

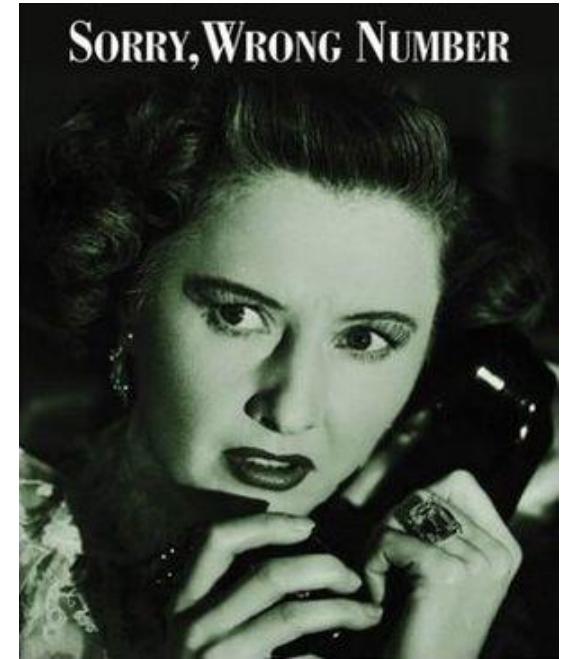
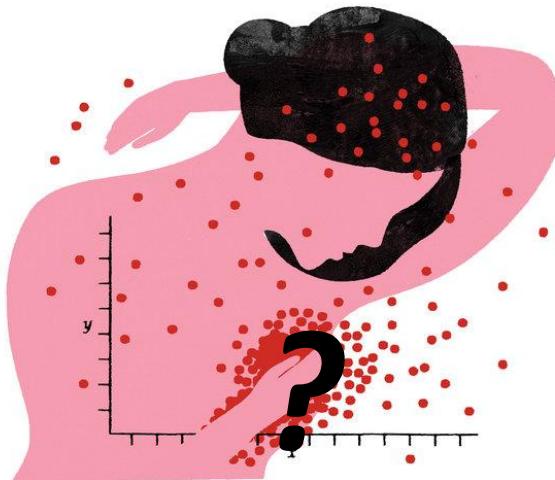
Workshop on Getting the Numbers Right on Cancer Screening

Ruth Etzioni, PhD
Fred Hutchinson Cancer Research Center
@retzoni



Interpreting Cancer Screening Studies

A workshop prepared for the
Dialogue on Cancer April 2015



Ruth Etzioni
Fred Hutchinson Cancer Research Center

 **FRED HUTCH**
40 YEARS OF CURES 1975–2015

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



STUART BRADFORD

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

Dr. Welch notes that clearly some women are helped by mammography screening, but the numbers are lower

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

Continued on Page 6

Vast Study Casts Doubts on Value of Mammograms

By GINA KOLATA FEB. 11, 2014

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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



HEALTH CARE

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Monday, September 15, 2014 | R1

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

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

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.

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.

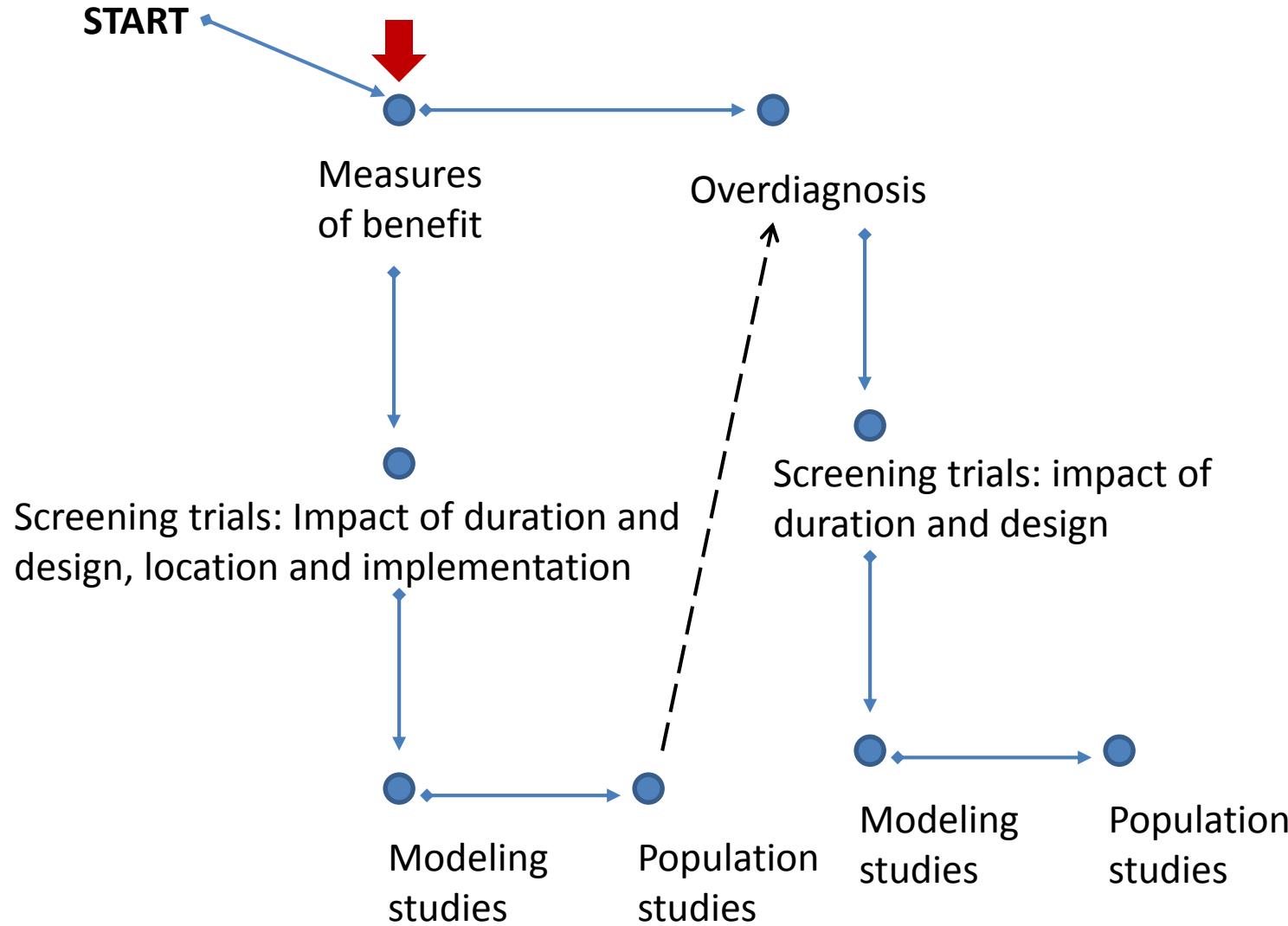
Overdiagnosis—the detection of tumors that aren't likely to cause harm—is now a hot topic in other cancers as well. A growing volume of studies estimate that as many as 30% of invasive breast cancers 18%

Making the Call

“I’m happy to accept the most favorable randomized trial as an estimate of benefit—on the order of one man avoiding a prostate cancer death out of 1000 men aged 55 to 69 years screened over 10 years—and ignore the less favorable data. Simply knowing that the overdiagnosis harm is somewhere around 30 to 100 times the estimated benefit—and knowing what treatment and its complications entail—is enough for me. I don’t need anymore data. My value judgment is simple: It’s an awful deal.”

H. Gilbert Welch, MD, MPH

A Map of Today's Workshop



Measures of Screening Benefit

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

RESULTS

After a median follow-up of 11 years in the core age group, the relative reduction in the risk of death from prostate cancer in the screening group was 21% (rate ratio, 0.79; 95% confidence interval [CI], 0.68 to 0.91; $P=0.001$), and 29% after adjustment for noncompliance. The absolute reduction in mortality in the screening group was 0.10 deaths per 1000 person-years or 1.07 deaths per 1000 men who underwent randomization. The rate ratio for death from prostate cancer during follow-up years 10 and 11 was 0.62 (95% CI, 0.45 to 0.85; $P=0.003$). To prevent one death from prostate cancer at 11 years of follow-up, 1055 men would need to be invited for screening and 37 cancers would need to be detected. There was no significant between-group difference in all-cause mortality.

Measures of Screening Benefit and Harm

BENEFIT

- Mortality rate ratio*: A / B
- Deaths prevented: A – B
- NNS: 1/(A-B)

OVERDIAGNOSIS

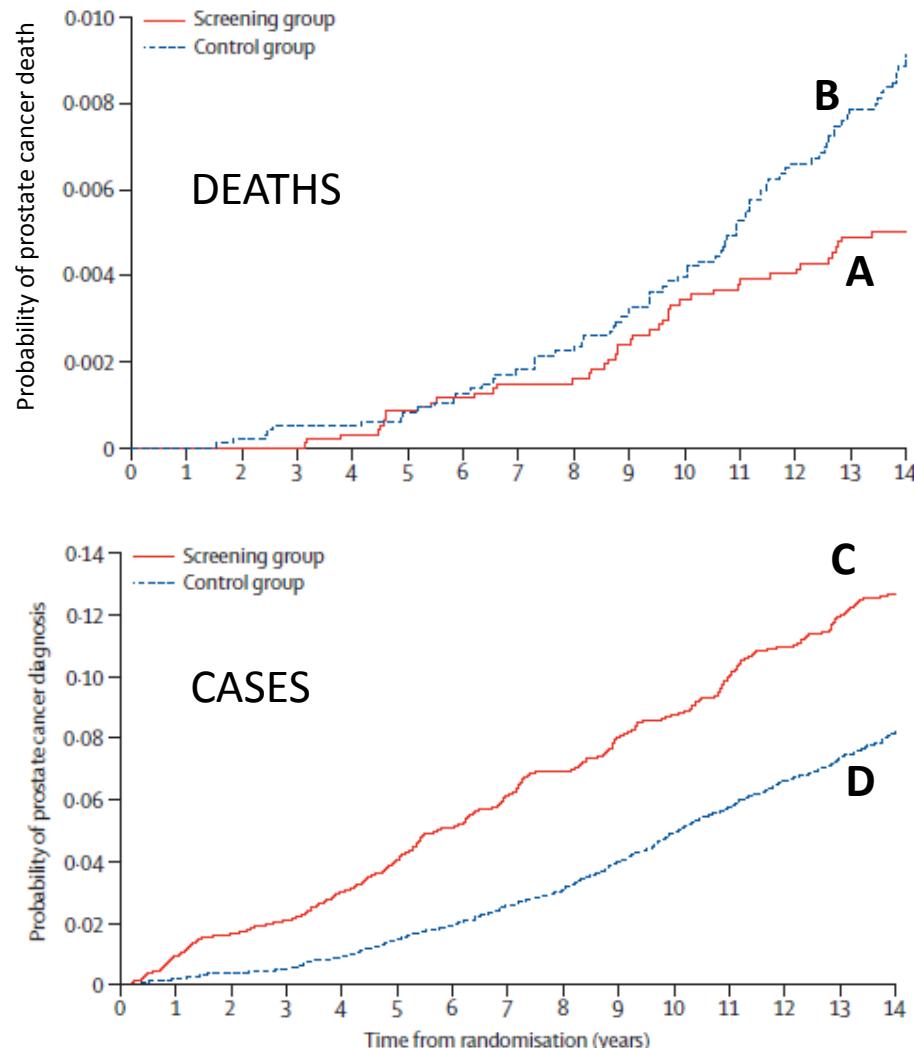
Cancer detected by screening that would not have been diagnosed without screening

Often estimated by excess incidence in screened group: C – D

NN

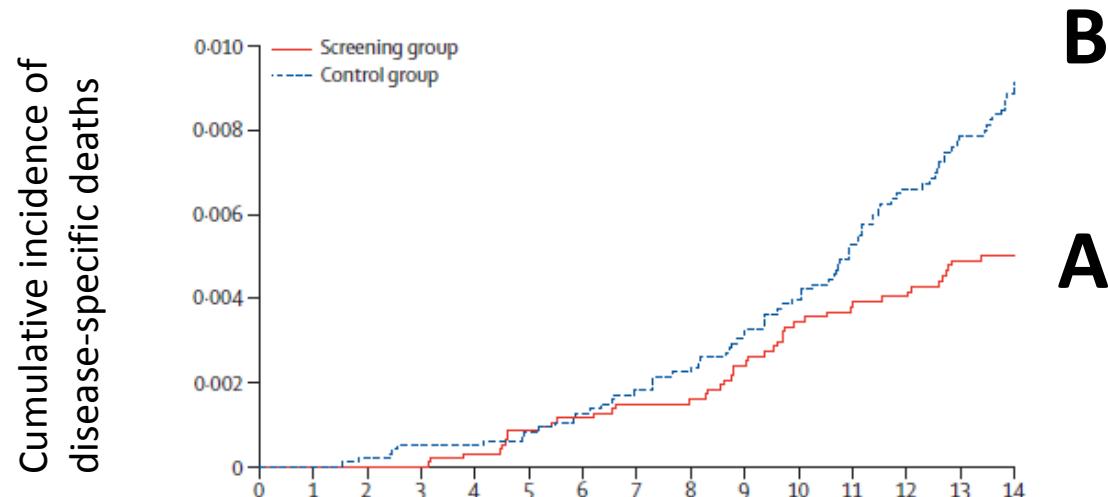
Overdiagnoses / deaths prevented

*: more or less



Measures of Benefit

- A and B represent the CUMULATIVE INCIDENCE of disease-specific mortality in the screen and control groups
 - Cumulative likelihood of disease-specific death **in the presence** of other-cause death
 - This is what is typically presented in screening trial reports
- But the comparison of the two is presented in terms of the MORTALITY RATE RATIO



Measures of Benefit

Mortality rate ratio

- Ratio of *cancer deaths/person years* between screening and control groups
- **NET quantity** – impact on risk of disease-specific mortality in absence of other-cause death
- May also be referred to as a **hazard ratio**

Absolute mortality difference or reduction

- Difference between cumulative incidence of disease-specific mortality in screening and control group
- Typically expressed as per 1000 or 10,000 persons screened

NNS – number needed to screen

- 1 / absolute mortality difference

Relative and Absolute Mortality may give Very Different Impressions

Mortality risk ratio = 0.8

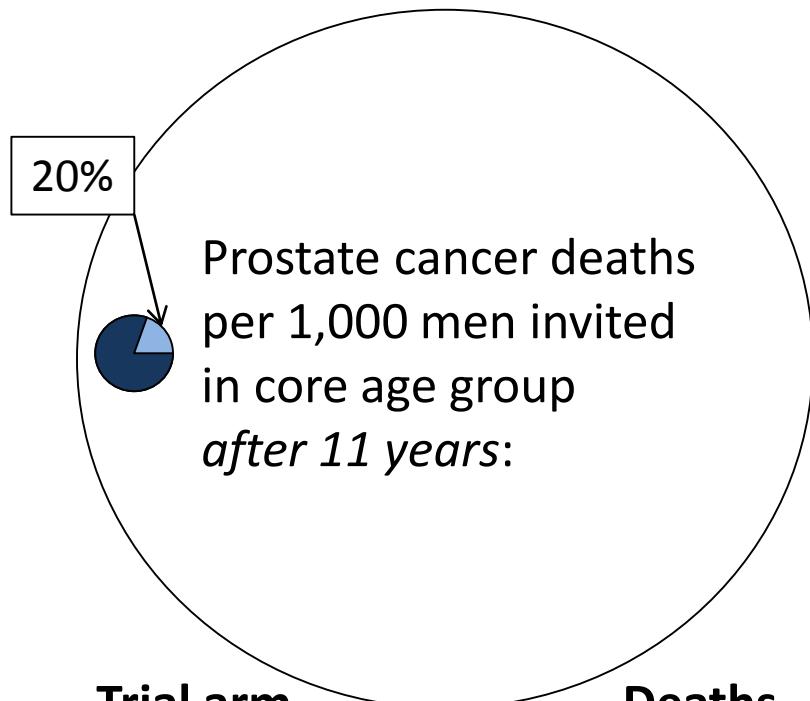
- For every 5 men who died of prostate cancer without screening (control group) one life was saved by screening
 - **Denominator is PC deaths without screening**

Absolute mortality reduction: 1.07 deaths per 1000

- For every 1000 men who entered screening one life was saved by screening
 - **Denominator is persons entering the screening program**
 - Depends on TWO THINGS
 - Baseline mortality without screening
 - Relative mortality reduction

Relative and Absolute Benefit Dependence on Baseline Mortality and Follow-up

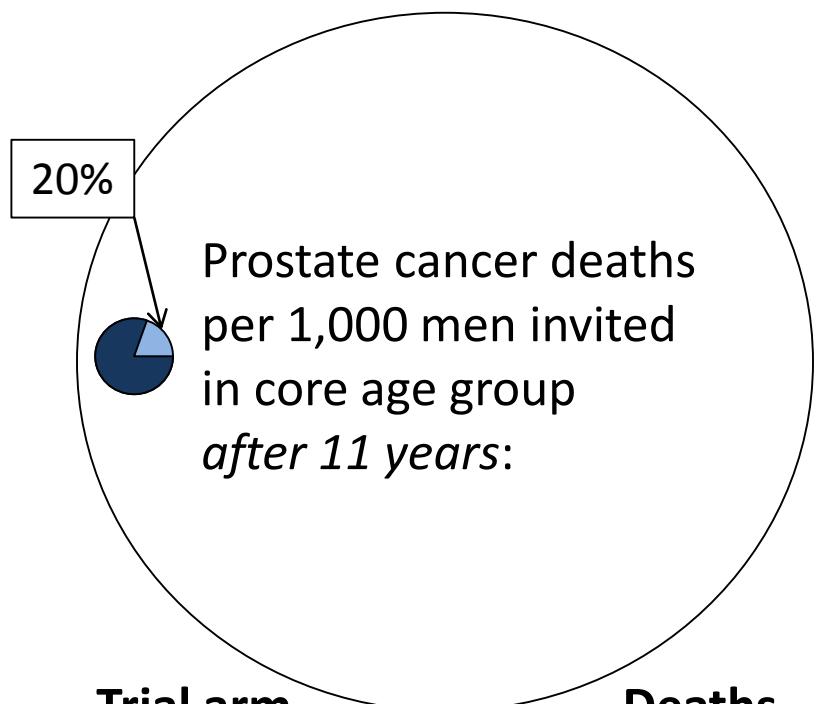
11-year follow-up (ERSPC)



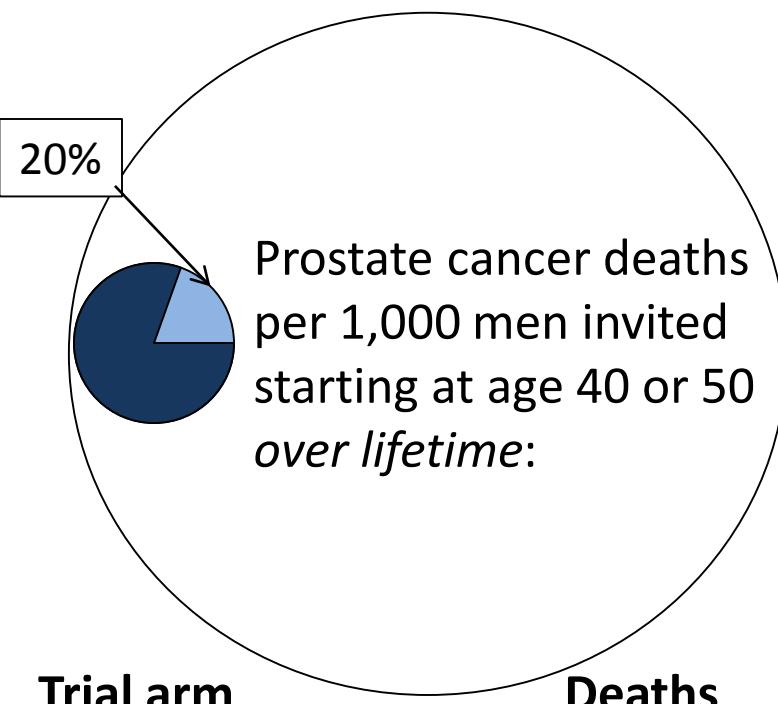
Trial arm	Deaths
Control	5.17
Screening	4.10
Absolute Difference	1.07
NNS	

Relative and Absolute Benefit Dependence on Baseline Mortality and Follow-up

11 year follow-up (ERSPC)



Long-term follow-up (SEER)



Trial arm	Deaths
Control	5.17
Screening	4.10
Absolute Difference	1.07
NNS	

Trial arm	Deaths
Control	30
Screening	24
Absolute Difference	6
NNS	

USPSTF

Infographic

1,000 men aged 55 to 69 screened every 1 to 4 years for 10 years with a PSA test

1,000 men screened.

Of these:

100-120

get false-positive results that may cause anxiety and lead to biopsy

(Possible side effects of biopsies include serious infections, pain, and bleeding)

110

get a prostate cancer diagnosis, and of these men:

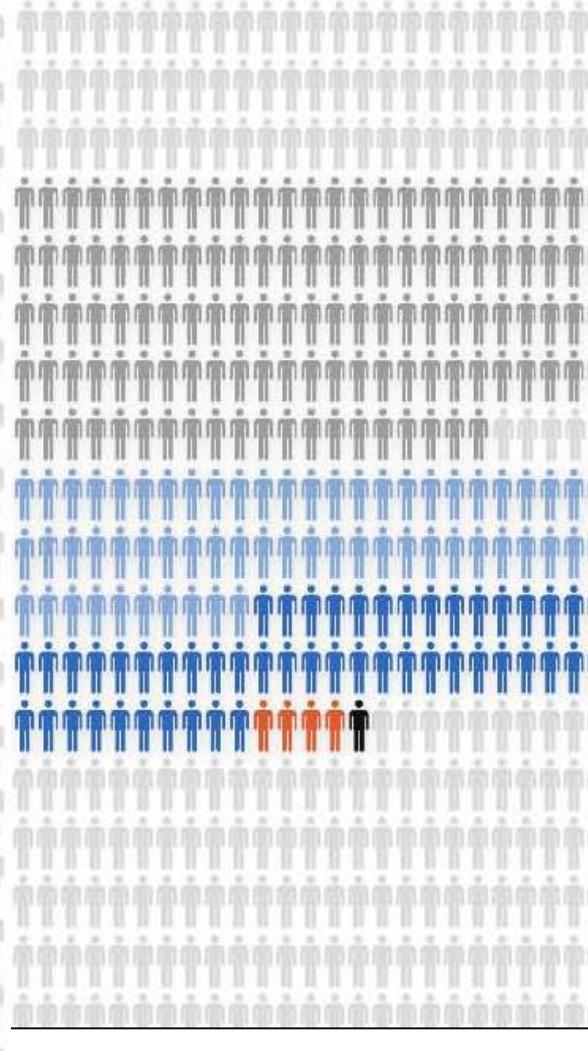
- at least 50 will have treatment complications, such as infections, sexual dysfunction, or bladder or bowel control problems

• 4-5

die from prostate cancer (5 die among men who do not get screened)

• 0-1

death from prostate cancer is avoided



A Breast Cancer Example

Special Communication

Quantifying the Benefits and Harms of Screening Mammography

H. Gilbert Welch, MD, MPH; Honor J. Passow, PhD

Table 1. Upper- and Lower-Bound Estimates for the Number of Breast Cancer Deaths Avoided
Because of a 10-Year Course of Annual Screening Mammograms^a

Data and Estimates	Notation and Calculation	Lower Bound (5% Reduction)			Upper Bound (36% Reduction)		
		Age 40 y	Age 50 y	Age 60 y	Age 40 y	Age 50 y	Age 60 y
SEER 15-y risk of dying from breast cancer per 1000 (2007-2009) ¹	a	3.27	6.45	9.87	3.27	6.45	9.87
Relative mortality reduction attributable to screening, %	b	5	5	5	36	36	36
Proportion screened (NHIS 2008), %	c	61	73	75	61	73	75
15-y Risk without screening per 1000	Baseline mortality		3.37	6.70	10.25	4.19	8.76
15-y Risk with screening per 1000	e = (1 - b) × d	3.20	6.36	9.74	2.68	5.61	8.66
10-y Absolute mortality reduction per 1000	Absolute mortality reduction		0.17	0.33	0.51	1.51	3.16
Calculated			0.1	0.3	0.5	1.6	3.2
Rounded	† (Rounded down for lower bound and up for upper bound)						4.9

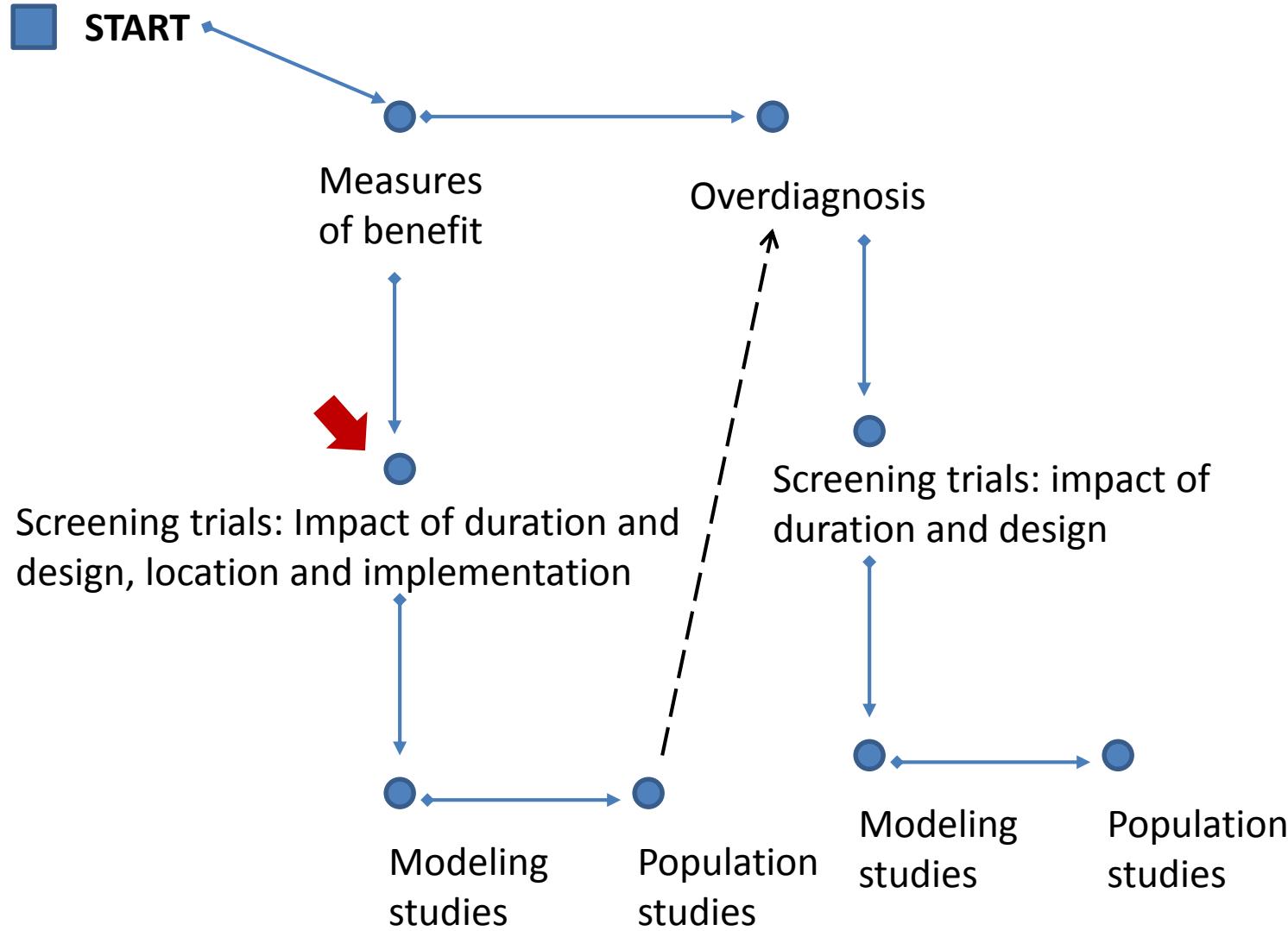
Summary: Screening Benefits

- There are different measures of benefit
 - Absolute versus Relative
 - Rates versus (cumulative) probabilities
- They can tell quite different stories
- Both depend on duration
 - Relative benefit estimates typically ignore this
 - Absolute benefit estimates are highly sensitive
- Focus on absolute benefit reduces the apparent impact of screening

WELL | Tara Parker-Pope

Mammogram's Role as Savior Is Tested

A Map of Today's Workshop



Screening Trials



Trials: Stop-Screen and Continuous Screen

Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening

Prostate Cancer Screening in the Randomized Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial: Mortality Results after 13 Years of Follow-up

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



OPEN ACCESS

Screening and Prostate-Cancer Mortality in a Randomized European Study

Benefit in Continuous Screen Trials

The Impact of Duration

*The NEW ENGLAND
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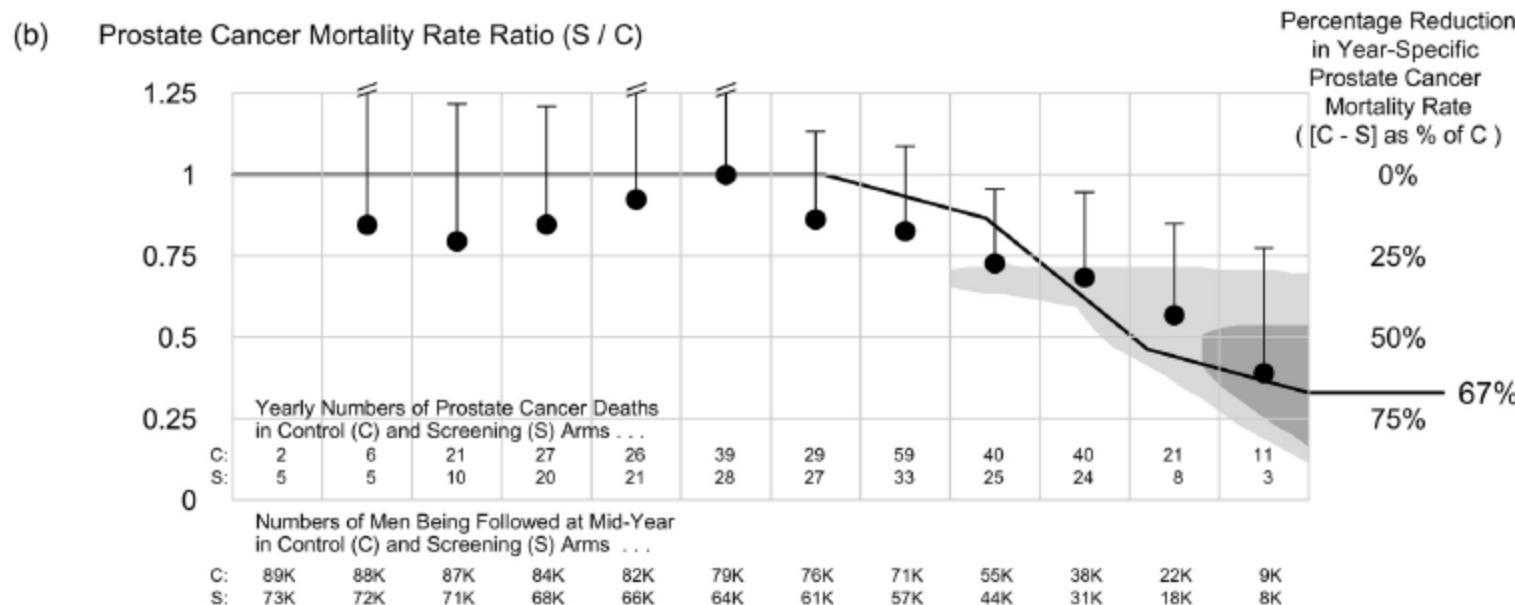
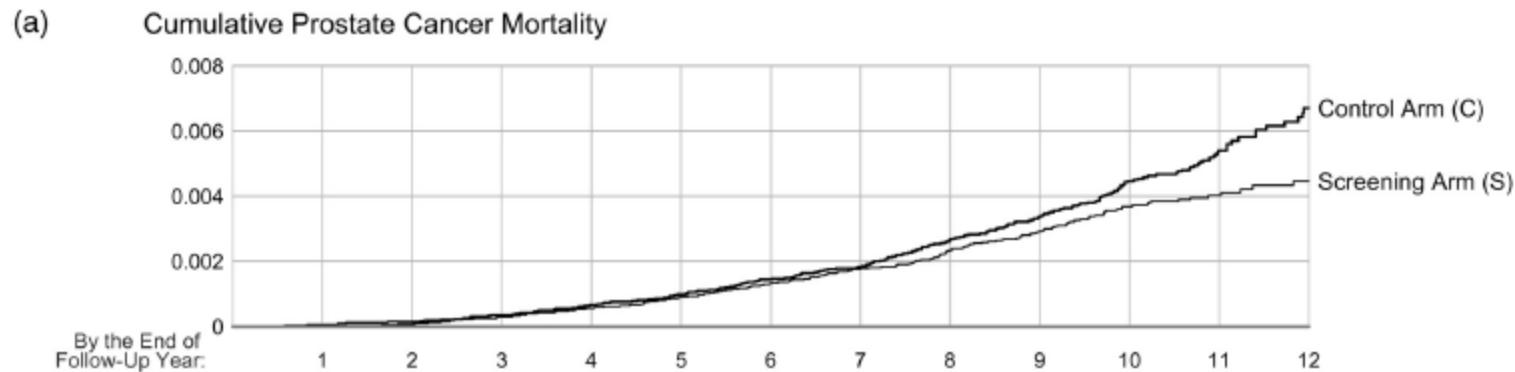
Prostate-Cancer Mortality at 11 Years of Follow-up

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)	0.09
8–9	71	122,867	0.58	118	151,319	0.78	0.74 (0.55 to 0.99)	0.04
10–11	56	97,994	0.57	111	120,900	0.92	0.62 (0.45 to 0.85)	0.003
1–11	245	706,846	0.35	385	866,812	0.44	0.79 (0.67 to 0.92)	0.003
≥12	54	57,387	0.94	77	66,241	1.16	0.80 (0.56 to 1.13)	0.21
Total	299	764,233	0.39	462	933,052	0.50	0.79 (0.68 to 0.91)	0.001

ORIGINAL ARTICLE

Mortality reductions produced by sustained prostate cancer screening have been underestimated

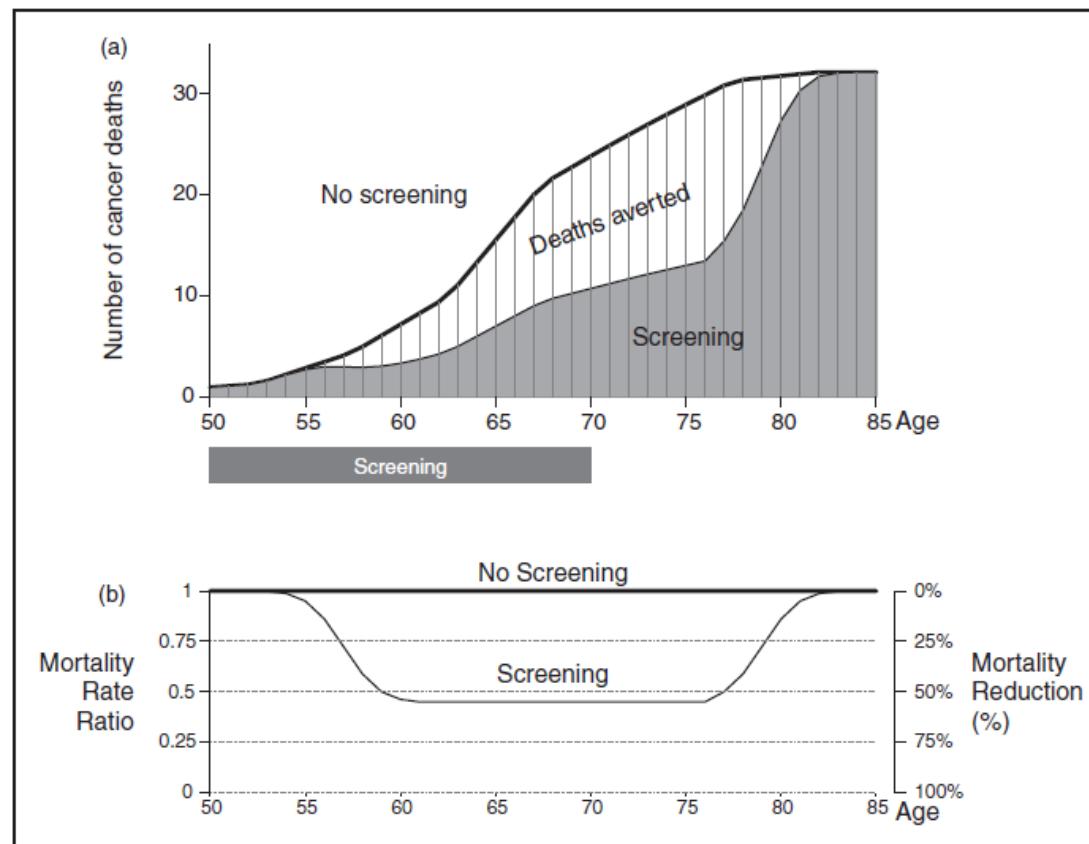
James A Hanley



Benefit in Stop-screen trials

Projecting the yearly mortality reductions due to a cancer screening programme

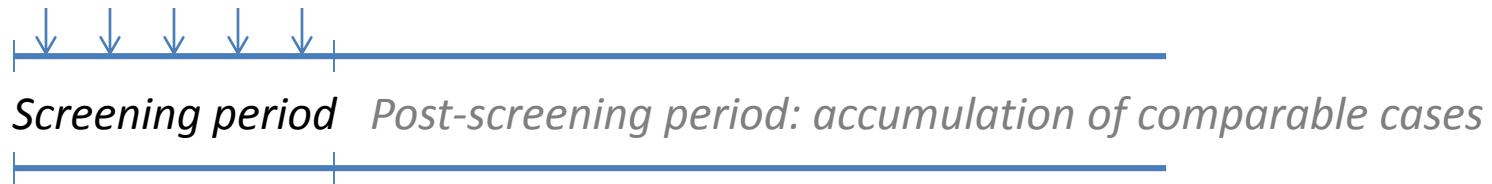
Zhihui (Amy) Liu, James A Hanley* and Erin C Strumpf



Analysis of Stop-Screen Trials

A Conundrum

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



(1) Classic analysis

- Ratio of mortality rates
 - For all subjects enrolled on screen relative to control arm
 - Why might this not be correct?

(2) Case-based analysis

- Ratio of mortality rates
 - Restrict to cases diagnosed during the screening period on screen relative to control arm
 - Why might this not be correct?

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

Results During the five year screening period, 666 invasive breast cancers were diagnosed in the mammography arm ($n=44\ 925$ participants) and 524 in the controls ($n=44\ 910$), and of these, 180 women in the mammography arm and 171 women in the control arm died of breast cancer during the 25 year follow-up period. The overall hazard ratio for death from breast cancer diagnosed during the screening period associated with mammography was 1.05 (95% confidence interval 0.85 to 1.30). The findings for women aged 40-49 and 50-59 were almost identical. During the entire study period, 3250 women in the mammography arm and 3133 in the control arm had a diagnosis of breast cancer, and 500 and 505, respectively, died of breast cancer. Thus the cumulative mortality from breast cancer was similar between women in the mammography arm and in the control arm (hazard ratio 0.99, 95% confidence interval 0.88 to 1.12). After 15 years of follow-up a residual excess of 106 cancers was observed in the mammography arm, attributable to over-diagnosis.

Case-based analysis
(2)

Classic analysis
(1)

The Impact of Location and Implementation

1. ERSPC and Goteborg

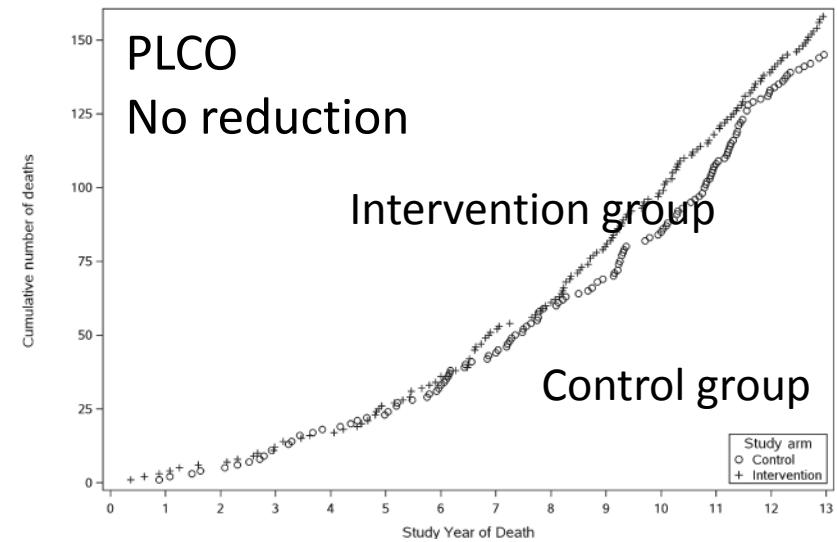
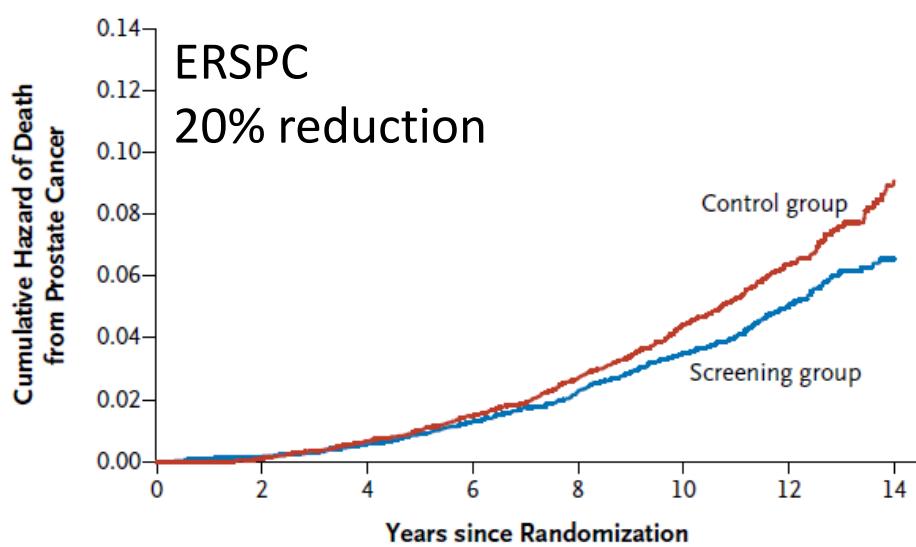
Mortality results from the Göteborg randomised population-based prostate-cancer screening trial

Jonas Hugosson, Sigrid Carlsson, Gunnar Aus, Svante Bergdahl, Ali Khatami, Pär Lodding, Carl-Gustaf Pihl, Johan Stranne, Erik Holmberg, Hans Lilja

Findings In each group, 48 men were excluded from the analysis because of death or emigration before the randomisation date, or prevalent prostate cancer. In men randomised to screening, 7578 (76%) of 9952 attended at least once. During a median follow-up of 14 years, 1138 men in the screening group and 718 in the control group were diagnosed with prostate cancer, resulting in a cumulative prostate-cancer incidence of 12·7% in the screening group and 8·2% in the control group (hazard ratio 1·64; 95% CI 1·50–1·80; $p<0\cdot0001$). The absolute cumulative risk reduction of death from prostate cancer at 14 years was 0·40% (95% CI 0·17–0·64), from 0·90% in the control group to 0·50% in the screening group ($p=0\cdot002$) compared to be

	ERSPC	Goteborg
Duration	11 years	14 years
Interval	Every 4 years mostly	Every 2 years
Biopsy compliance	Variable	Excellent (93%)
Mortality rate ratio	0.79	0.56
Absolute mortality difference	1.07 per 1000 participants	3.40 per 1000

2. ERSPC and PLCO Trials

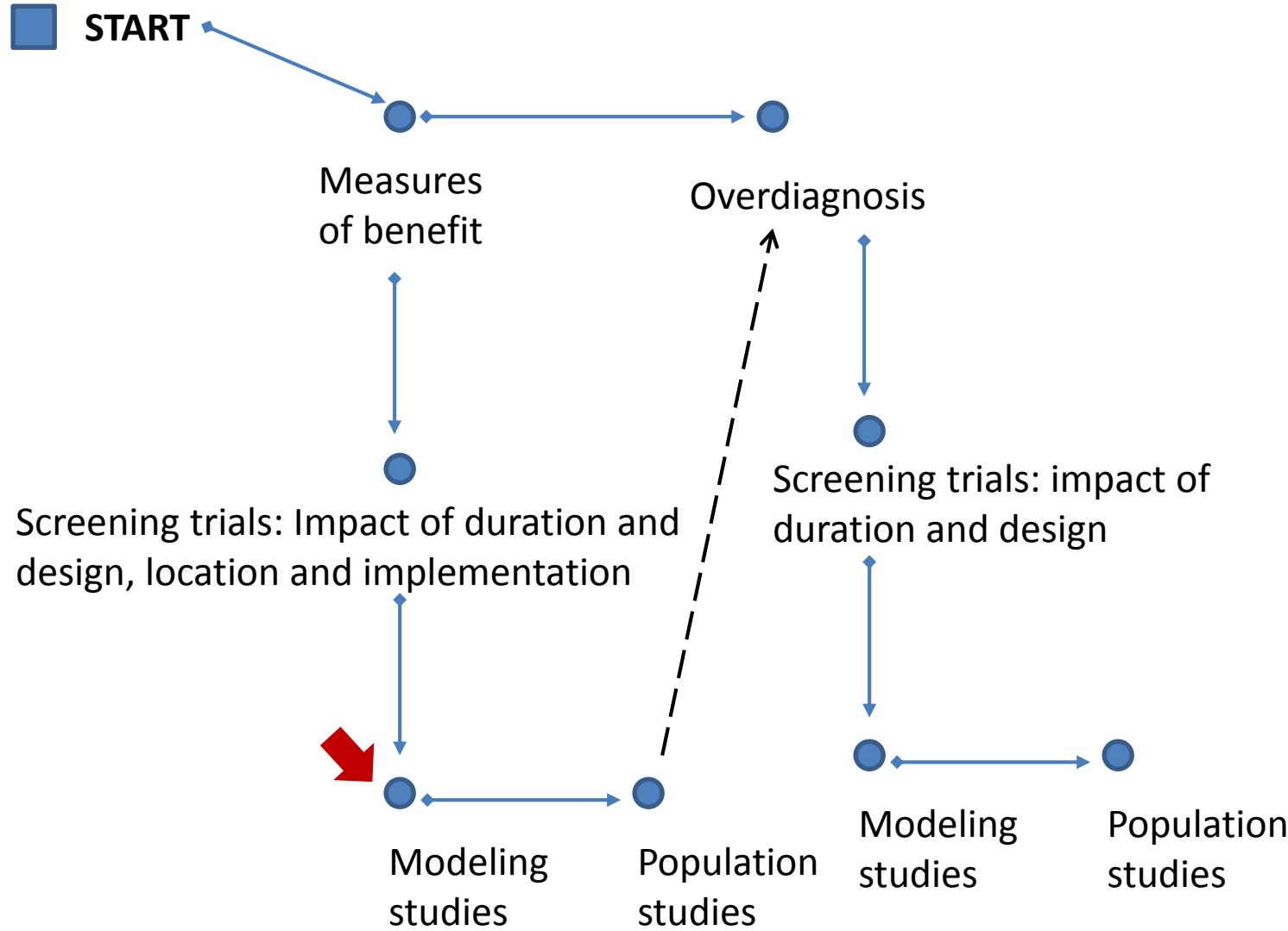


	ERSPC Continuous Screen	PLCO Stop Screen
Duration	11 years	11 years
Interval	Every 4 years mostly	Every year for 6 years
Contamination	Not much	Extensive
Compliance	Relatively good	Quite poor
Mortality rate ratio	0.79	1.09

Trials - Summary

- Not all trials are created equal
 - Results depend on design and duration
- Continuous-screen trials
 - Full relative benefit observed only years after start of trial
- Stop-screen trials
 - Dilution of relative benefit once screening starts
- Results depend on circumstances of implementation
 - Protocols
 - Baseline risks
 - Contamination and compliance
- No trials provide
 - Lifetime benefits
 - Results for strategies other than those examined

A Map of Today's Workshop



Modeling Studies



Modeling Studies

What is a model?

- A virtual representation of disease progression and survival in a population
 - In the absence of screening
 - In the presence of screening
- Any framework for integrating available information or data to project outcomes that are typically not empirically observable

Why do we model?

- Because we can't empirically observe what we want to know
 - e.g. Long-term effects of screening, comparative benefits of different screening strategies

What do we need to build a defensible model?

- Adequate data to inform the framework (e.g. model parameters)
- Assumptions or mechanism for the parts for which we don't have data

Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms

Jeanne S. Mandelblatt, MD, MPH; Kathleen A. Cronin, PhD; Stephanie Bailey, PhD; Donald A. Berry, PhD; Harry J. de Koning, MD, PhD; Gerrit Dralsma, PhD; Hui Huang, MS; Sandra J. Lee, DSc; Mark Munsell, MS; Sylvia K. Plevritis, PhD; Peter Ravdin, MD, PhD; Clyde B. Schechter, MD, MA; Bronislava Sigal, PhD; Michael J. Venler, MS; Marvin Zelen, PhD; and Eric J. Feuer, PhD
Modeling Network (CISNET)*

Special Communication

Quantifying the Benefits and Harms of Screening Mammography

H. Gilbert Welch, MD, MPH; Honor I. Passow, PhD

Cost-Effectiveness of CT Screening in the National Lung Screening Trial

William C. Black, M.D., Ilana F. Gareen, Ph.D., Samir S. Soneji, Ph.D., JoRean D. Sicks, M.S., Emmett B. Keeler, Ph.D., Denise R. Aberle, M.D., Arash Naeim, M.D., Timothy R. Church, Ph.D., Gerard A. Silvestri, M.D.,

Jeremy Gorelick, Ph.D.
for the National Lung

Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force

Harry J. de Koning, MD; Rafael Meza, PhD; Sylvia K. Plevritis, PhD; Kevin ten Haaf, MSc; Vludit N. Munshi, MS; Jihyoun Jeon, PhD; Saadet Ayca Erdogan, PhD; Chung Yin Kong, PhD; Summer S. Han, PhD; Joost van Rosmalen, PhD; Sung Eun Choi, SM; Paul F. Pinsky, PhD; Amy Berington de Gonzalez, PhD; Christine D. Berg, MD; William C. Black, MD; Martin C. Tammemägi, PhD; William D. Hazelton, PhD; Eric J. Feuer, PhD*; and Pamela M. McMahon, PhD*

Quantifying the Benefits and Harms of Screening Mammography

H. Gilbert Welch, MD, MPH; Honor J. Passow, PhD

What do they want to know?

- Breast cancer deaths avoided by annual mammography over 15 years in the US population

What data do they have?

1. Chance of dying of breast cancer over the next 15 years based on BC mortality rates in SEER 2007-2009. This case population is a mixture of screen- and non-screen-detected cases
2. Relative frequency of screening in the population
3. Assumed relative benefit of screening on BC mortality from trials

What is the “model”

- Simple calculator to extract baseline risk of BC mortality (without screening) over 15 years
- Then apply their relative benefit in (3.) above to calculate an absolute mortality reduction over this interval

Quantifying the Benefits and Harms of Screening Mammography

H. Gilbert Welch, MD, MPH; Honor J. Passow, PhD

**“Modelled”
Baseline mortality**

Relative Benefit

**Table 1. Upper- and Lower-Bound Estimates for the Number of Breast Cancer Deaths Avoided
Because of a 10-Year Course of Annual Screening Mammograms^a**

Data and Estimates	Notation and Calculation	Lower Bound (5% Reduction)			Upper Bound (36% Reduction)		
		Age 40 y	Age 50 y	Age 60 y	Age 40 y	Age 50 y	Age 60 y
SEER 15-y risk of dying from breast cancer per 1000 (2007-2009) ¹	a	3.27	6.45	9.87	3.27	6.45	9.87
Relative mortality reduction attributable to screening, %	b	5	5	5	36	36	36
Proportion screened (NHIS 2008), %	c	61	73	75	61	73	75
15-y Risk without screening per 1000	d = a/[c × (1 - b) + (1 - c)]	3.37	6.70	10.25	4.19	8.76	13.51
15-y Risk with screening per 1000	e = (1 - b) × d	3.20	6.36	9.74	2.68	5.61	8.66
10-y Absolute mortality reduction per 1000							
Calculated		0.17	0.33	0.51	1.51	3.16	4.87
Rounded		0.1	0.3	0.5	1.6	3.2	4.9

Absolute mortality reduction

^a (Rounded down for lower bound and up for upper bound)

Cost-Effectiveness of CT Screening in the National Lung Screening Trial

What do they want to know?

- Costs per quality-adjusted life year saved by CT screening as conducted in the trial over the trial horizon and over a lifetime horizon

What data do they have?

- NLST data: smoking histories, diagnosis dates with and without screening, lung cancer and other-cause survival for the duration of the trial

What is the “model”?

- Trial horizon: Model is essentially an accounting device
- Lifetime horizon:
 - Model is an extrapolation of survival for cases and non-cases beyond the trial horizon
 - SEER data (for cases) and life tables adjusted for smoking (for non-cases) used to project long-term survival

Cost-Effectiveness of CT Screening in the National Lung Screening Trial

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Arash Naeim, M.D., Timothy R. Church, Ph.D., Gerard A. Silvestri, M.D.,
Jeremy Gorelick, Ph.D., and Constantine Gatsonis, Ph.D.,
for the National Lung Screening Trial Research Team*

Strategy	Life Expectancy		QALE	Incremental Costs [†]	Incremental Life Expectancy		Cost per Life-Yr	Cost per QALY
	Cost U.S. \$	life-yr			QALY	U.S. \$	life-yr	QALY
CT screening	3,074	14.7386	10.9692	1,631	0.0316	0.0201	52,000 (34,000–106,000)	81,000 (52,000–186,000)
Radiographic screening	1,911	14.7071	10.9491	469	0	0	NA	NA

CONCLUSIONS

We estimated that screening for lung cancer with low-dose CT would cost \$81,000 per QALY gained, but we also determined that modest changes in our assumptions would greatly alter this figure. The determination of whether screening outside the trial will be cost-effective will depend on how screening is implemented. (Funded

Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force

Harry J. de Koning, MD; Rafael Meza, PhD; Sylvia K. Plevritis, PhD; Kevin ten Haaf, MSc; Vudit N. Munshi, MS; Jiyoung Jeon, PhD; Saadet Ayca Erdogan, PhD; Chung Yin Kong, PhD; Summer S. Han, PhD; Joost van Rosmalen, PhD; Sung Eun Choi, SM; Paul F. Pinsky, PhD;

What do they want to know?

- Benefits and harms for a range of Lung CT policies varying by ages to start and stop, minimum pack years smoked and maximum years since quitting

What data do they have?

1. NLST and PLCO trials – incidence, screening rates, treatment, mortality
2. US trends in disease incidence and smoking patterns

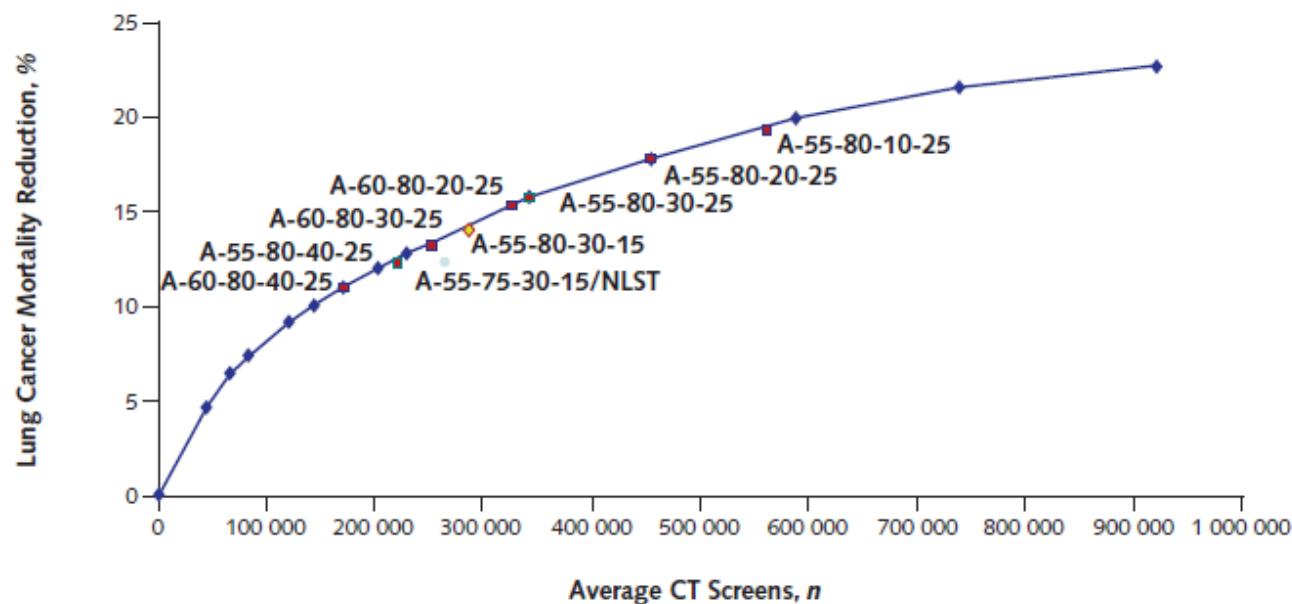
What is the “model?”

1. Multiple simulation models of disease
2. The models generate disease histories for a population with a specified range of smoking histories
3. Disease histories include latent events in disease onset and progression and are calibrated to replicate disease incidence in NLST
4. Models also include a mechanism for how early detection impacts survival and are calibrated to replicate disease mortality in NLST

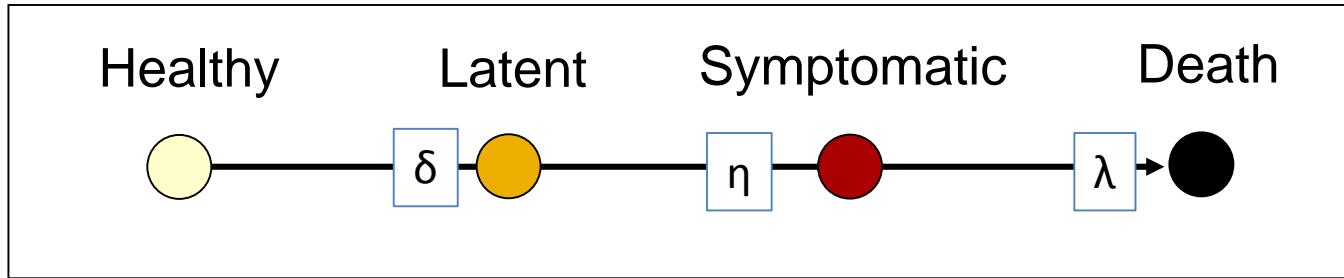
Benefits and Harms of Computed Tomography Lung Cancer Screening Strategies: A Comparative Modeling Study for the U.S. Preventive Services Task Force

Harry J. de Koning, MD; Rafael Meza, PhD; Sylvia K. Plevritis, PhD; Kevin ten Haaf, MSc; Vidit N. Munshi, MS; Jiyoung Jeon, PhD; Saadet Ayca Erdogan, PhD; Chung Yin Kong, PhD; Summer S. Han, PhD; Joost van Rosmalen, PhD; Sung Eun Choi, SM; Paul F. Pinsky, PhD; Amy Berrington de Gonzalez, PhD; Christine D. Berg, MD; William C. Black, MD; Martin C. Tammemägi, PhD; William D. Hazelton, PhD; Eric J. Feuer, PhD*; and Pamela M. McMahon, PhD*

Figure 1. Estimated lung cancer mortality reduction (as percentage of total lung cancer mortality in cohort) and life-years gained (averages of 5 models) from annual CT screening, for programs with minimum eligibility age of 55 years and maximum of 80 years at different smoking eligibility cutoffs and NLST scenario (A-55-75-30-15).



Modeling Disease I



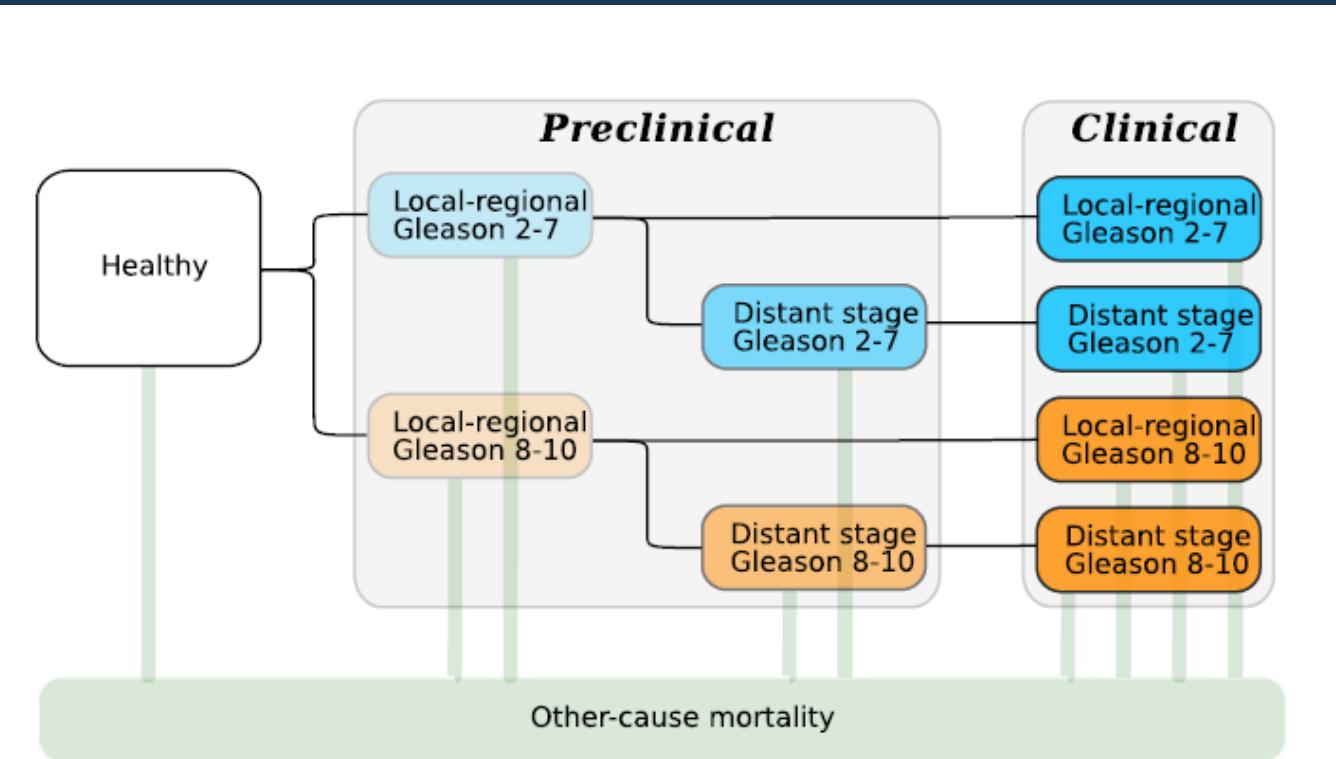
Natural history depends on

- Risk of onset
- Risk of becoming symptomatic
- Survival with and without screening
 - Baseline survival
 - Screening benefit

Data required

- Disease incidence with and without screening
- Screening frequency
- Baseline survival without screening
- Screening trial data or mechanism for screening benefit

Modeling Disease II

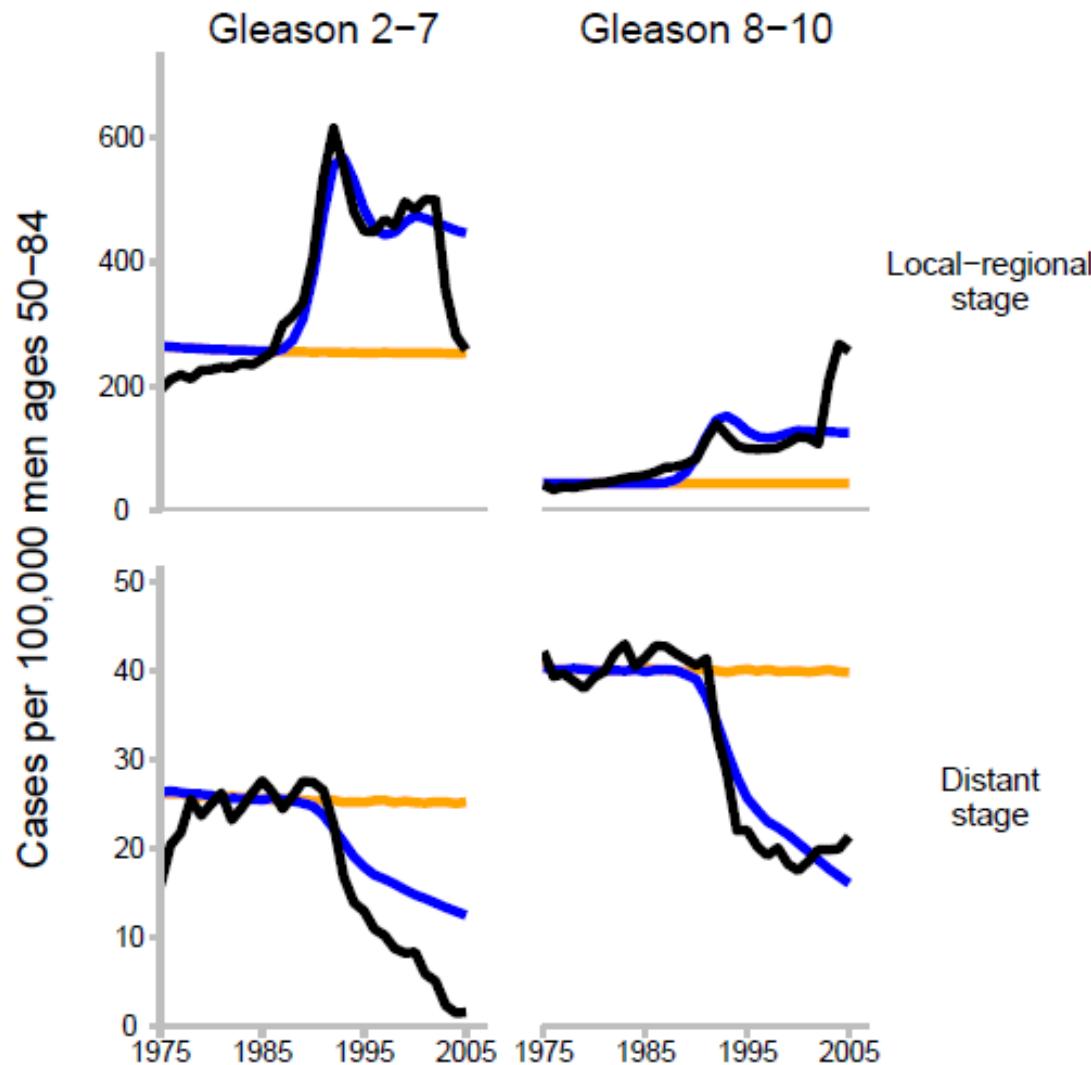


Data required:

- Disease incidence with and without screening **by stage/grade**
- Population screening patterns
- Baseline survival without screening **by stage/grade**
- Note: model allows **STAGE-SHIFT** mechanism for screening benefit

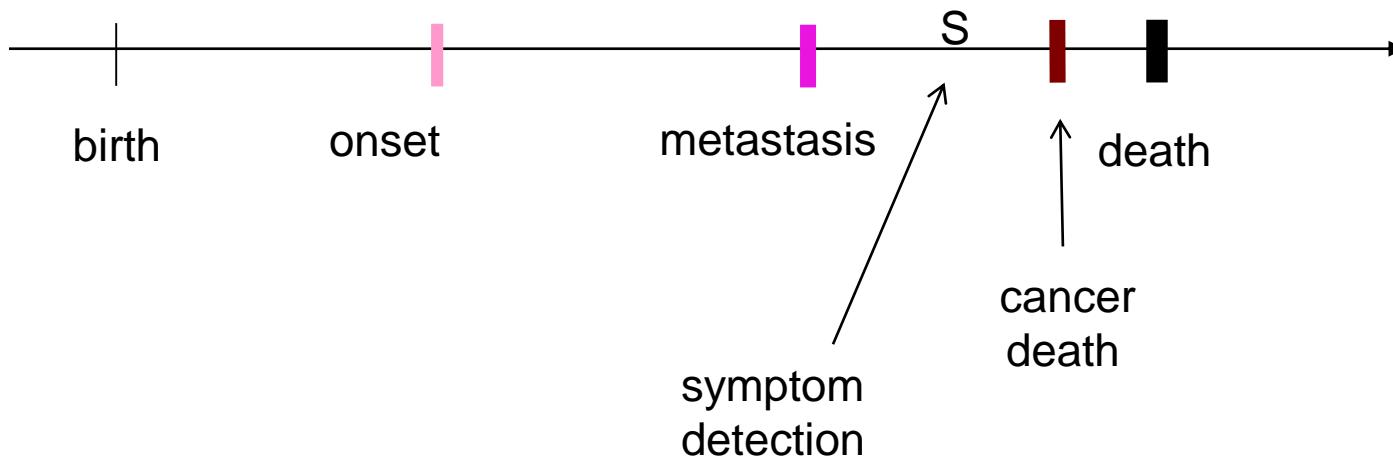
Model Fit to SEER Incidence

Always ask: How is the model calibrated?

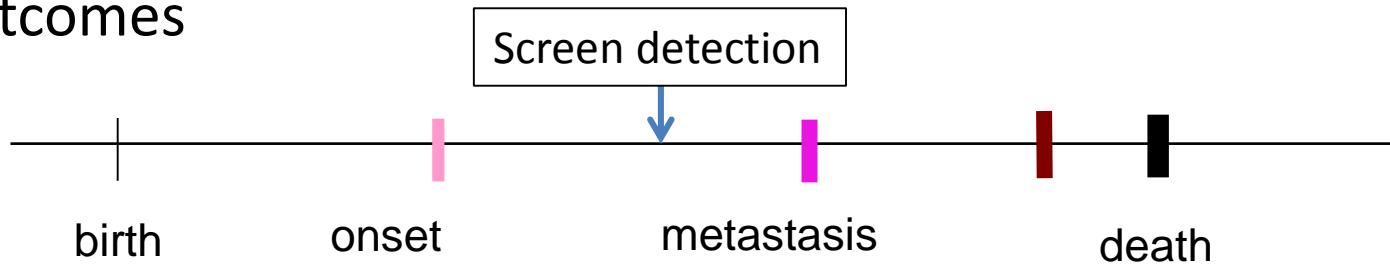


Using the Model in Practice

- Use the fitted model to simulate a population of disease histories without screening



- Superimpose screening and project the resulting change in outcomes



Modeling a Virtual Trial

Comparative Effectiveness of Alternative Prostate-Specific Antigen-Based Prostate Cancer Screening Strategies

Model Estimates of Potential Benefits and Harms

Roman Gulati, MS; John L. Gore, MD; and Ruth Etzioni, PhD

Background: The U.S. Preventive Services Task Force recently concluded that the harms of existing prostate-specific antigen (PSA) screening strategies outweigh the benefits.

Objective: To evaluate comparative effectiveness of alternative PSA screening strategies.

Design: Microsimulation model of prostate cancer incidence and mortality quantifying harms and lives saved for alternative PSA screening strategies.

Data Sources: National and trial data on PSA growth, screening and biopsy patterns, incidence, treatment distributions, treatment efficacy, and mortality.

Target Population: A contemporary cohort of U.S. men.

Time
Perspective
Intervention
ages, screening

men aged 50 to 74 years annually with a PSA threshold for biopsy referral of 4 $\mu\text{g/L}$ reduces the risk for prostate cancer death to 2.15% with risk for overdiagnosis of 3.3%. A strategy that uses higher PSA thresholds for biopsy referral in older men achieves a similar risk for prostate cancer death (2.23%) but reduces the risk for overdiagnosis to 2.3%. A strategy that screens biennially with longer screening intervals for men with low PSA levels achieves similar risks for prostate cancer death (2.27%) and overdiagnosis (2.4%) but reduces total tests by 59% and false-positive results by 50%.

Results of Sensitivity Analysis: Varying incidence inputs or reducing the survival improvement due to screening did not change conclusions.

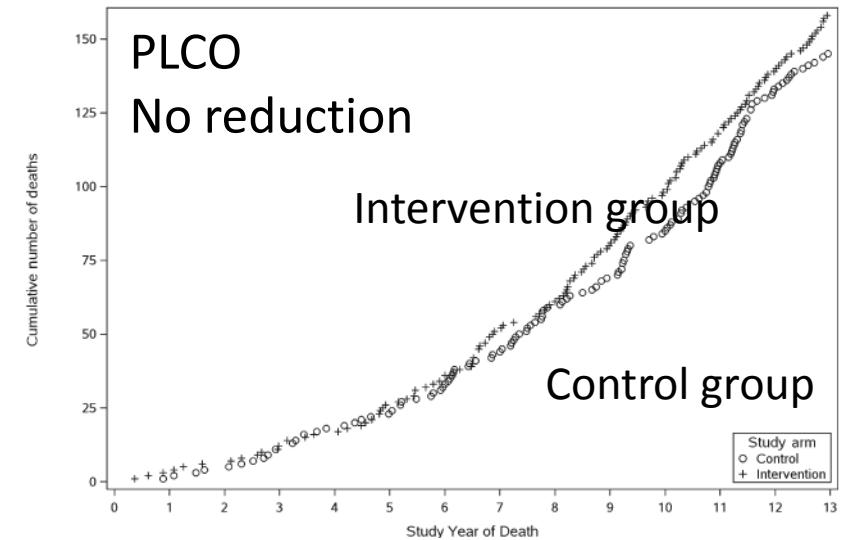
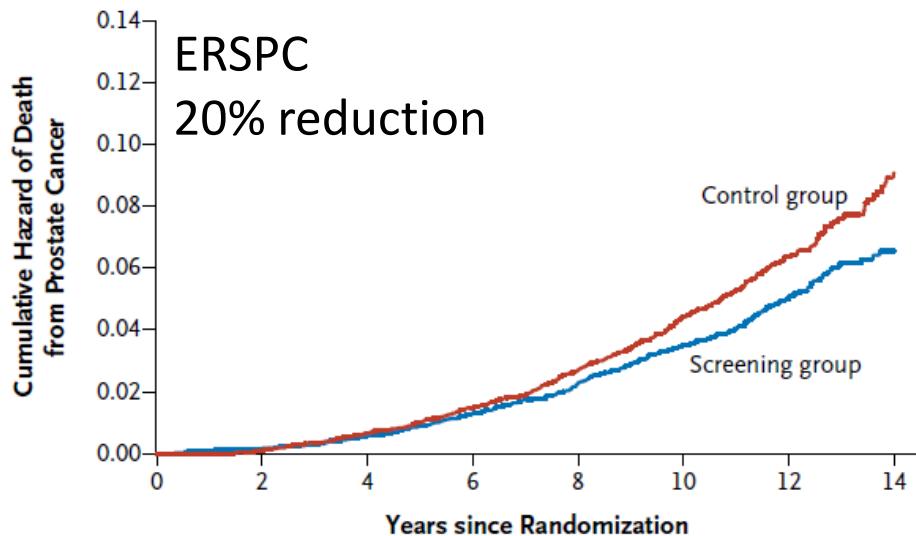
Limitations: The model is a simplification of complex clinical scenarios.

"This modeling study compared 35 screening strategies that differed by ages to start and stop screening, screening intervals, and thresholds for biopsy."

Outcomes of Candidate Screening Policies

Screening policy components	Policy 1	Policy 2	Policy 3	Policy 4	Policy 5
Screening ages	45-75	50-75	40-75	50-75	40-75
Interscreening interval	age-specific	biennial	biennial	annual	annual
PSA test-positive threshold	4.0	4.0	age-specific	4.0	4.0
Outcomes	3% die of prostate cancer in absence of screening				
Average number of PSA tests	8.3	10.6	15.5	20.3	30.0
Probability of at least 1 false positive	18.8%	19.7%	14.2%	21.4%	21.8%
Probability of cancer diagnosis	14.4%	14.7%	13.8%	15.3%	15.5%
Probability of overdiagnosis	2.4%	2.7%	1.8%	3.3%	3.5%
Probability of life saved	0.6%	0.6%	0.5%	0.7%	0.7%

2. ERSPC and PLCO Trials



Take the screening benefit from this trial Simulate it under the conditions of this trial



ERSPC and PLCO Trials

Impact of implementation Differences

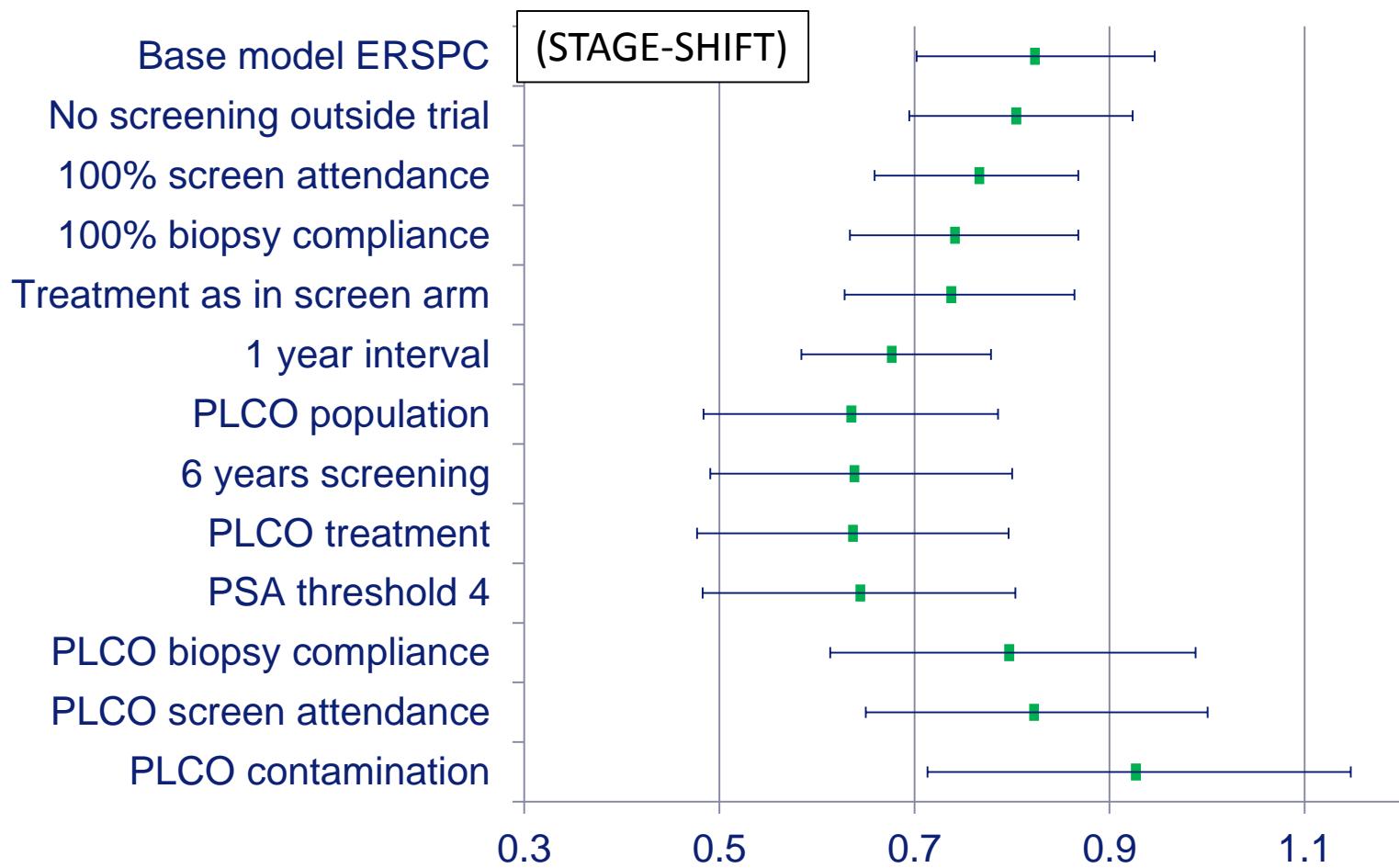
The impact of PLCO control arm contamination on perceived PSA screening efficacy

Roman Gulati · Alex Tsodikov · Elisabeth M. Wever ·
Angela B. Mariotto · Eveline A. M. Heijnsdijk ·
Jeffrey Katcher · Harry J. de Koning · Ruth Etzioni

An excess of deaths on the screened arm is not unlikely

The power of the trial to detect a difference in mortality even if screening is beneficial is very low (less than 25%)

Decomposing Factors Impacting Benefit Results



Modeling Studies - Summary

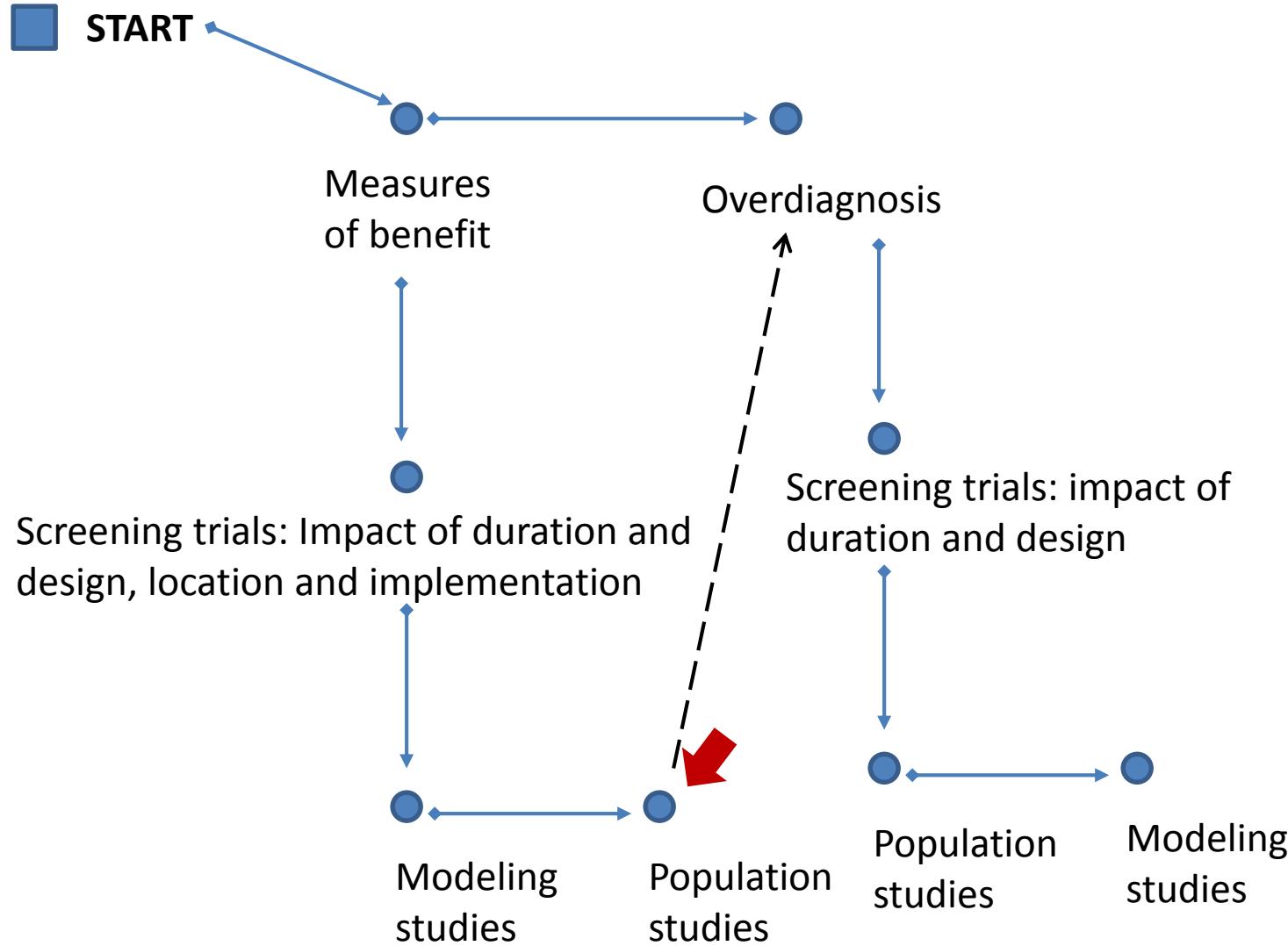
There are different types of models

- Some are essentially accounting exercises
 - Some develop elaborate abstractions of the underlying biology
- ALL make assumptions

Natural history /microsimulation models have two pieces

- Disease progression piece
 - Survival piece including screening benefit mechanism
- BOTH should be clearly specified
-
- Need to make sure that the data available are adequate to inform the model. This can be very challenging!
 - Always ask: “how is the model calibrated?”
 - Variation in results across models is to be expected and welcomed!
 - But also needs to be explained

A Map of Today's Workshop



Population Studies of Benefit

Surveillance studies of cancer trends

- Link changes in care with changes in disease mortality
- Frequently speculative (but see modeling studies later)

Ecologic studies comparing incidence and mortality across areas

- Not useful without data on trends in patterns of care such as screening and treatment
- Need to be very carefully scrutinized for alternative explanations
- Any effects observed not interpretable on individual level

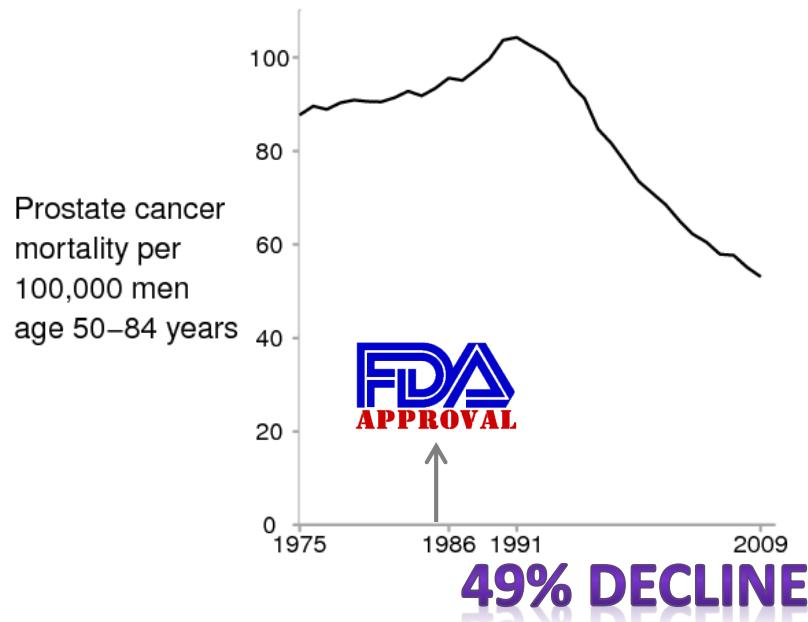
Case-control studies

- Many sources of bias
- Difficult to do right!

Prostate Cancer Screening— The Evidence, the Recommendations, and the Clinical Implications

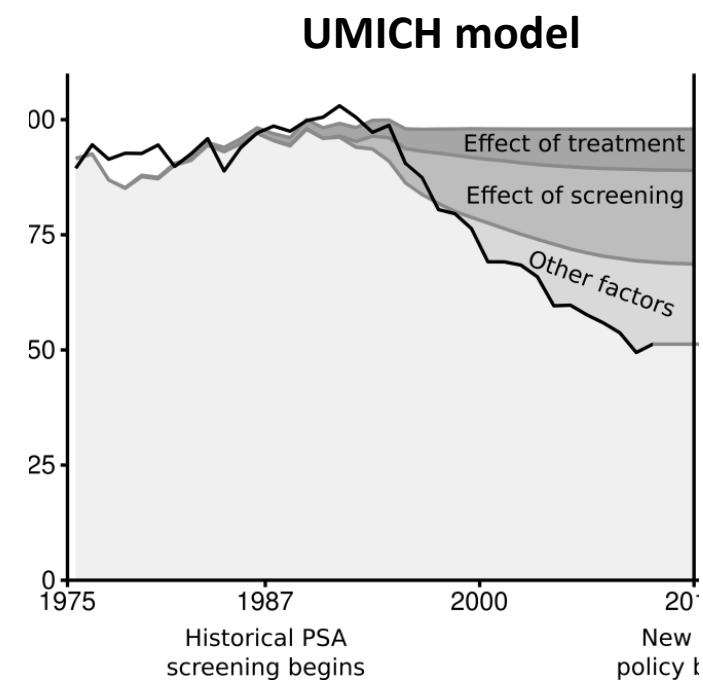
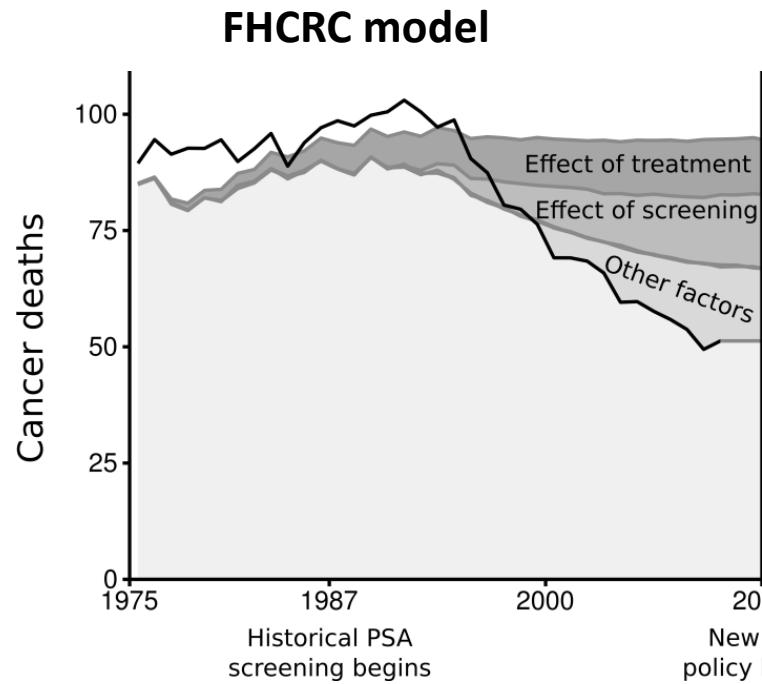
Roger Chou, MD

Michael L. LeFevre, MD, MSPH



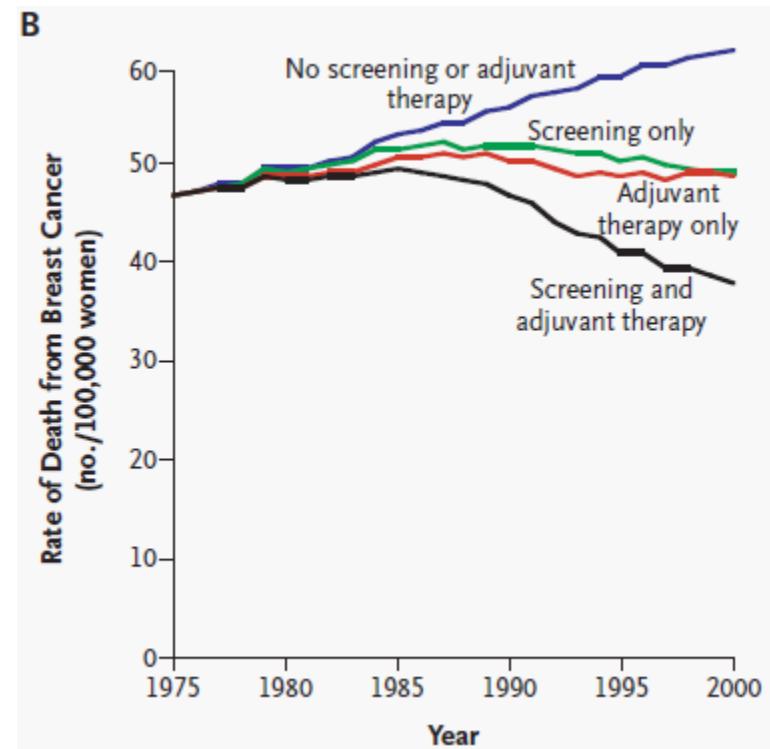
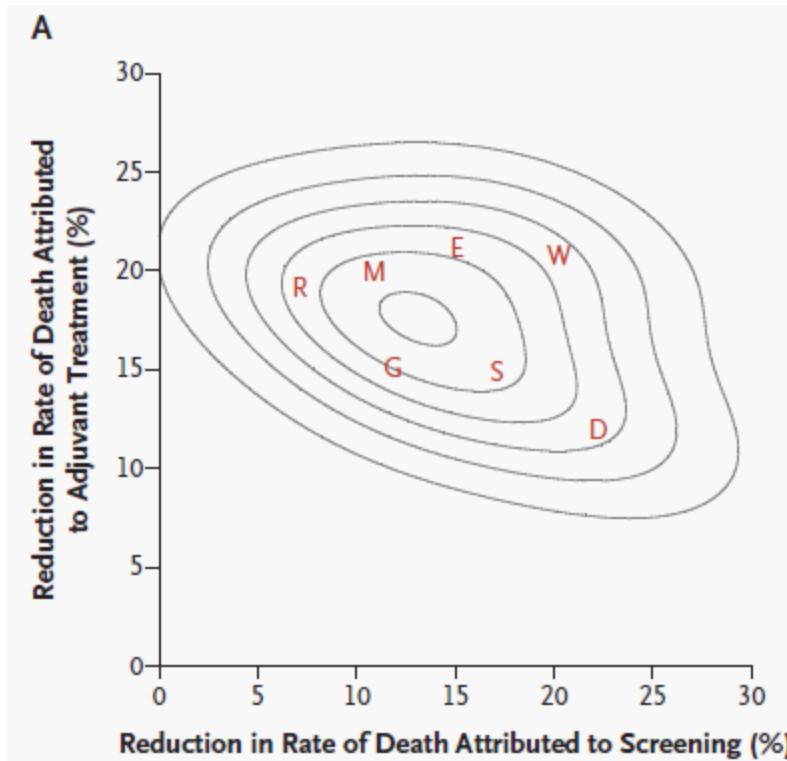
"ERSPC clearly showed that if PSA screening reduces prostate cancer mortality, it does not occur for 7 to 10 years. Therefore, the decline observed from the 1990s to about 2000 could not be from screening but was probably due to other factors such as more effective treatments."

Modeling the Impact of Screening and Treatment



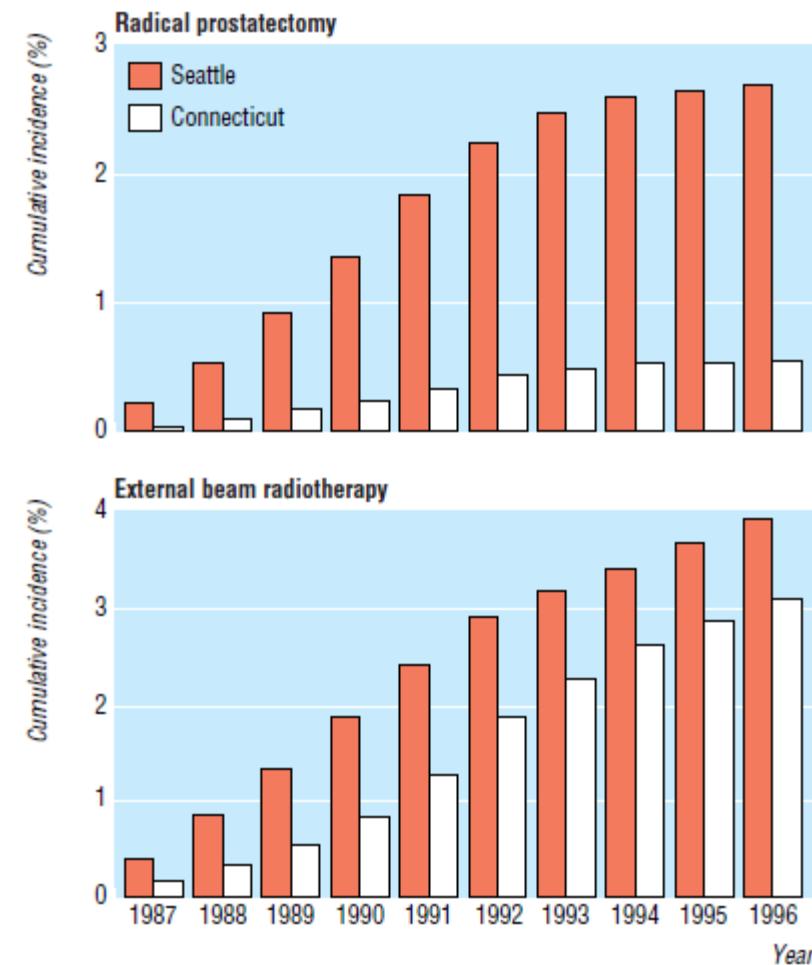
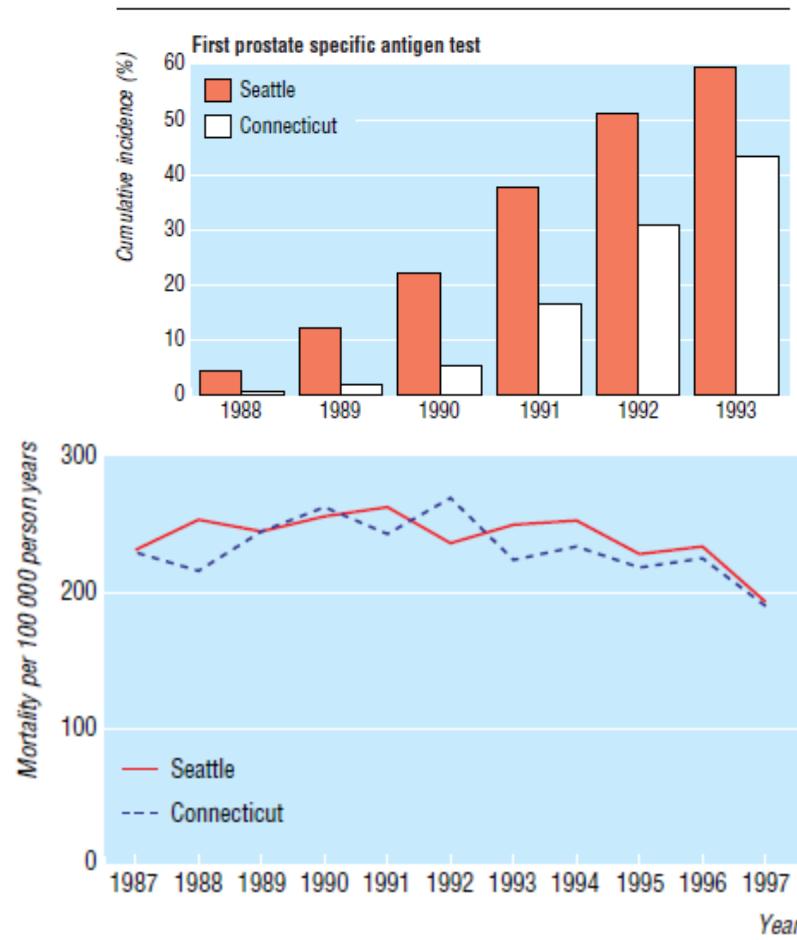
Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer

Donald A. Berry, Ph.D., Kathleen A. Cronin, Ph.D., Sylvia K. Plevritis, Ph.D.,
Dennis G. Fryback, Ph.D., Lauren Clarke, M.S., Marvin Zelen, Ph.D.,
Jeanne S. Mandelblatt, Ph.D., Andrei Y. Yakovlev, Ph.D., J. Dik F. Habbema, Ph.D.,
and Eric J. Feuer, Ph.D., for the Cancer Intervention and Surveillance
Modeling Network (CISNET) Collaborators*



Natural experiment examining impact of aggressive screening and treatment on prostate cancer mortality in two fixed cohorts from Seattle area and Connecticut

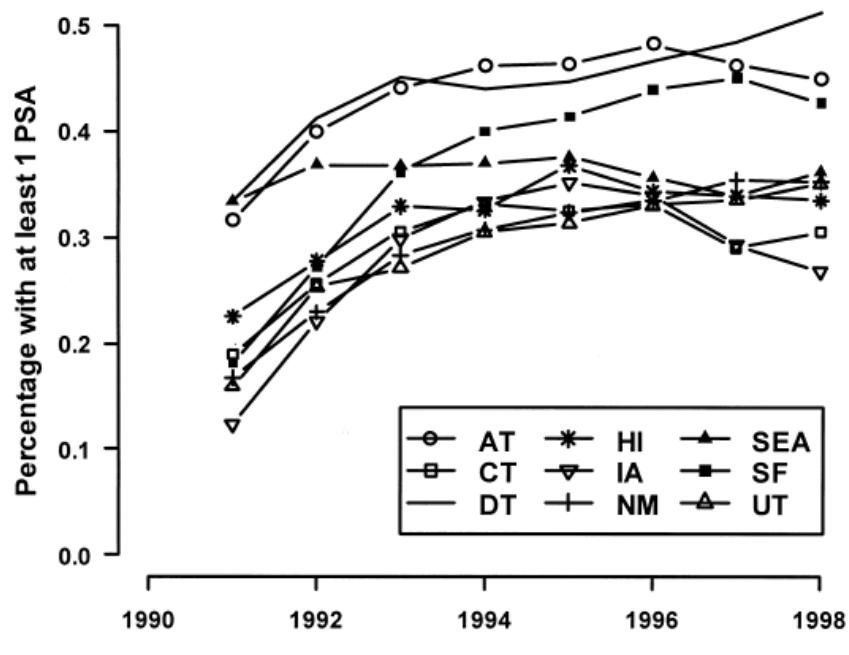
Grace Lu-Yao, Peter C Albertsen, Janet L Stanford, Therese A Stukel, Elizabeth S Walker-Corkery, Michael J Barry



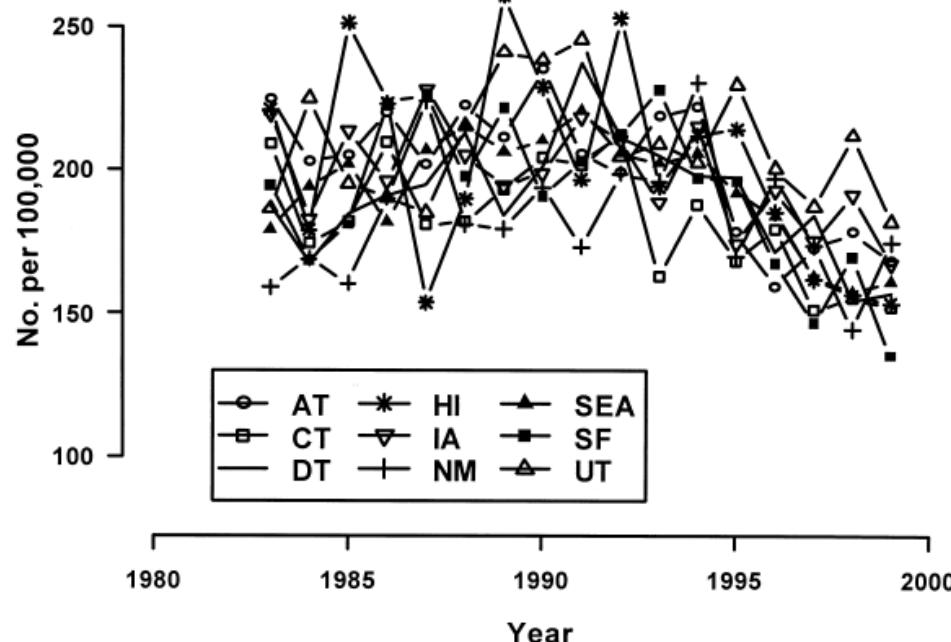
An Ecologic Study of Prostate-specific Antigen Screening and Prostate Cancer Mortality in Nine Geographic Areas of the United States



Pamela A. Shaw^{1,2}, Ruth Etzioni¹, Steven B. Zeliadt¹, Angela Mariotto³, Kent Karnofski¹, David F. Penson⁴, Noel S. Weiss^{1,5}, and Eric J. Feuer³

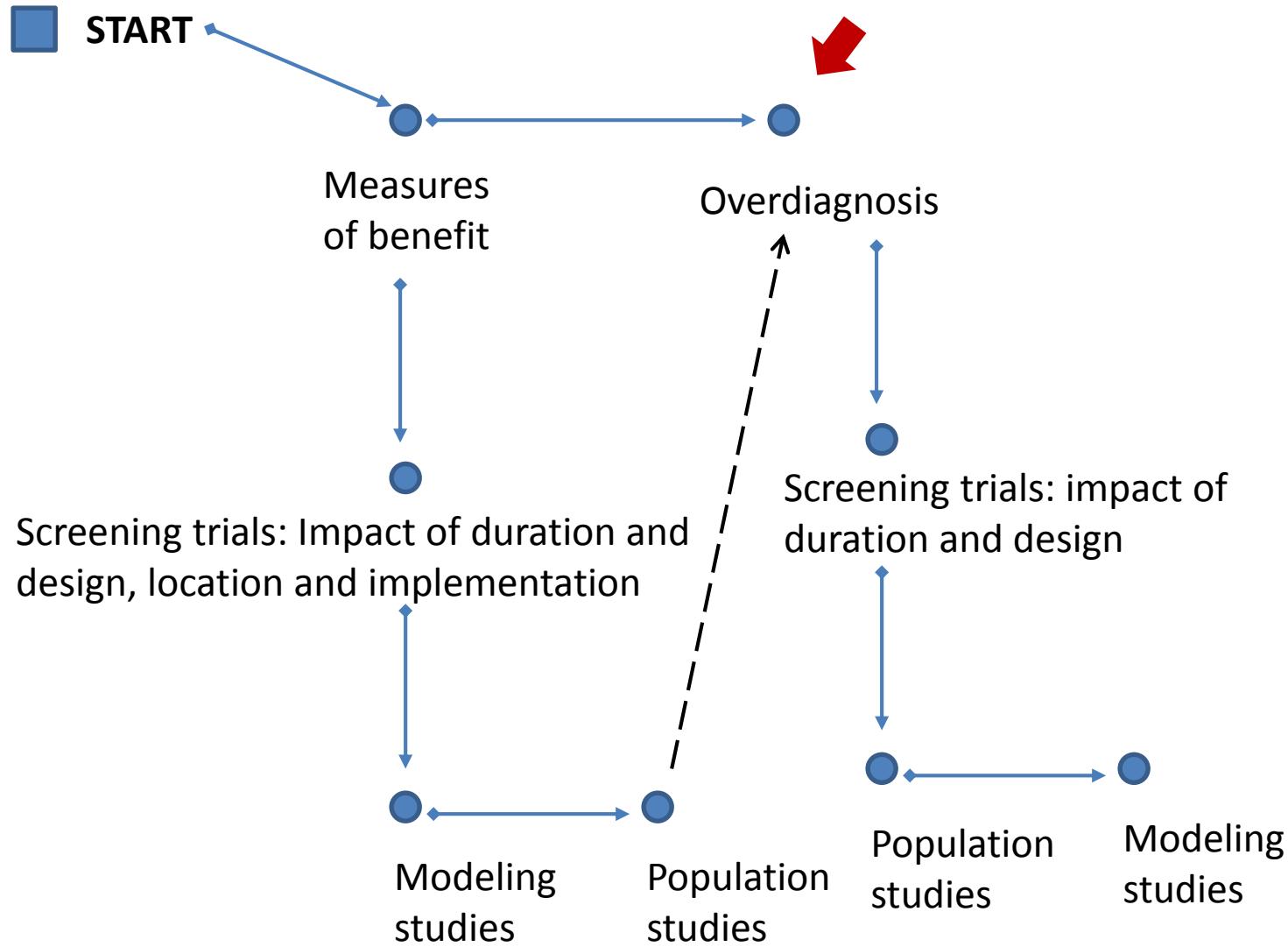


Screening

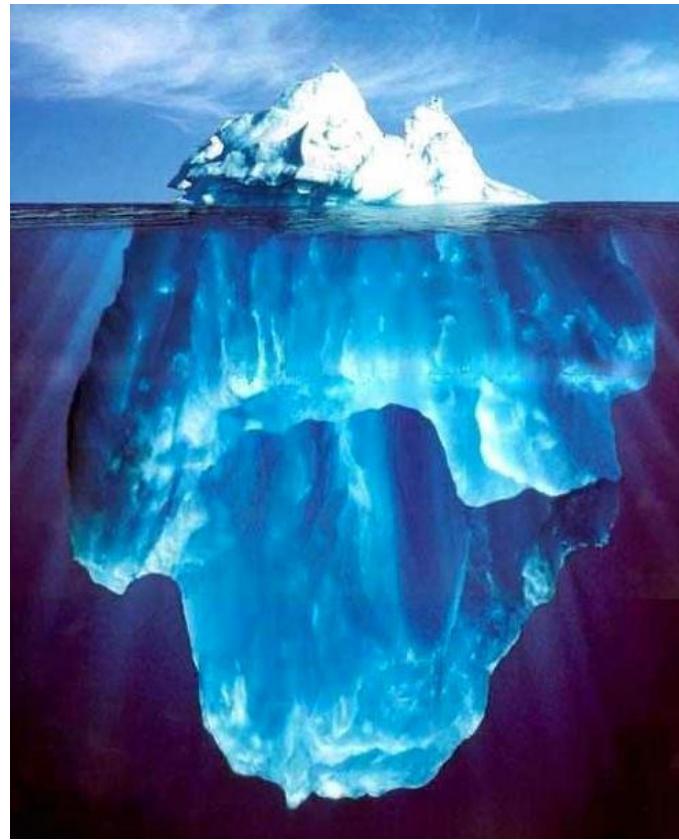


Mortality

A Map of Today's Workshop

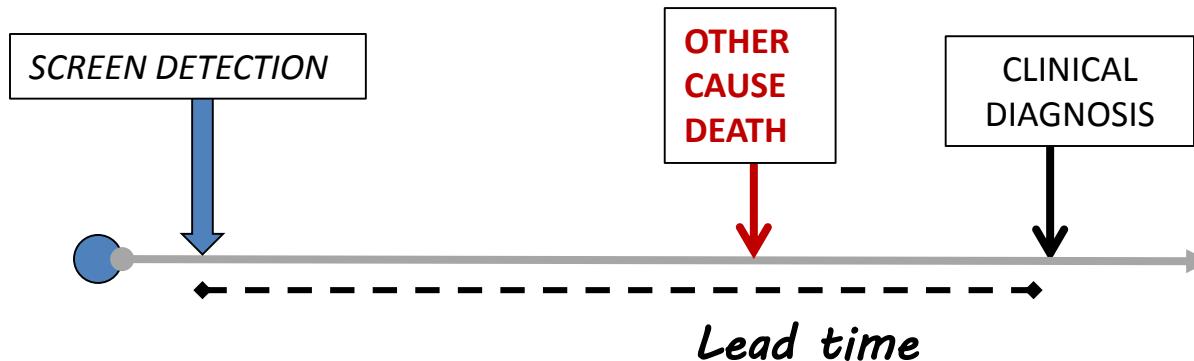


Overdiagnosis



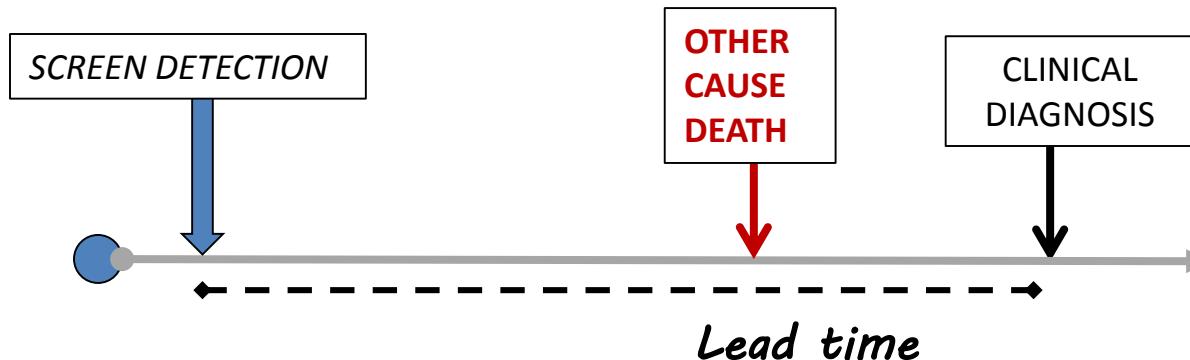
Overdiagnosis

Definition: A screen-detected case that would not have been diagnosed in the absence of screening



Overdiagnosis

Definition: A screen-detected case that would not have been diagnosed in the absence of screening



Measures of overdiagnosis

- (1) As a fraction of screen-detected cases (only LT approach)
- (2) As a fraction of all cases diagnosed
- (3) Relative to incidence expected in the absence of screening
- (4) As a fraction of cases screened
- (5) Relative to lives saved by screening (aNND)

Many articles do not clearly specify the denominator in their abstracts

Overdiagnosis of Invasive Breast Cancer Due to Mammography Screening: Results From the Norwegian Screening Program

Mette Kalager, MD; Hans-Olov Adami, MD, PhD; Michael Bretthauer, MD, PhD; and Rulla M. Tamimi, ScD

18-25%: Denominator is incidence in absence of screening

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

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

31%: Denominator is all cases detected

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

22%: Denominator is cases detected on the screening arm (mammo or CBE)

50%: Denominator is mammogram-only cases on the screening arm

Two Ways People Learn About Overdiagnosis

(1) Count excess cases in the presence of screening

“EXCESS INCIDENCE APPROACH”

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

“LEAD TIME APPROACH”

KEY LESSON: APPROACH MATTERS

Lead-Time vs Excess Incidence: Breast Cancer

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

Overdiagnosis of Invasive Breast Cancer Due to Mammography Screening: Results From the Norwegian Screening Program

Mette Kalager, MD; Hans-Olov Adami, MD, PhD; Michael Bretthauer, MD, PhD; and Rulla M. Tamimi, ScD

**Excess
Incidence**

18-25%: Denominator is incidence in absence of screening

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

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**Excess
Incidence**

31%: Denominator is all cases detected

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

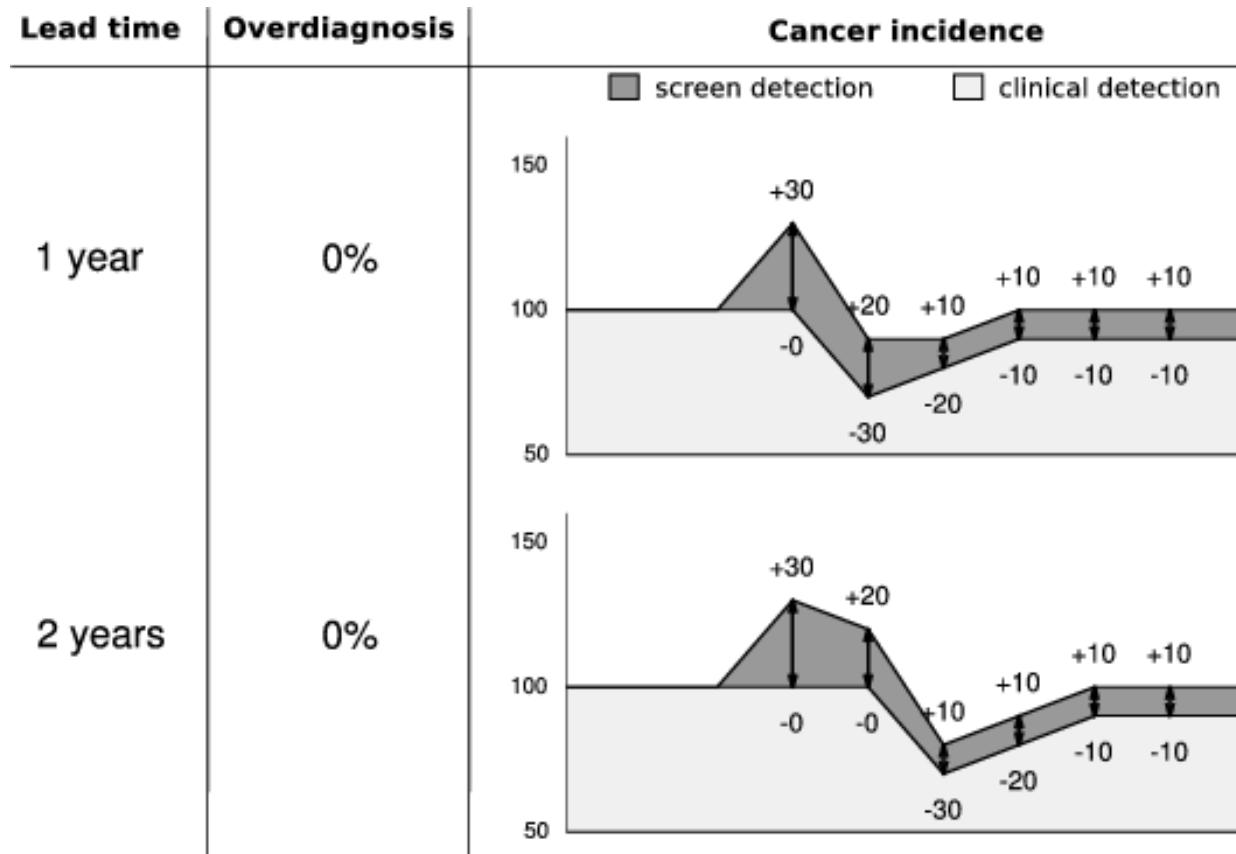
**Excess
Incidence**

22%: Denominator is cases detected on the screening arm (mammo or CBE)

50%: Denominator is mammogram-only cases on the screening arm

A Closer Look at Excess Incidence

Note: two types of excess incidence – point (annual) or cumulative



Timing

- Wait to calculate point excess incidence
- Cumulative excess incidence persistently biased

Counterfactual

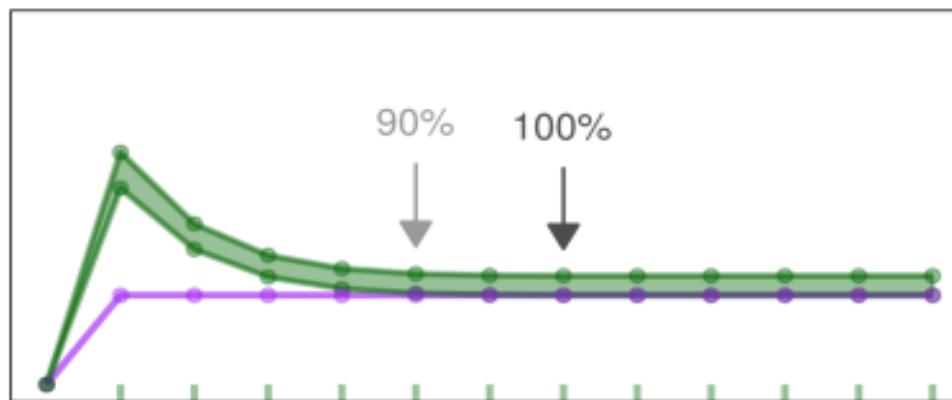
- Impute incidence in absence of screening

How long to wait?

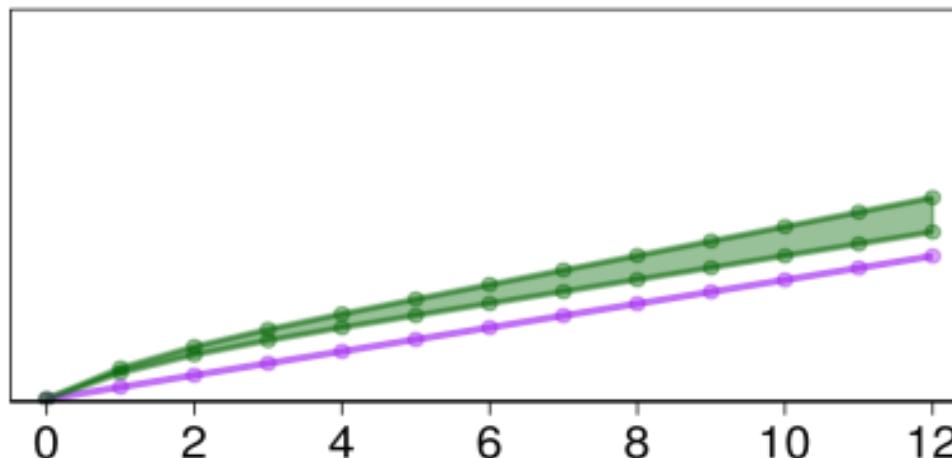
Continuous Screen Trial

Continuous-screen trial with preclinical period 0-6 years, overdx 25% of screen-detections

Screen arm receives tests in all years
Control arm receives no tests



Annual
Incidence

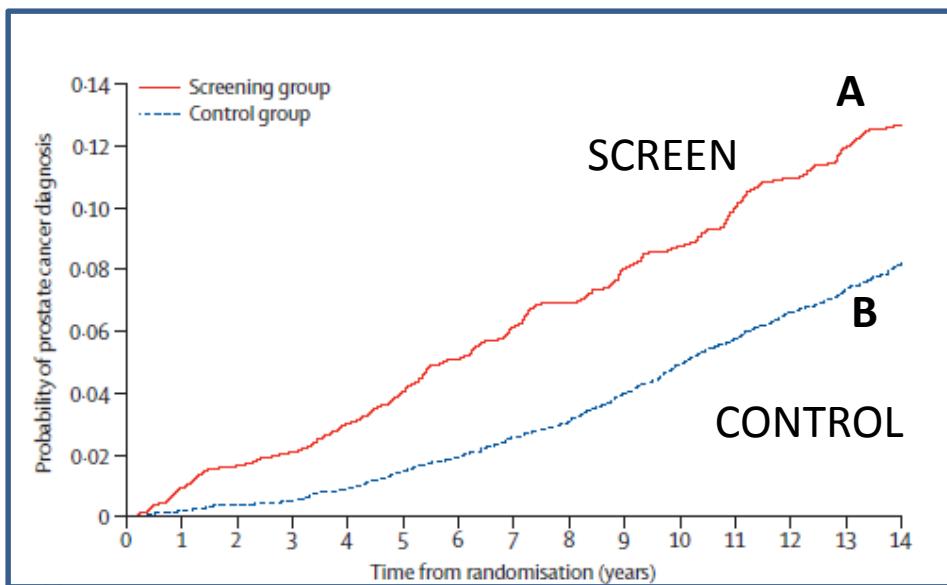


Cumulative
Incidence

Overdiagnosis in the ERSPC

A Continuous Screen Trial

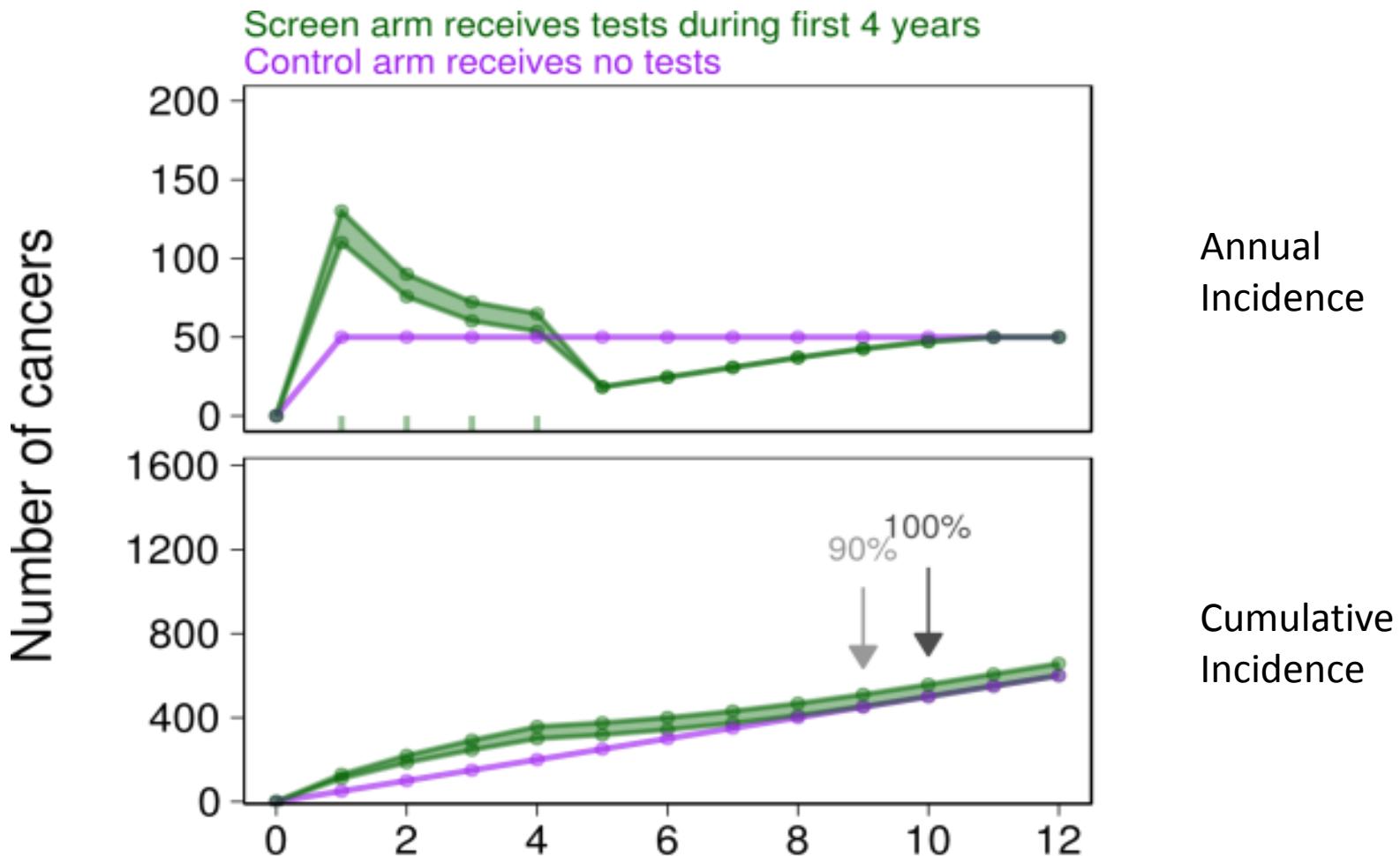
Screening and Prostate-Cancer Mortality
in a Randomized European Study



	Cumulative Incidence
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%

How long to wait? Stop-screen Trial

Stop-screen trial with preclinical period 0-6 years; overdiagnosis 25%



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

Table 1 | Number of breast cancers diagnosed in mammography arm and control arm, by study year

Year of study	Mammography arm (n=44 925)		Control arm (n=44 910)	
	No of cancers detected	Mean size (cm)	No of cancers detected	Mean size (cm)
1	253	1.87	170	2.03
2	109	2.05	89	2.19
3	101	1.64	89	2.11
4	111	2.01	86	2.08
5	92	1.98	90	2.13
Subtotal years 1-5	666	1.91	524	2.10
6	83	2.15	83	2.42
7	82	1.99	93	2.24
8	107	2.01	133	2.04
9	115	1.86	119	1.90
10	127	1.69	128	1.71
Subtotal years 6-10	514	1.93	556	2.05

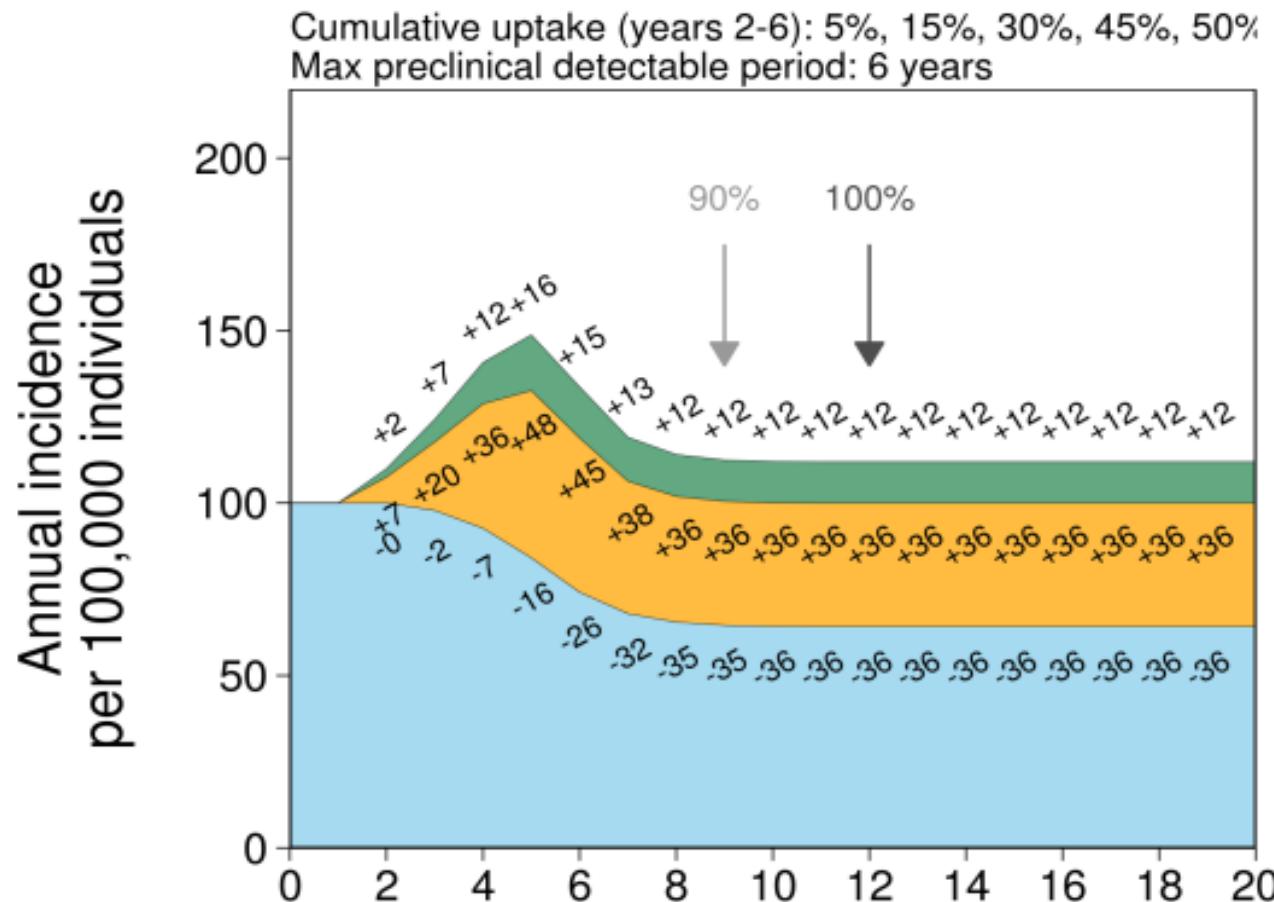
End
of
screening

484 of 666
mammogram
detected

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.

Difference
= 106
at 15 years

How long to wait? Population setting



Annual excess incidence eventually becomes unbiased; cumulative excess always biased
(Given the correct counterfactual incidence which is generally not observable)

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

H. Gilbert Welch, Peter C. Albertsen

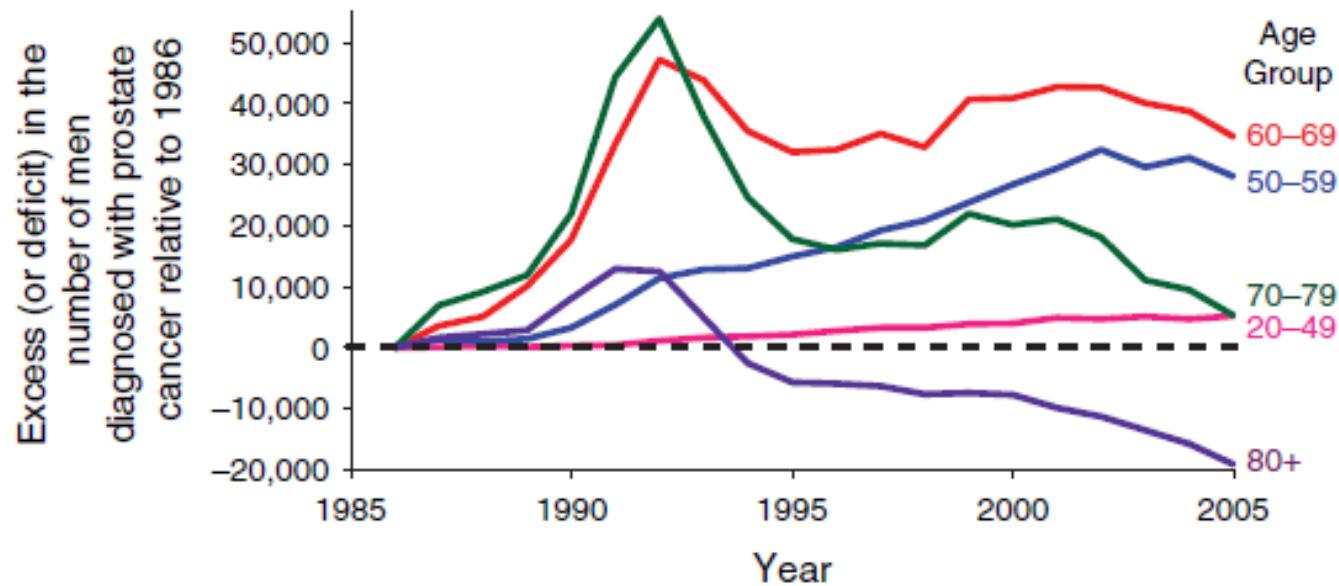


Figure 2. Excess (or deficit) in the number of men diagnosed with prostate cancer relative to 1986.

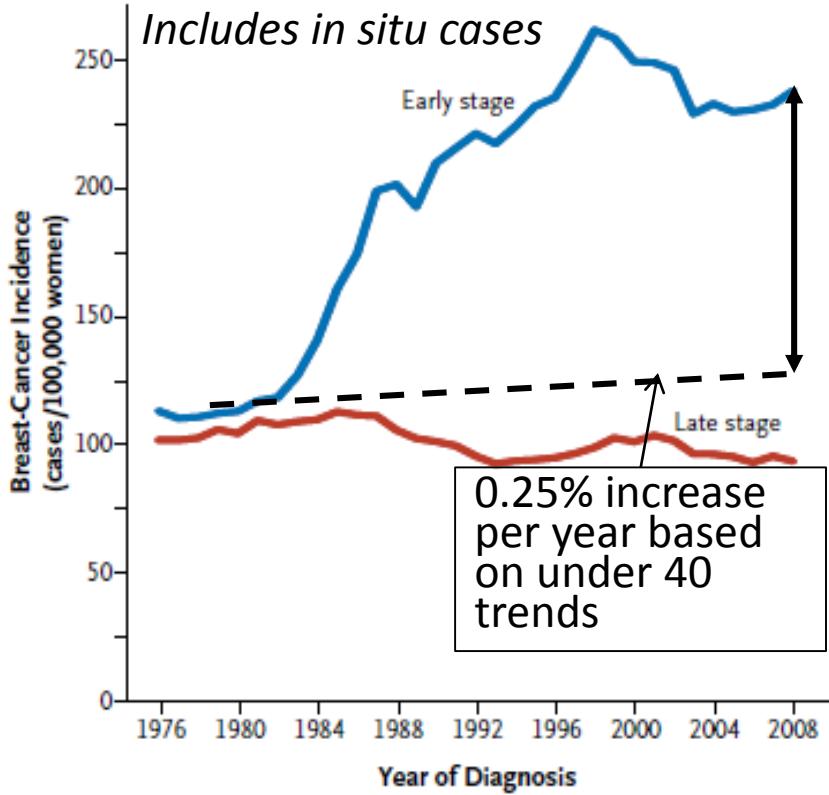
Since 1986, an estimated additional 1 305 600 men were diagnosed with prostate cancer.

What About the Counterfactual?

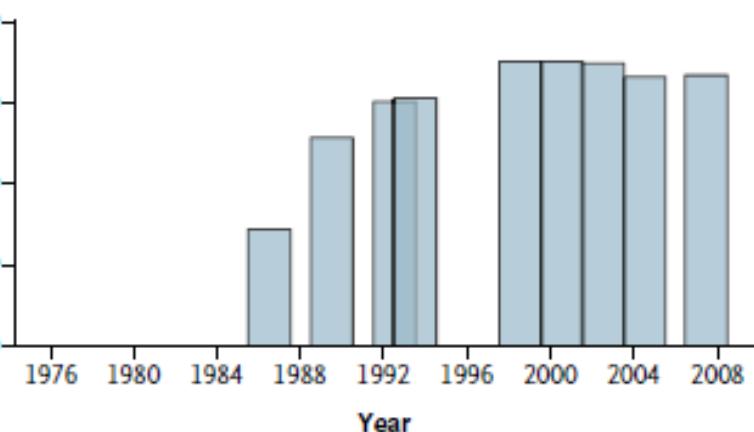
Bleyer and Welch

Screening Uptake

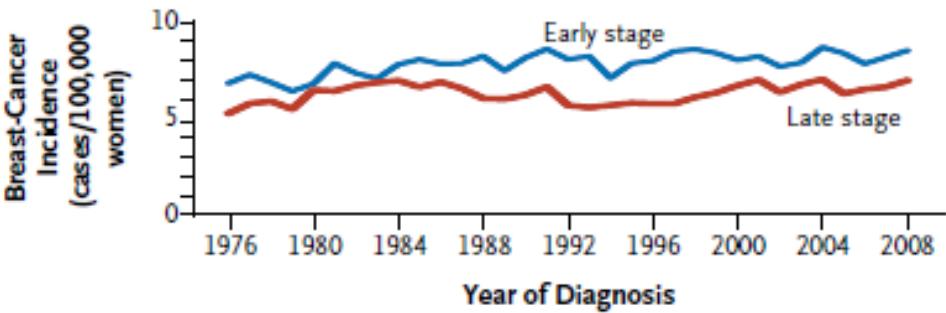
Incidence by Stage: Age 50+



Women Who Underwent Screening Mammography (%)



Incidence by Stage: Age 40-49

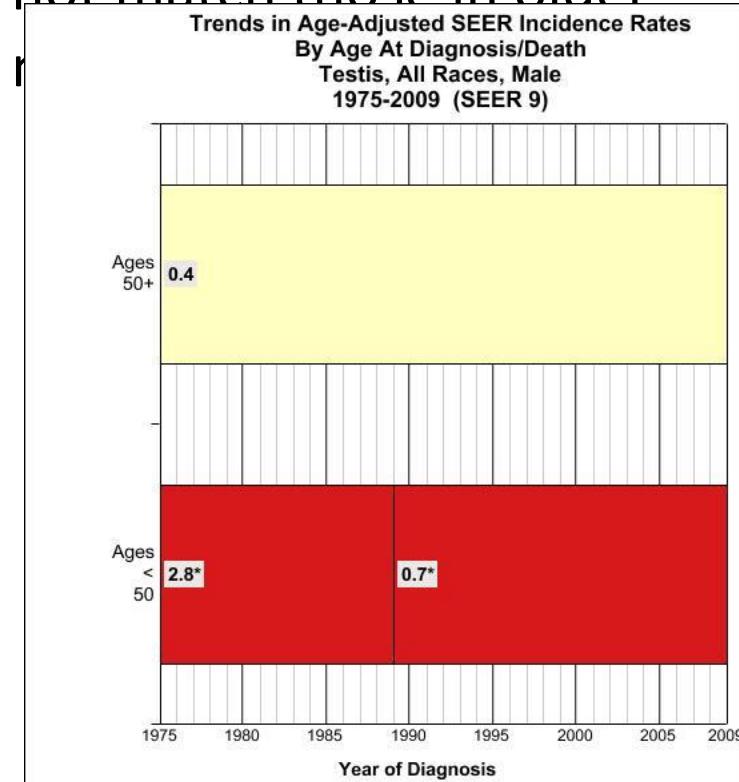


Cumulative: Over 1 million women overdiagnosed

Annual: 31% of cancers diagnosed in 2008

Trends in Testicular Cancer Incidence

Trends in younger men do not match those in older

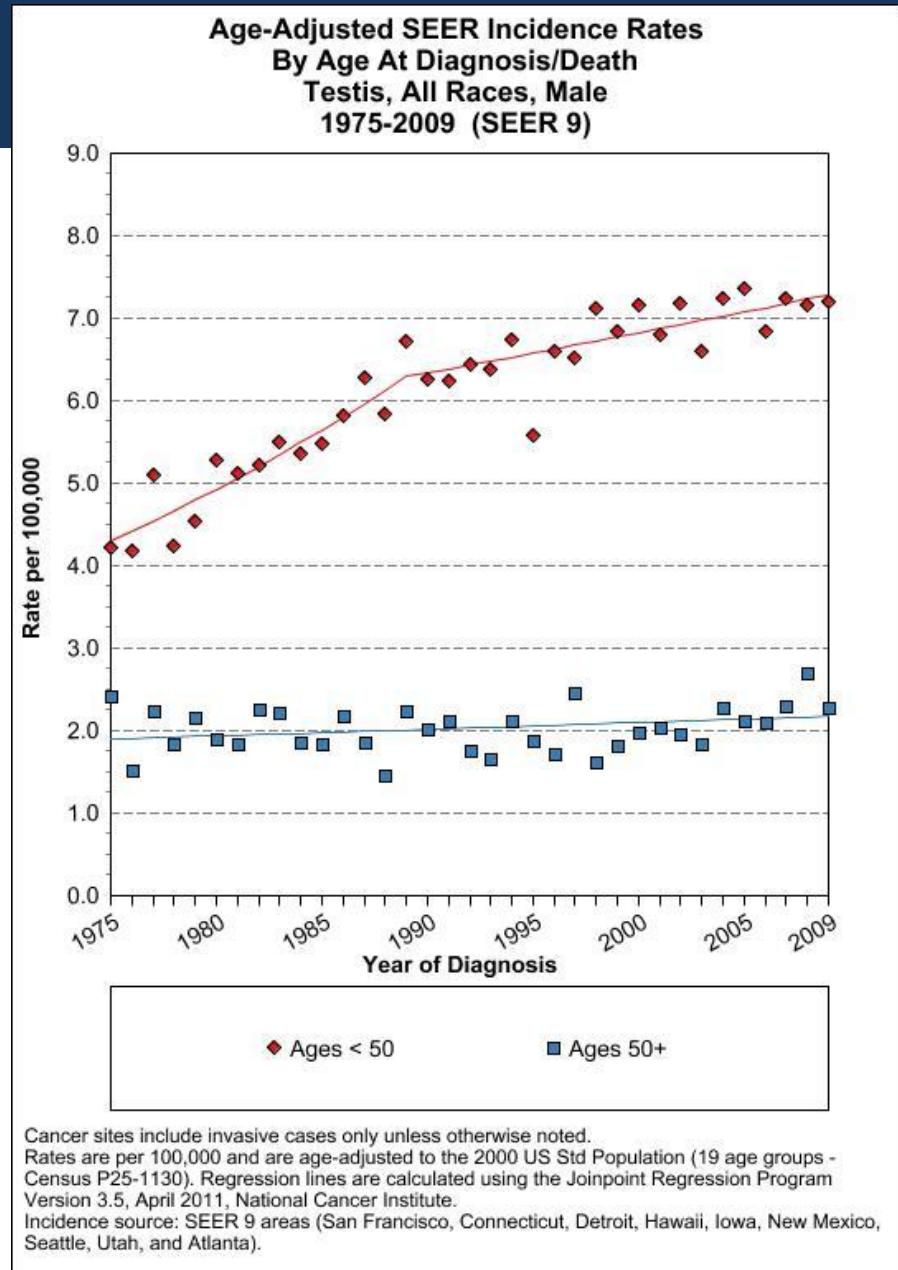


Cancer sites include invasive cases only unless otherwise noted.

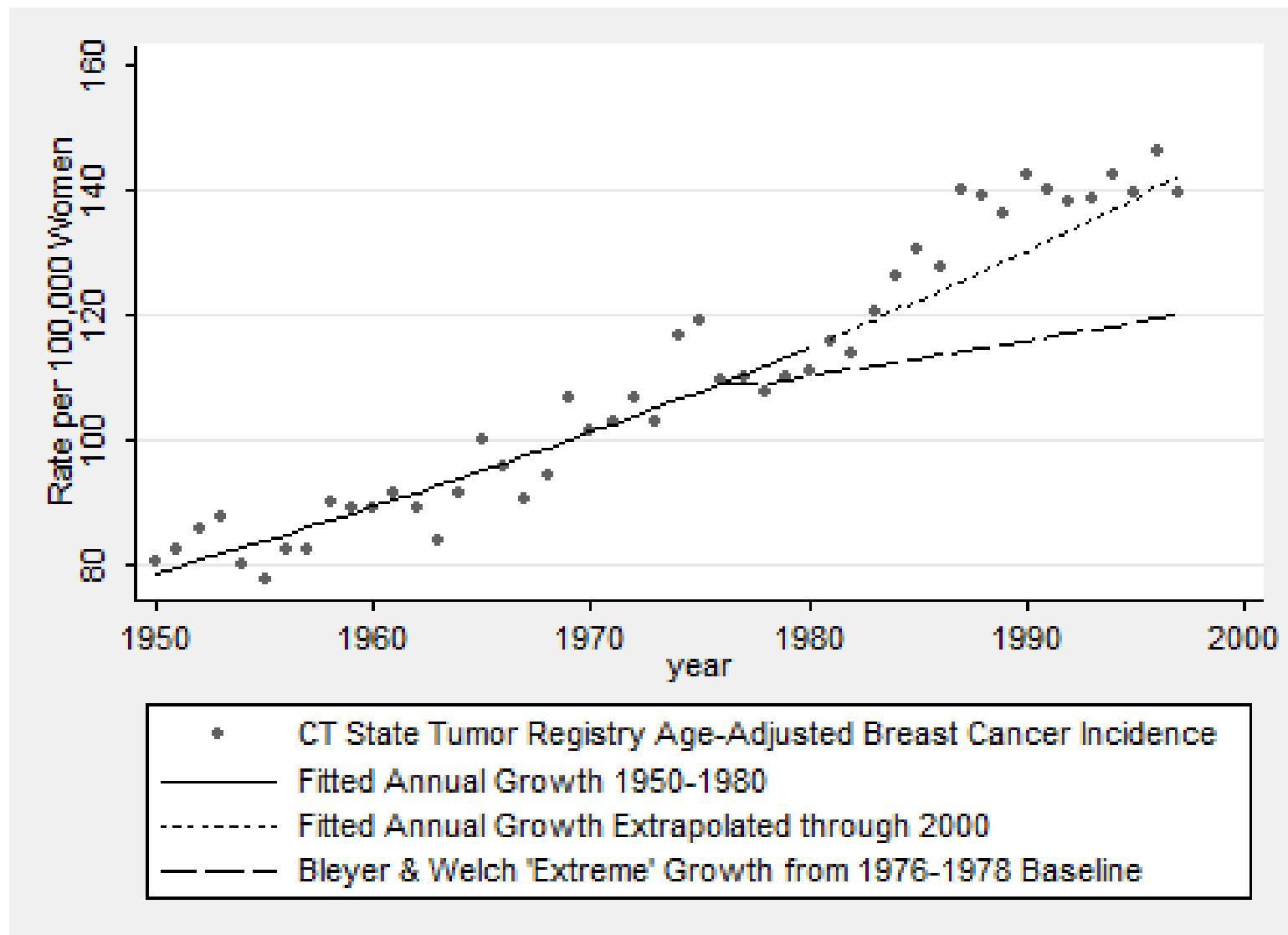
The APC is the Annual Percent Change based on rates age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). The APCs were calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute (<http://surveillance.cancer.gov/joinpoint/>).

* The APC is statistically significant from zero ($p < .05$).

Incidence source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).



Counterfactual Incidence From Connecticut Registry



Excess Incidence: Lessons

Method counts

Estimates based on cumulative excess incidence always biased
(Exception: stop-screen trials given adequate waiting time)

Counterfactual is important

In population setting, you most often cannot observe the counterfactual incidence without screening

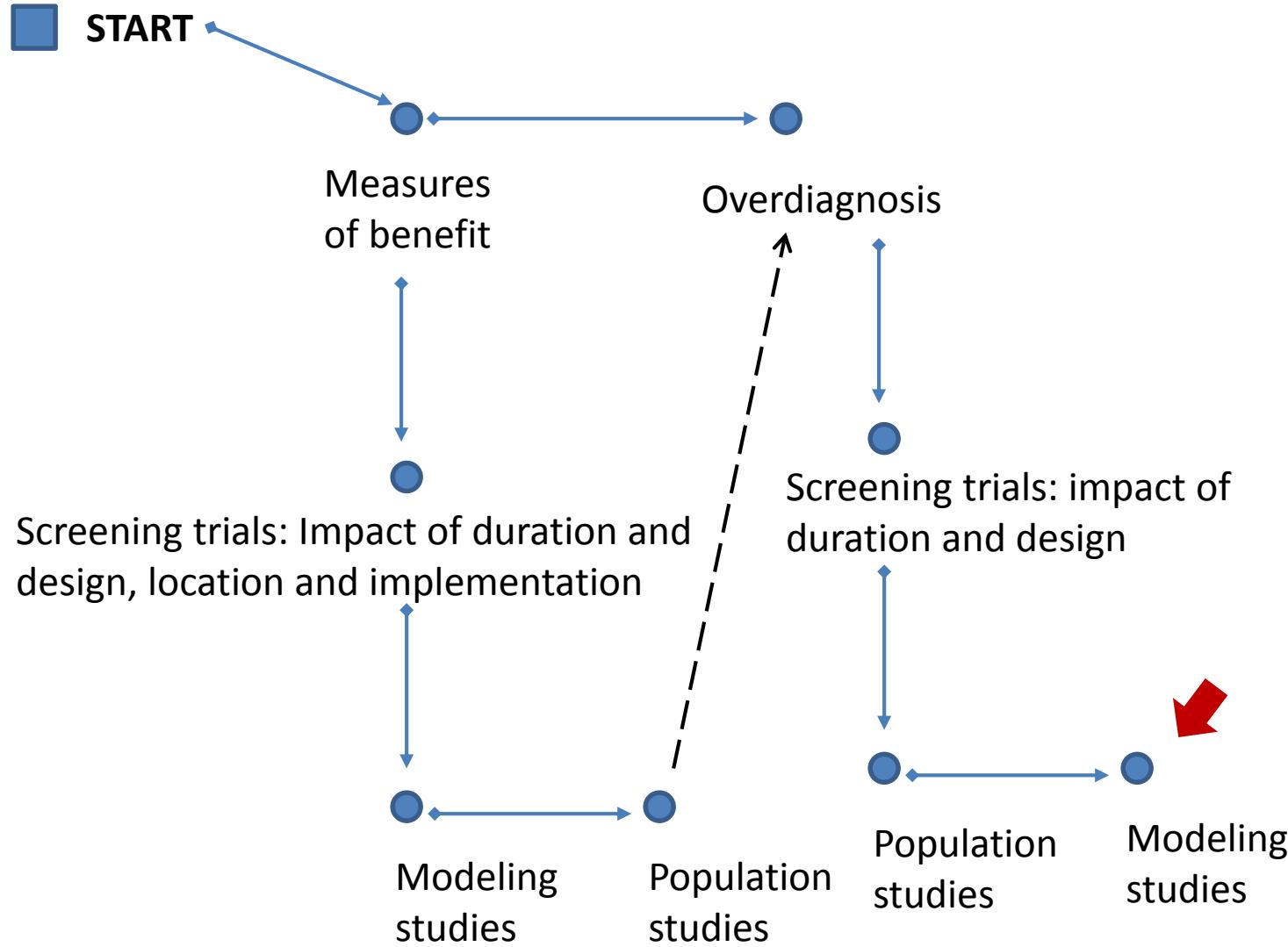
Duration counts

Excess incidence estimates biased in the early years of screening
Cumulative excess incidence estimates always biased

How long to wait?

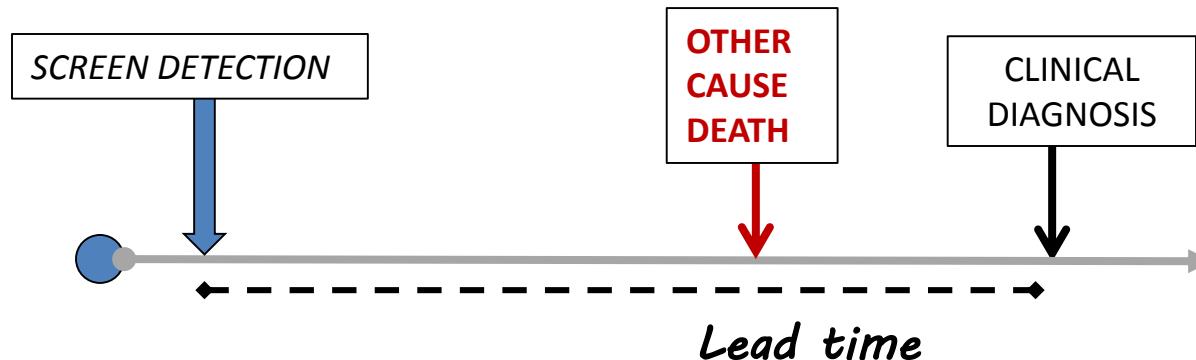
Till screening stabilizes plus maximum preclinical duration

A Map of Today's Workshop



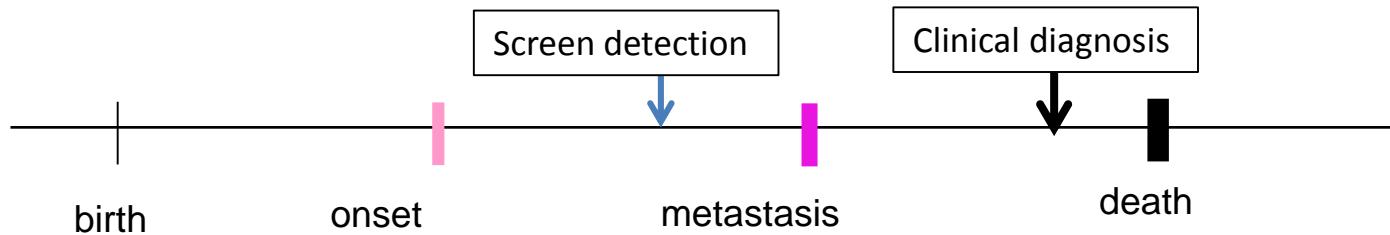
Modeling

Modeling studies base estimation on the notion that overdiagnosis occurs when the lead time is longer than life expectancy



Probability overdiagnosed = Prob (lead time > time to other-cause death)

- Lead time distribution – estimate from models fit to data on disease incidence with and without screening
 - **Statistical models** estimate preclinical duration, then derive lead time
 - **Computer simulation** models produce individual lead times from natural history



Statistical Models of Lead Time applied to data from screened cohorts

Screening Sensitivity and Sojourn Time From Breast Cancer Early Detection Clinical Trials: Mammograms and Physical Examinations

By Yu Shen and Marvin Zelen

	MST	
	Years	SD
HIP	2.5	1.2
Sweden	5.5	.61
Malmö	2.1	.37
Stockholm+	2.6	1.3
40-49	4.3	1.2
50-59	1.9	.94
Edinburgh		
Canada 1		
Canada 2		

Consensus estimate: 40 months

Lead Time from Simulation Models

- Three models of prostate cancer progression, detection and survival in the US
- Calibrated to US prostate cancer incidence trends given PSA screening patterns and assuming constant background incidence in absence of screening
- Calibrated models provide rates of natural history events
 - Onset
 - Progression to metastatic state(s)
 - Clinical diagnosis in the absence of screening
 - Age at disease-specific and other-cause death

	UMICH	MISCAN	FHCRC
Mean lead time (years)	5.4	6.9	5.9
Fraction overdiagnosed given screen detected	23%	42%	28%

Consistency of Lead Time and Excess Incidence

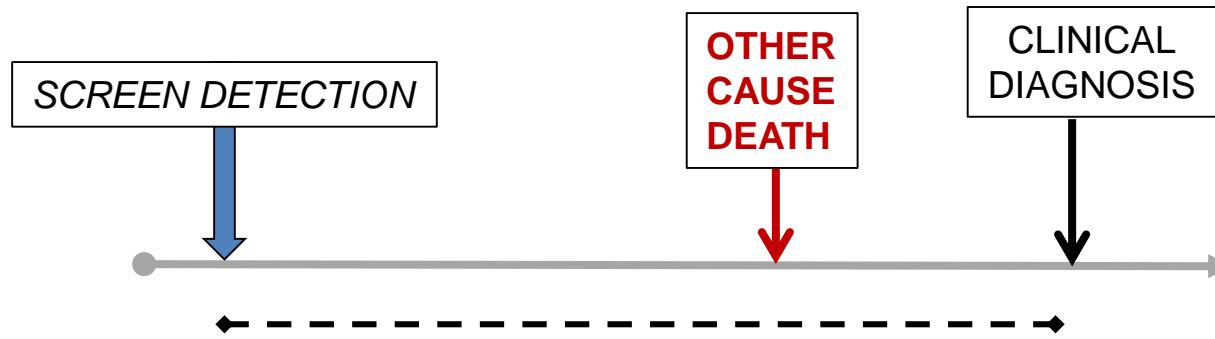
An observation

Excess incidence and Lead-time approaches are almost never used together

Idea

IF Lead time + OC death \Rightarrow Overdiagnosis

THEN (maybe) Overdiagnosis + OC death \Rightarrow Lead time



Objective

Lead time

Derive the mean lead time implied by the 31% estimate of overdiagnosis for breast cancer in the US and compare with published studies

Results

A Reality Check for Overdiagnosis Estimates Associated With Breast Cancer Screening

Ruth Etzioni, Jing Xia, Rebecca Hubbard, Noel S. Weiss, Roman Gulati

Frequency of overdiagnosis among localized invasive breast cancers (percent)

Mean lead time among localized invasive breast cancers, λ	LTdist*: Exponential	
	HR† = 0.75	HR† = 0.85
2	3.3	4.0
4	7.0	8.2
6	11.3	13.5
8	15.5	17.3
10	20.4	21.3
12	24.3	24.9

The mean lead time that best matches 18% overdiagnosed is about 9 years. Published estimates are around 2-4 years

Skepticism of Models

Lead-Time Models Should Not Be Used to Estimate Overdiagnosis in Cancer Screening

Per-Henrik Zahl, DrMedSci¹, Karsten Juhl Jørgensen, DrMedSci², and Peter C. Gøtzsche, DrMedSci²

Lead Time and Overdiagnosis

Stuart G. Baker, Philip C. Prorok, Barnett S. Kramer

Are the assumptions made by statistical and simulation models reasonable?

- Form of lead time distribution or components of natural history
 - Do models allow for a mixture of lead times representing progressive and indolent cases?
 - If not they may underestimate overdiagnosis

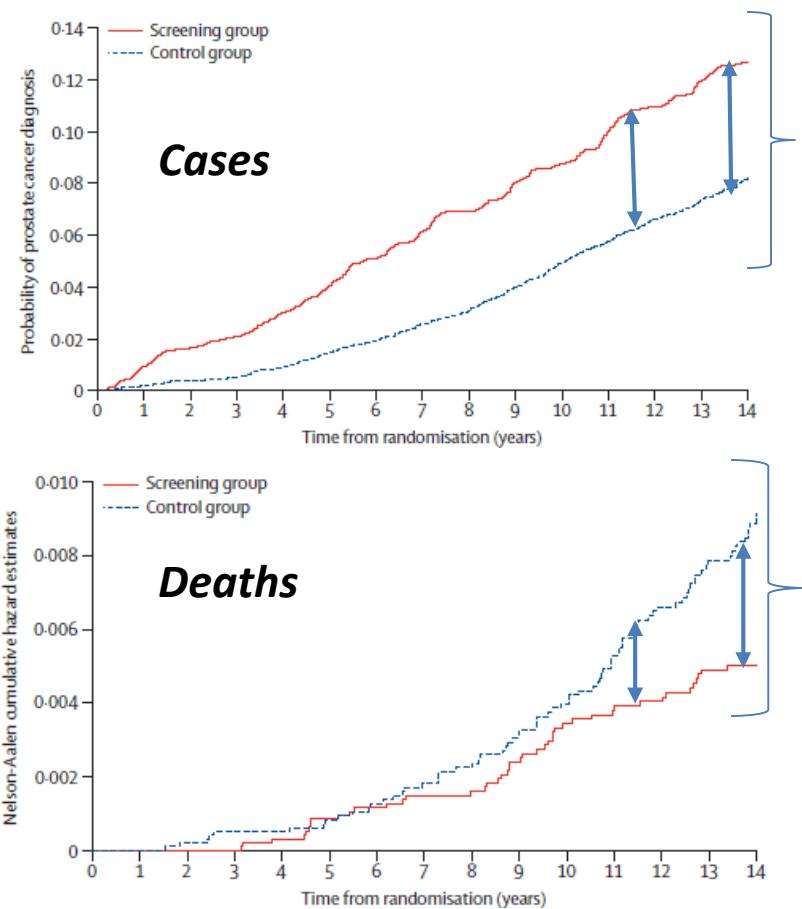
Number Needed to Detect (NND)

ORIGINAL ARTICLE

Screening and Prostate-Cancer Mortality in a Randomized European Study

“During a median follow-up of 9 years, the rate ratio for death from prostate cancer in the screening group, as compared with the control group, was 0.80. The absolute risk difference was 0.71 death per 1000 men. This means that 1410 men would need to be screened and **48 additional cases of prostate cancer would need to be treated** to prevent one death from prostate cancer.

ERSPC Estimate of NND



$$\begin{array}{r} 8.2\% \\ - 4.8\% \\ \hline 3.4\% \\ \div 0.07\% \\ \hline 48 \end{array}$$

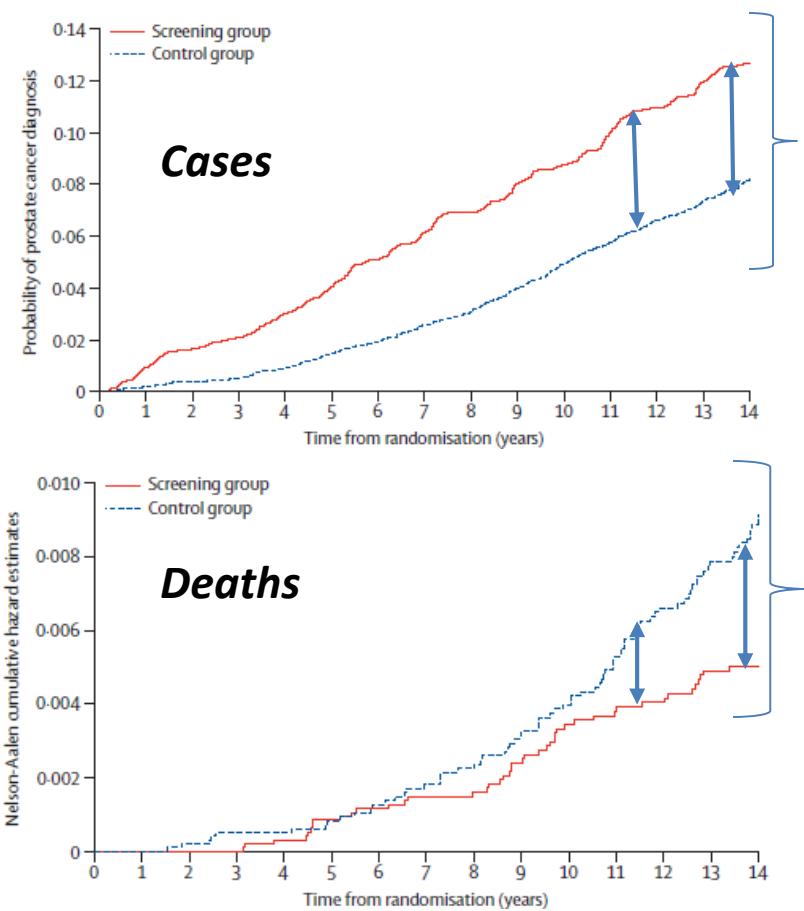
of screened group diagnosed

of control group diagnosed

excess incidence
lives saved after 9 years

NND

ERSPC Estimate of NND



$$\begin{array}{r} 8.2\% \\ - 4.8\% \\ \hline 3.4\% \\ \div 0.07\% \\ \hline 48 \end{array}$$

of screened group diagnosed

of control group diagnosed

excess incidence

lives saved after 9 years

NND (37 in updated report)

! Excess incidence overestimates
overdiagnosis

! Lives saved is time-sensitive;
increases with follow-up

Short Term versus Long Term NND

JOURNAL OF CLINICAL ONCOLOGY

STATISTICS IN ONCOLOGY

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

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

18

At 12 years

**Journal of
Clinical
Epidemiology**

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

Roman Gulati^a, Angela B. Mariotto^b, Shu Chen^a, John L. Gore^c, Ruth Etzioni^{a,*}

9

At 25 years

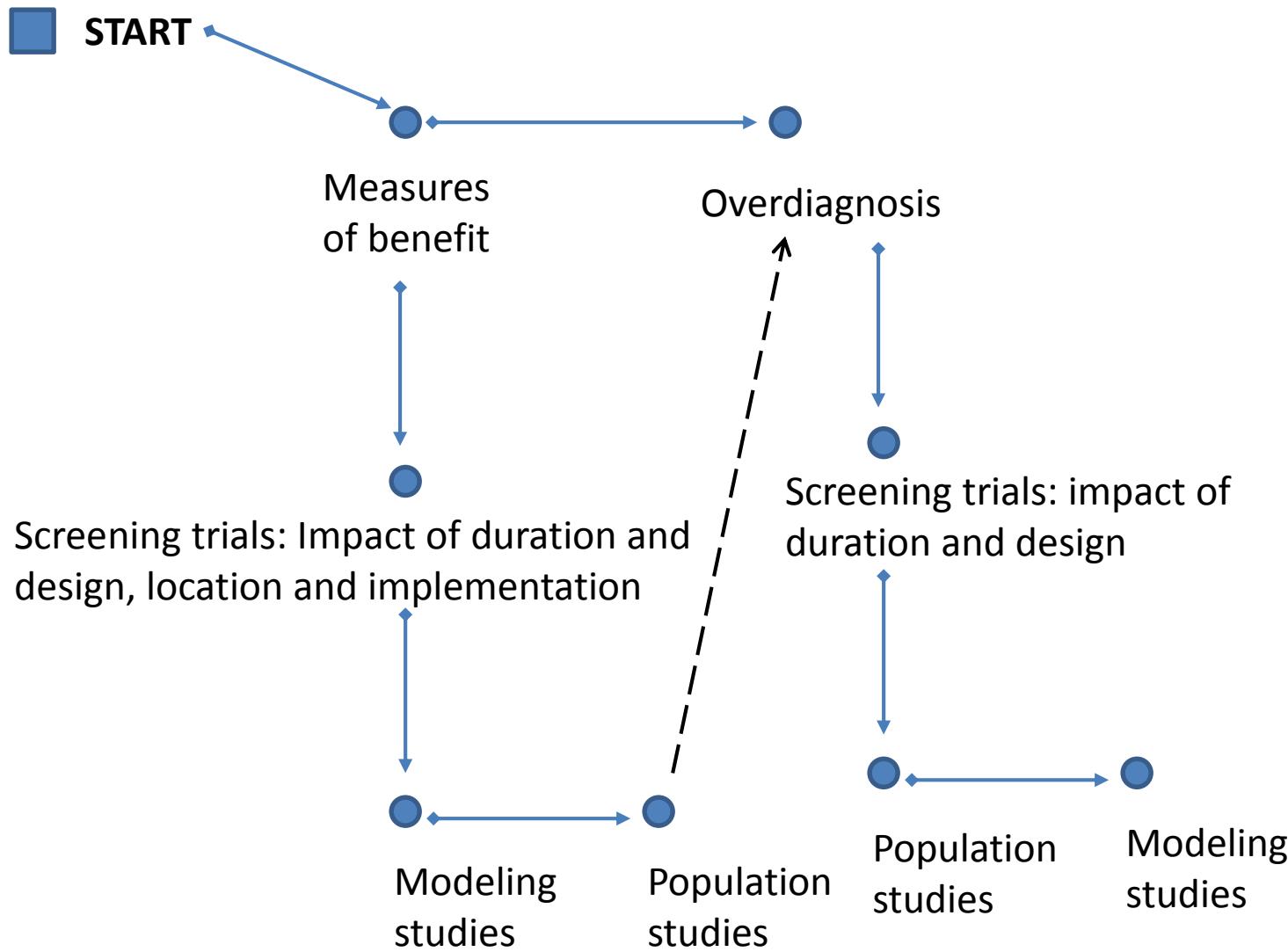
The NEW ENGLAND
JOURNAL of MEDICINE

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

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

5

Recap



WELL | Tara Parker-Pope

Mammogram's Role as Savior Is Tested

Has the power of the mammogram been oversold?

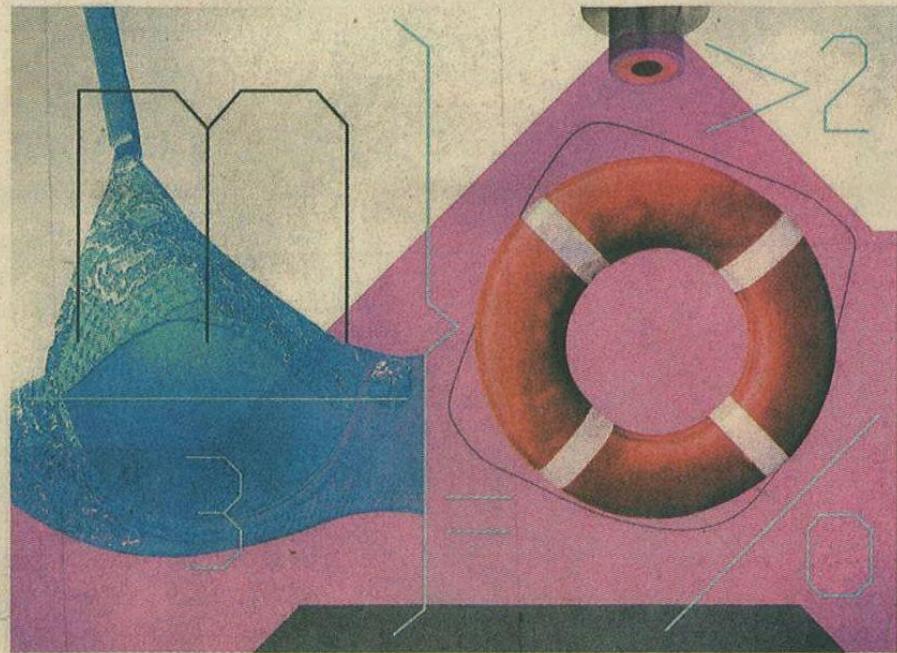
At a time when medical experts are rethinking screening guidelines for prostate and cervical cancer, many doctors say it's also time to set the record straight about mammography screening for breast cancer. While most agree that mammograms have a place in women's health care, many doctors say

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



STUART BRADFORD

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

Dr. Welch notes that clearly some women are helped by mammography screening, but the numbers are lower

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

Continued on Page 6

Vast Study Casts Doubts on Value of Mammograms

By GINA KOLATA FEB. 11, 2014

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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



HEALTH CARE

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THE WALL STREET JOURNAL.

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Monday, September 15, 2014 | R1

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

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

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.

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%

Making the Call

“I’m happy to accept the most favorable randomized trial as an estimate of benefit—on the order of one man avoiding a prostate cancer death out of 1000 men aged 55 to 69 years screened over 10 years—and ignore the less favorable data. Simply knowing that the overdiagnosis harm is somewhere around 30 to 100 times the estimated benefit—and knowing what treatment and its complications entail—is enough for me. I don’t need anymore data. My value judgment is simple: It’s an awful deal.”

H. Gilbert Welch, MD, MPH

Assessing Mammography's Benefits and Harms

By Charlie Schmidt

Canadian Trial

Findings from one of the largest studies of mammography ever conducted reverberated around the world in February, after results showed that breast cancer death rates were unaffected by routine screening over 25 years of follow-up. Nearly 90,000 women aged 45–59 years were randomized either to mammography screening or no mammography, and their breast cancer deaths—numbering 505 and 500 respectively—were virtually identical, according to conclusions published in the *British Medical Journal*.

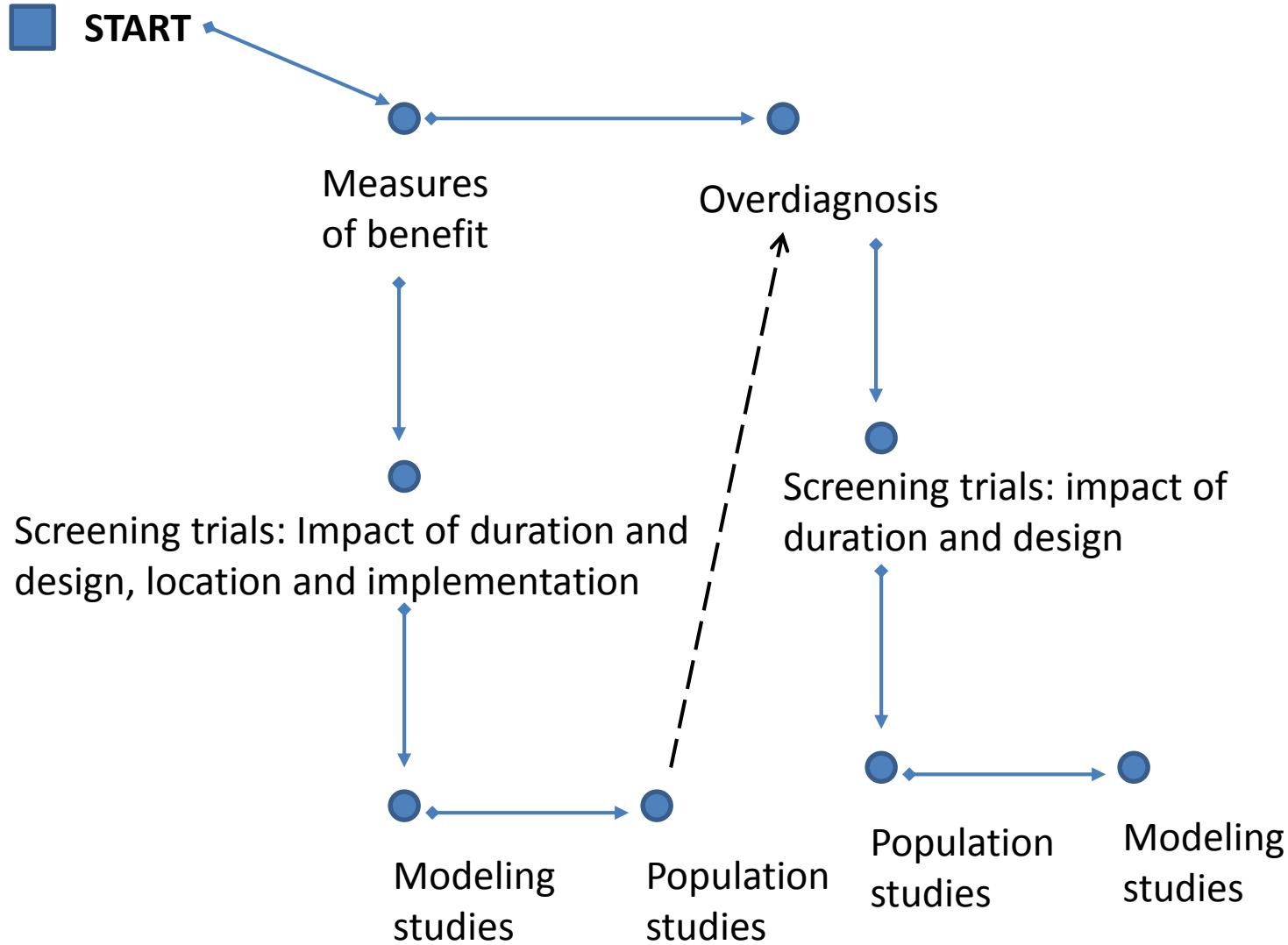
These latest findings fanned a growing controversy, as experts debate how to balance mammography's benefits with the associated risk of over-diagnosis and treatment of cancers that might never be life-threatening. In December 2013, H. Gilbert Welch, MD, MPH, a professor at Dartmouth's Geisel School of Medicine in Hanover, NH, published a review in *JAMA Internal Medicine* of nine randomized trials of mammography. Among 1,000 50-year-old American

Welch and Passow 20%

women of average risk who were screened annually for a decade, at most three (and perhaps none) will avoid death from cancer; up to 670 will have at least one false-positive diagnosis; and three to 14 will be needlessly treated, his results showed. During a plenary talk at the December 2013 San Antonio Breast Cancer Symposium, Welch added that mammography had made virtually no contribution to the 30% reduction in breast cancer mortality observed during the last two decades in the United States. Most of that reduction, he said, was due to improvements in treatment. Welch's conclusion has its detractors—during his talk at the conference, Robert Smith, PhD, an epidemiologist at the American Cancer Society, emphasized that screening benefits become apparent with follow-up of two decades or more.

Bleyer and Welch

Thank You!



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NCI

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- Eric Feuer



Cancer Intervention and
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