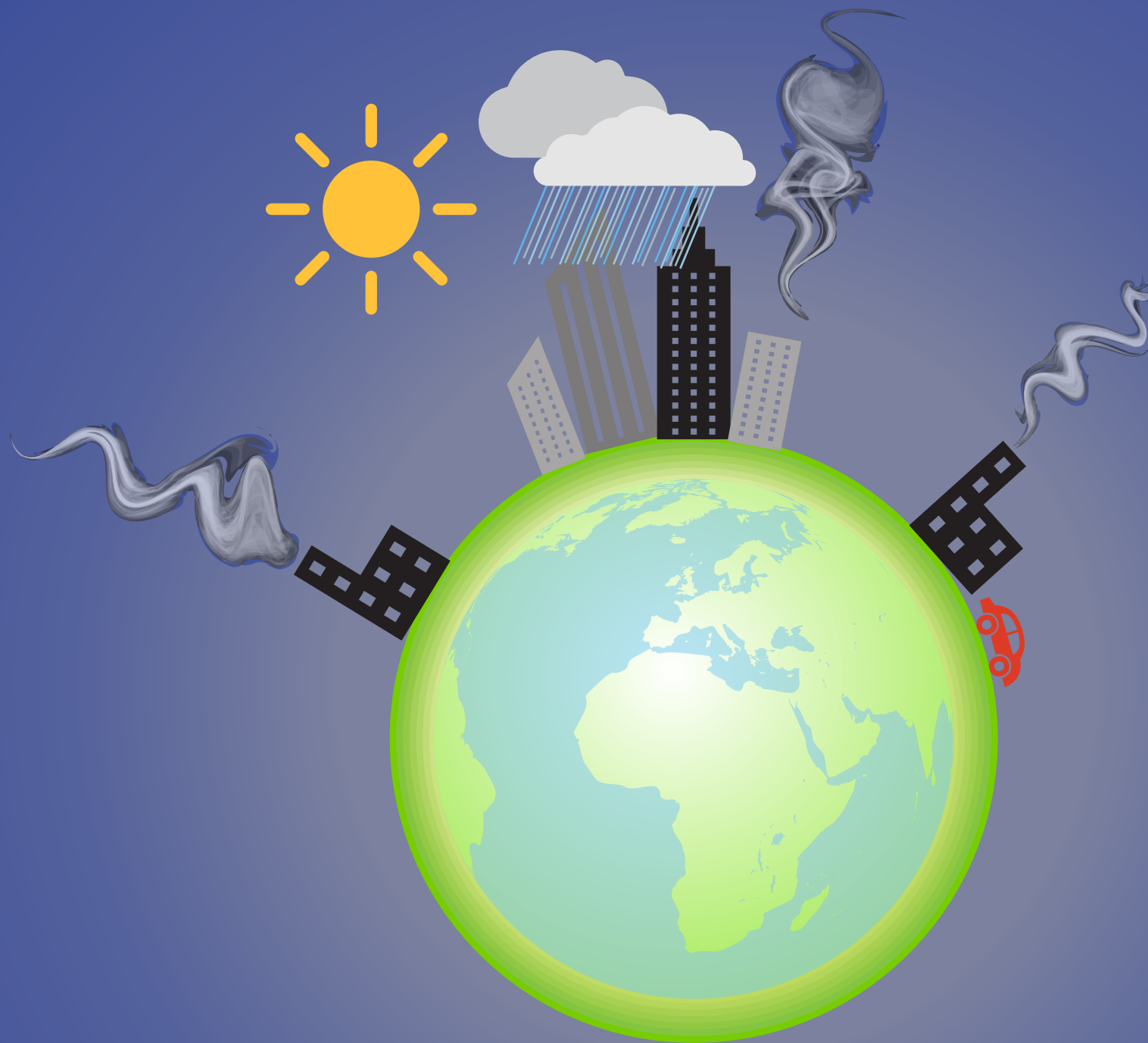




Screening Tests

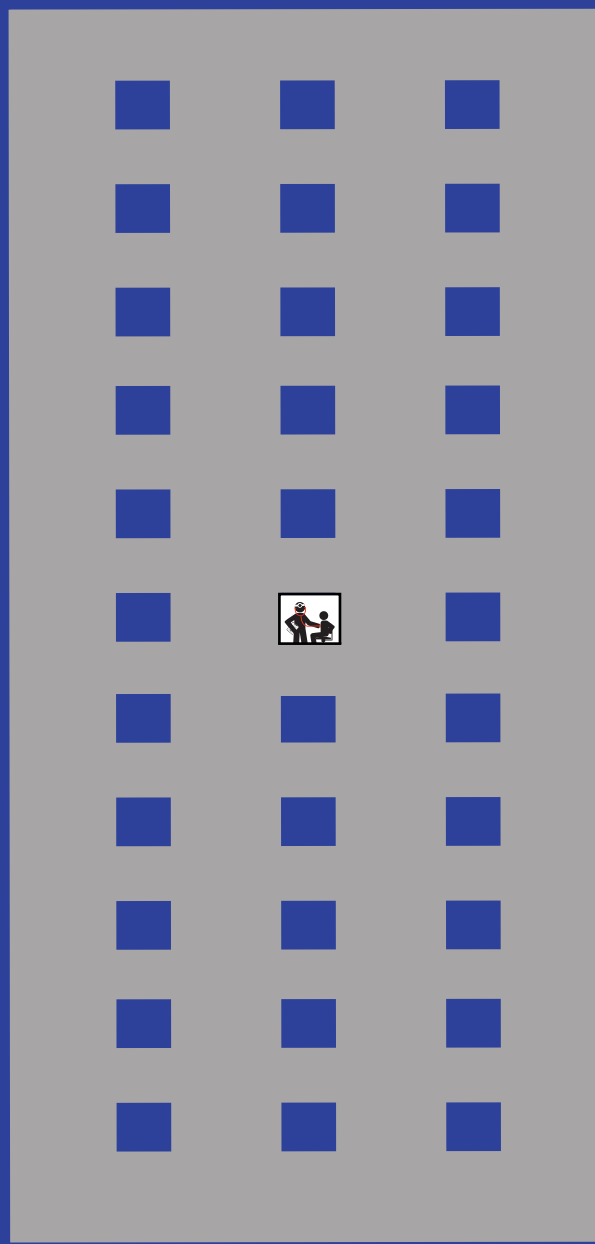
Martina Steurer, MD MAS
Thomas Newman, MD MPH

November 14th, 2019

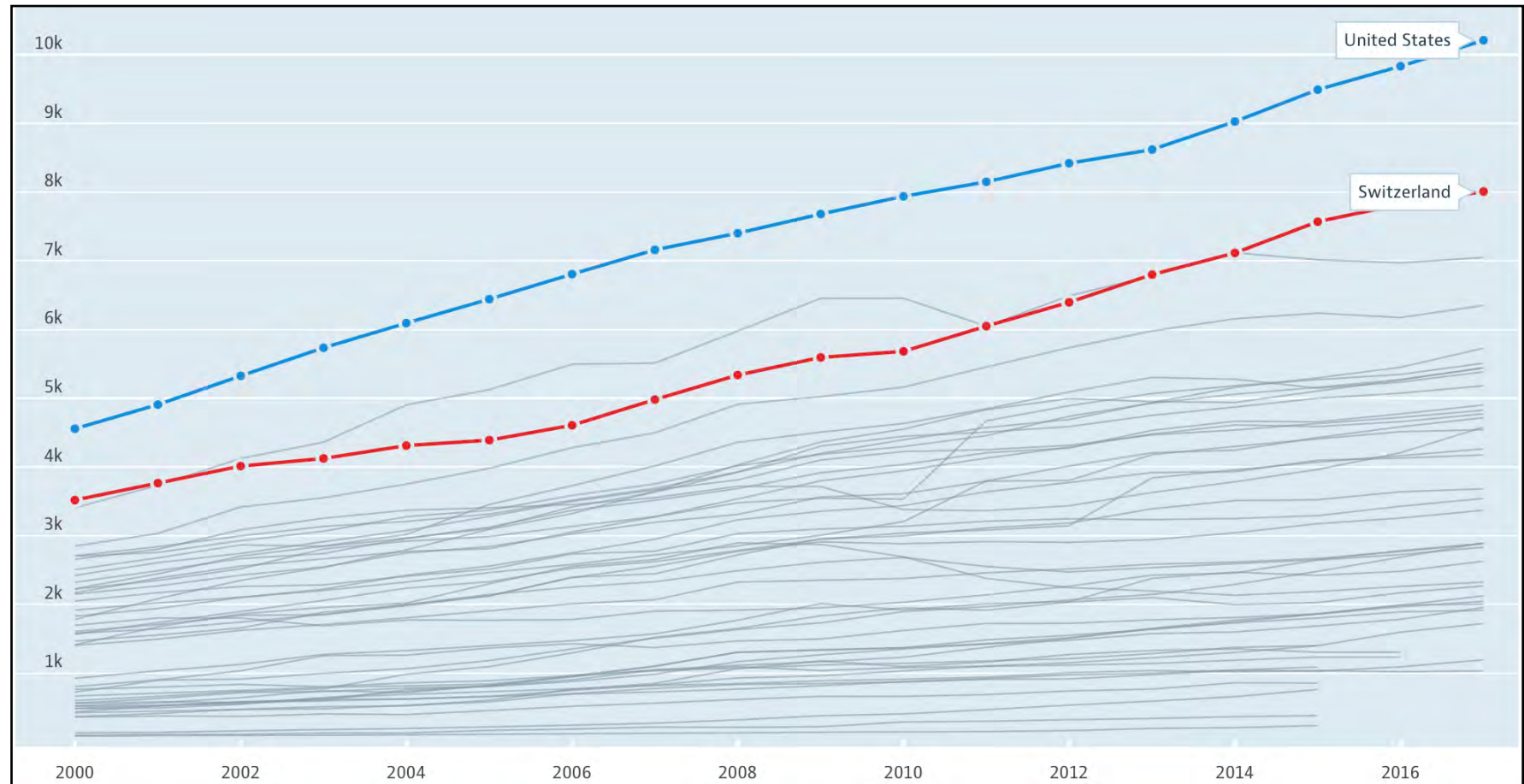


A WASTEFUL WORLD





Health care spending per capita



Source: OECD Health Data

Definition of screening

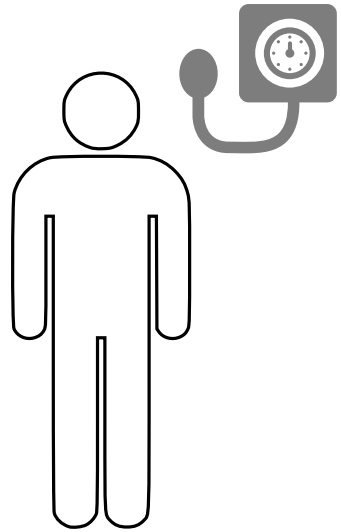
Common definition: testing to detect asymptomatic disease

Better definition*: application of a test to detect a potential disease or condition in people with no known signs or symptoms of that disease or condition.

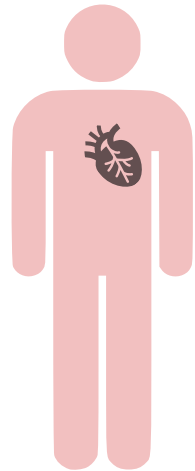
- Disease vs. condition
- Asymptomatic vs. no known signs or symptoms

*Common screening tests. David M. Eddy, editor. Philadelphia, PA: American College of Physicians, 1991

Spectrum of screening



risk factor



presymptomatic disease



unrecognized
symptomatic disease



recognized
symptomatic disease

more people recognized and treated
harder to demonstrate benefit
more potential for harm

fewer labeled and treated
easier to demonstrate benefit
less potential for harm

hypercholesterolemia

neonatal hypothyroidism

iron deficiency anemia

HIV

vision and hearing problems
in young children

prostate cancer

Harm from screening?



Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report

EXPERT PANEL ON INTEGRATED GUIDELINES FOR
CARDIOVASCULAR HEALTH AND RISK REDUCTION IN
CHILDREN AND ADOLESCENTS

ABBREVIATIONS

CVD—cardiovascular disease
NHLBI—National Heart, Lung, and Blood Institute
RCT—randomized controlled trial
PDAY—Pathobiological Determinants of Atherosclerosis in Youth
BP—blood pressure
HDL—high-density lipoprotein
DM—diabetes mellitus
CMT—carotid intima-media thickness
LDL—low-density lipoprotein
T1DM—type 1 diabetes mellitus
T2DM—type 2 diabetes mellitus
TC—total cholesterol
DGA—American Academy of Pediatrics
NCEP—National Cholesterol Education Program
DASH—Dietary Approaches to Stop Hypertension
CHILD—Cardiovascular Health Integrated Lifestyle Diet
FLP—fasting lipid profile
CDC—Centers for Disease Control and Prevention
AMA—American Medical Association
MCHB—Maternal and Child Health Bureau
FDA—Food and Drug Administration
AHA—American Heart Association

www.pediatrics.org/cgi/doi/10.1542/peds.2009-2107C
doi:10.1542/peds.2009-2107C
Accepted for publication Sep 8, 2011
Address correspondence to Janet M. de Jesus, MD, RD, 31
Center Dr, Building 31, Room 4A17, MSC 2480, Bethesda, MD
20892. E-mail: dejesusj@nhlbi.nih.gov

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Copyright © 2011 by the American Academy of Pediatrics
for Abbott Laboratories. Dr Daniels has served as a consultant
received funding/grant support for research from the National
Institutes of Health (NIH). Dr Gidding has received funding/grant
support for research from GlaxoSmithKline. Dr Gillman has
received funding/grant support for research from Mead
Johnson. Dr Gidding has received funding/grant support
from the Health Advisory Board, Child Development Council of
Franklin County, was a consultant to Early Head Start for Region
5B, has written for Village and taught classes through Garrison

(Continued on last page)

1. INTRODUCTION

Atherosclerotic cardiovascular disease (CVD) remains the leading cause of death in North Americans, but manifest disease in childhood and adolescence is rare. By contrast, risk factors and risk behaviors that accelerate the development of atherosclerosis begin in childhood, and there is increasing evidence that risk reduction delays progression toward clinical disease. In response, the former director of the National Heart, Lung, and Blood Institute (NHLBI), Dr Elizabeth Nabel, initiated development of cardiovascular health guidelines for pediatric care providers based on a formal evidence review of the science with an integrated format addressing all the major cardiovascular risk factors simultaneously. An expert panel was appointed to develop the guidelines in the fall of 2006.

The goal of the expert panel was to develop comprehensive evidence-based guidelines that address the known risk factors for CVD (Table 1-1) to assist all primary pediatric care providers in both the promotion of cardiovascular health and the identification and management of specific risk factors from infancy into young adult life. An innovative approach was needed, because a focus on cardiovascular risk reduction in children and adolescents addresses a disease process (atherosclerosis) in which the clinical end point of manifest CVD is remote. The prevention of risk-factor development (primordial prevention) and the prevention of future CVD by effective management of identified risk factors (primary prevention).

The evidence review also required an innovative approach. Most systematic evidence reviews include 1 or at most, a small number of finite questions that address the impact of specific interventions on specific health outcomes, and a rigorous literature review often results in only a handful of in-scope articles for inclusion. Typically, evidence is limited to randomized controlled trials (RCTs), systematic reviews, and meta-analyses published over a defined time period. There is a defined format for abstracting studies, grading the evidence, and presenting of results. The results of the review lead to the conclusions, independent of interpretation.

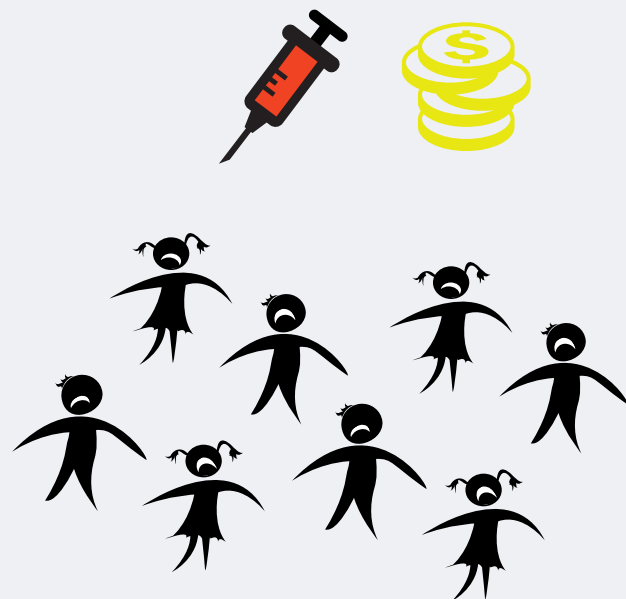
By contrast, given the scope of the charge to the expert panel, this evidence review needed to address a broad array of questions concerning the development, progression, and management of multiple risk factors extending from birth through 21 years of age, including studies with follow-up into later adult life. The time frame extended back to 1985, ~5 years before the review for the last NHLBI guideline addressing lipids in children published in 1992.¹ This evidence is largely available in the form of epidemiologic observational studies

Harm from screening:

Lipid screening in childhood



harm to those not
tested ?

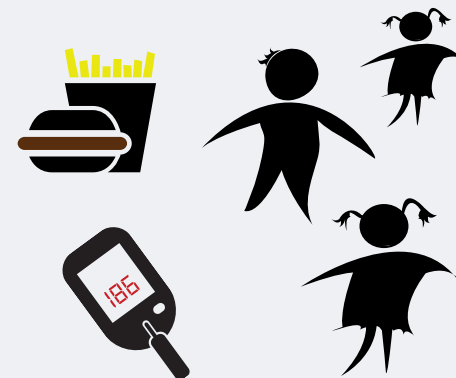


harm to all tested
cost
discomfort/pain

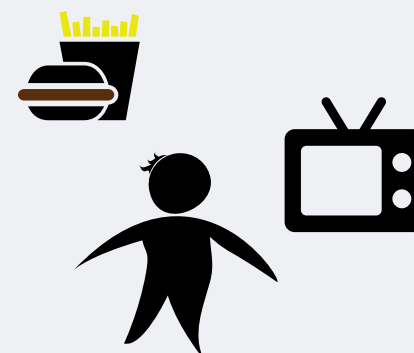
+ result



- result



harm to those with
positive results
follow up testing
harmful treatment
unnecessary treatment



harm to those with
negative results
inappropriate reassurance
leading to delay in
diagnosis or unhealthy
decisions

Harm from screening

Editorial | October 2016

LESS IS MORE

Lipid Screening in Children Low-Value Care

Thomas B. Newman, MD, MPH^{1,2}; Alan R. Schroeder, MD³; Mark J. Pletcher, MD, MPH^{2,4}

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JAMA Intern Med. 2016;176(10):1437-1438. doi:10.1001/jamainternmed.2016.5114.



Harm from screening ?

**THERE'S NO
PRENATAL
TEST FOR
AWESOME**



Excessive screening?

Nearly every body part susceptible to cancer now has an advocacy group, politician or athlete with a public awareness campaign to promote routine screening tests — even though it is well established that many of these exams offer little benefit for the general public.

The New York Times

FORTY YEARS' WAR; In Push for Cancer Screening, Limited Benefits

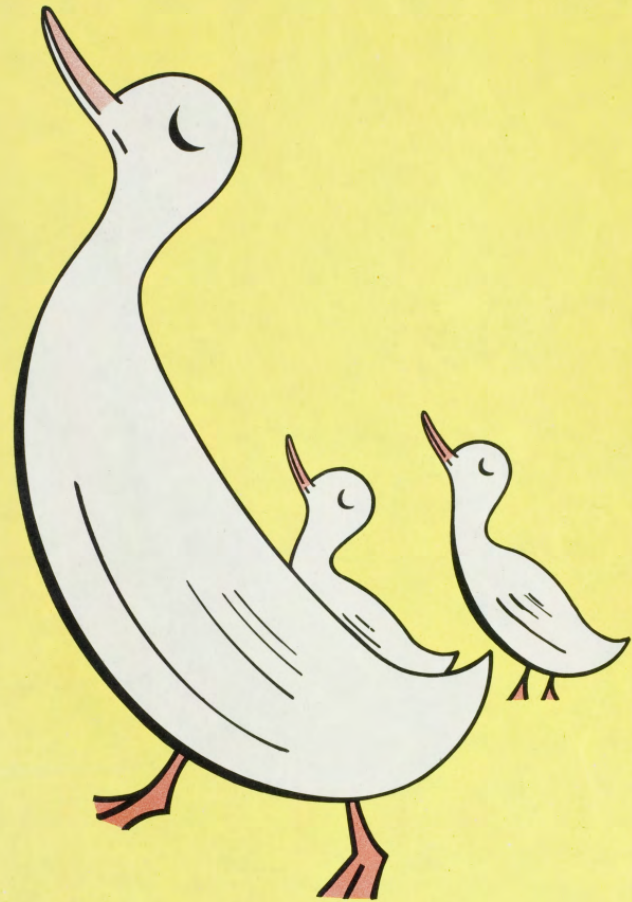
By NATASHA SINGER

Published: July 17, 2009

Forces behind excessive screening

- ◆ Companies selling instruments to do the test
- ◆ Companies selling the test itself
- ◆ Companies selling products to treat the condition
- ◆ Clinicians who treat the condition
- ◆ Politicians who are (or want to appear) sympathetic
- ◆ Disease research and advocacy groups
- ◆ Academics who study the condition
- ◆ Clinicians doing or interpreting the test
- ◆ Managed care organizations
- ◆ The public

CONFIDENCE

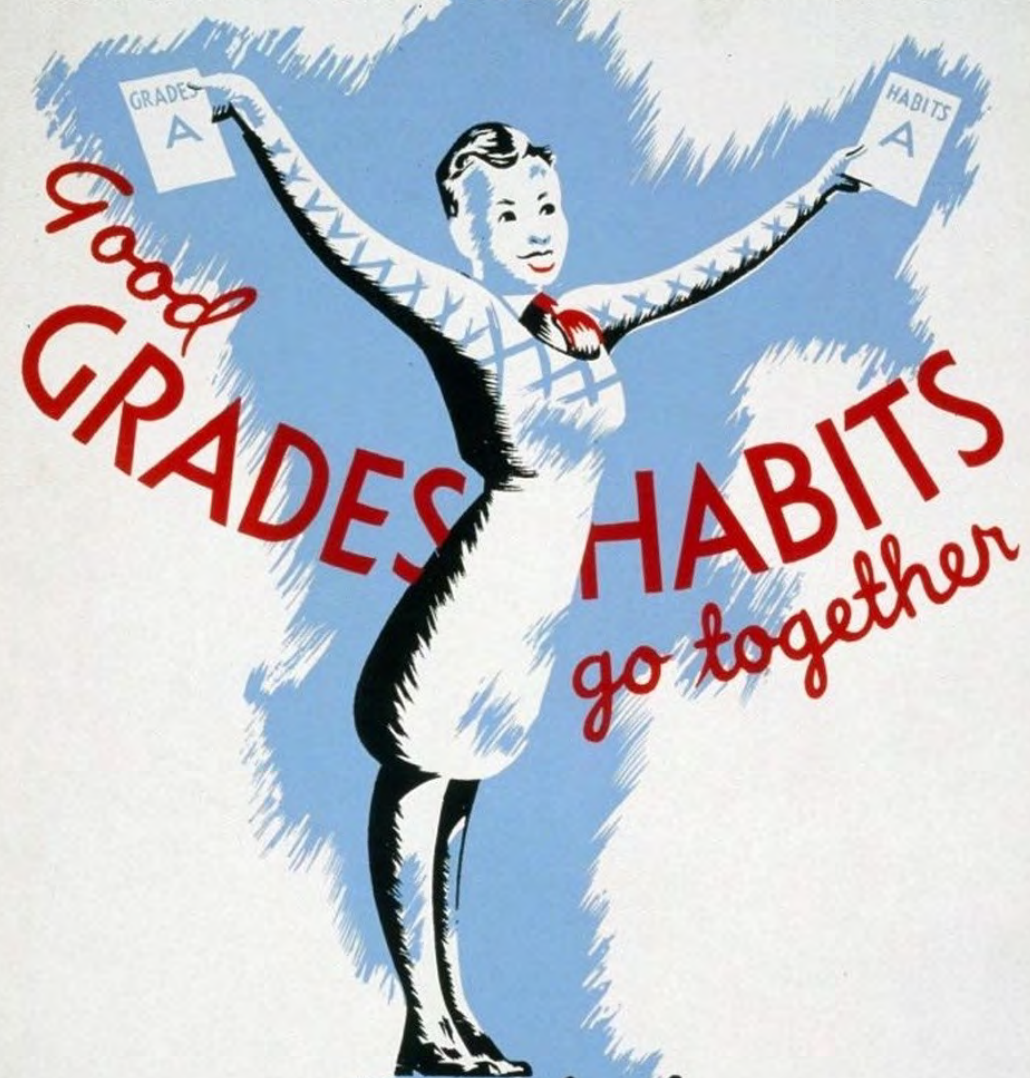


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LA ROCHE-POSAY
LABORATOIRE DERMATOLOGIQUE

**IF YOU CARE FOR SOMEBODY,
CHECK THEIR BEAUTY SPOTS.**





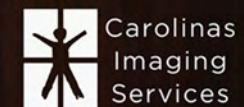
Remember to ask your doctor to check your neck for thyroid cancer.  Light of Life Foundation
checkyourneck.com



Concerned about lung cancer?

Lung cancer is by far the leading cause of cancer death among both men and women, and nearly half of all cases are in the most advanced stage at diagnosis. Fortunately, Carolinas Imaging Services now offers a lung cancer screening that can detect cancer before it becomes symptomatic. The National Comprehensive Cancer Network recommends the screening for individuals 55+ with a history of heavy smoking (at least 30 pack-years), and individuals 50+ with a 20-pack-year history coupled with another risk factor, such as asbestos exposure. The cost is only \$250—well worth the peace of mind that comes with finally having answers.

Schedule your lung cancer screening today at 704.442.4390.



What's key
to surviving
breast cancer?

You

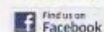
GET SCREENED NOW



LESS TALK. MORE ACTION.

Early detection saves lives. **The 5-year survival rate for breast cancer when caught early is 98%. When it's not? 23%.**

Visit komen.org/getscreened or scan this code with a QR reader app on your smart phone to start making a difference.

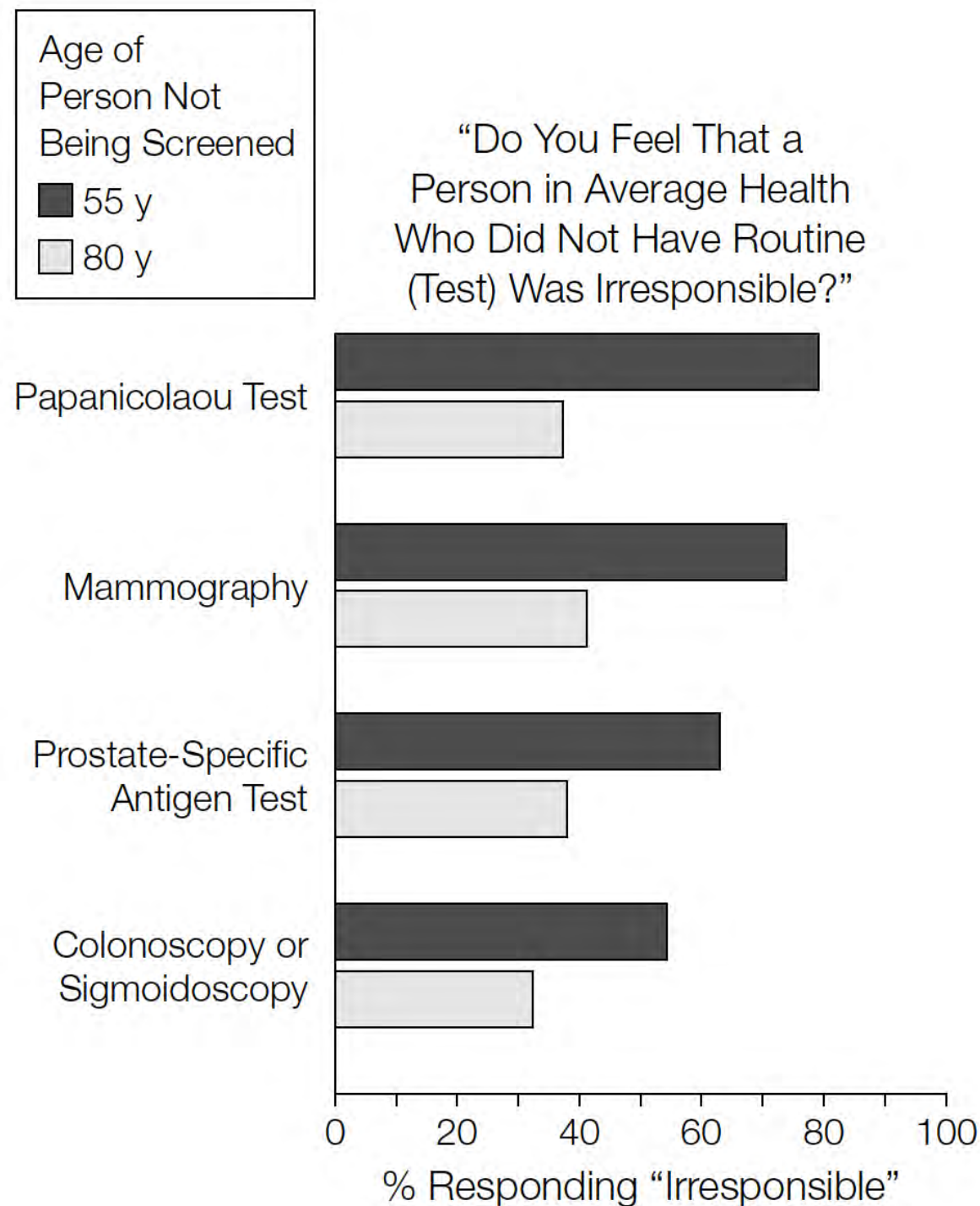


©2011 Susan G. Komen for the Cure™

**susan g.
komen.** 

Screening as an obligation ?

Enthusiasm for Cancer Screening in the US, Schwartz LM et al, JAMA 2004



Too Many Older Patients Get Cancer Screenings



Molly Ferguson

By Liz Szabo, Kaiser Health News

Dec. 19, 2017

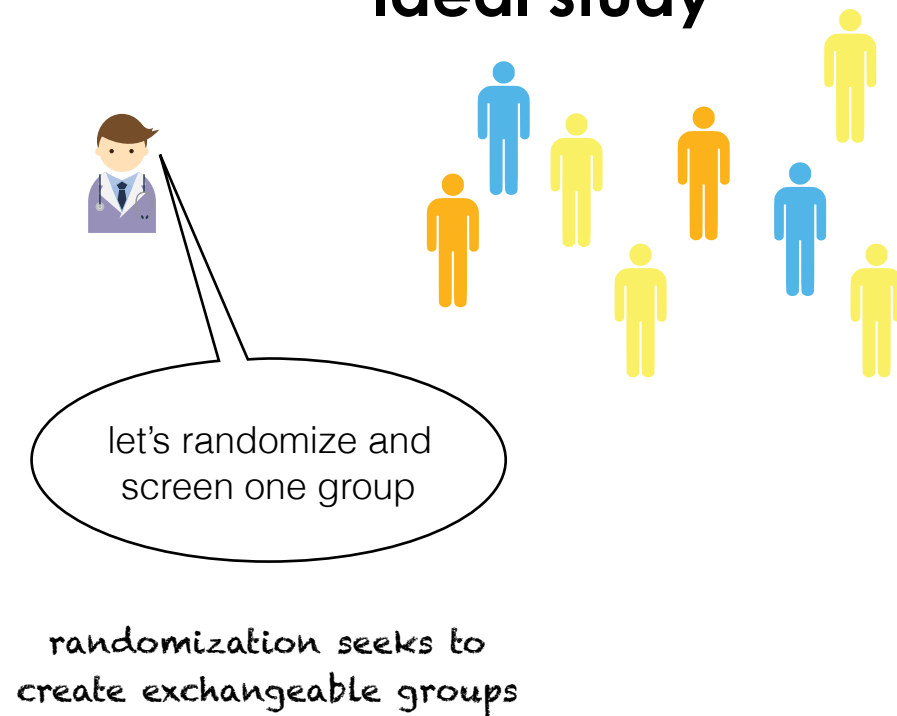


Elena Altemus is 89 and has dementia. She often forgets her children's names, and sometimes can't recall whether she lives in Maryland or Italy.

Mrs. Altemus, who entered a nursing home in November, was screened for breast cancer this summer. "If the screening is not too invasive, why not?" asked her daughter, Dorothy Altemus. "I want her to have the best quality of life possible."

Evaluating studies of screening

Ideal study

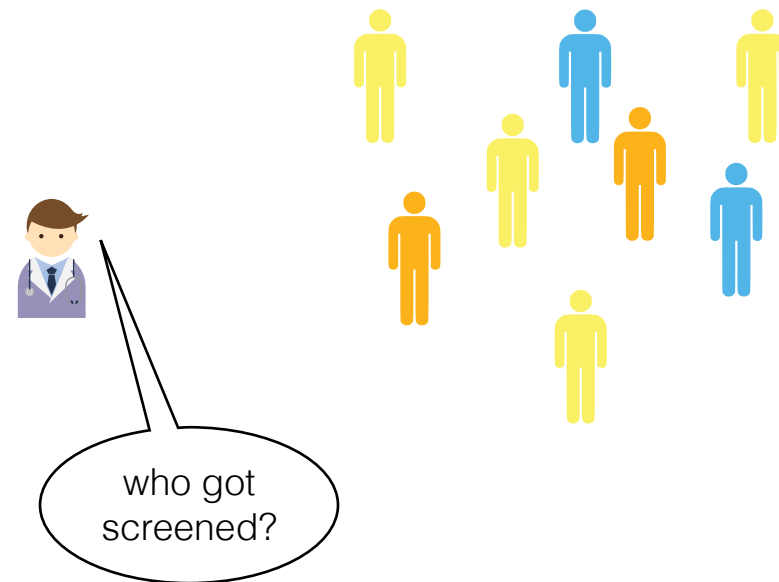


not screened

screened

compare mortality of ENTIRE screened group and ENTIRE NOT screened group

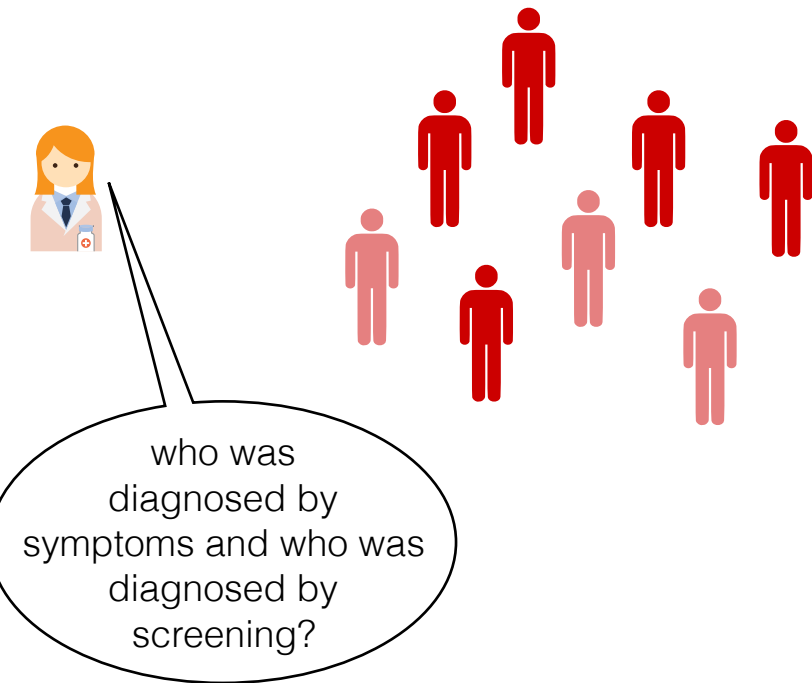
Observational study



not screened

screened

compare mortality between those screened and those not screened

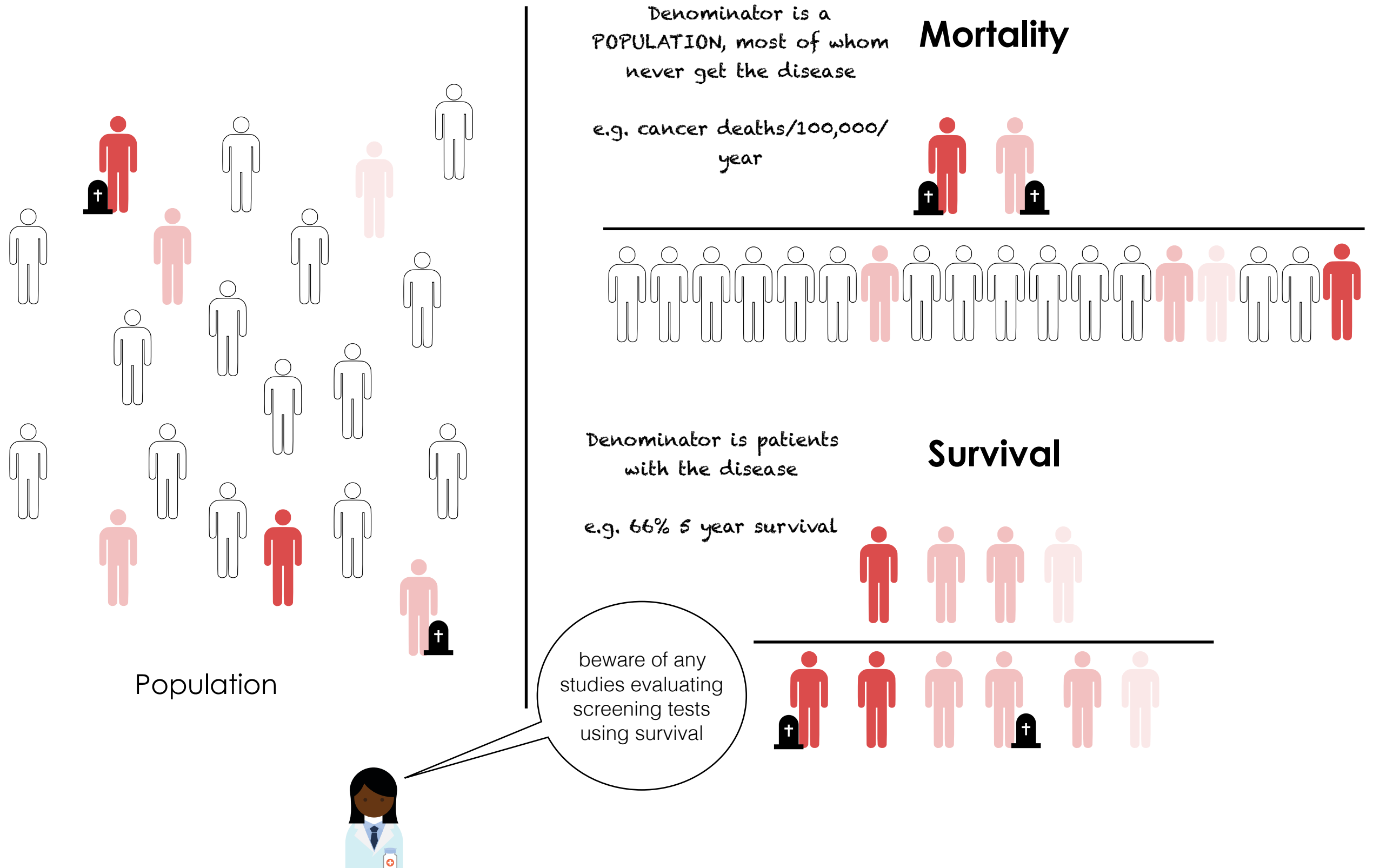


symptoms

screened

compare mortality between those diagnosed by screening and those diagnosed by symptoms

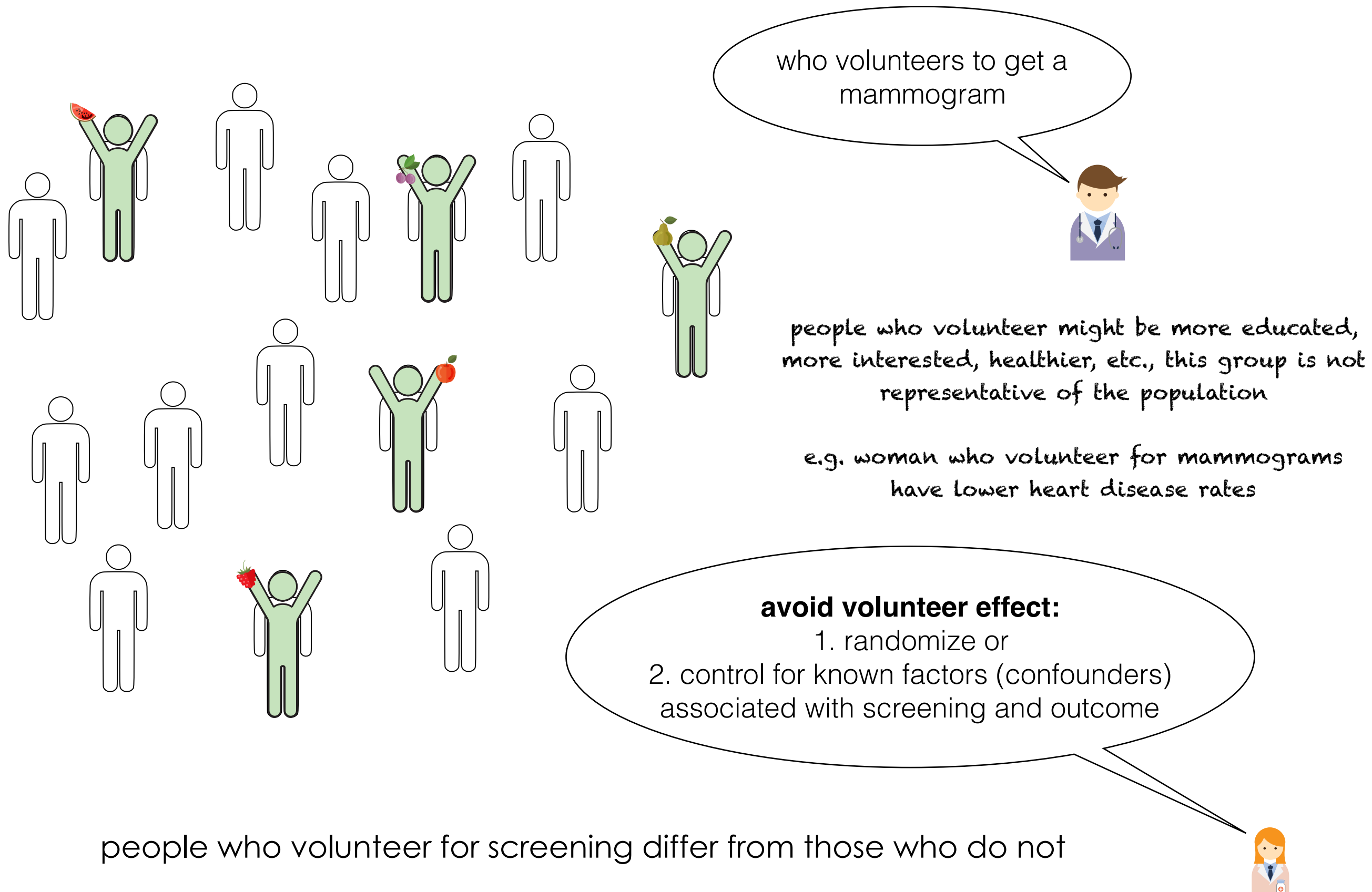
Mortality versus Survival



Possible Biases in Observational Studies of Screening Test

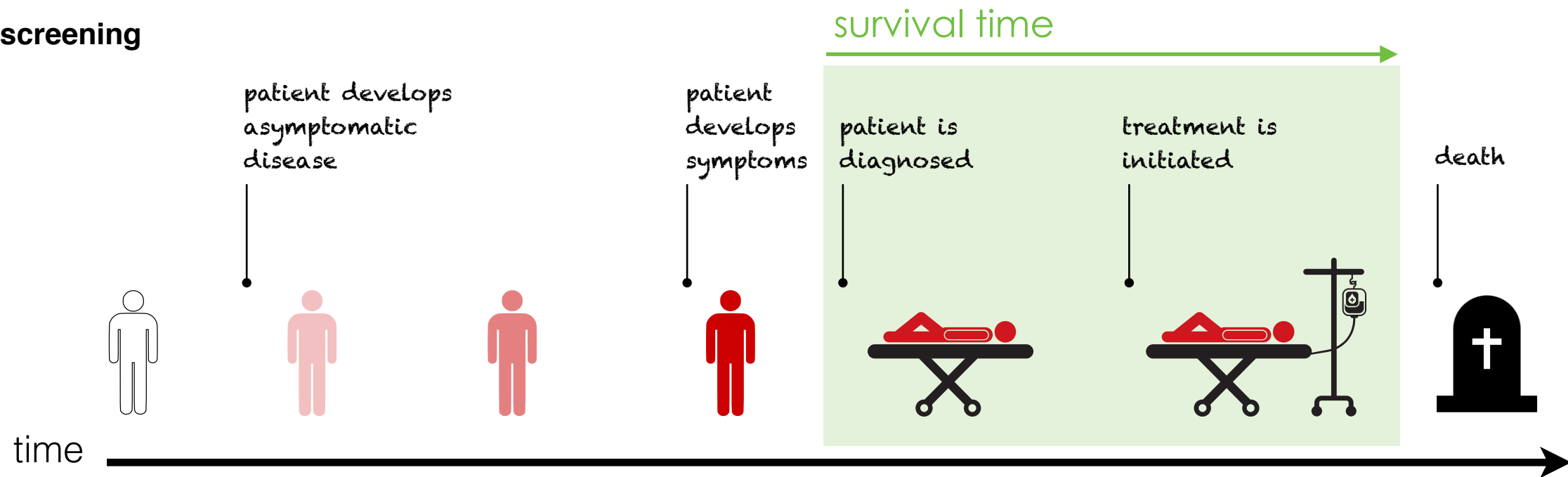
- ◆ Volunteer bias
- ◆ Lead time bias
- ◆ Length time bias
- ◆ Stage migration bias
- ◆ Pseudodisease

Volunteer Effect

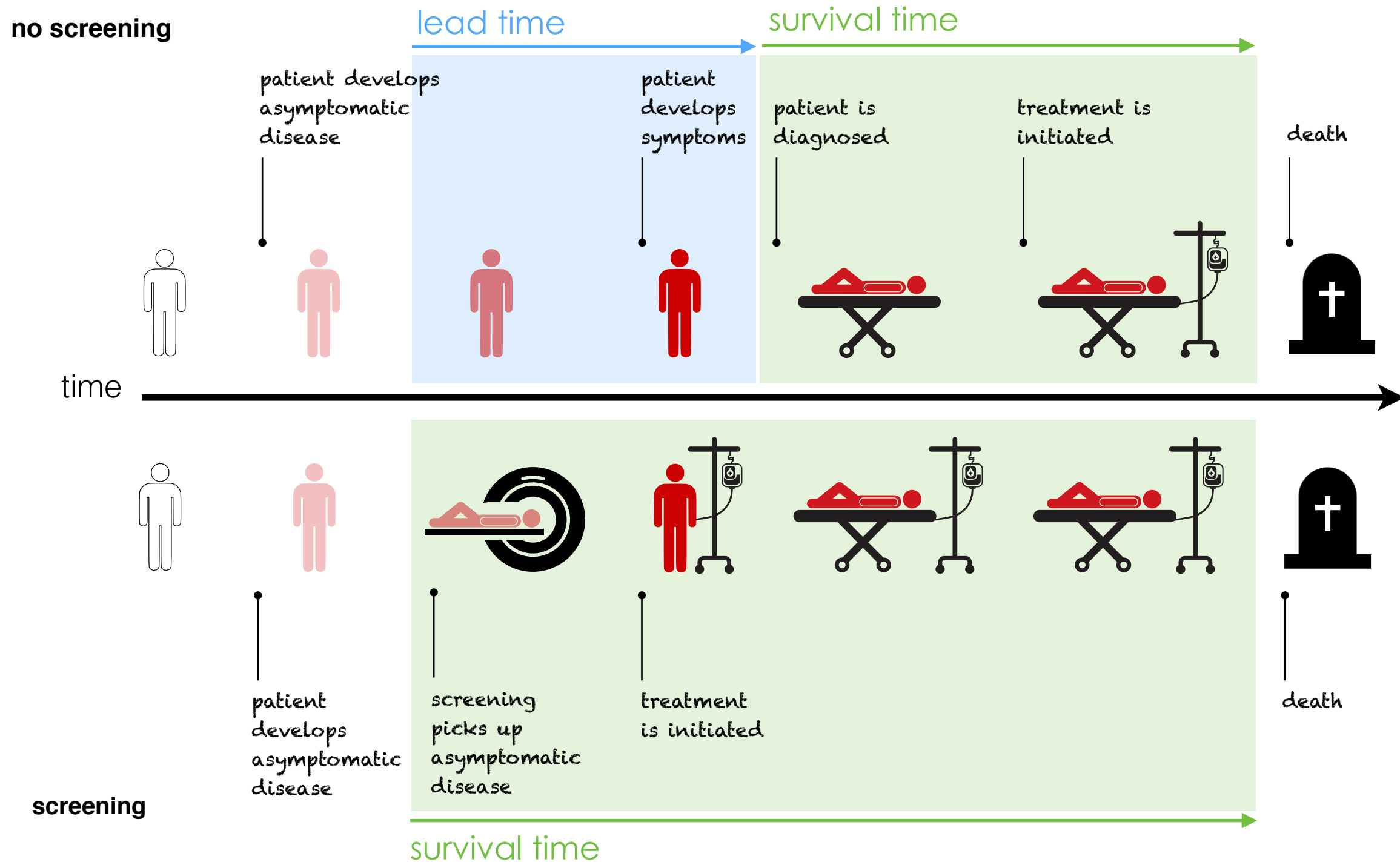


Lead Time Bias

no screening

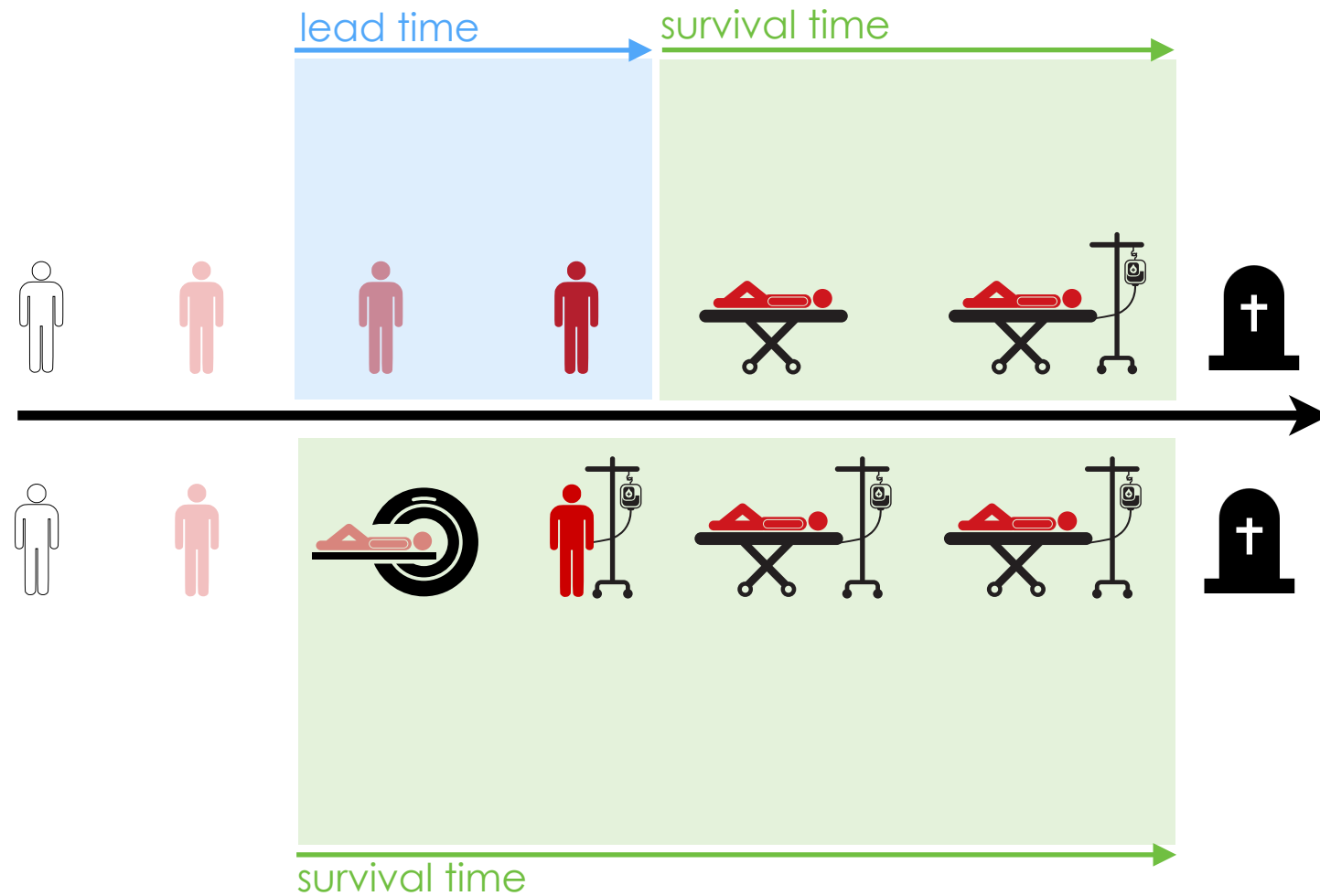


Lead Time Bias



Screening identifies disease during a latent period before it becomes symptomatic. If survival is measured from time of diagnosis, screening will always improve survival even if there is no benefit of early diagnosis

Lead Time Bias



lead time bias is only present when survival from diagnosis compared between diseased persons

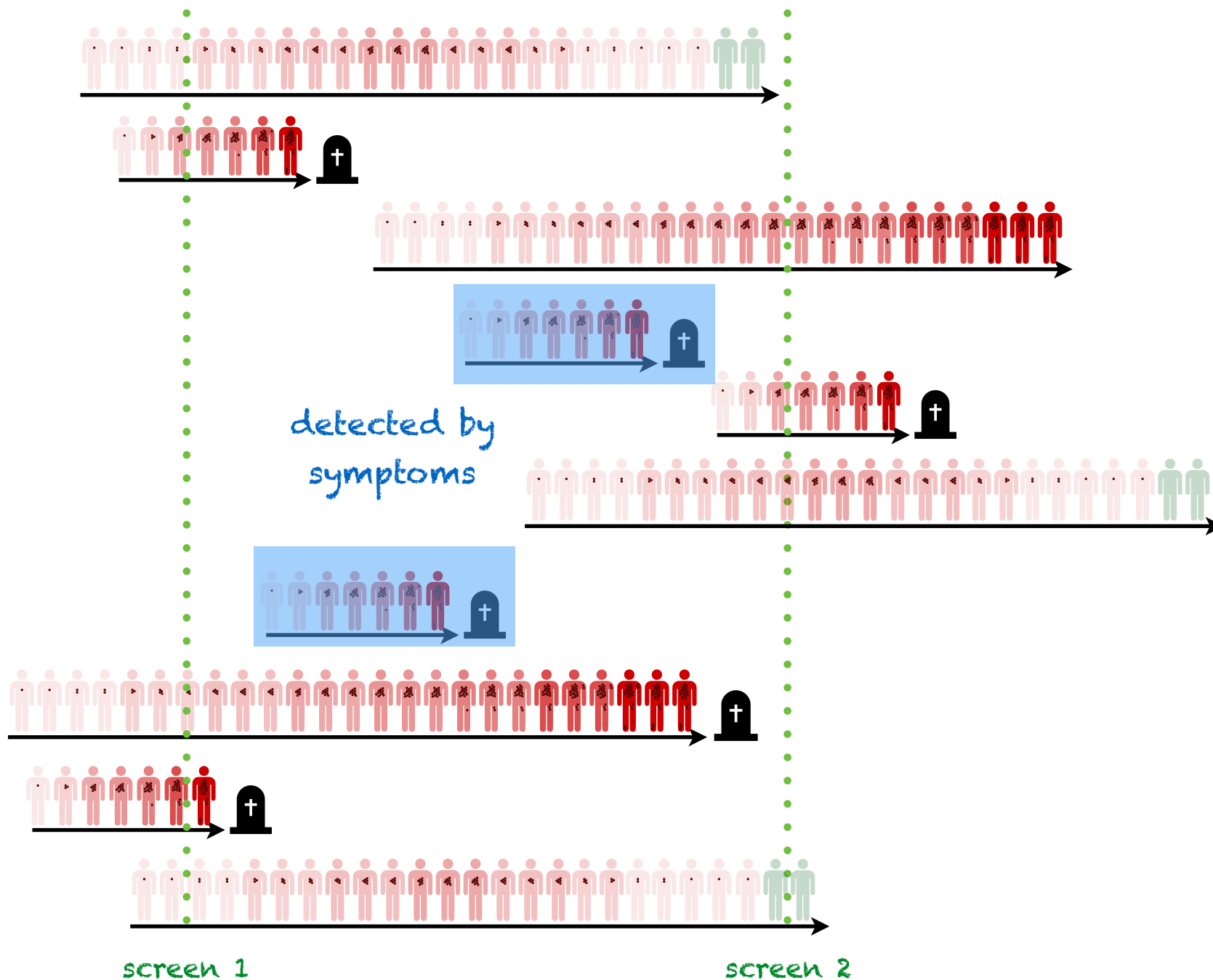
- screened vs. not screened
- diagnosed by screening vs. by symptoms
- diagnosed at different stages

avoid lead time bias

1. measure mortality, not survival
2. count from date of randomization



Length Time Bias



Prevalence = incidence x duration

Slower growing tumors have greater duration in the pre-symptomatic phase, therefore greater prevalence

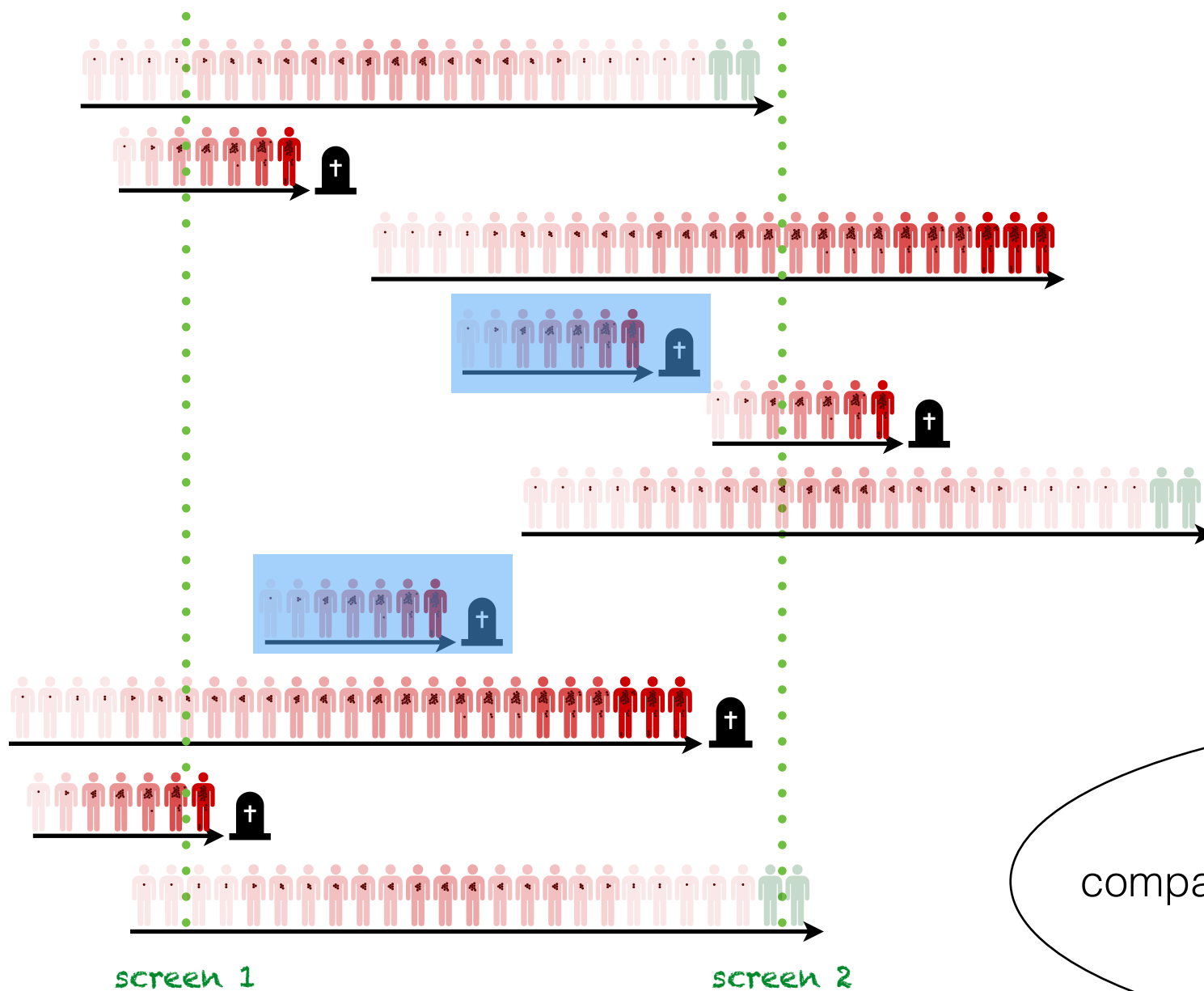
Screening picks up *prevalent* cases, which therefore will be disproportionately slower growing

Screen 1 and **screen 2** detect a total of 8 tumors: 5/8 have a good prognosis, 3/8 have a bad prognosis.

Symptoms lead to detection of 2 tumors - both of them had a bad prognosis.

Screening picks up prevalent disease, benign courses of disease have a greater prevalence

Length Time Bias



length bias is only present when survival from diagnosis is compared AND disease is heterogeneous

lead time bias usually present as well

avoiding length bias:
compare mortality in the ENTIRE screened group to the ENTIRE unscreened group





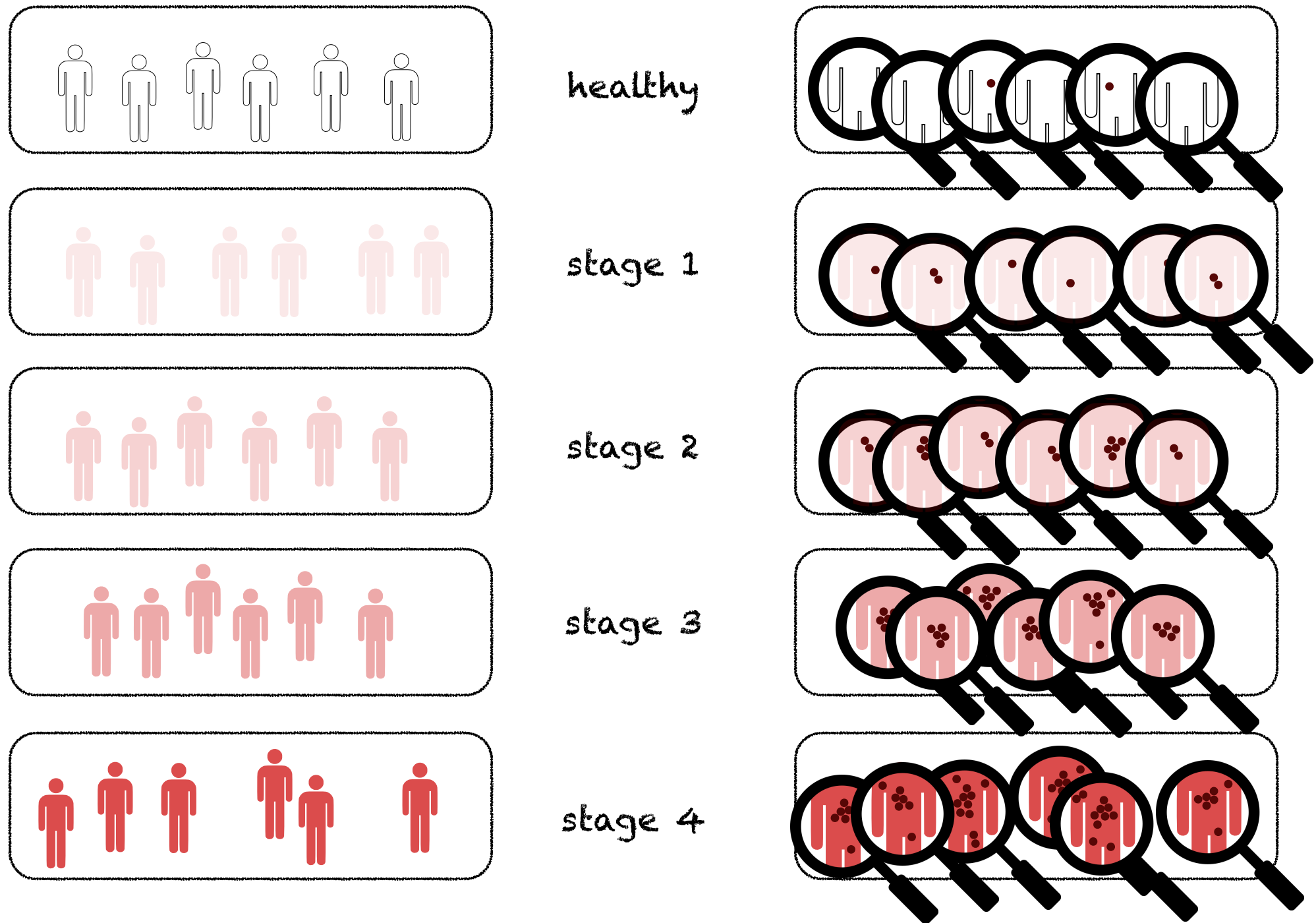
Will Rogers Phenomenon

The Will Rogers phenomenon: Stage migration and new diagnostic techniques as a source of misleading statistics for survival in cancer, Feinstein AR et al, NEJM 1985

When the Okies left Oklahoma and moved to California, they raised the average intelligence level in both states.

- Will Rogers

Stage Migration Bias



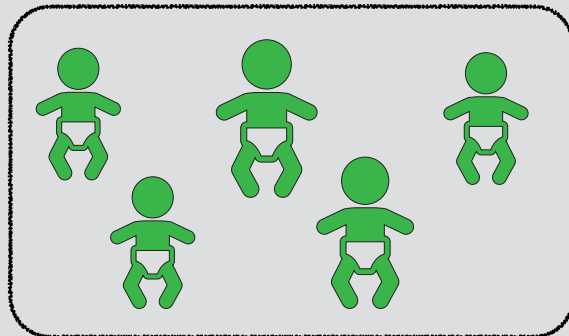
Newer tests classify people into more advanced stages. Stage specific survival improves.

Birth weight strata and Factor X

BW strata

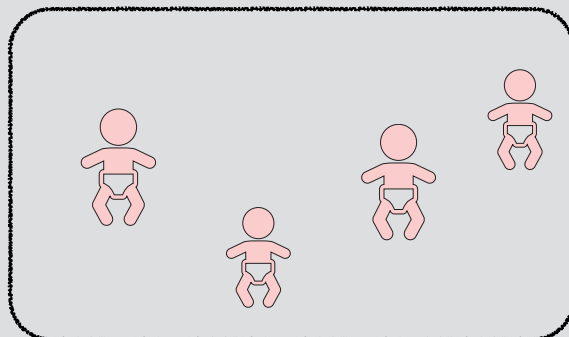
Normal birth weight

Factor X absent



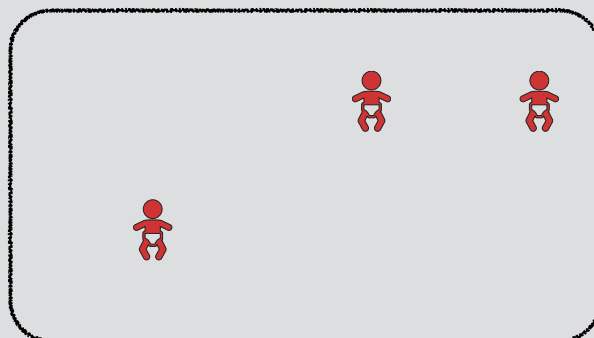
Mortality 1%

Low birth weight



Mortality 3%

Very low birth weight



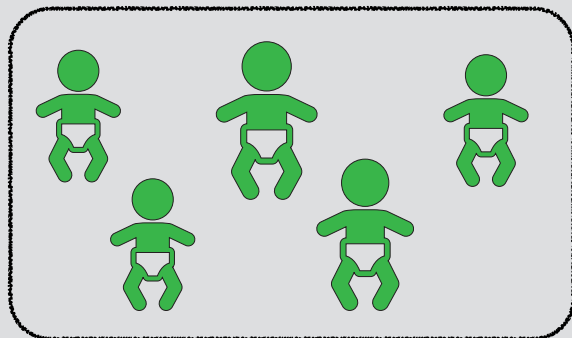
Mortality 5%

Birth weight strata and Factor X

BW strata

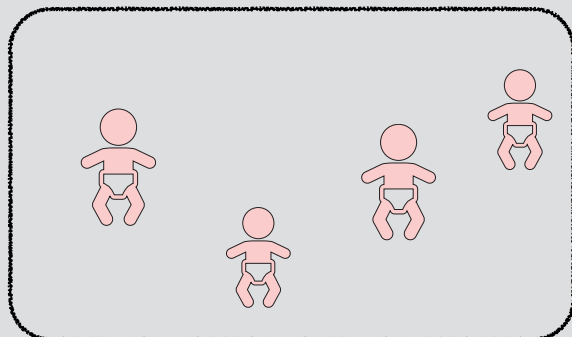
Normal birth weight

Factor X absent



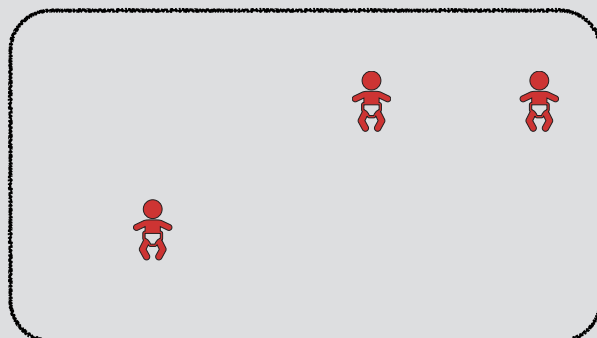
Mortality 1%

Low birth weight



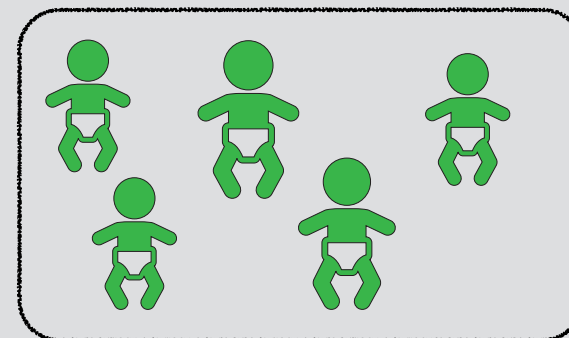
Mortality 3%

Very low birth weight

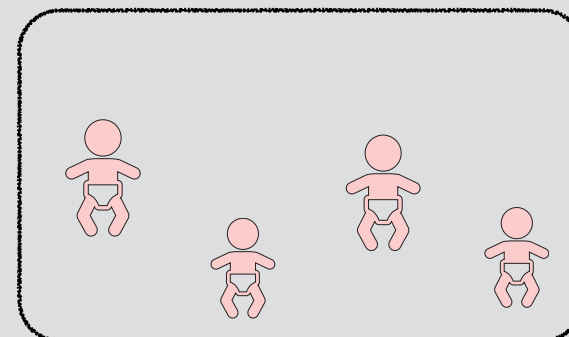


Mortality 5%

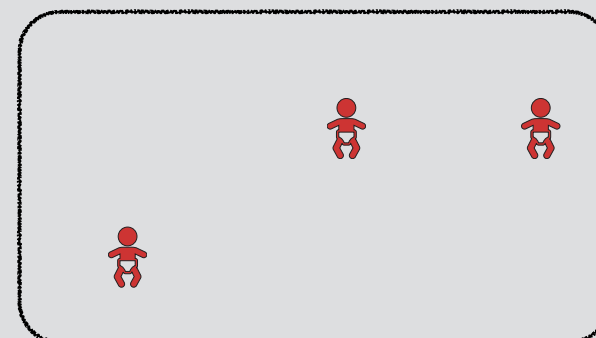
Factor X present



Mortality 0.5%



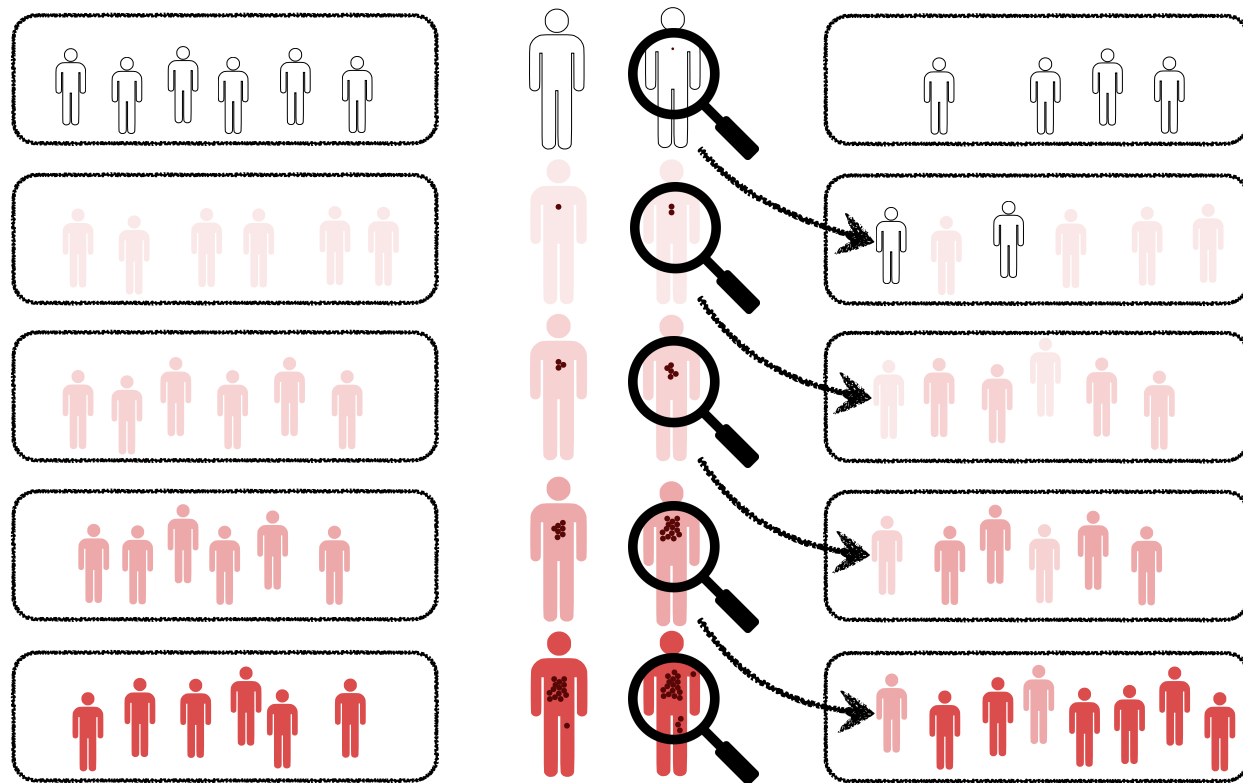
Mortality 2%



Mortality 4%

What happened? Is factor X good or bad?

Stage Migration Bias



the harder you look for disease, and the more advanced the technology the higher the prevalence, the higher the stage, and the better the (apparent) outcome for the stage

avoid stage migration bias

1. beware of stage migration in any stratified analysis: check OVERALL survival in screened vs. unscreened group
2. more generally do not stratify on factors distal in a causal pathway to the factor you wish to evaluate



Summary

Volunteer bias

people who volunteer for screening differ from those who do not

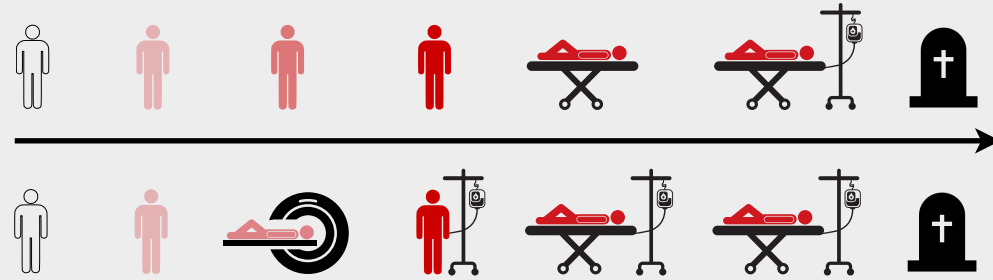


how to avoid

- * randomize people to screened and unscreened
- * otherwise, try to control for factors (confounders) associated with both screening and outcome

Lead time bias

screening identifies disease during a latent period before it becomes symptomatic - screening appears to improve survival

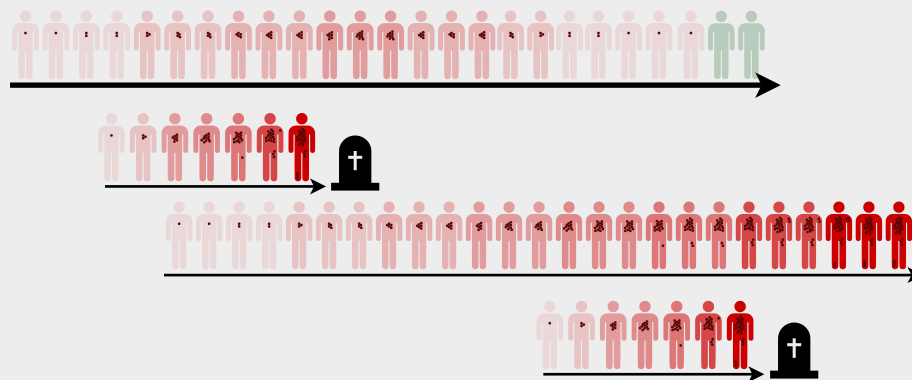


how to avoid

- * measure mortality and not survival
- * count from date of randomization

Length time bias

screening picks up prevalent disease and benign courses of disease have a greater prevalence

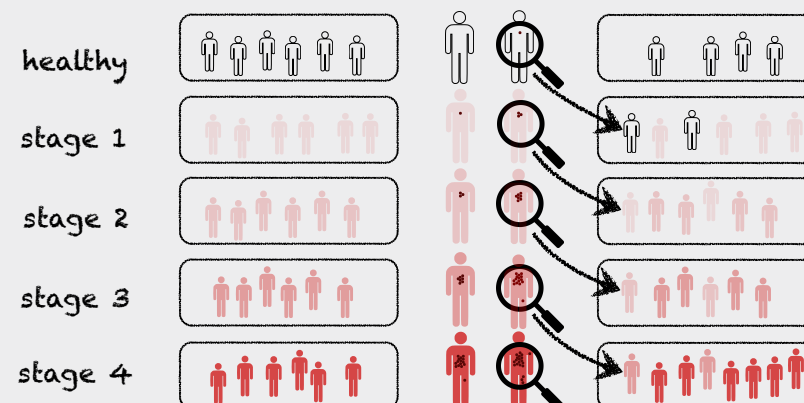


how to avoid

- * compare mortality in the ENTIRE screened group to the ENTIRE unscreened group

Stage migration bias

newer tests classify people into more advanced stages - stage specific survival improves.



how to avoid

- * beware of stage migration in any stratified analysis
- * check OVERALL survival in screened vs. unscreened group



Summary

Volunteer bias

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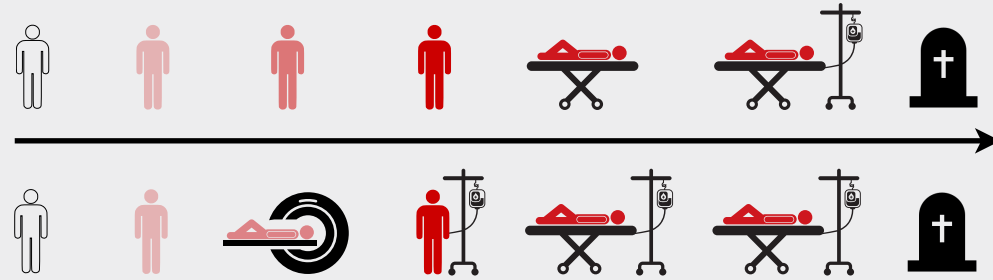


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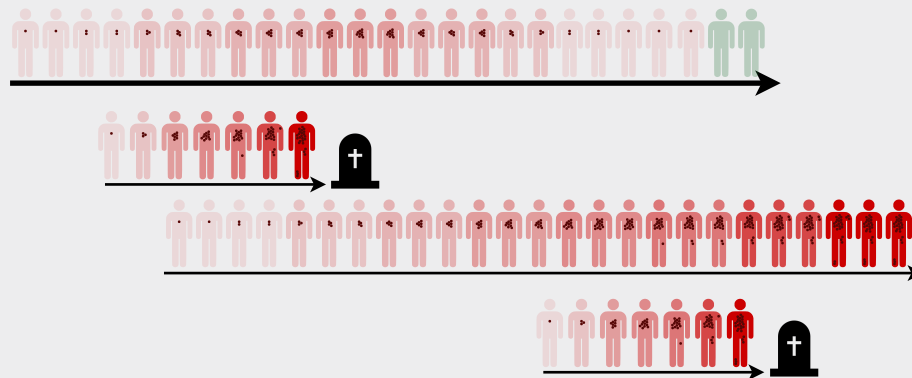


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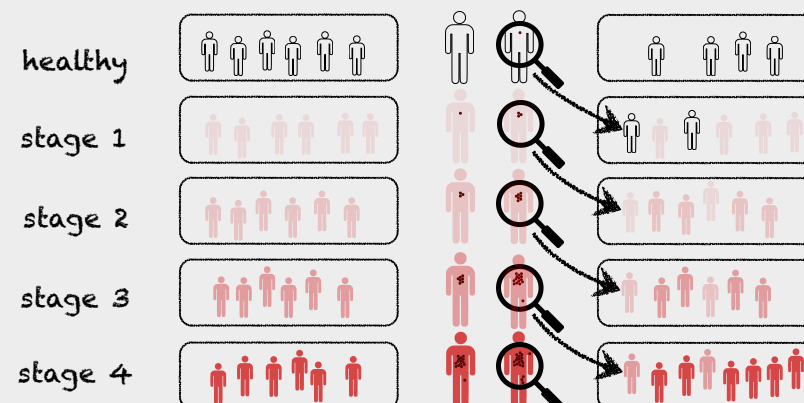


how to avoid

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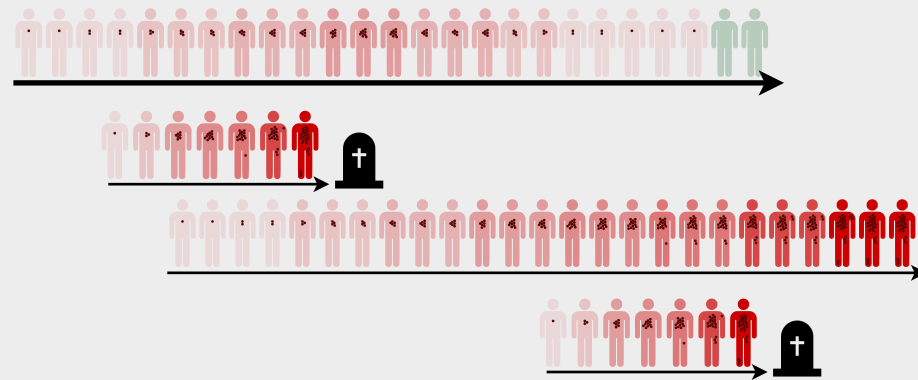
how to avoid

- * beware of stage migration in any stratified analysis
- * check OVERALL survival in screened vs. unscreened group

A special case of Length Bias!

Length bias

screening picks up prevalent disease and benign courses of disease have a greater prevalence



how to avoid

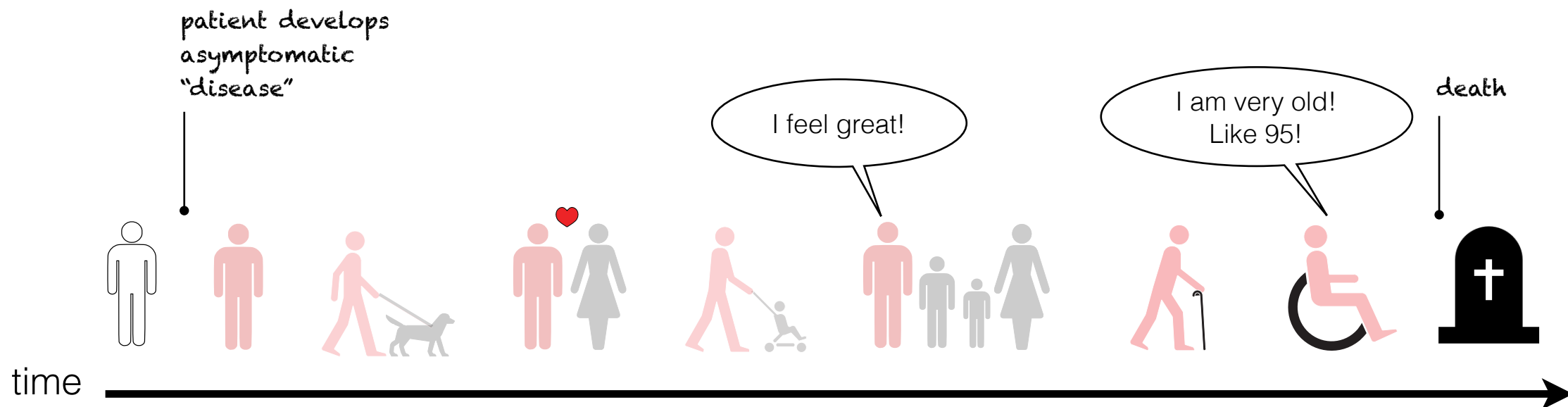
- * compare mortality in the ENTIRE screened group to the ENTIRE unscreened group

Pseudodisease or Overdiagnosis

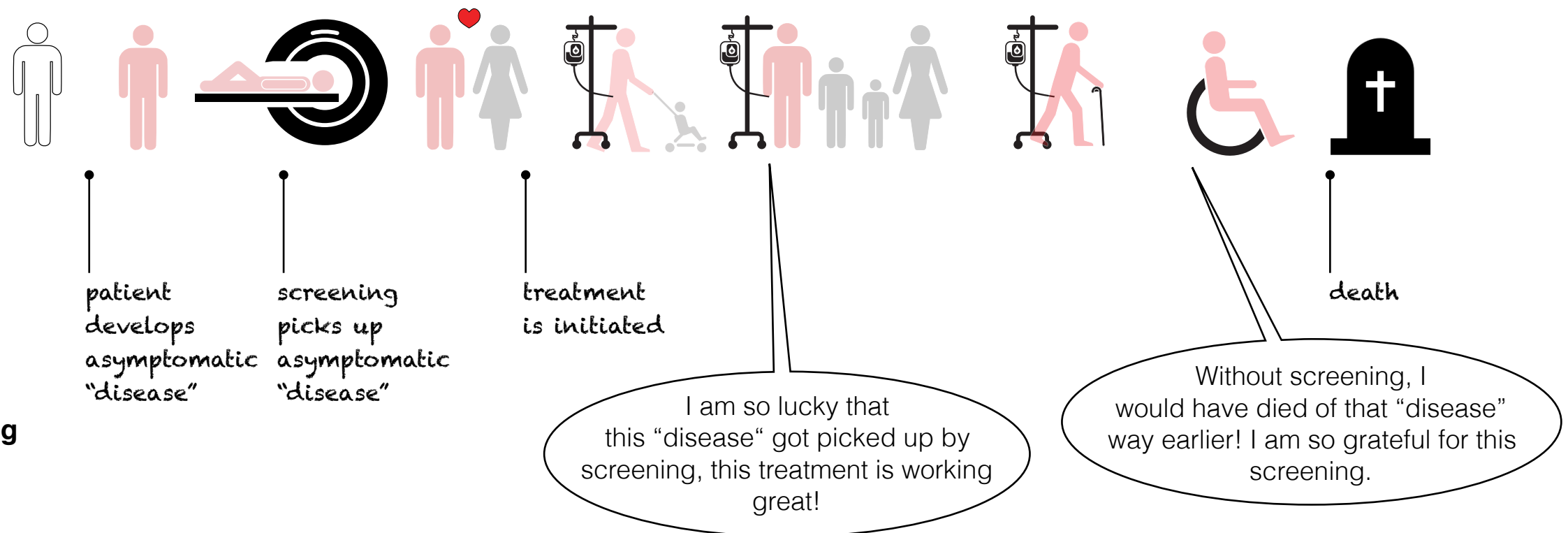
Overdiagnosis is sort of like length bias. That is, the disease would NEVER have become symptomatic if it had not been diagnosed by screening.

Pseudodisease or Overdiagnosis

no screening

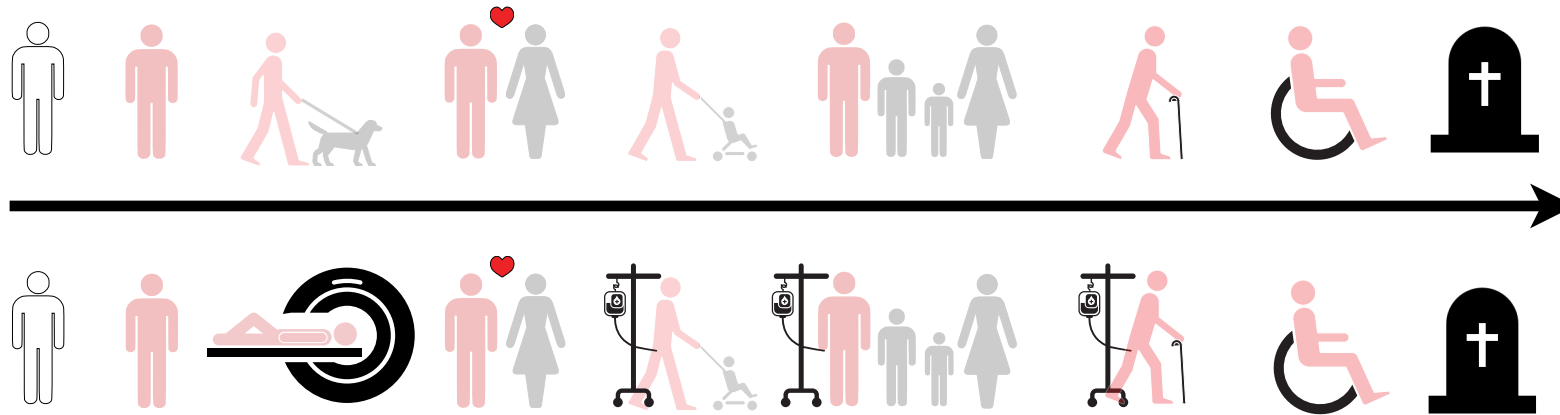


screening



Pseudodisease is a condition that looks just like the disease, but never would have bothered the patient

Pseudodisease or Overdiagnosis



two types of pseudodisease:

Type 1: disease which would never cause symptoms

Type 2: preclinical disease in people who will die from another cause before disease presents

associated with increasing incidence and survival but stable mortality from disease

in an INDIVIDUAL TREATED PATIENT it is IMPOSSIBLE to distinguish pseudo disease from successfully treated asymptomatic disease

1. Treating pseudo disease will always be successful
2. Treating pseudo disease can only cause harm
(but treated patients are grateful)

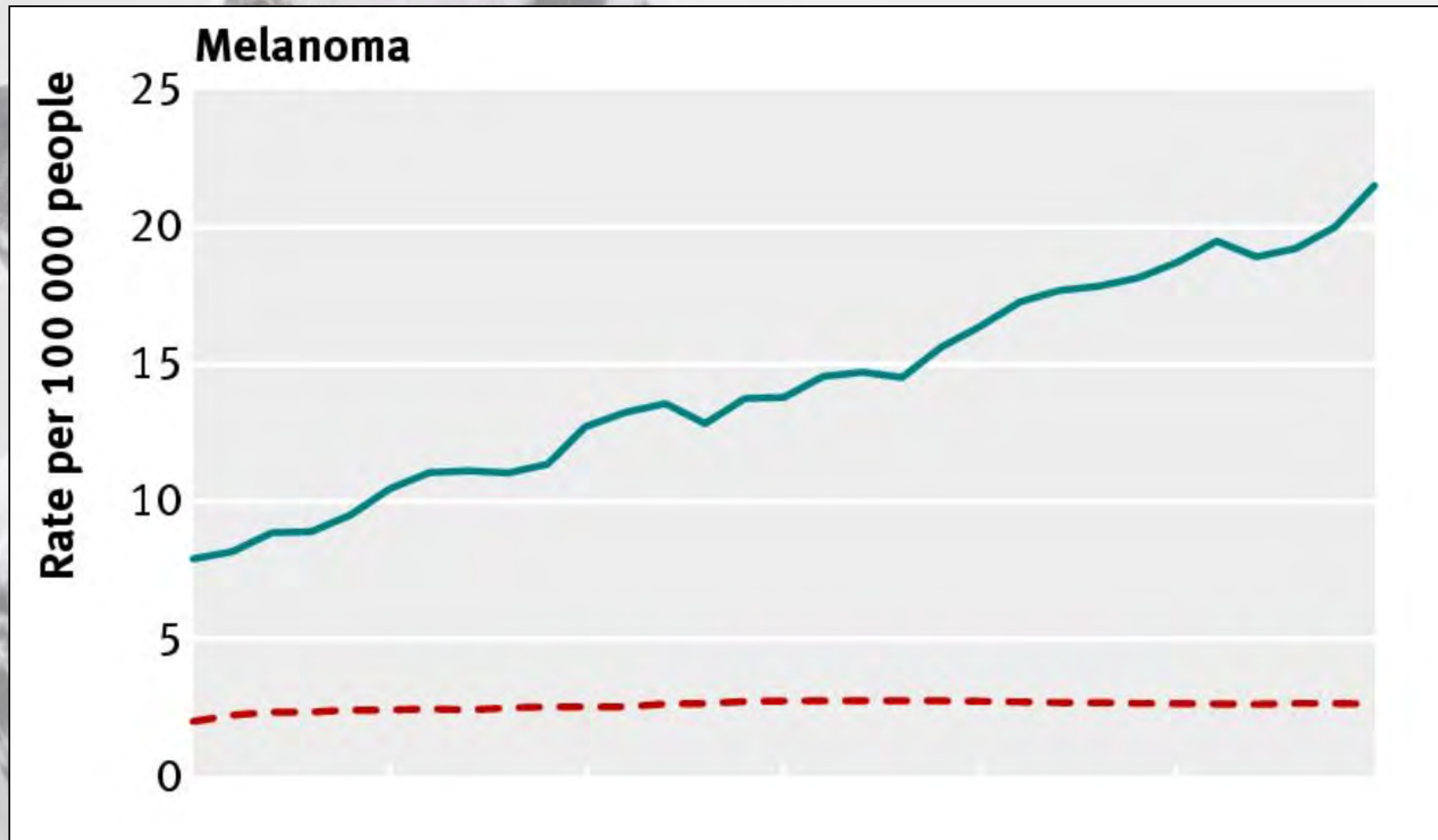




LA ROCHE-POSAY
LABORATOIRE PHARMACEUTIQUE

Pseudodisease or Overdiagnosis

Moynihan et al., BMJ 2012;344:e3502

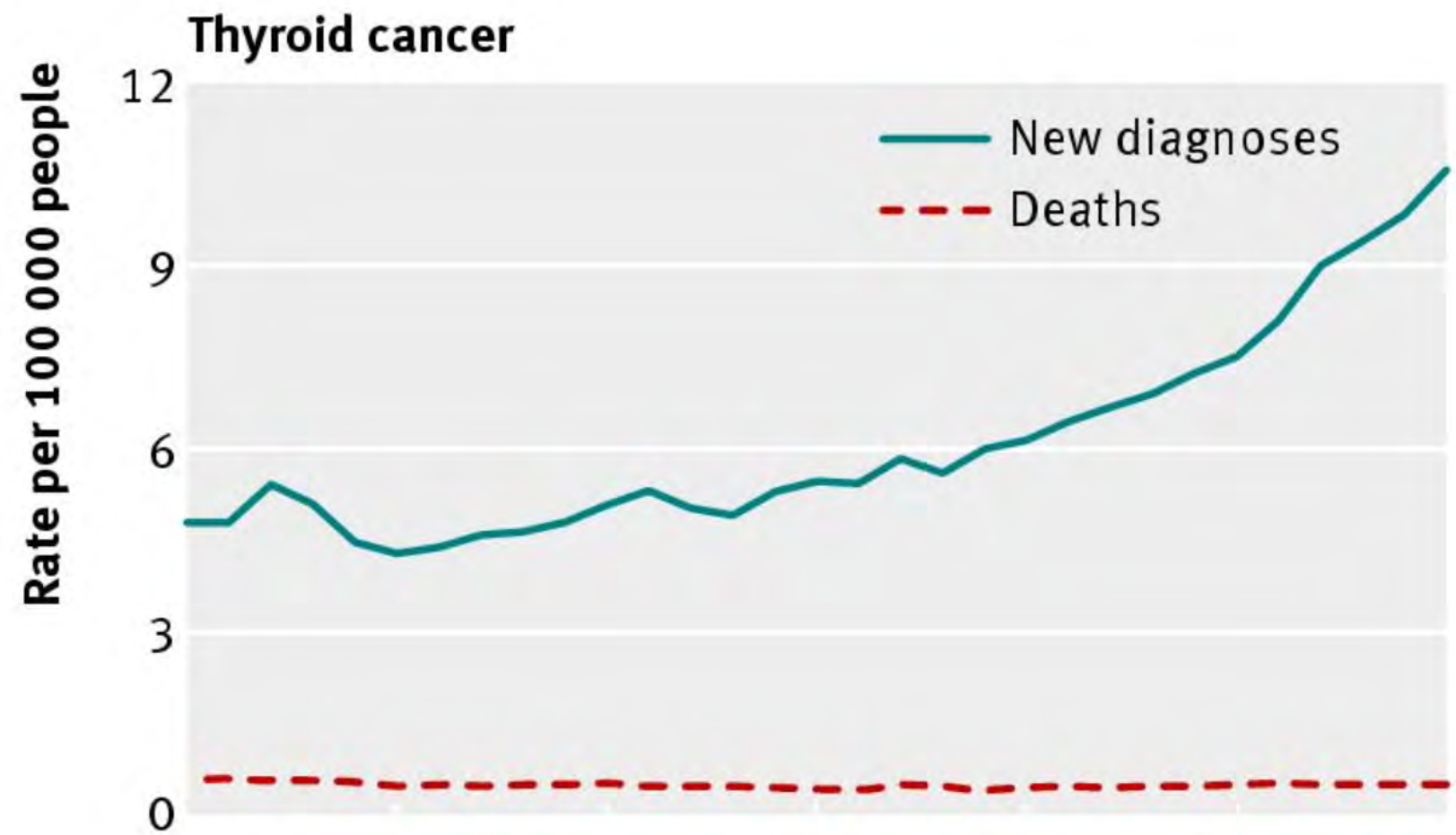


Pseudodisease or Overdiagnosis

Moynihan et al., BMJ 2012;344:e3502



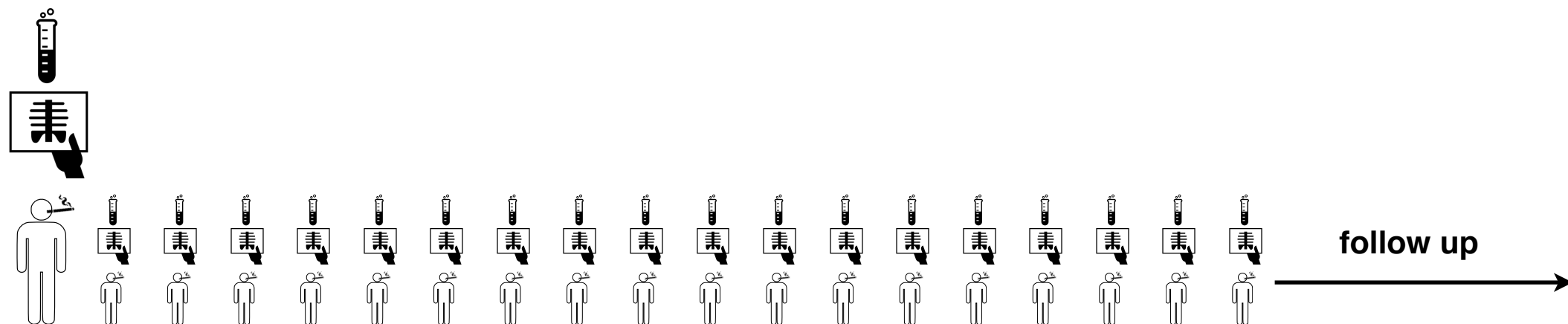
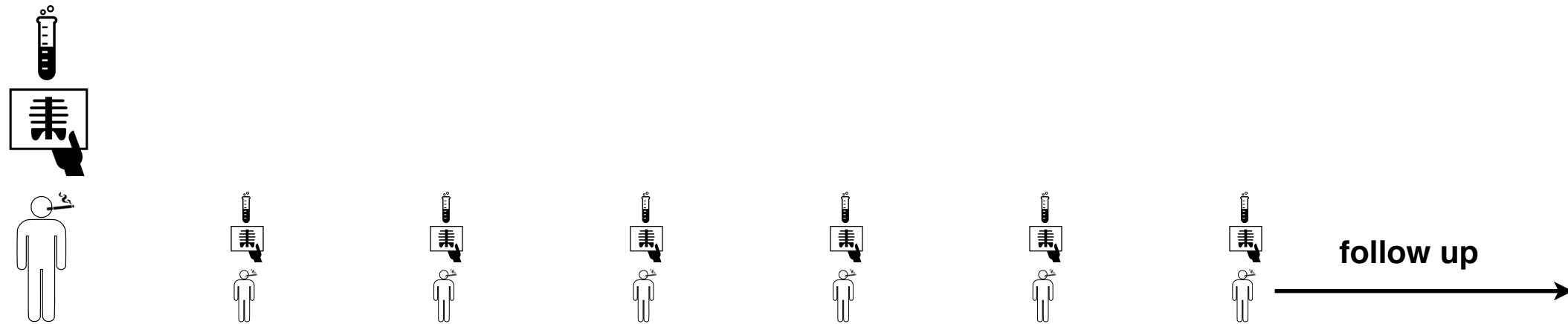
Ask your doctor to check for thyroid cancer.  Light of Life Foundation
checkyourneck.com



Mayo Lung Project: an RCT

Marcus et al., JNCI 2000;92:1308-16

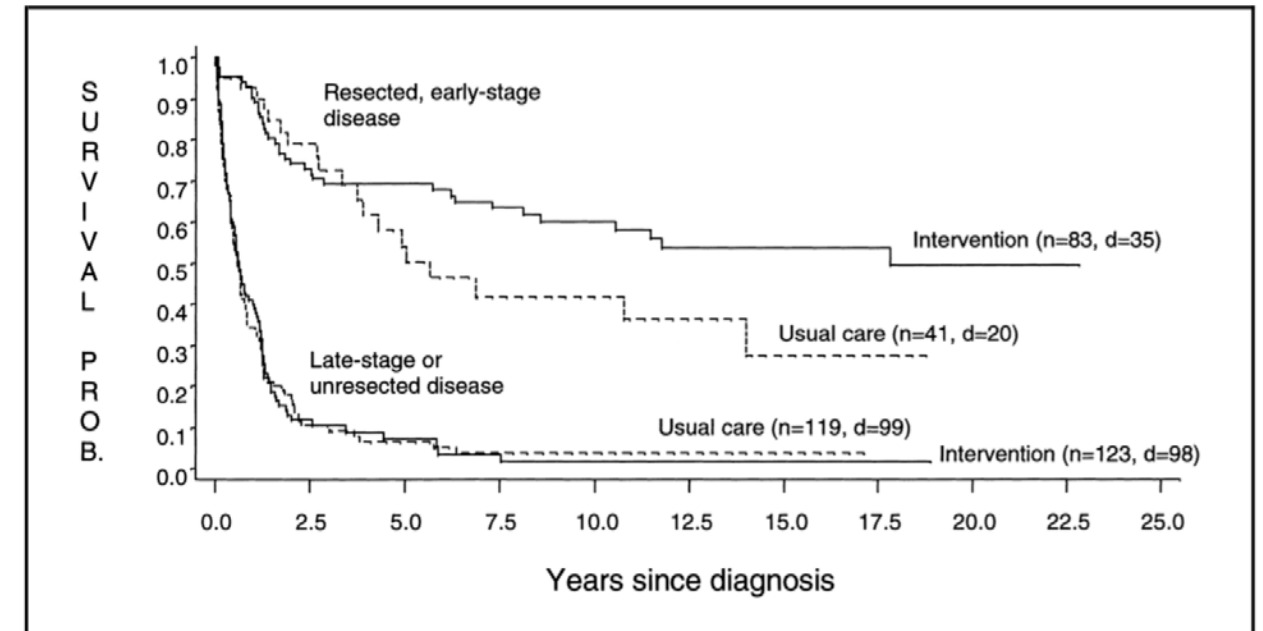
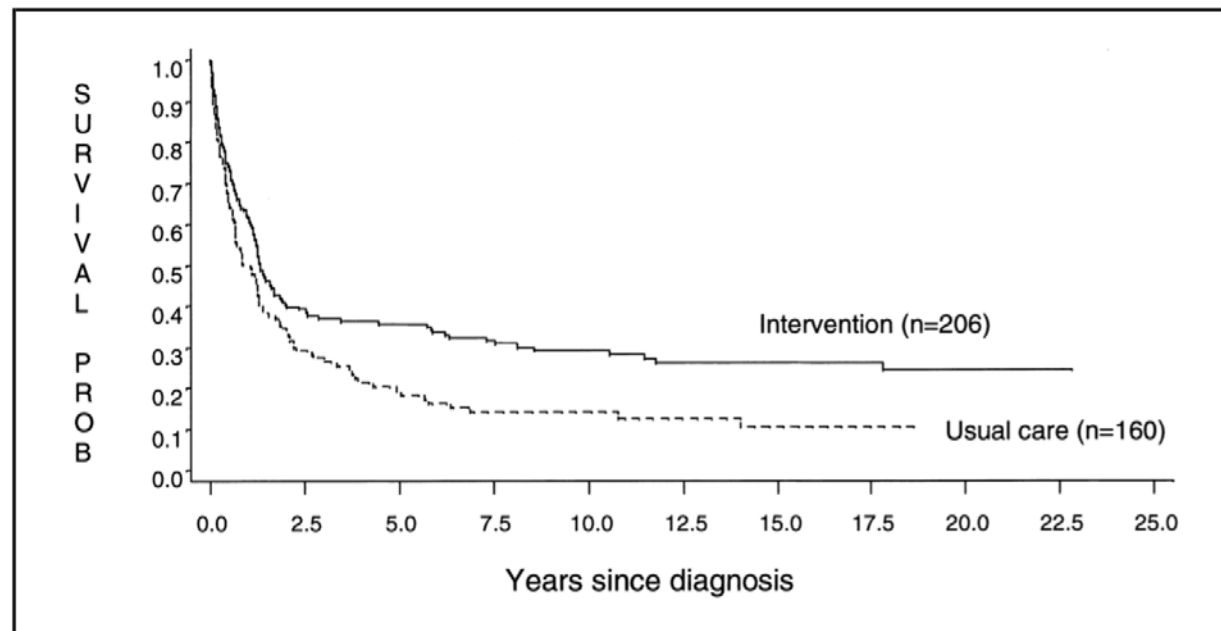
standard group



intervention group

Mayo Lung Project: Results

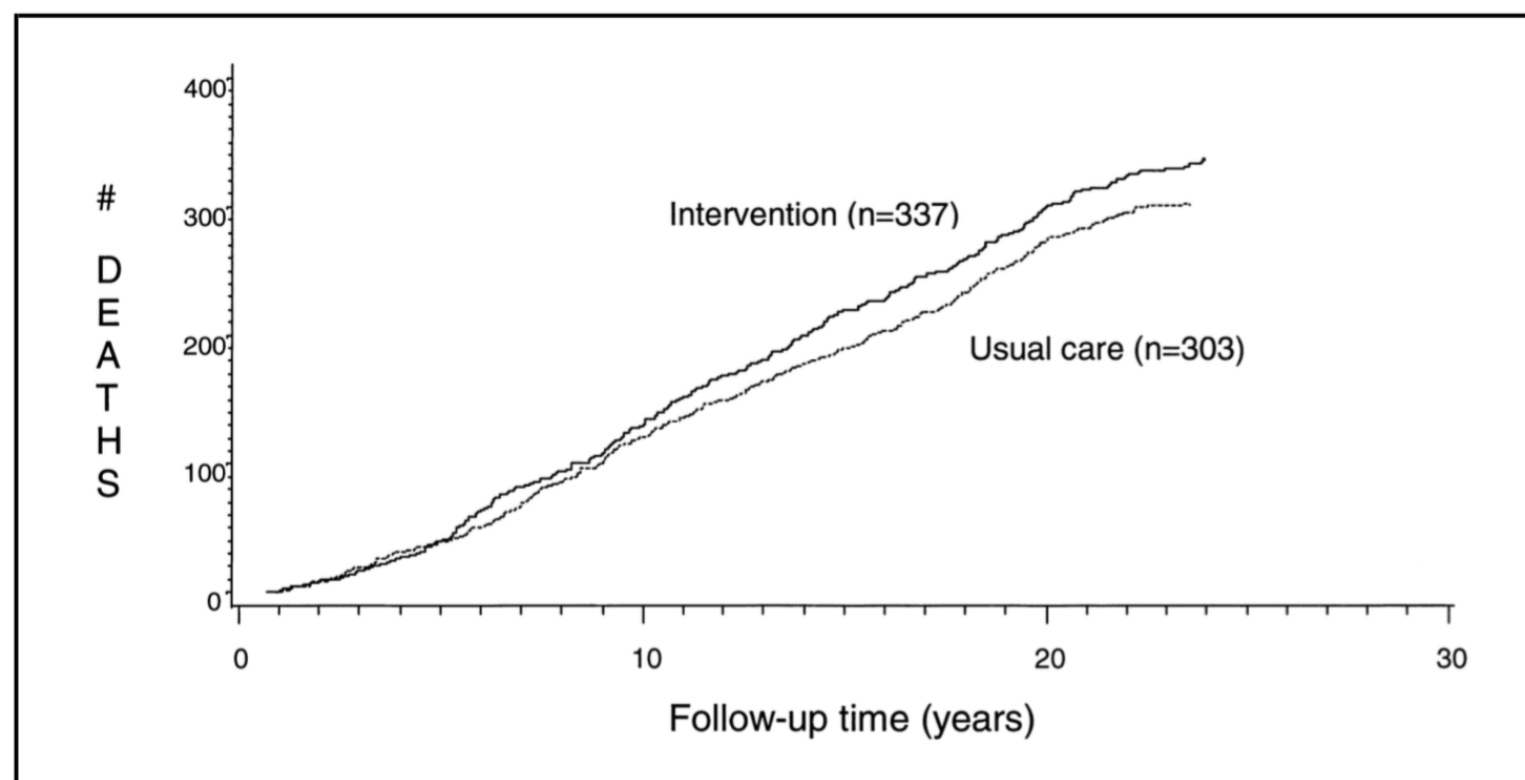
Marcus et al., JNCI 2000;92:1308-16



What happened?

Mayo Lung Project: Results

Marcus et al., JNCI 2000;92:1308-16



After 20 years of follow up:

- * increased mortality in the intervention group
- * significant increase (29%) in the total number of lung cancers in the screened group with excess of tumors in early stage and no decrease in late stage tumors





Mammography confusion

SYLVIA SOO
ACTRESS,
BARING IT ALL,
DIAGNOSED AT 25

*This might be her first film,
but it's certainly not*
HER FIRST SCREENING.



PHOTOGRAPHED BY NIKKI ORMEROD; HAIR AND MAKEUP BY JUKKA SUUTARI; WARDROBE STYLED BY SHEA HURLEY; PROP STYLED BY SUZANNE CAMPOS; ASSISTANTS THOMAS DAGG AND NICK WONG

BREAST FEST 
A RETHINK BREAST CANCER EVENT
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ORIGINAL RESEARCH | **7 MARCH 2017**

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 (); Per-Henrik Zahl, MD, DrMedSci (*)*

[Article, Author, and Disclosure Information](#)

What's key
to surviving
breast cancer?

You

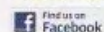
GET SCREENED NOW



LESS TALK. MORE ACTION.

Early detection saves lives. **The 5-year survival rate for breast cancer when caught early is 98%. When it's not? 23%.**

Visit komen.org/getscreened or scan this code with a QR reader app on your smart phone to start making a difference.



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**susan g.
komen.** 

A MAMMOGRAM THAT'S MORE LIKE A DAY AT THE SPA.
THAT'S PURE.

PURE Mammography is not only about convenience, but also comfort. Our facility was created in collaboration with a world leader in spa design and management. So for your next mammogram experience, think warm robes, relaxing music, and a café latte.

SPA-LIKE, PAINLESS MAMMOGRAM EXPERIENCE ON LONG ISLAND



IMPORTANCE
OF SCREENING
MAMMOGRAMS



ADVANTAGES
OF 3D
MAMMOGRAPHY



HOW PURE
MAMMOGRAPHY
IS DIFFERENT



Bias of screening tests in RCT

- ◆ Poor quality of randomization
- ◆ Poor choice of outcome variable:
cause specific mortality

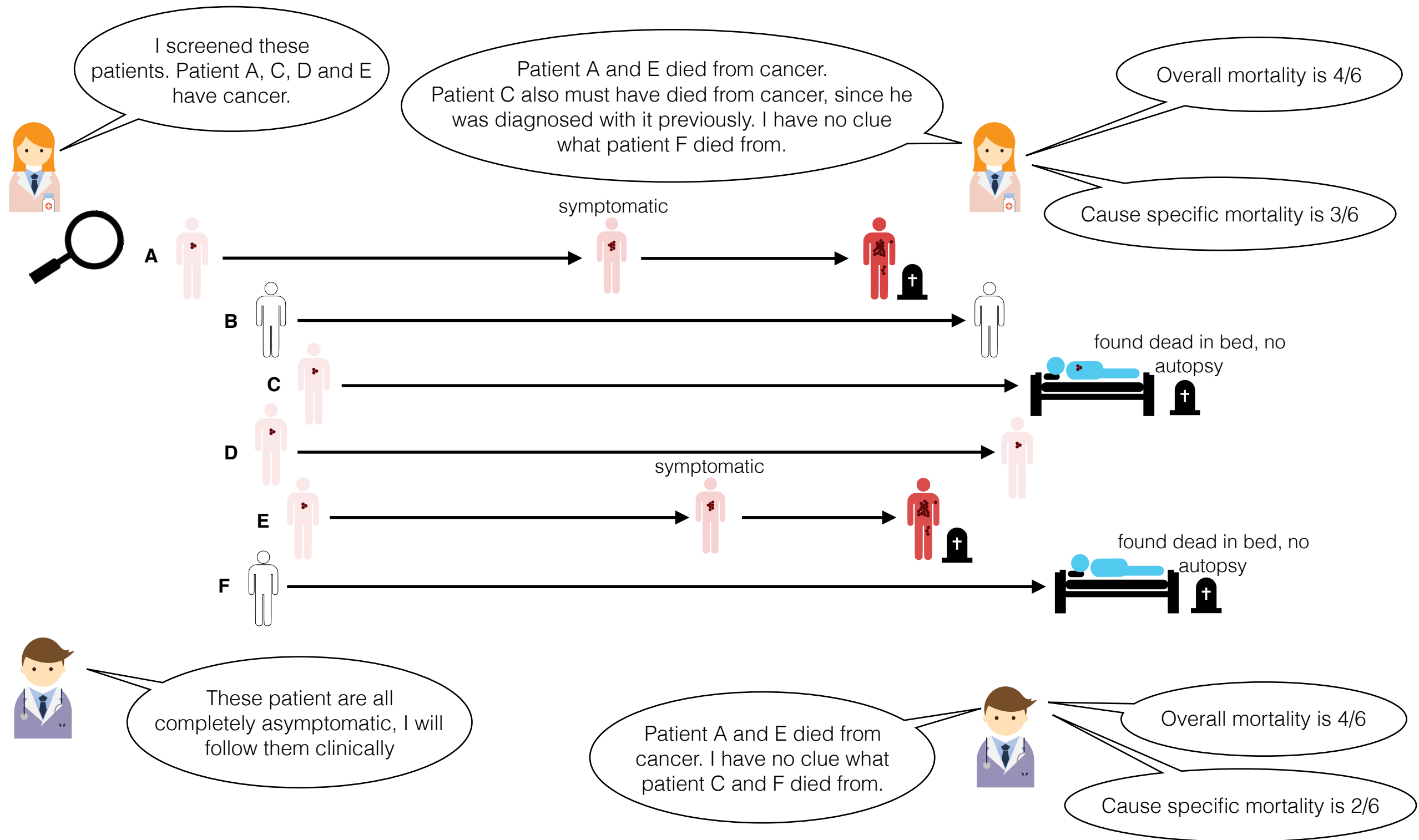
Poor quality of randomization

Edinburgh Trial

Br J Cancer. 1994 September; 70(3): 542–548

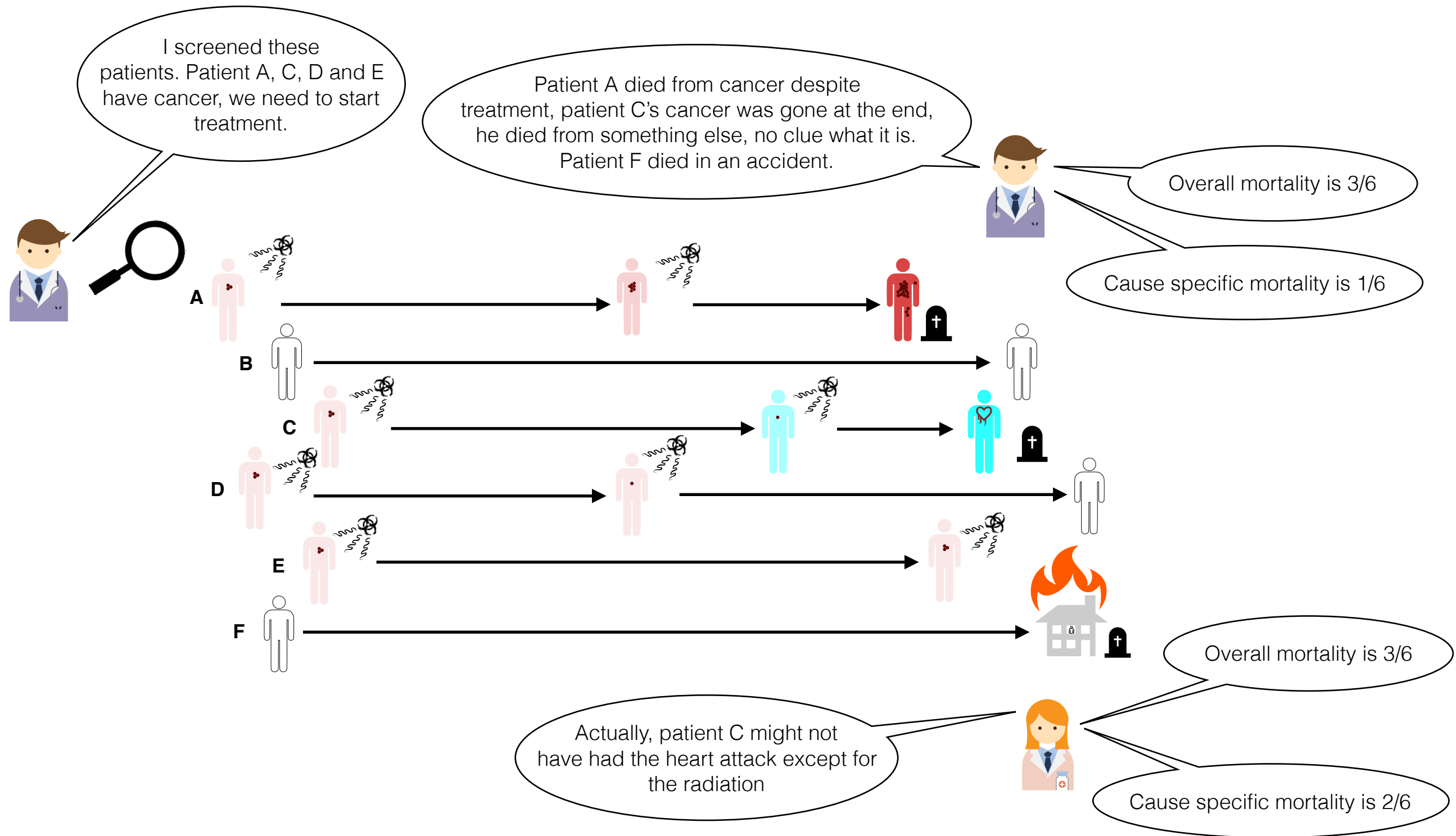
- ♦ Randomization by *practice* (N=87?), not by woman
- ♦ 7 practices changed allocation status
- ♦ Highest SES
 - ♦ 26% of women in control group
 - ♦ 53% of women in screening group
- ♦ 26% reduction in cardiovascular mortality in mammography group

Cause-specific mortality: Sticky diagnosis bias



Overestimation of cause-specific mortality due to incorrect assignment of cause of death. Can be avoided by measuring all cause mortality.

Cause-specific mortality: Slippery linkage bias



Underestimation of cause-specific mortality due to incorrect assignment of cause of death. Late deaths due to complications of screening or treatment will not be counted in cause-specific mortality. Can be avoided by measuring all cause mortality.

Cause-specific mortality: Slippery linkage bias

Early Breast Cancer Trialists Collaborative Group

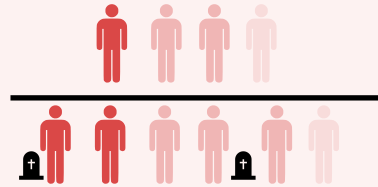
Meta-analysis of radiotherapy for early breast cancer

Lancet 2000;355:1757

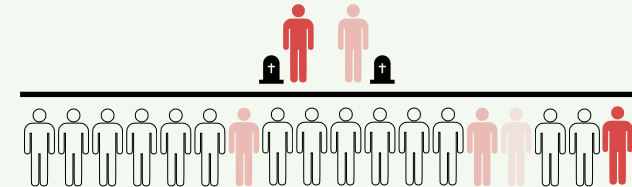
- ◆ Meta-analysis of 40 RCTs
- ◆ Central review of individual-level data; N = 20,000
- ◆ Breast cancer mortality reduced (20-yr absolute risk reduction 4.8%; P = .0001)
- ◆ Mortality from other causes increased (20-yr absolute risk **increase** 4.3%; P = 0.003)

Summary: Outcome variable and biases

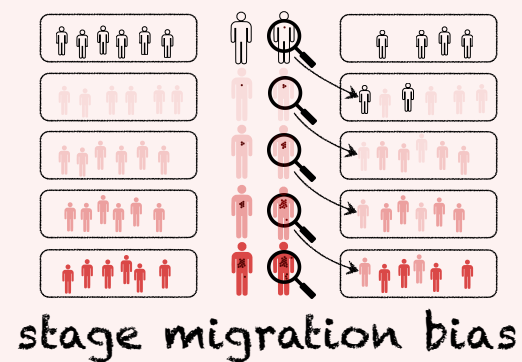
survival



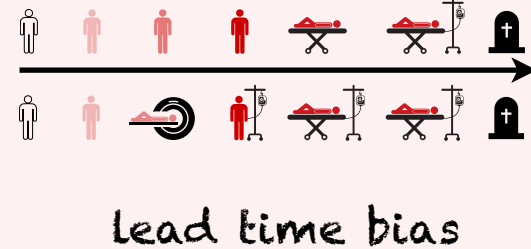
mortality



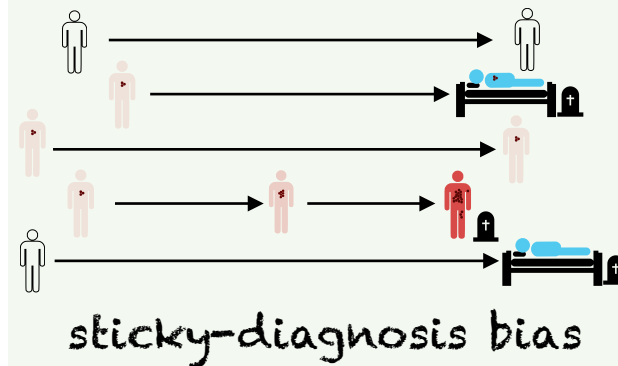
stratified survival



overall survival



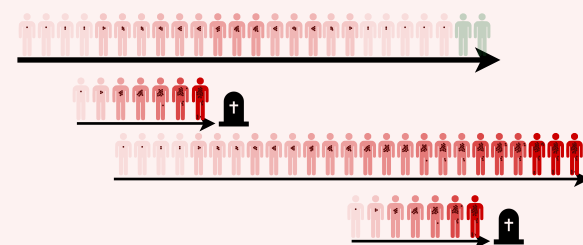
cause-specific mortality



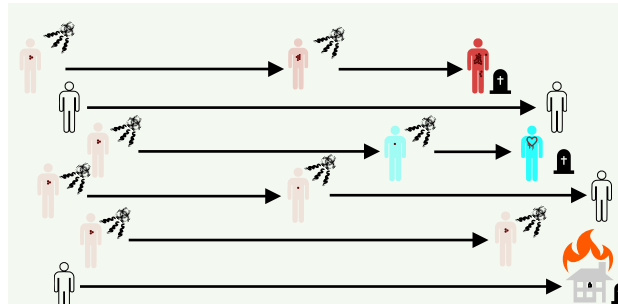
overall mortality



length time bias



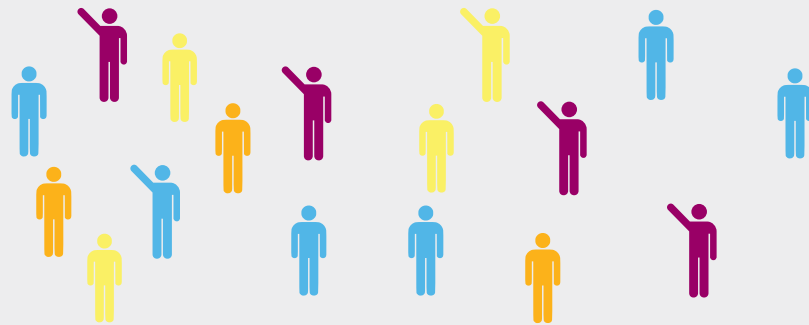
slippery-linkage bias



Summary

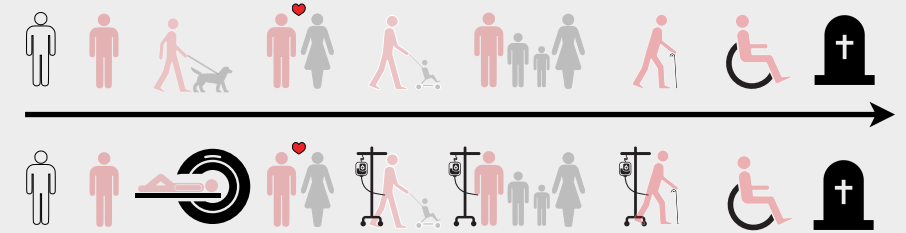
Volunteer bias

people who volunteer
for screening differ
from those who do
not



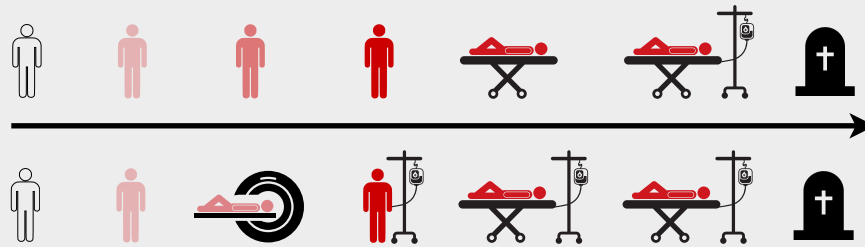
Pseudodisease

condition that looks
just like the disease,
but never would
have bothered the
patient



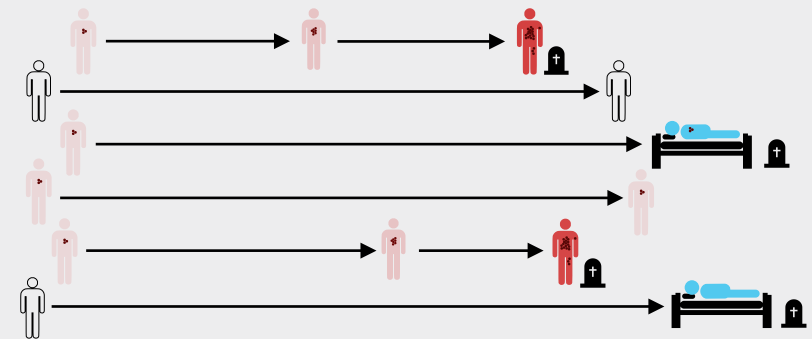
Lead time bias

screening identifies disease during a latent period before it becomes symptomatic
- screening appears to improve survival



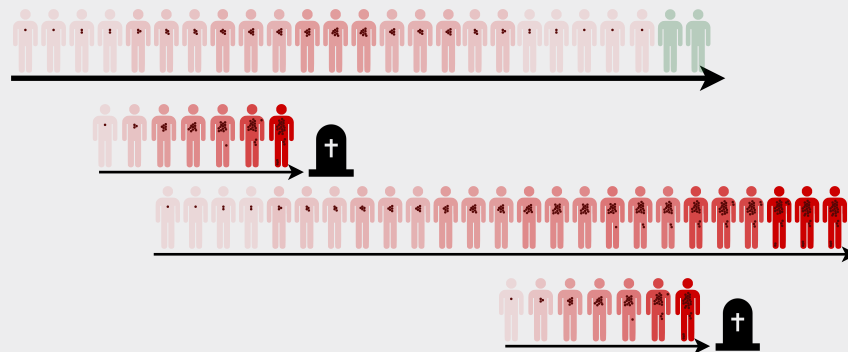
Sticky diagnosis bias

overestimation of cause-specific mortality due to incorrect assignment of cause of death



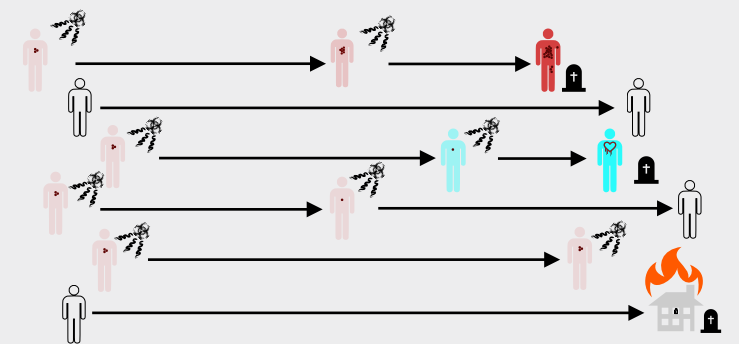
Length time bias

screening picks up
prevalent disease and
benign courses of
disease have a greater
prevalence



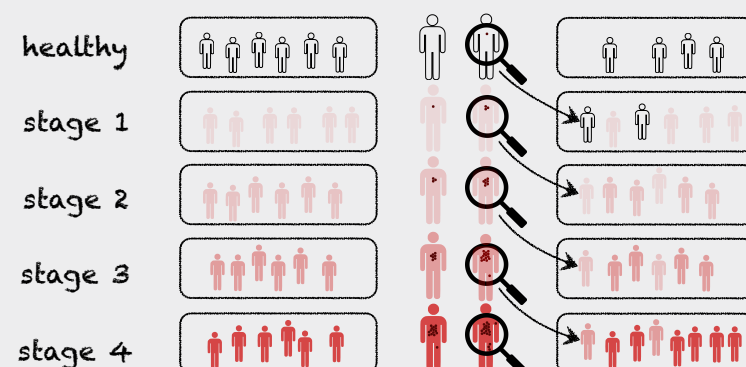
Slippery linkage bias

underestimation of cause-specific mortality due to incorrect assignment of cause of death



Stage migration bias

newer tests classify people into more advanced stages - stage specific survival improves.



Thank you!