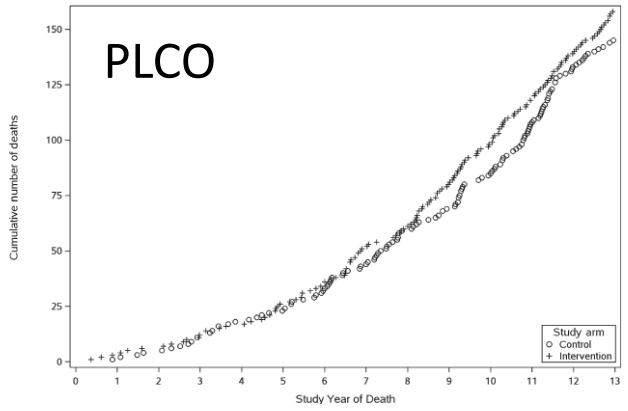
15% reduction in risk of ovarian cancer death in MMS arm compared to no screening (p=0.1)

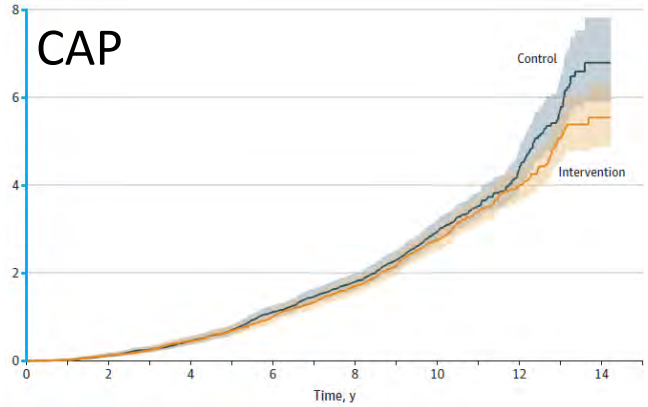


3. Prostate cancer screening doesn’t save lives

Prostate cancer trials: key differences in execution





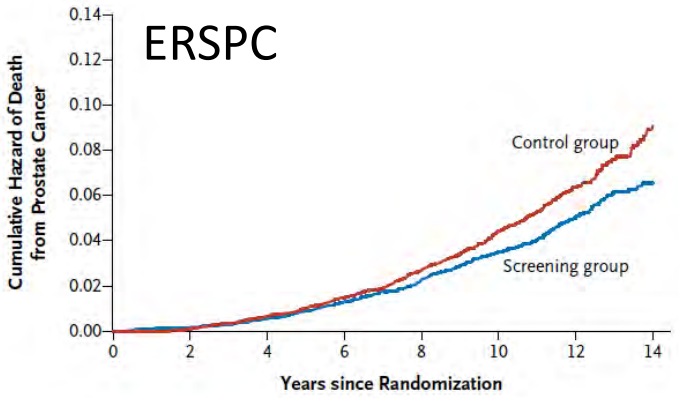


	ERSPC	PLCO	CAP
Screening interval	4 years (most centers) 2 years (Sweden)	Annual for 5 years	One screen at start of trial
Screening on control arm	Infrequent	74% at least one test 50% tested each year	Infrequent
Compliance with screening	Relatively good	Relatively good	Only 36% of eligible men were screened
Compliance with biopsy	80%	40%	85%

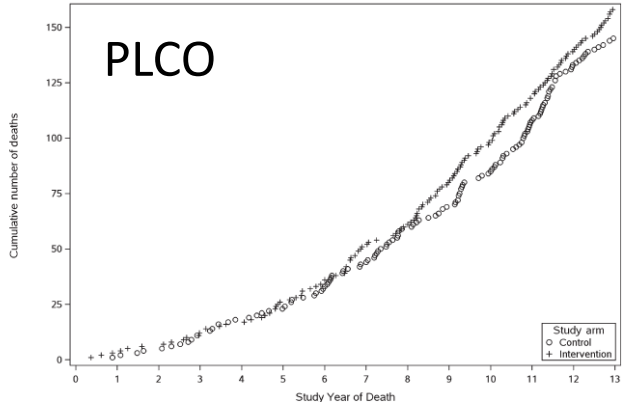
Schröder et al., N Engl J Med, 2012; Andriole et al., J Natl Cancer Inst, 2012; Martin et al, JAMA 2018

Prostate cancer trials: more similar than they appear

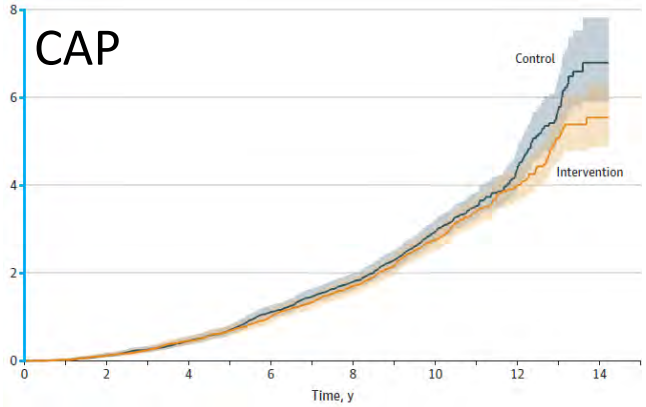
ERSPC



PLCO



CAP



Annals of Internal Medicine ORIGINAL RESEARCH

Reconciling the Effects of Screening on Prostate Cancer Mortality in the ERSPC and PLCO Trials

Alex Tsodikov, PhD; Roman Gulati, MS; Eveline A.M. Heijnsdijk, PhD; Paul F. Pinsky, PhD; Sue M. Moss, PhD; Sheng Qiu, MS; Tiago M. de Carvalho, MS; Jonas Hugosson, MD; Christine D. Berg, MD; Anssi Auvinen, MD; Gerald L. Andriole, MD; Monique J. Roobol, PhD; E. David Crawford, MD; Vera Nelen, MD; Maciej Kwiatkowski, MD; Marco Zappa, PhD; Marcos Luján, MD; Arnauld Villers, MD; Eric J. Feuer, PhD; Harry J. de Koning, MD; Angela B. Mariotto, PhD; and Ruth Etzioni, PhD

Background: The ERSPC (European Randomized Study of Screening for Prostate Cancer) found that screening reduced prostate cancer mortality, but the PLCO (Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial) found no reduction.

Objective: To evaluate whether effects of screening on prostate cancer mortality relative to no screening differed between the ERSPC and PLCO.

Design: Cox regression of prostate cancer death in each trial group, adjusted for age and trial. Extended analyses accounted for increased incidence due to screening and diagnostic work-up in each group via mean lead times (MLTs), which were estimated empirically and using analytic or microsimulation models.

Results: Estimated MLTs were similar in the ERSPC and PLCO intervention groups but were longer in the PLCO control group than the ERSPC control group. Extended analyses found no evidence that effects of screening differed between trials ($P = 0.37$ to 0.47 [range across MLT estimation approaches]) but strong evidence that benefit increased with MLT ($P = 0.0027$ to 0.0032). Screening was estimated to confer a 7% to 9% reduction in the risk for prostate cancer death per year of MLT. This translated into estimates of 25% to 31% and 27% to 32% lower risk for prostate cancer death with screening as performed in the ERSPC and PLCO intervention groups, respectively, compared with no screening.

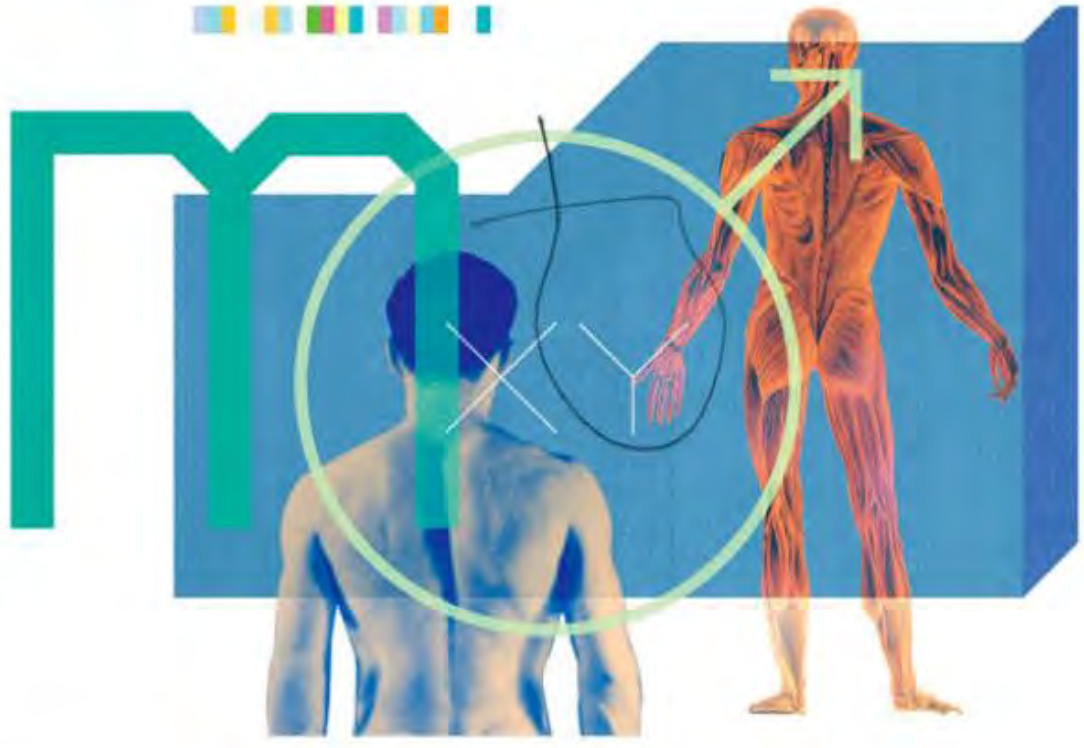
Limitation: The MLT is a simple metric of screening and diagnostic work-up.

PSA screening as conducted in the trials reduced prostate cancer mortality by 25-32% compared with no screening

Tsodikov et al, Annals of Internal Medicine 2018

The New York Times

New Study Offers Support for Prostate Testing



STUART BRADFORD

By RONI CARYN RABIN
SEPTEMBER 4, 2017

For men who are weighing the pros and cons of prostate cancer screening, a new study strengthens the evidence that testing can reduce deaths from this cancer, something two earlier large landmark clinical trials appeared to reach different conclusions about.

New studies lend support for PSA screening for prostate cancer

CBS NEWS

PSA screening can catch prostate cancer early, but in many cases may lead to unnecessary treatments. GETTY IMAGES/ISTOCKPHOTO

Despite ongoing debate over the value of prostate cancer screening, a new review says it can indeed reduce a man's risk of dying from the disease.

Early tumor detection using the prostate-specific antigen (PSA) blood test lowers a man's risk of prostate cancer death by 25 percent to 32 percent, the new analysis of two major trials of PSA testing found.

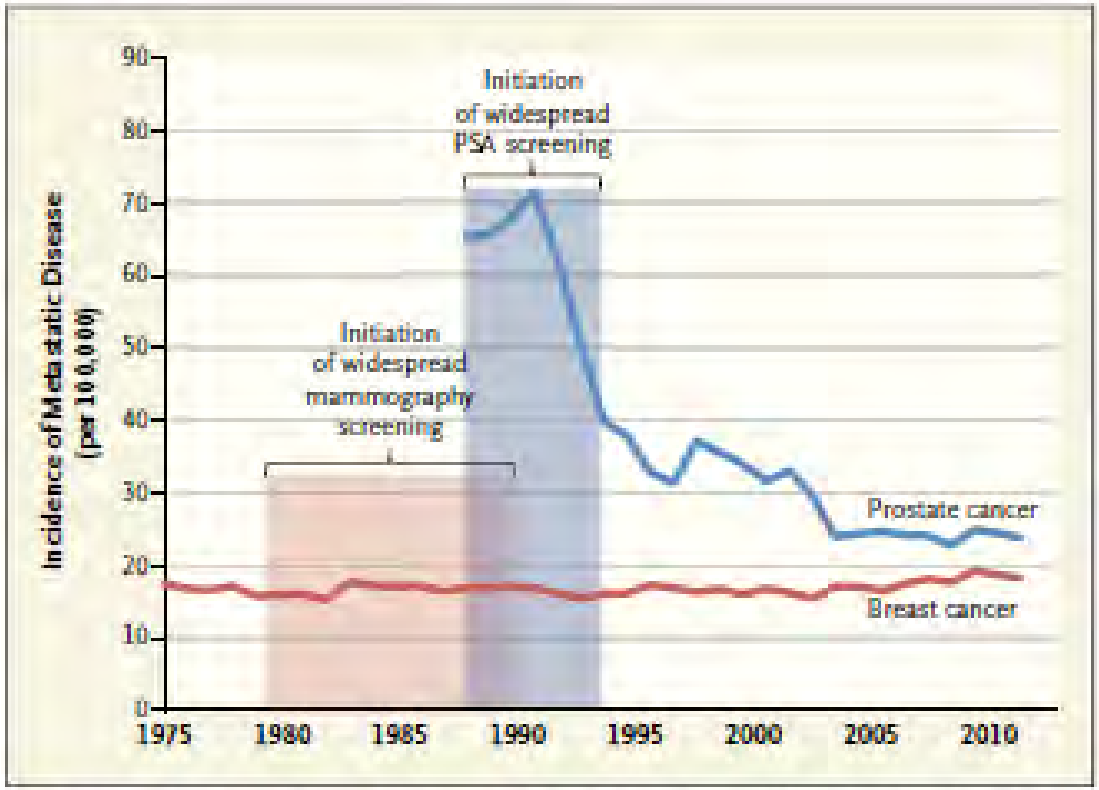
4. Breast cancer screening doesn’t work because advanced-stage incidence has not gone down

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.

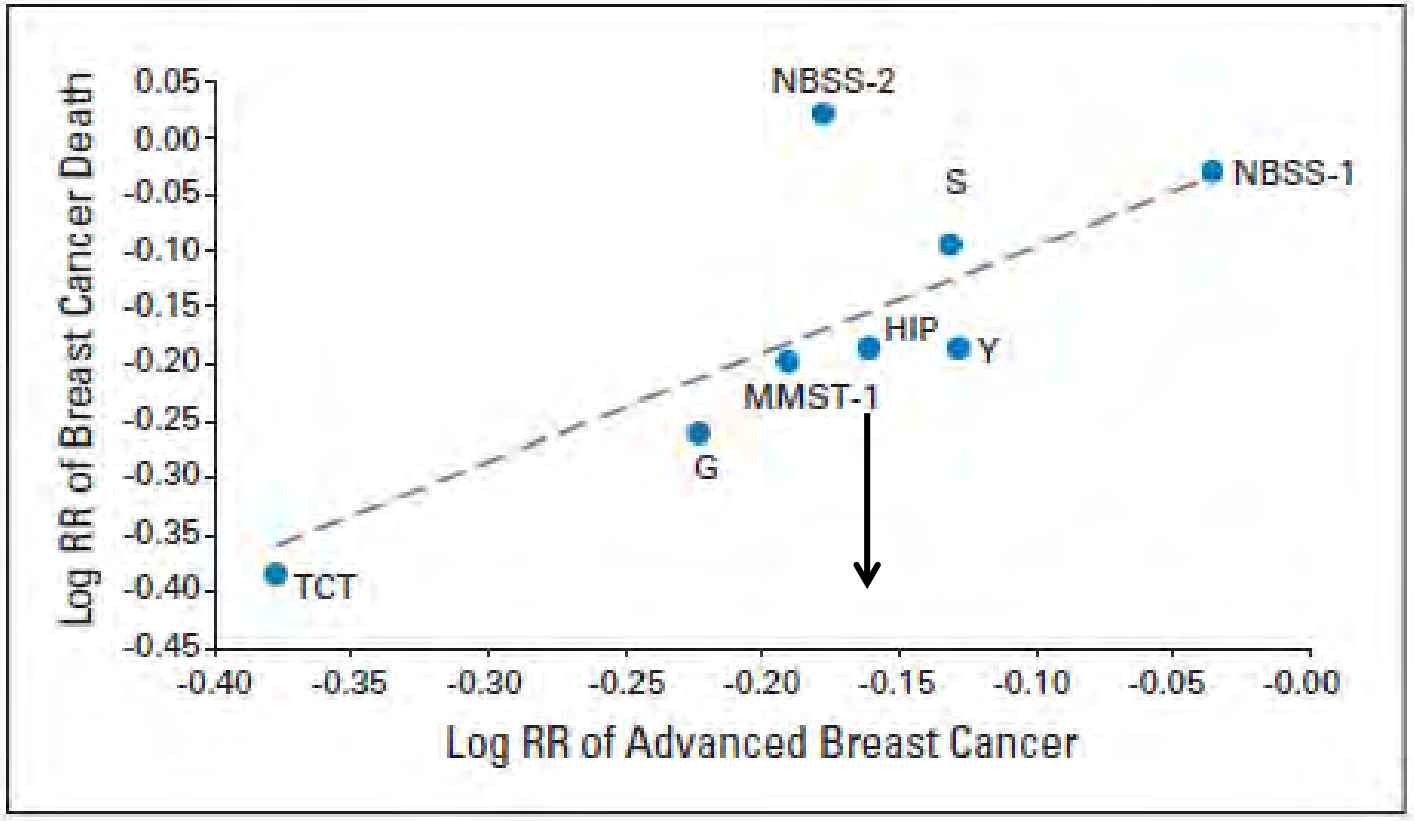
No reduction observed in the population over time

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

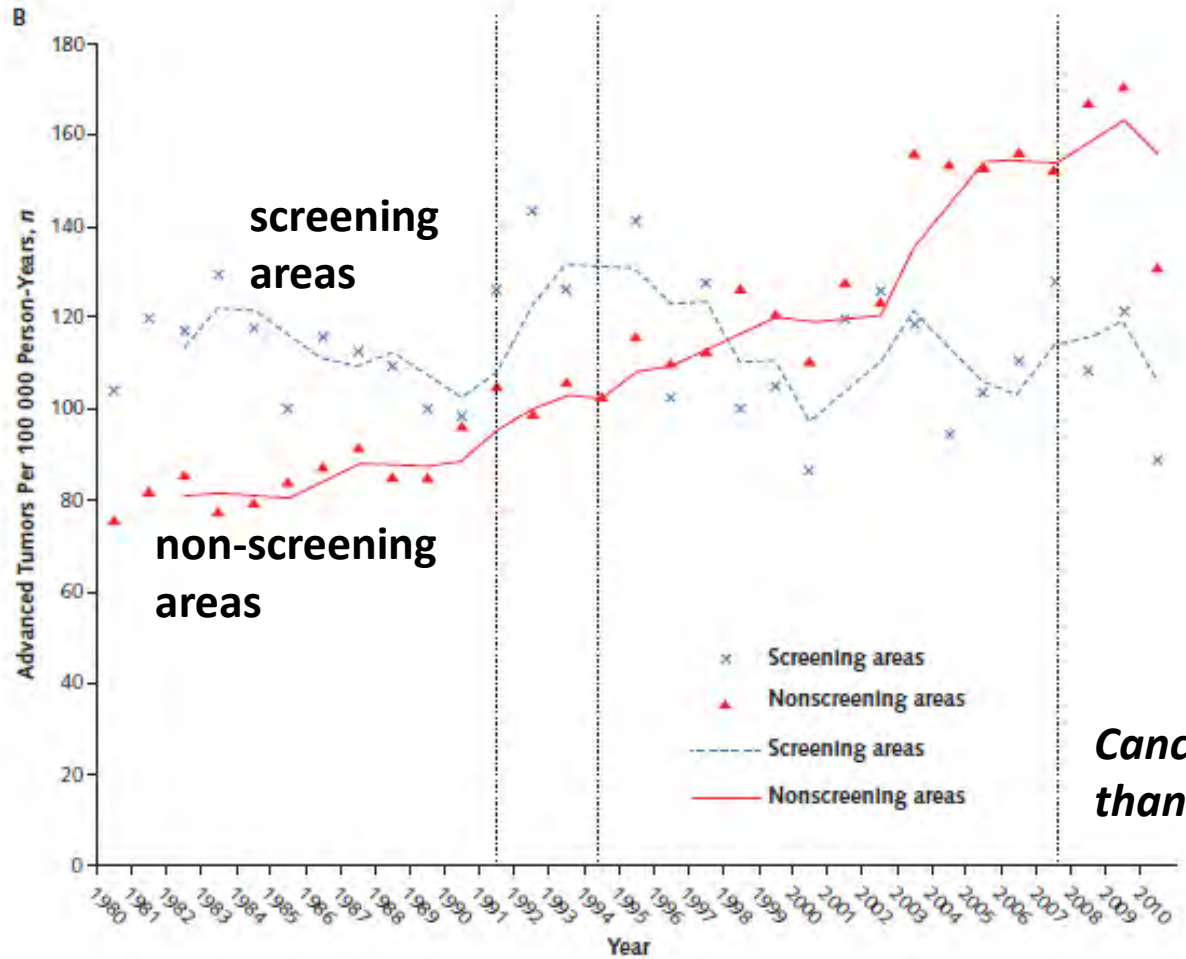
ORIGINAL RESEARCH

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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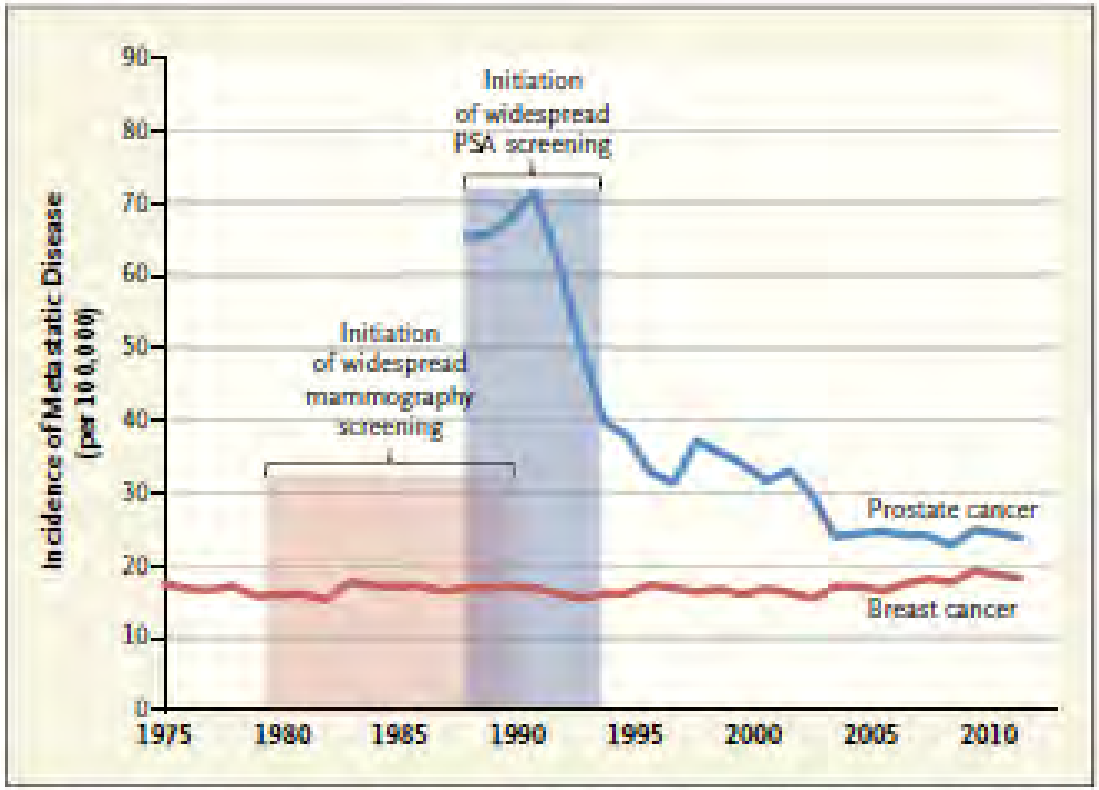


Incidence of Cancer That Was Metastatic at First Presentation, United States, 1975–2012.

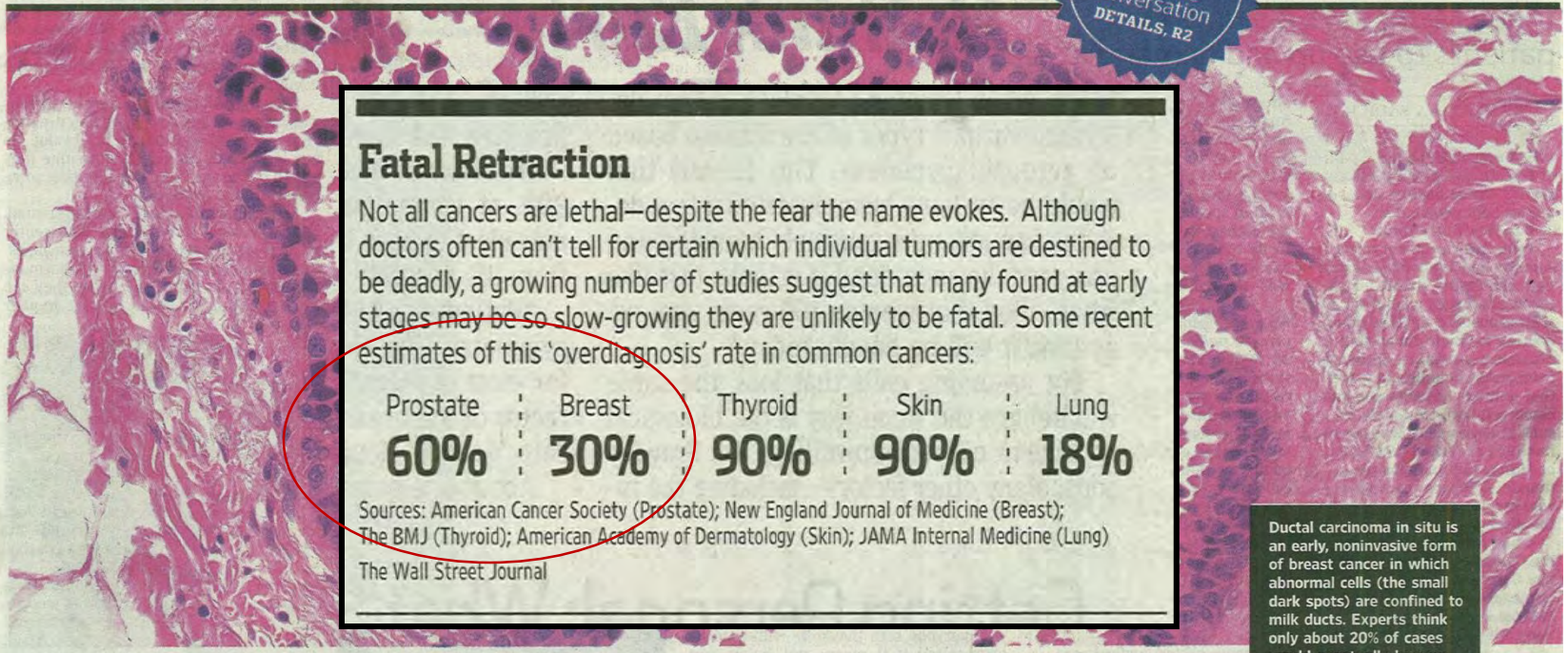
- Changes in technology for identifying advanced disease?
- Greater availability of imaging and surgery to stage new cases
- Changes in medical record and registry coding practices?
- True background trend increasing?

5. 30 percent of breast cancers and 60 percent of prostate cancers are overdiagnosed

HEALTH CARE

THE WALL STREET JOURNAL.

Follow The Experts
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

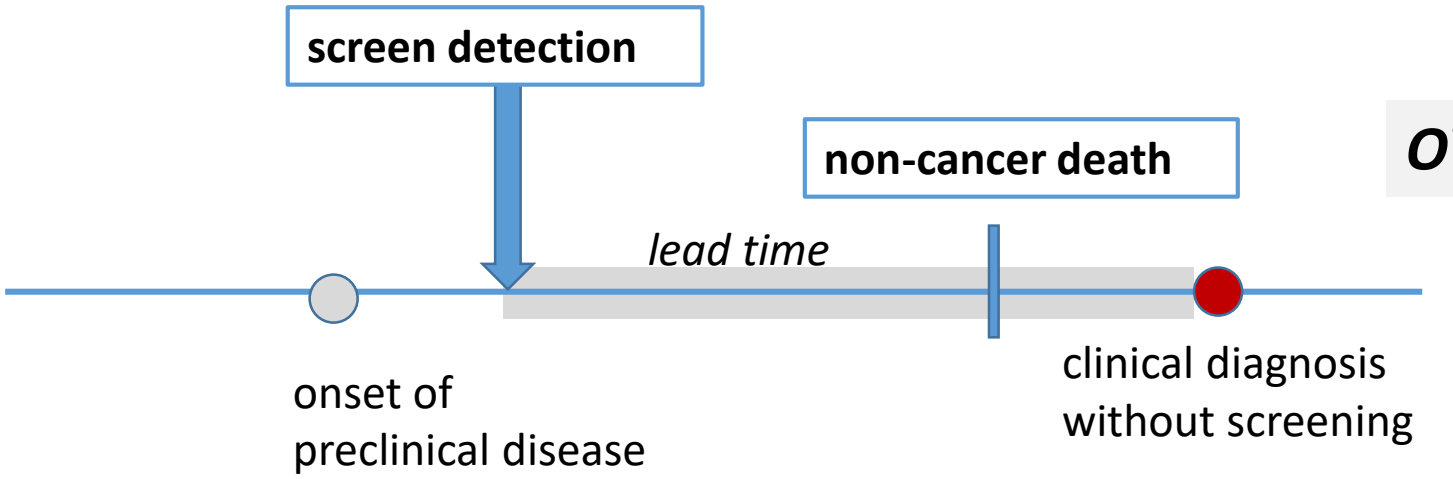
Gleason score of 6 or below "benign lesions"—although others note that that would mean half of the men treated for prostate cancer in the past 20 years didn't have cancer after all.

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%

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



OVERDIAGNOSED

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

Two ways to estimate overdiagnosis

- Lead time approach – first calculate the lead time then infer overdiagnosis
- Excess incidence – incidence with minus incidence without screening

Thirty percent of breast cancers overdiagnosed

The NEW ENGLAND JOURNAL of MEDICINE

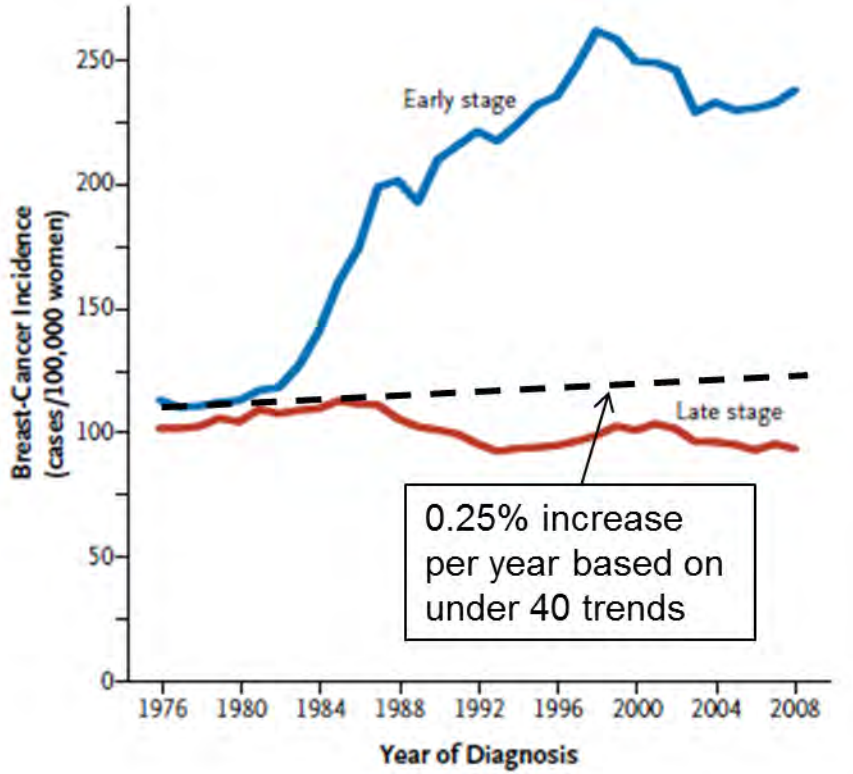
ORIGINAL ARTICLE

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

Thirty percent of breast cancers overdiagnosed

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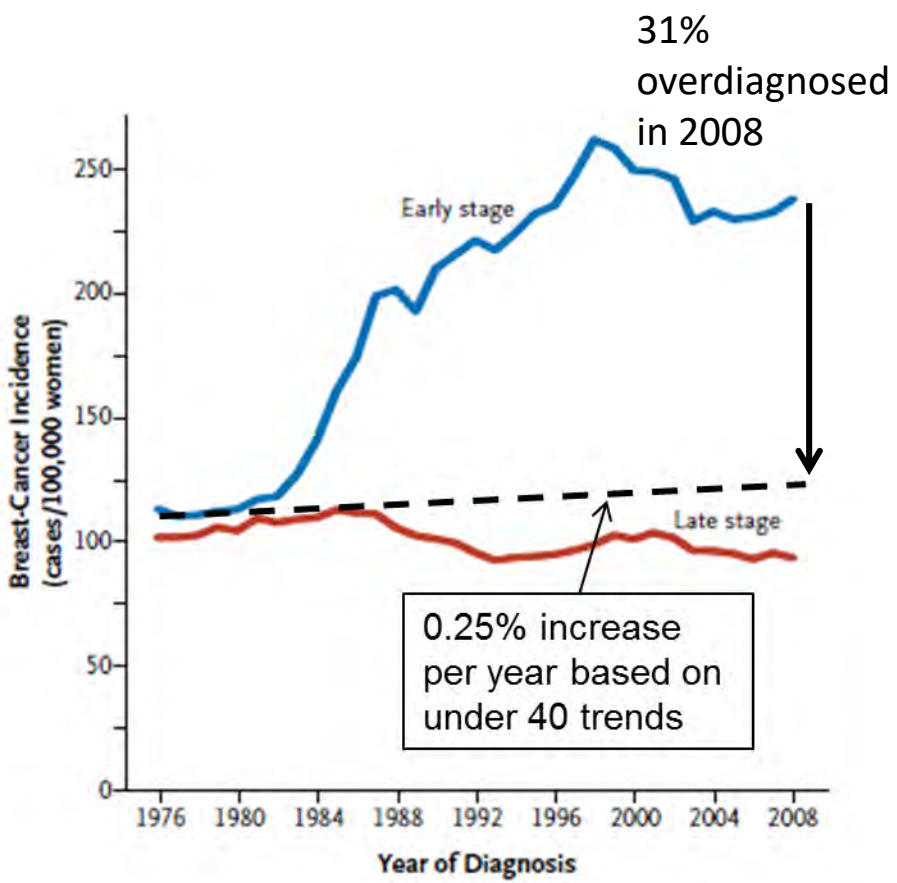
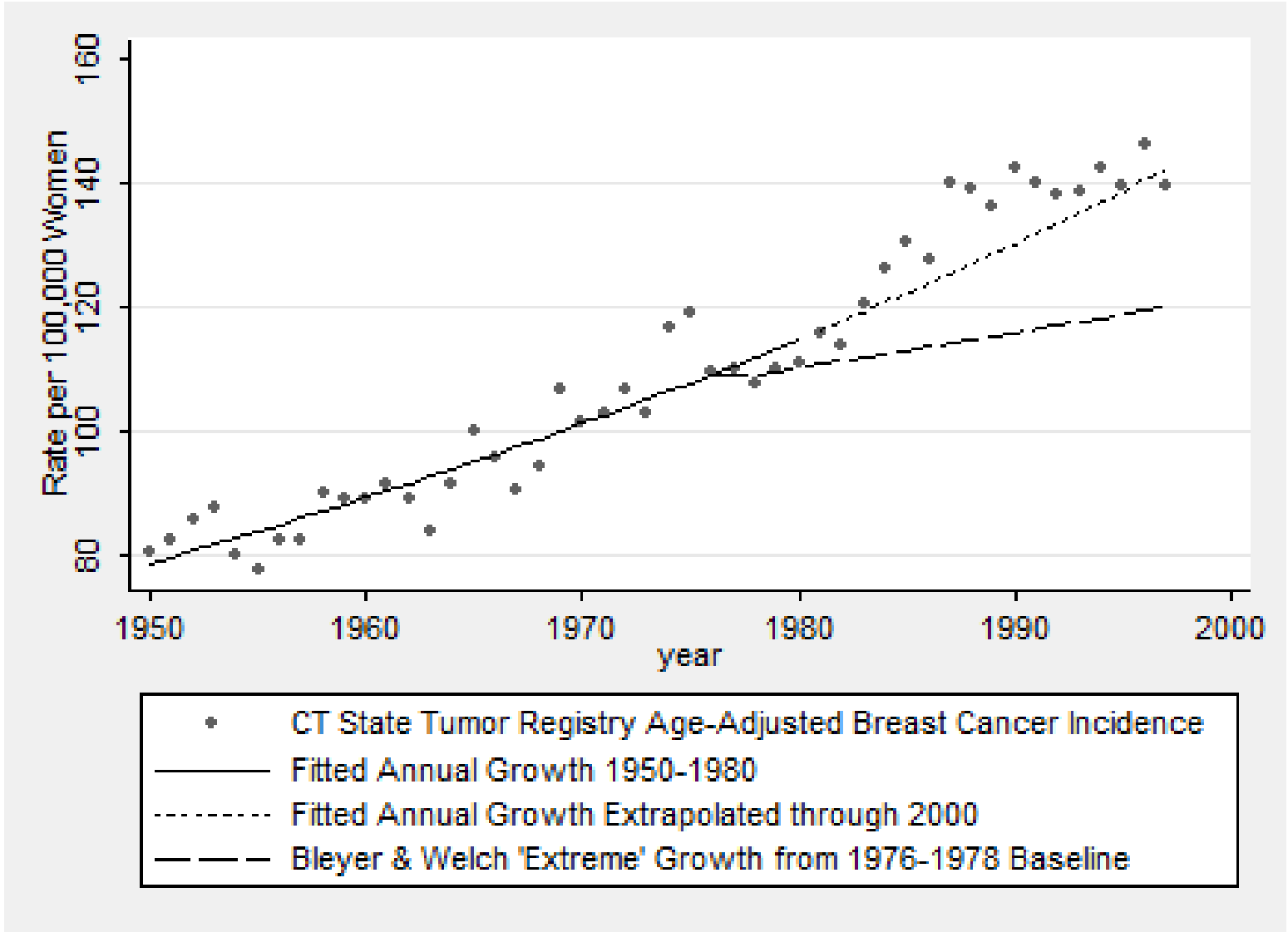
- Attribute all excess cases to overdiagnosis – 31% of all cancers

NEJM 2012

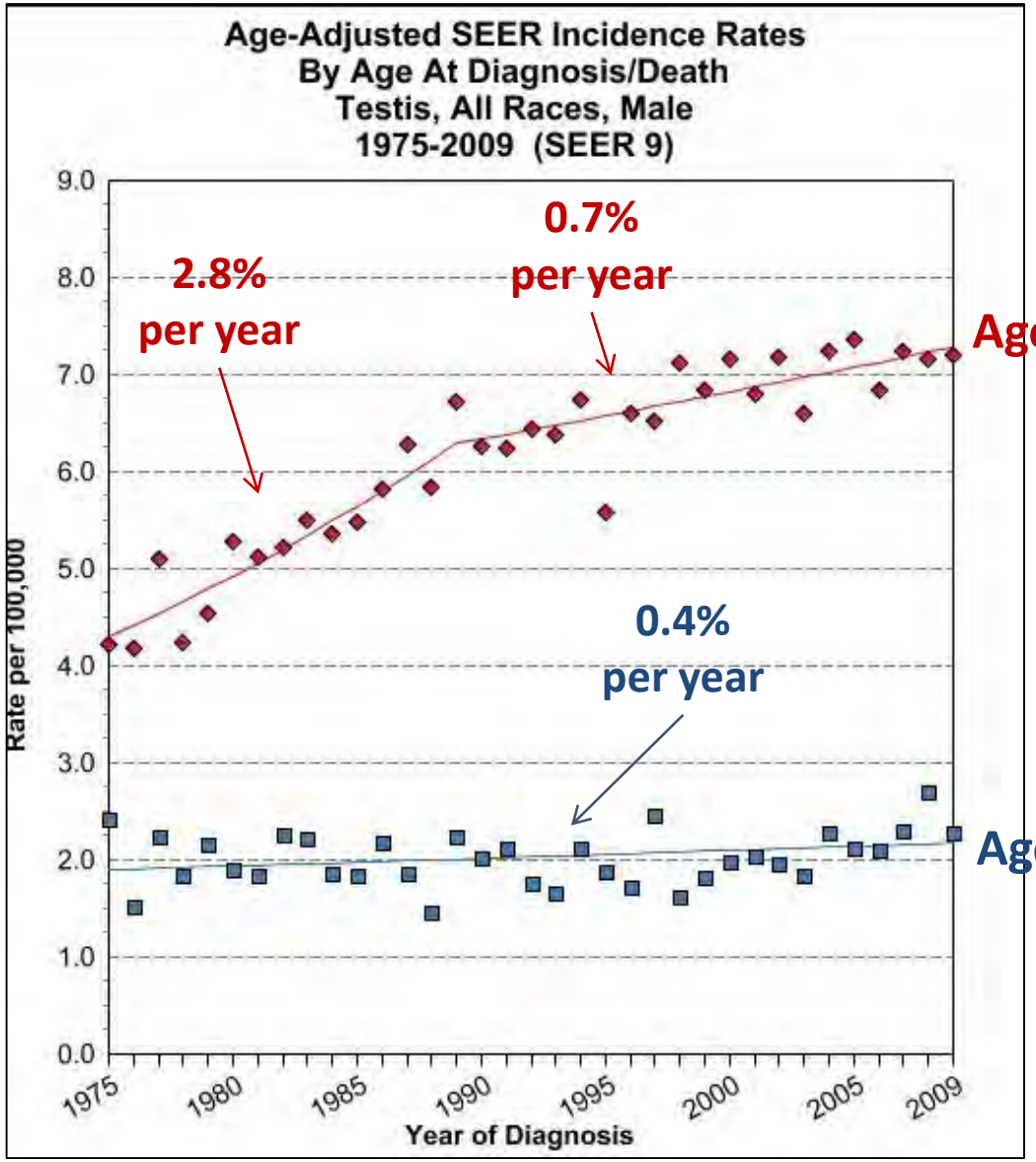
Incidence in women 40 and older
By calendar year and stage



Questioning the background trend



Trends in Testicular Cancer Incidence

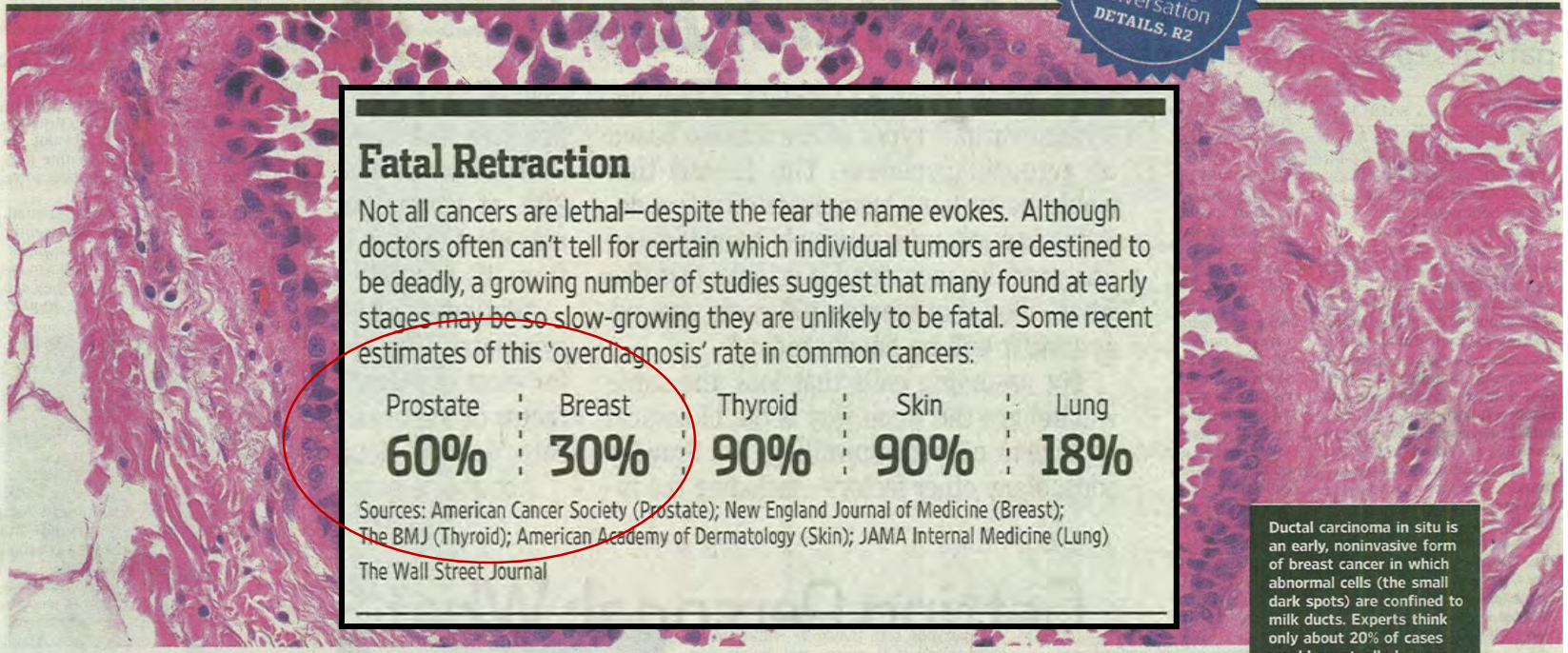


Trends in younger men do not match trends in older men

HEALTH CARE

THE WALL STREET JOURNAL.

Follow The Experts
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.

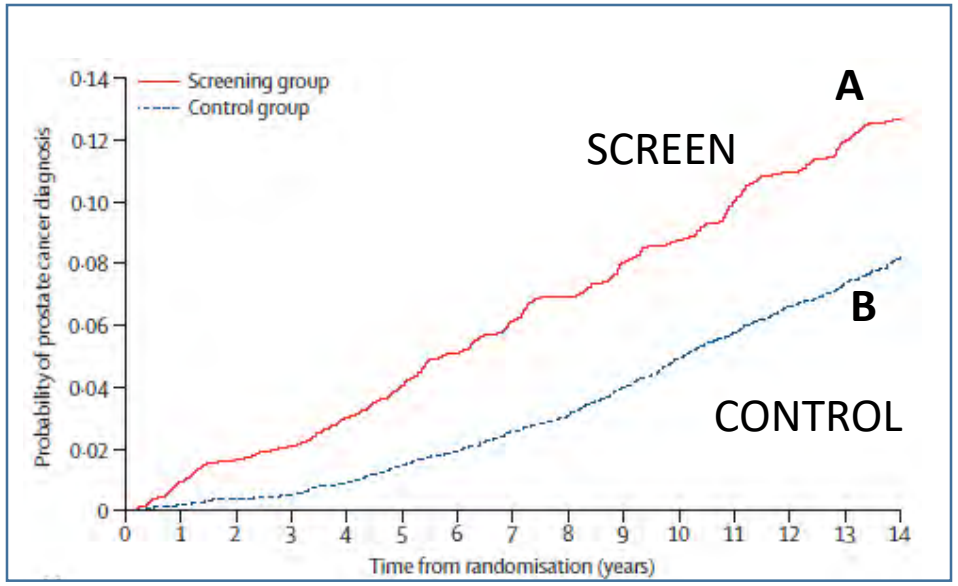
While it's clear that early-stage cancers are more treatable than late-stage ones, some leading cancer

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%

Screening and Prostate-Cancer Mortality in a Randomized European Study

Prostate cancer incidence in ERSPC

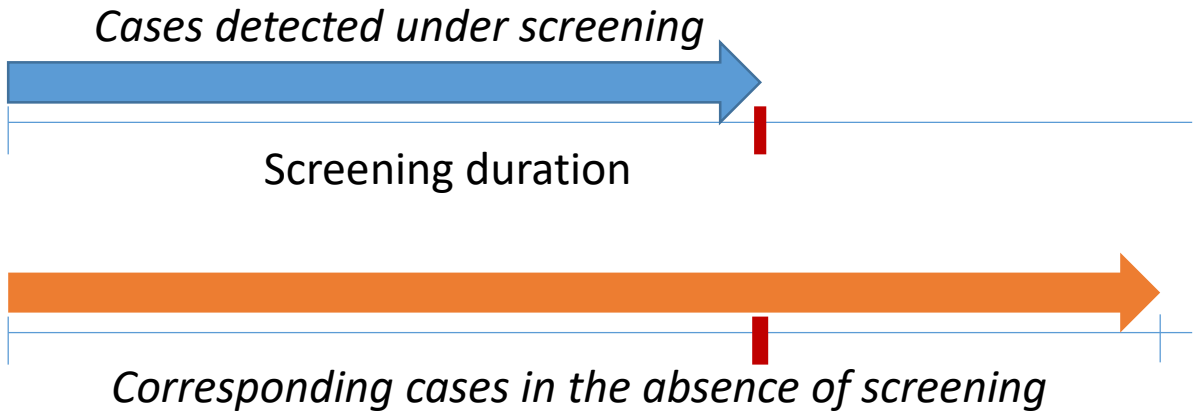


	Cumulative Incidence at 9 years
Screened arm (Screen-detected)	8.2% (**5.8%**)
Control arm	4.8%
Excess	**8.2% - 4.8% = 3.4%**
Excess/screen-detected	**3.4/5.8 = 58%**

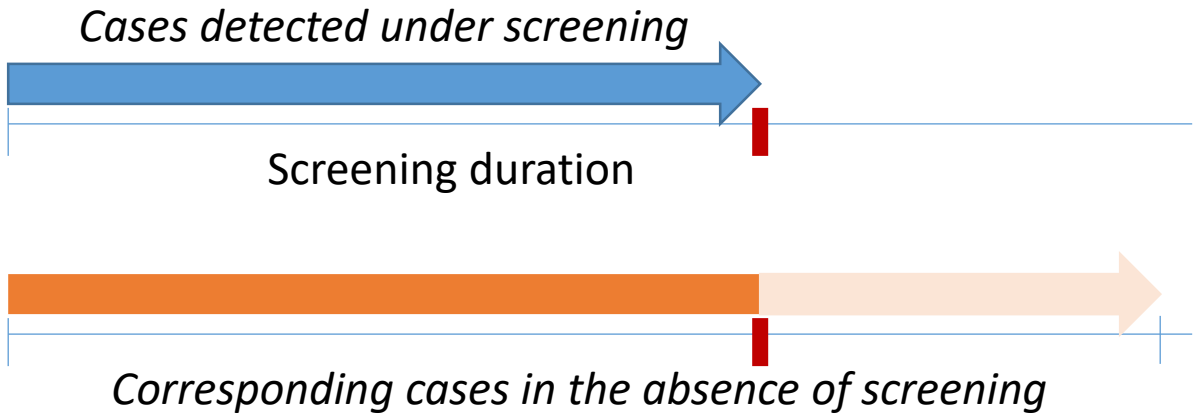
Schroder et al
NEJM 2009

The problem with excess incidence in the ERSPC

- What we know
  Cases diagnosed during the trial reflect cases that would have been diagnosed both during and after the trial in the absence of screening

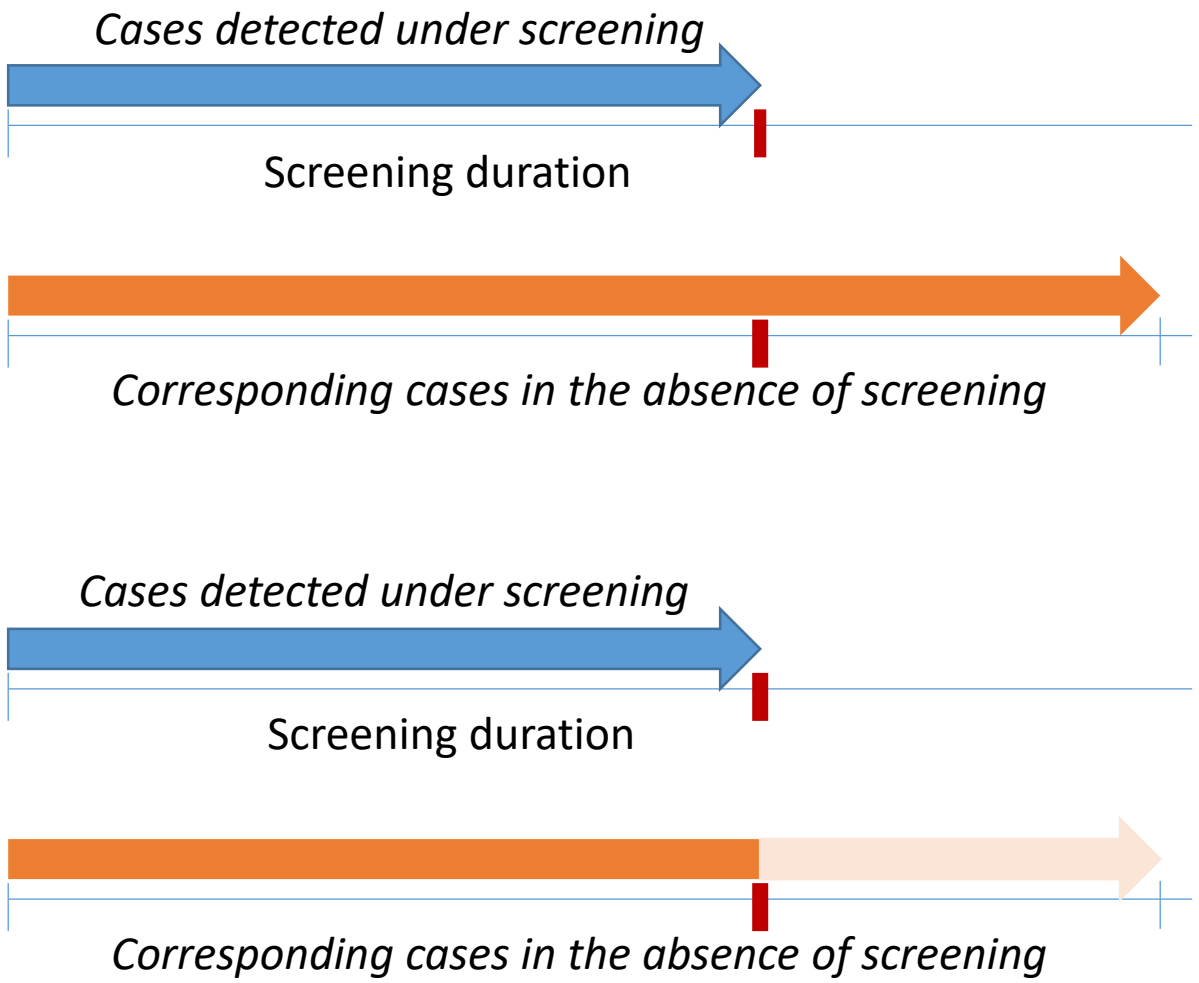


- Continued screen trial stops counting cases in the screen and control groups at the same time!



The problem with excess incidence in the ERSPC

In this setting cumulative excess incidence will always be greater than zero even if there is NO overdiagnosis!



So how many prostate cancers are overdiagnosed?

Study	Mean lead time (years)	Overdiagnosis (percent of screen detected)
Telesca	4.6 (white men)	**23%**
Biometrics 2008	6.8 (black men)	**34%**
Draisma JNCI 2009	5.9	**28%**
Gulati		**4%** age 50-54 with high grade, high PSA
CEBP 2012		**70%** age 75-79 with low grade, low PSA

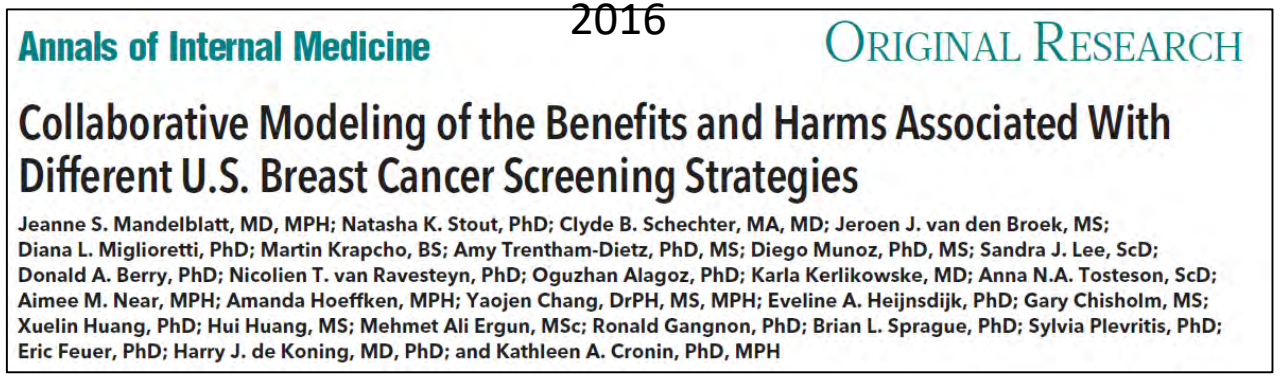
All estimates based on prostate cancer incidence in the US assuming incidence would have been flat without PSA

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 lead time from incidence trends
  - Infer overdiagnosis rates based on lead time
  - Sensitive to modeling assumptions
  - Data inadequate to get sharp estimates if we allow that some cancers don't progress

- Our best estimate at this time:
  - About 10-15% of cancers detected
- Likely 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

6. Ovarian cancer screening doesn’t work

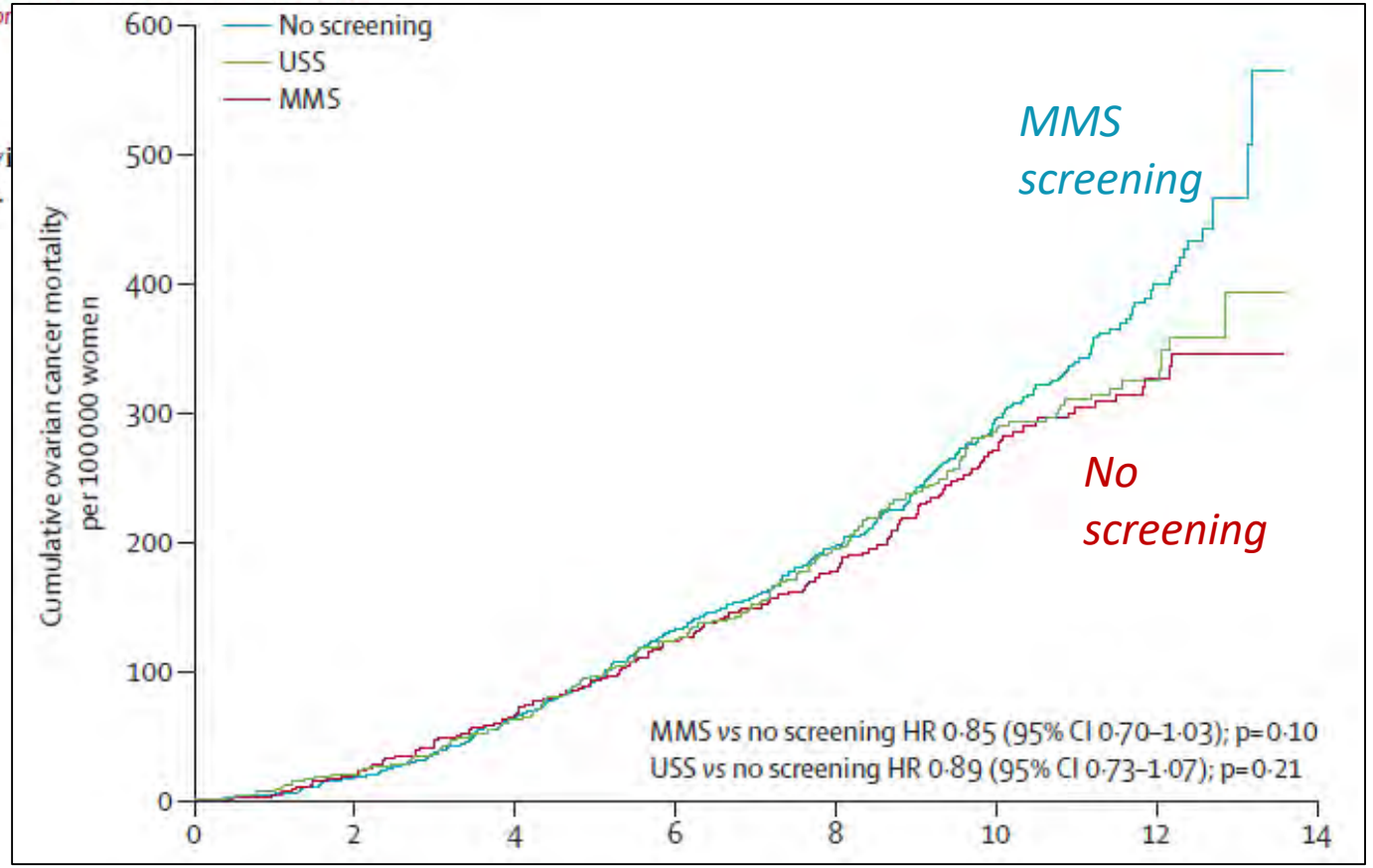
Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial

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

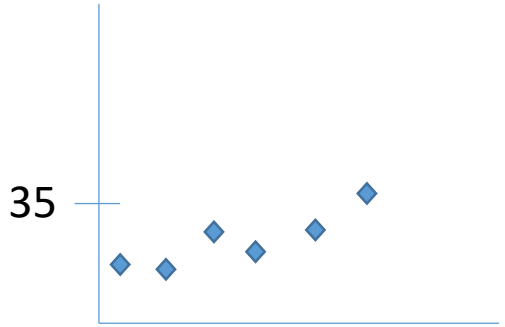
MMS uses ROCA algorithm – learns by observing serial CA125 trajectories over time

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

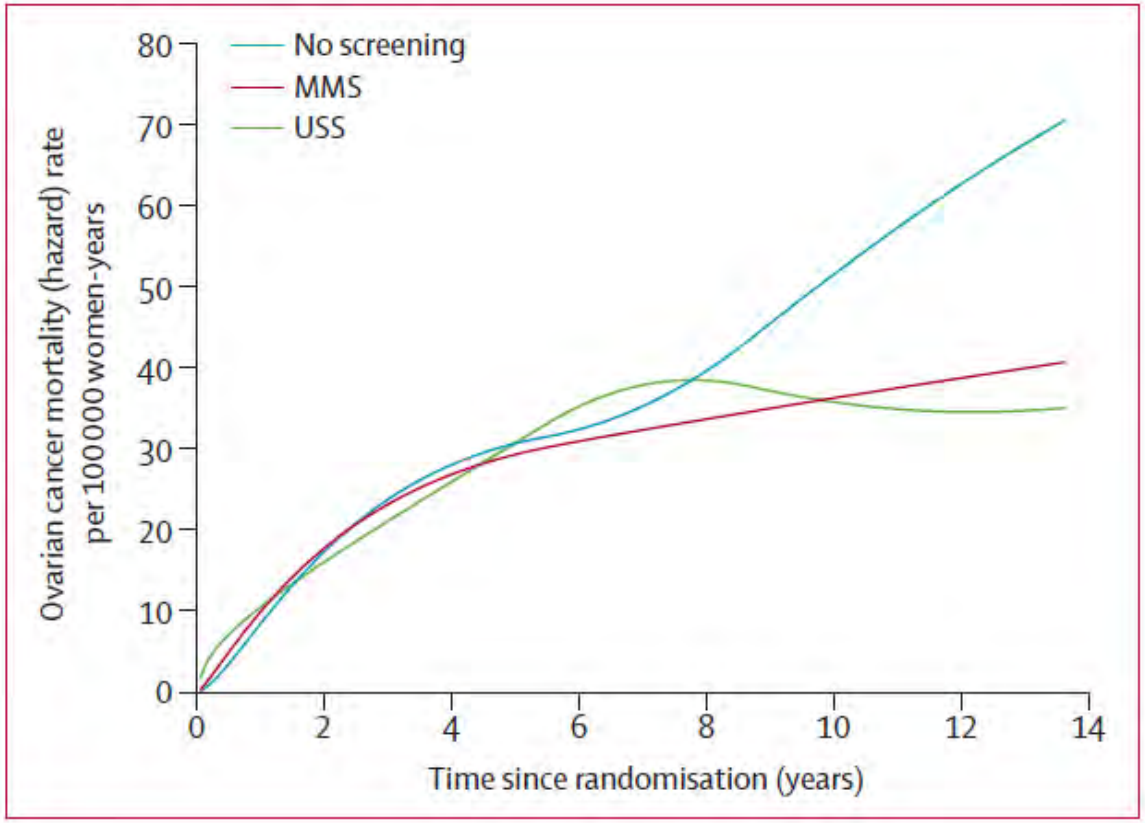
Understanding the UKTOCS trial

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
- It is likely that those women diagnosed early had shorter lead times than those referred later



7. 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]

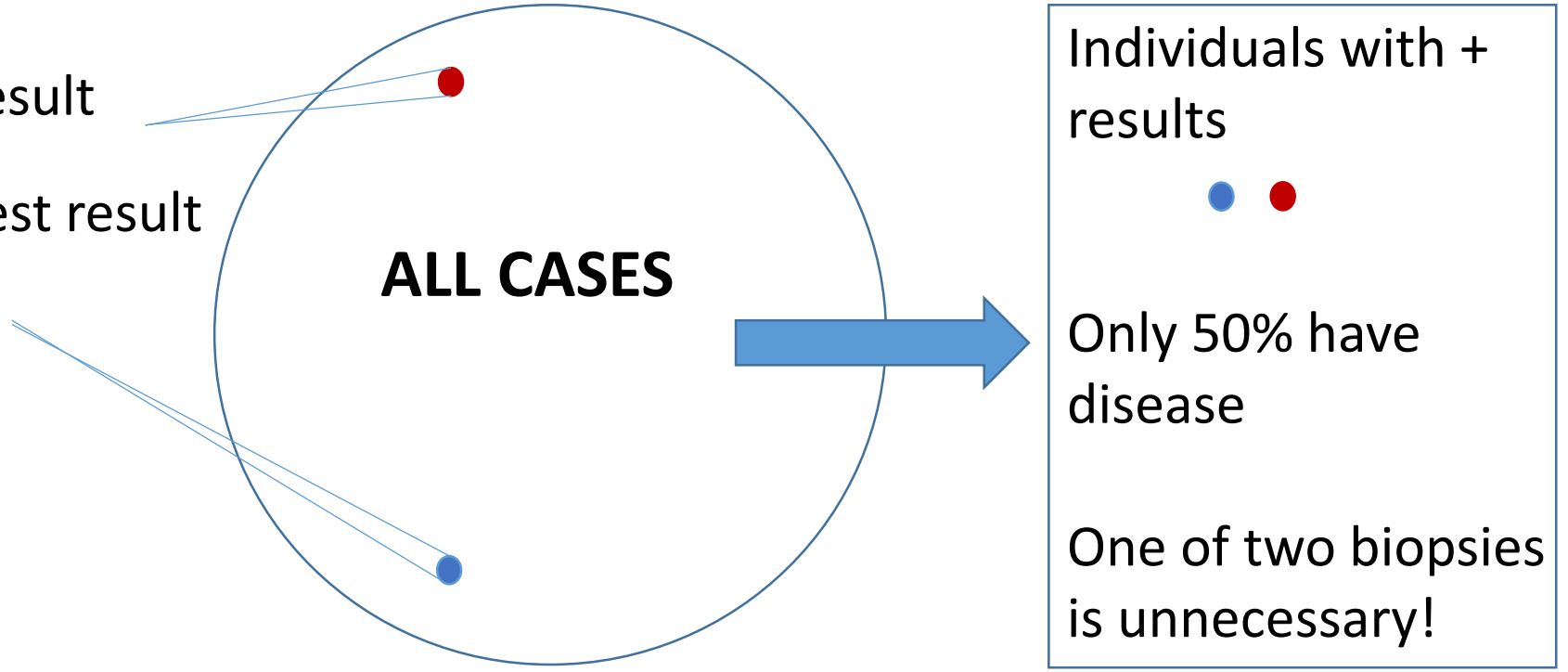
Earlier detection is key to redu[illegible] can detect eight common cancer[illegible] and mutations in cell-free DNA. W[illegible] with nonmetastatic, clinically d[illegible] esophagus, colorectum, lung, o[illegible] 70% of the eight cancer types. [illegible] of five cancer types (ovary, liver, stomach, 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

Excitement about liquid biopsies for early detection of rare cancers but

- Tests need to be extremely specific – almost not false positive tests
- 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

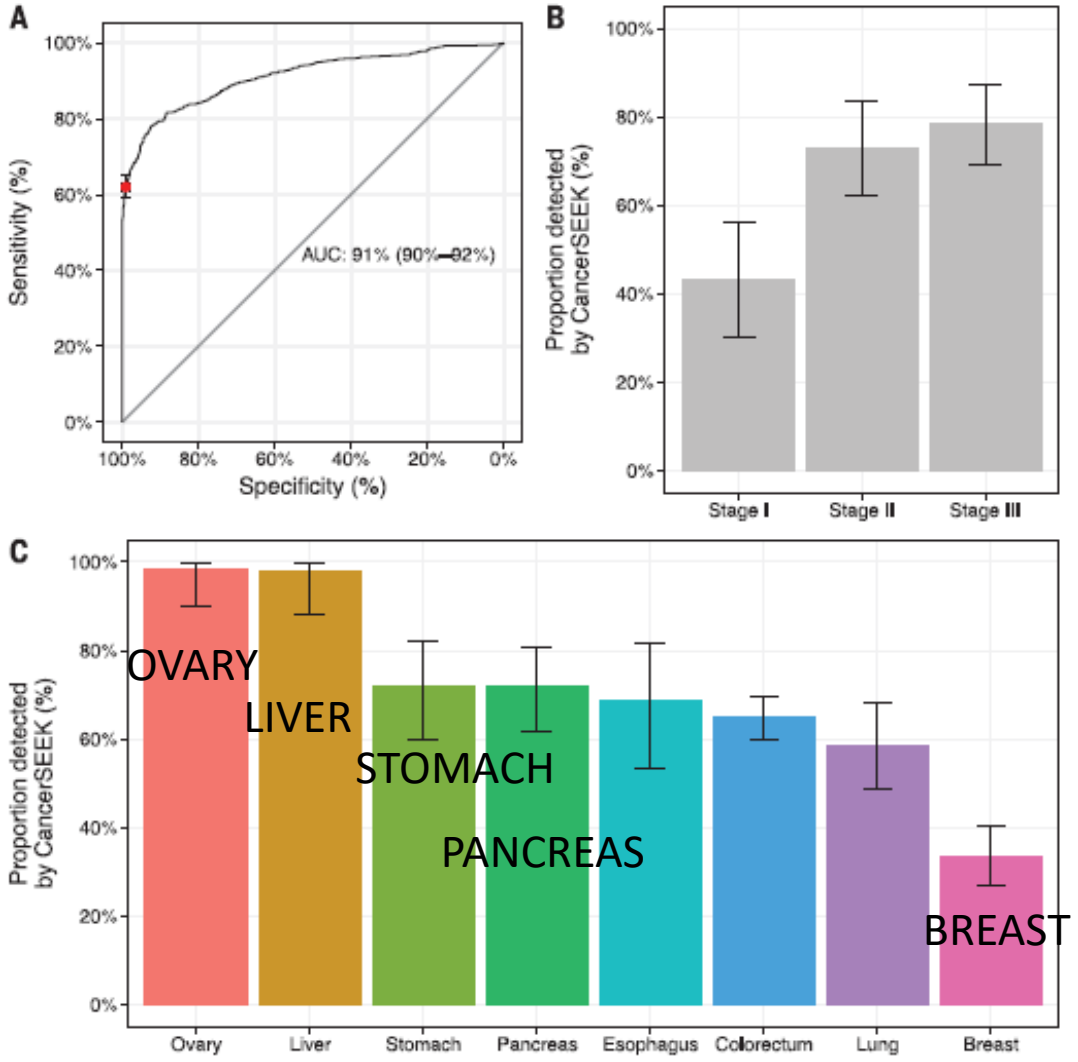
Confirmatory diagnostics for very early cancers need to be developed

- 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



8. Excess body weight causes cancer

Excess weight and cancer risk

SPECIAL REPORT

Body Fatness and Cancer — Viewpoint of the IARC Working Group

JAMA Oncology | Original Investigation

Proportion of Cancer Cases Attributable to Excess Body Weight by US State, 2011-2015

Farhad Islami, MD, PhD; Ann Goding Sauer, MSPH; Susan M. Gapstur, PhD; Ahmedin Jemal, DVM, PhD

Original Investigation

Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk

A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials

VIEWPOINT

Excessive Weight Gain, Obesity, and Cancer

Opportunities for Clinical Intervention

ORIGINAL ARTICLE

Overweight, Obesity, and Mortality from Cancer in a Prospectively Studied Cohort of U.S. Adults

Excess weight and cancer risk

- Many studies point to an association between excess weight and cancer risk
- Several cohort studies have long-term information on BMI and cancer
  - Women's Health Initiative
  - Nurses Health Study
  - Cancer Prevention Study II
- Studies differ in timing of BMI measurements
  - Concurrent with diagnosis
  - Prior to diagnosis

Body Fatness and Cancer — Viewpoint of the IARC Working Group

Cancer Site or Type	Relative Risk of the Highest BMI Category Evaluated versus Normal BMI (95% CI)‡
Esophagus: adenocarcinoma	4.8 (3.0–7.7)
Gastric cardia	1.8 (1.3–2.5)
Colon and rectum	1.3 (1.3–1.4)
Liver	1.8 (1.6–2.1)
Gallbladder	1.3 (1.2–1.4)
Pancreas	1.5 (1.2–1.8)
Breast: postmenopausal	1.1 (1.1–1.2)§
Corpus uteri	7.1 (6.3–8.1)
Ovary	1.1 (1.1–1.2)
Kidney: renal-cell	1.8 (1.7–1.9)

All of these studies are observational

- Studies show association but not causation
  - Excess weight affects estrogens and insulin but more research needed
- Other factors not accounted for may explain finding
  - Health seeking behaviors may differ by BMI
  - Screening tests may have different performance by BMI
- Story is likely more complicated than it appears
  - But there is a tendency to oversimplify

Health & Science

The disturbing links between too much weight and several types of cancer

The Washington Post
Democracy Dies in Darkness

April 15 2019

> Being obese and overweight — long implicated in heart disease and diabetes — has been associated in recent years with an increased risk of getting at least 13 types of cancer, including stomach, pancreatic, colorectal and liver malignancies, as well as postmenopausal breast cancer.

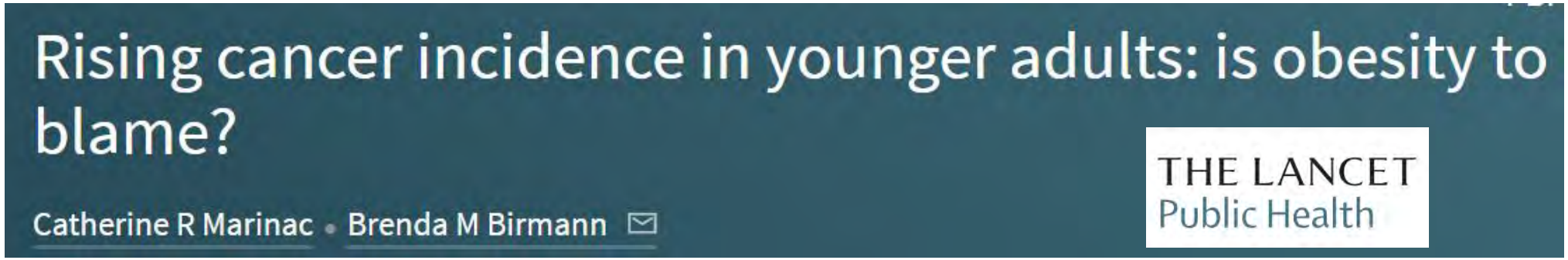
most alarming, young people, who as a group are heavier than their parents, are developing weight-related malignancies, including colorectal cancer, at earlier ages than previous generations, experts say.

Can increasing BMI explain colorectal cancer trends in younger cases?

Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry

Hyuna Sung, Rebecca L Siegel, Philip S Rosenberg, Ahmedin Jemal

- Studied 12 “obesity-related cancers” and 18 other cancers
- For 6 of 12 “obesity-related cancers” estimated incidence was increasing at younger ages
  - Multiple myeloma, colorectal, uterine, kidney, gallbladder, pancreas
- For 5 of the 6, estimated incidence was also increasing at older ages
  - All except colorectal



"Sung and colleagues did not comment on why only some obesity-related cancers, and not all 12, showed temporal trends of markedly rising younger adult incidence, or why some obesity-related cancers appeared to have declining rather than increasing incidence in the older age groups. **Such observations could reflect varying influences of other risk factors across such cancer types and age groups, and warrant further investigation**."

9. Alcohol consumption increases your chance of getting breast and some other cancers

Alcohol and cancer risk

- Many studies point to an association between drinking and cancer risk
- Recent studies have shown an increase in risk even with very modest intake
- Some biological basis for the link
- Questions about
  - Which is the best measure of alcohol consumption?
  - What is the timing that matters most?

Some alcohol-related cancers

Liver

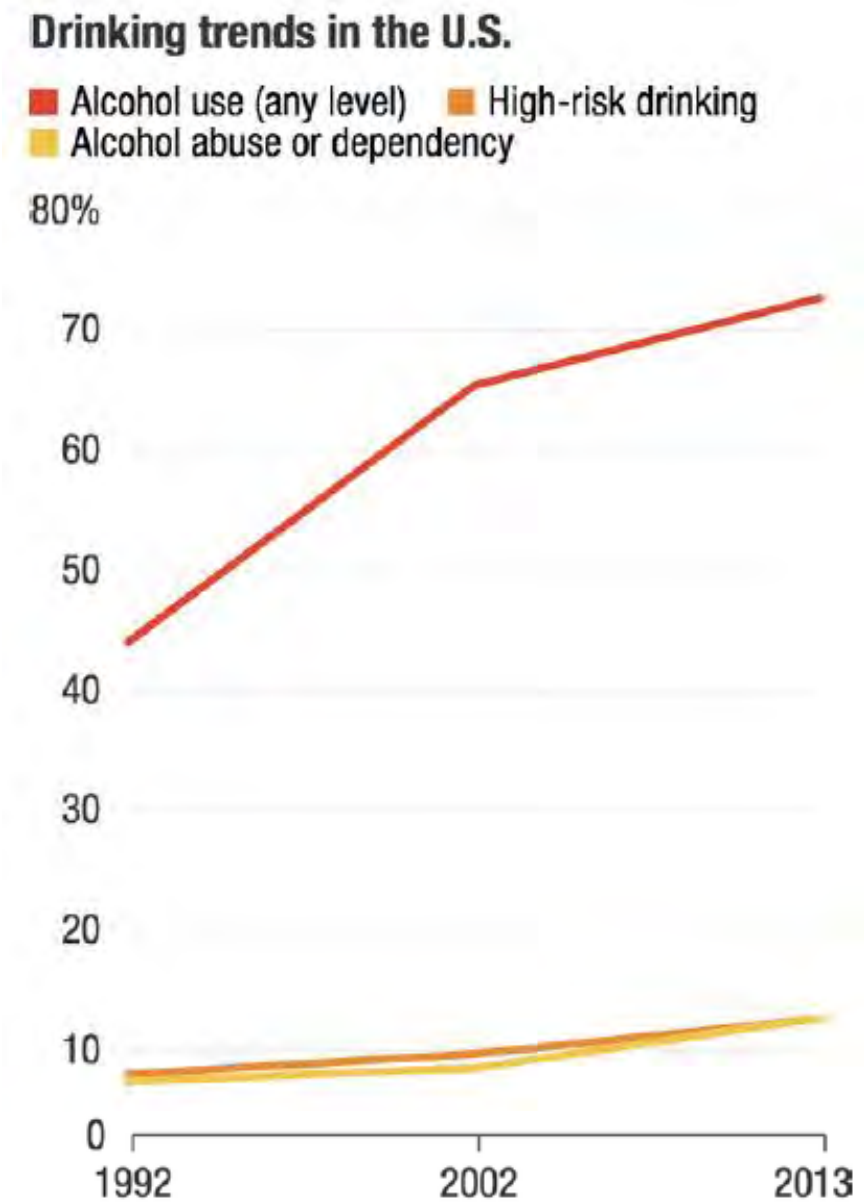
Esophagus

Throat

Breast

Colorectal

Could increased alcohol consumption at younger ages explain colorectal cancer trends?



All of these studies are observational

- All of these studies are observational
- Alcohol consumption is usually self-reported
  - Many people understate their alcohol intake
  - Reports of modest intake could reflect higher consumption
- Have to balance effect of alcohol on cancer risk with effect on general health
  - Positive effects of modest intake on cardiovascular disease
  - Known beneficial effects of red wine

HEALTHNEWSREVIEW.ORG
IMPROVING YOUR CRITICAL THINKING ABOUT HEALTH CARE

Observational studies & the health messaging merry-go-round: Moderate alcohol, once “healthy,” now “not so good for you after all”

Review

1. Most screen-detected cases are not saved by screening T F
2. Clinical trials are the most reliable sources of evidence about screening benefit T F
3. Prostate cancer screening doesn't save lives T F
4. Breast cancer screening doesn't work because advanced-stage incidence is flat T F
5. 30% of breast cancers and 60% of prostate cancers are overdiagnosed T F
6. Ovarian cancer screening doesn't work T F
7. New blood-based screening tests are going to solve all of our problems T F
8. Excess body weight causes cancer T F
9. Alcohol consumption increases your chance of getting breast and some other cancers T F
10. Women with dense breasts have a greater risk of getting breast cancer T F