

Will CT screening reduce overall lung cancer mortality?

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Screening - Requirements

- important health problem
- detectable risk factor or disease marker
- simple, safe, precise and validated test
- the screening program is effective

Screening - Requirements

- lung cancer - important health problem
 - frequent and lethal
 - Canada 2008
 - 23,900 new diagnoses
 - 20,200 deaths
 - 5-year survival rate 15%

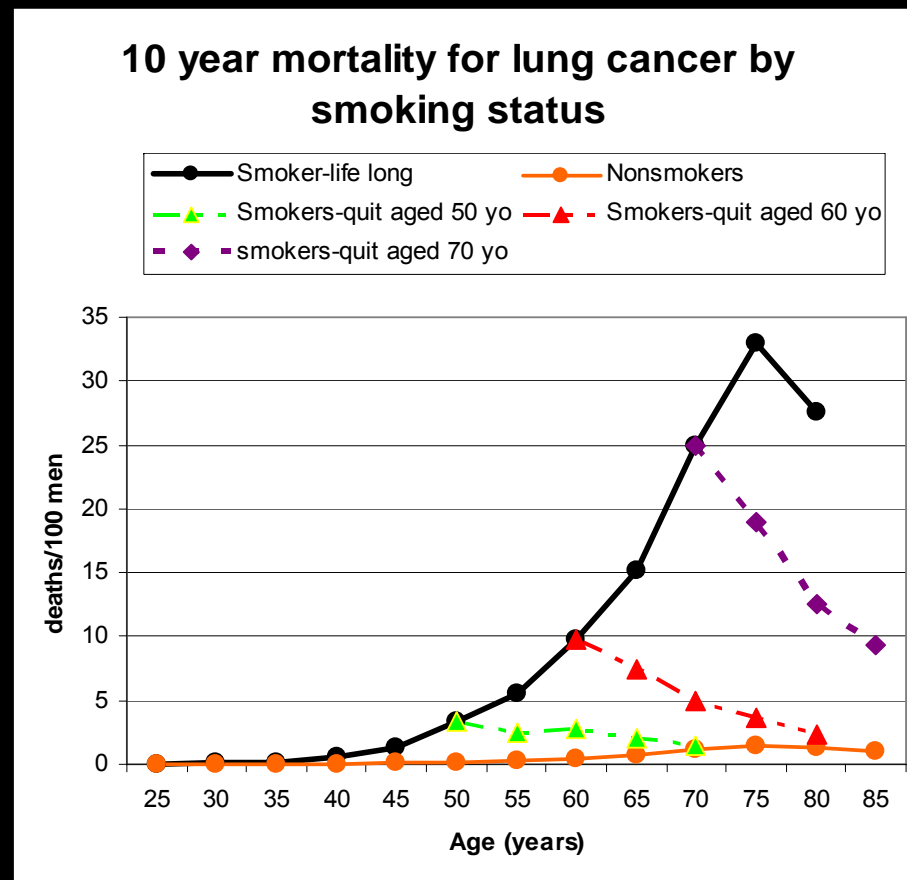
Screening - Requirements

- important health problem
- detectable risk factor or disease marker
 - smoking cessation programs in effect
 - large smoking population



Screening - Requirements

- detectable risk factor or disease marker
 - large ex-smoking population



courtesy
N Young, NZ

Screening - Requirements

- important health problem
- detectable risk factor or disease marker
- simple, safe, precise and validated test

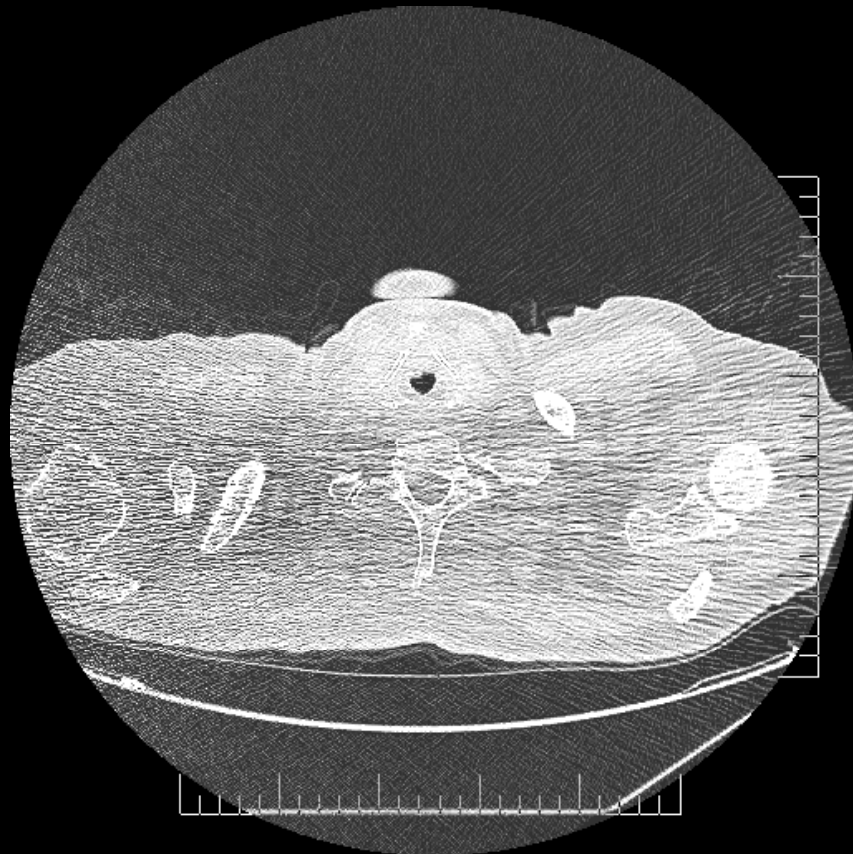
Screening - Requirements

- simple, safe, precise and validated test
 - Low-Dose Computed Tomography



Low-Dose CT

- helical CT
- multi-slice
- 120 kV,
40-80 mA,
1.25 mm



LDCT for lung cancer screening

- 1st landmark publication:
C Henschke et al. ELCAP
Lancet 1999

The New York Times
ON THE WEB

“CAT SCAN PROCESS
COULD CUT DEATHS
FROM LUNG CANCER”

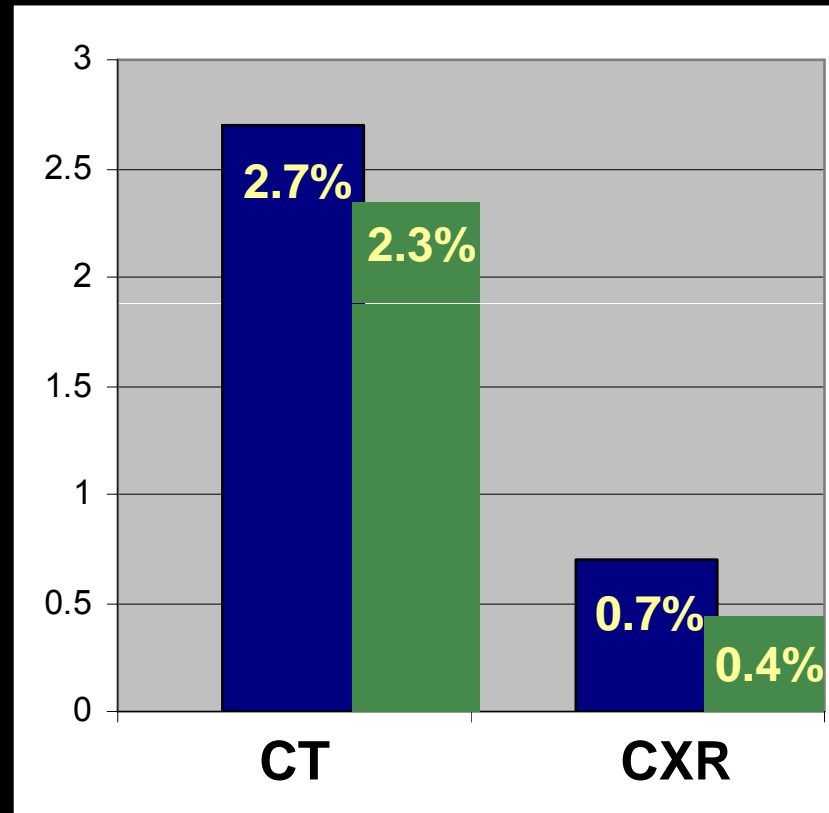
TIME

“Spotting
Lung
Cancer
Before It's
Too Late”

ELCAP: Screening Results

% cancers found

% Stage I
cancers found



LDCT detects Stage I lung cancers

PMH screening results

- first 1,000
- 2.2% malignancies
- 2% lung cancer
- 78% Stage 1



Screening - Requirements

- important health problem
- detectable risk factor or disease marker
- simple, safe, precise and validated test
- the screening program is effective

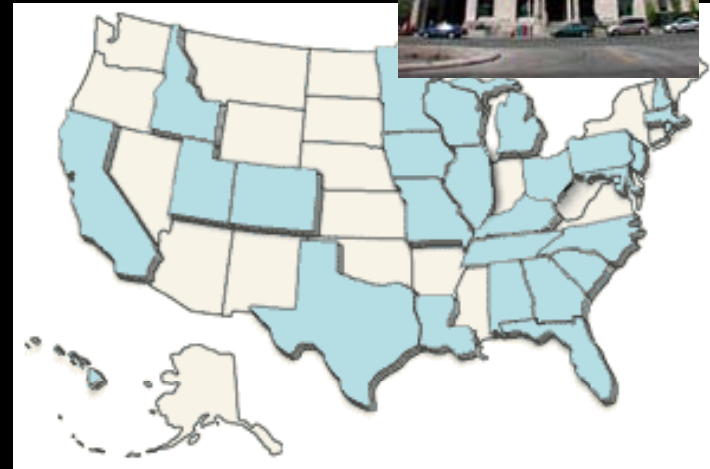
heated discussion

Screening effectiveness

- measured as *survival*

I-ELCAP

- 27,456
- non-randomized
- 10-year-survival
- up to 92%*



SCREENING IS EFFECTIVE
NOT SCREENING CAUSES HARM

Henschke et al,
New Eng J Med 2006

Screening effectiveness

- measured as *mortality*
- can only be addressed in *randomized* trials

NELSON trial

ITALUNG

Netherlands, Belgium, Denmark

20,000

LDCT vs. general care

3,000

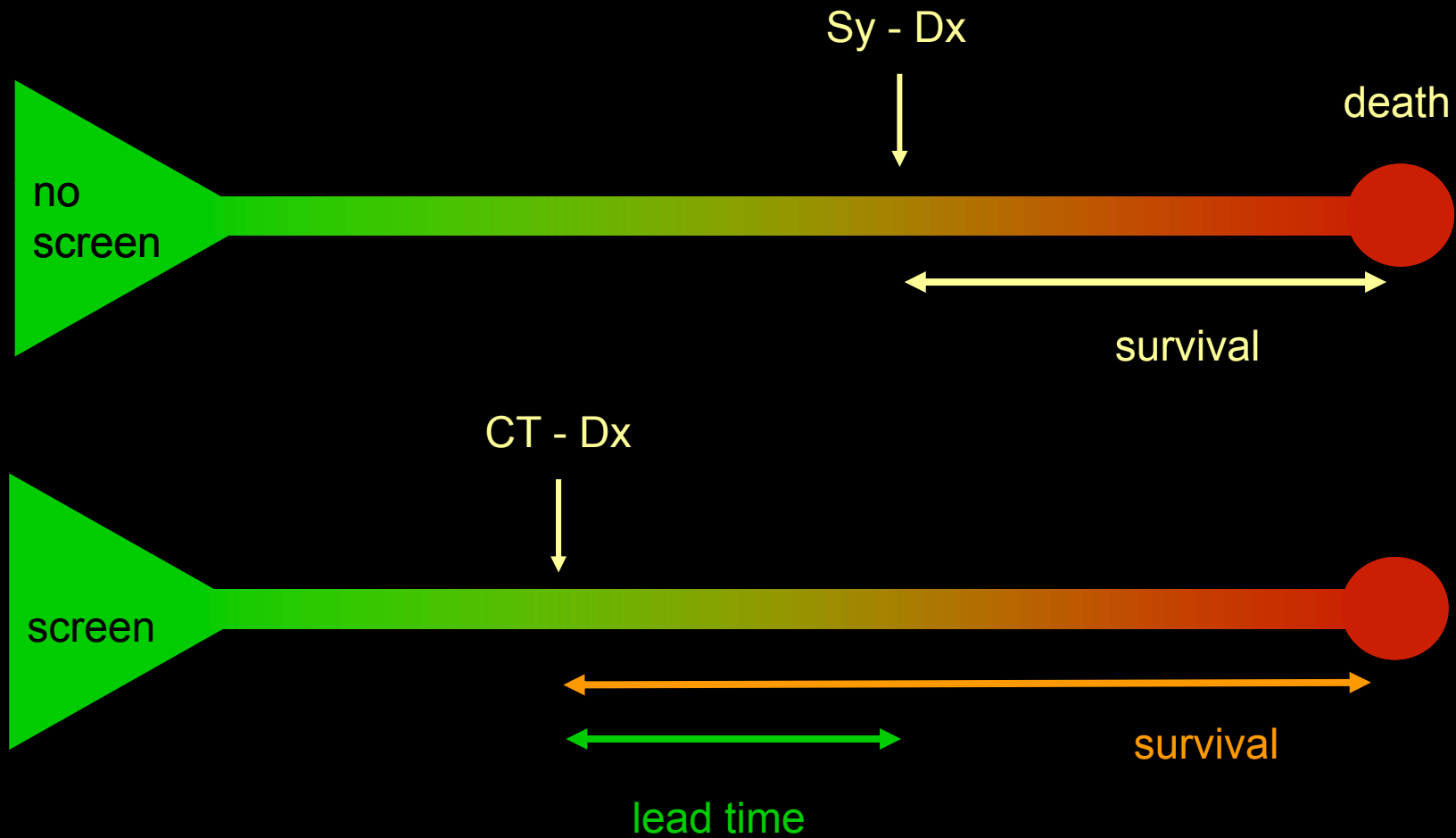
LDCT vs. general care

MORTALITY BENEFIT NOT PROVEN
EFFECTIVENESS OF SCREENING UNPROVEN
SCREENING CAUSES HARM

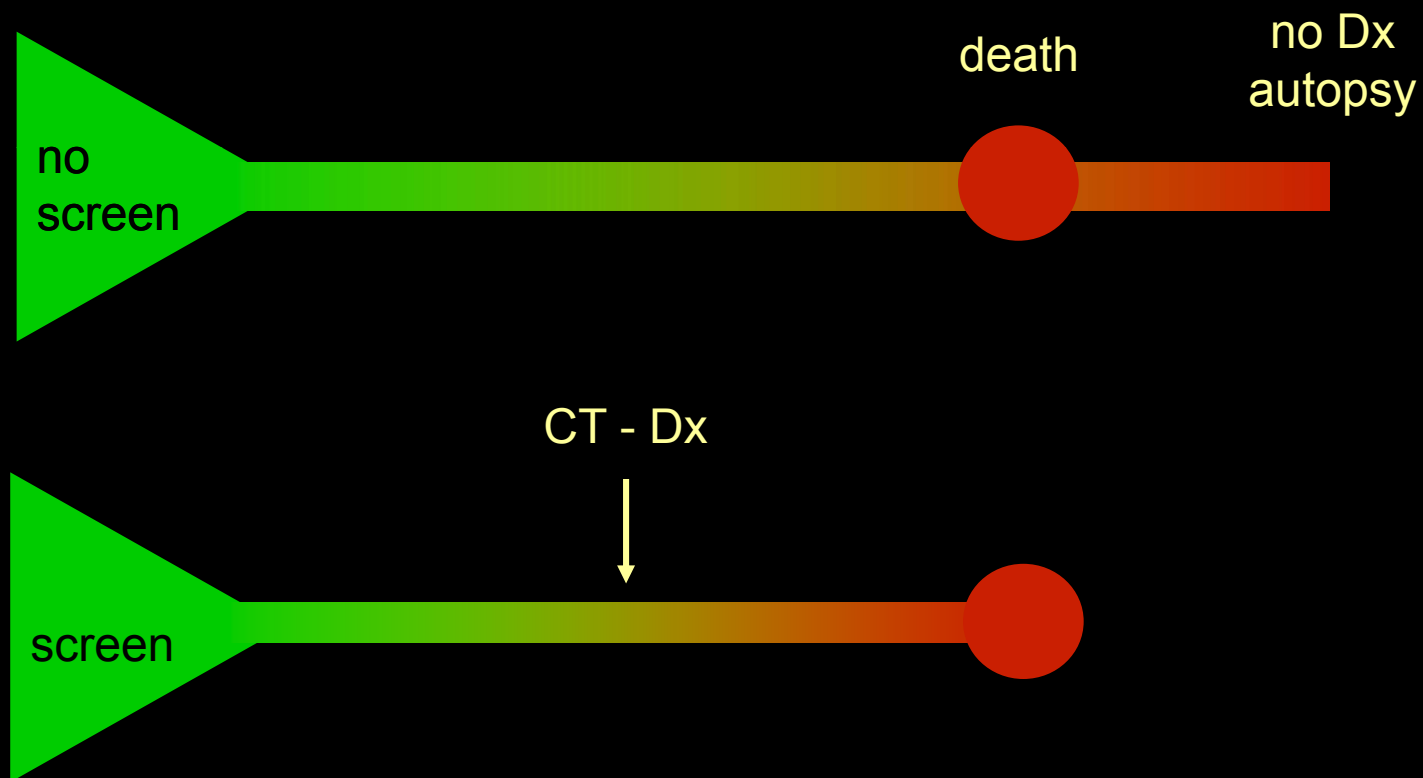
Survival vs. Mortality

- 10-year survival up to 92%
- longer survival \neq reduced mortality
- survival biased by
 - lead time bias
 - length time bias
 - overdiagnosis

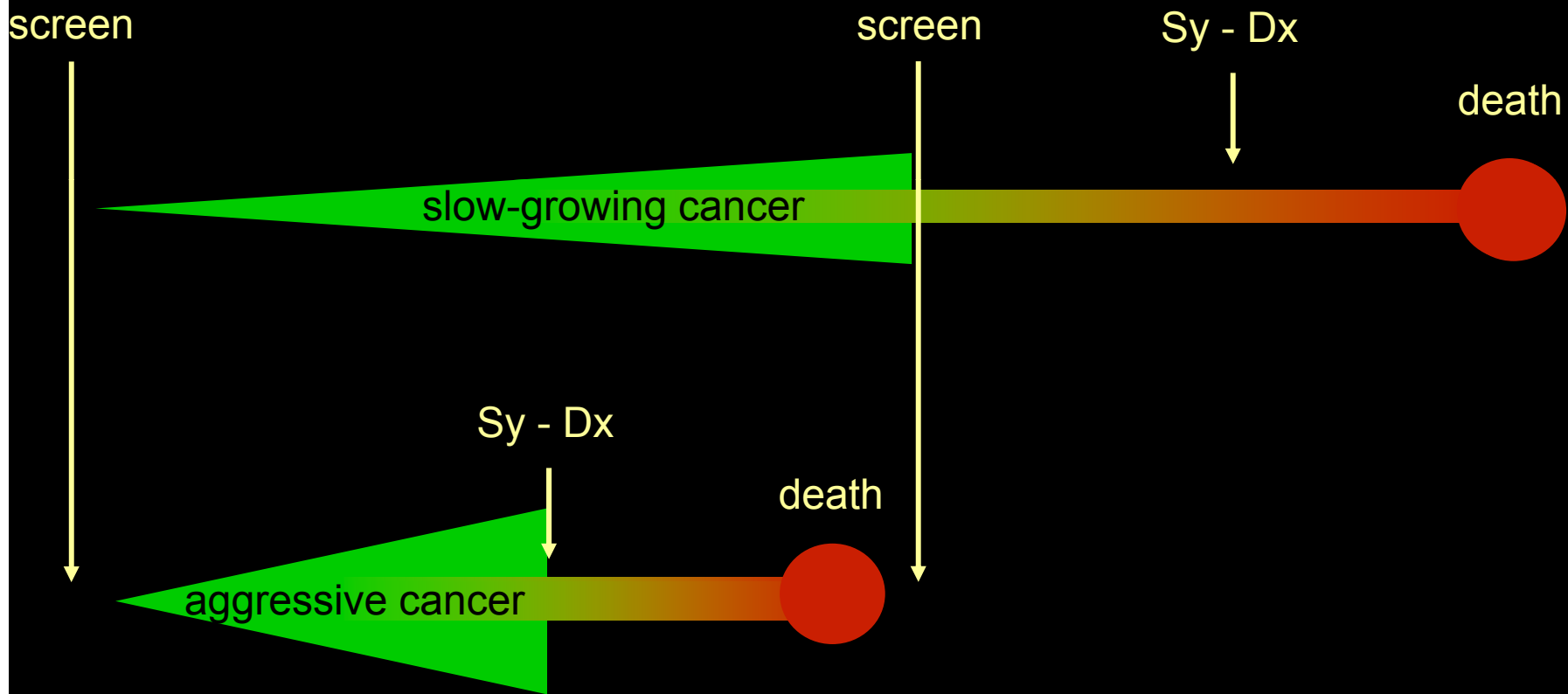
Lead time bias



Overdiagnosis bias

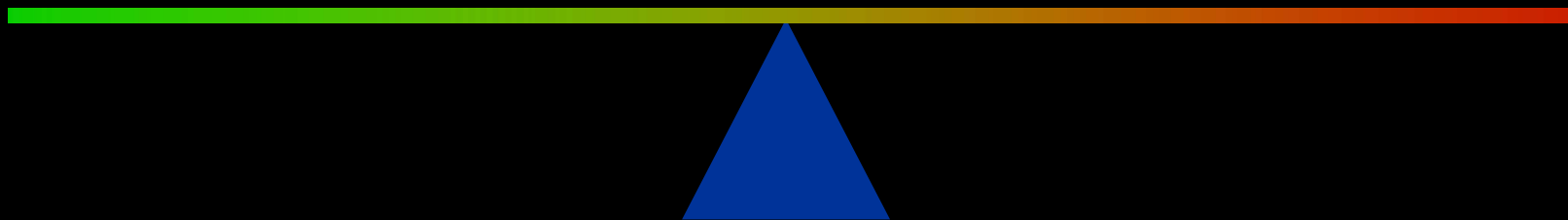


Length time bias



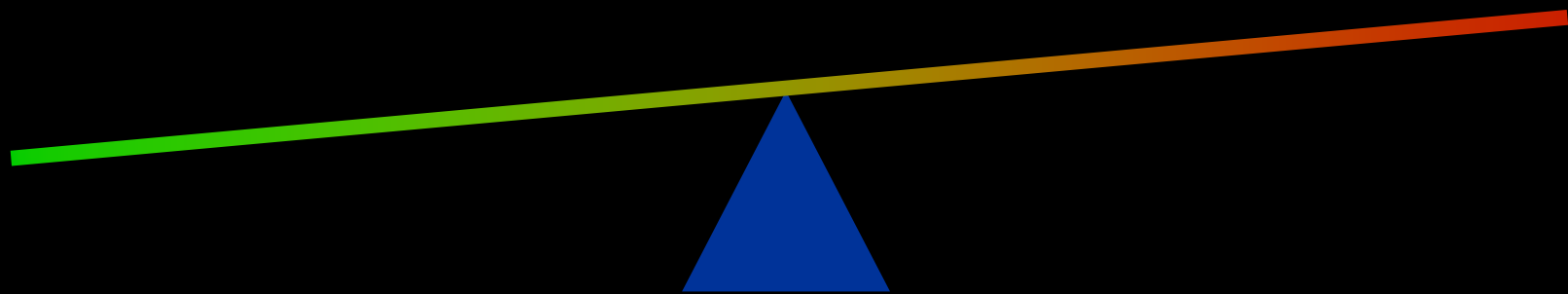
screening detects slow-growing cancers
aggressive cancers elude screening tests

Does CT screening reduce mortality?



Does CT screening reduce mortality?

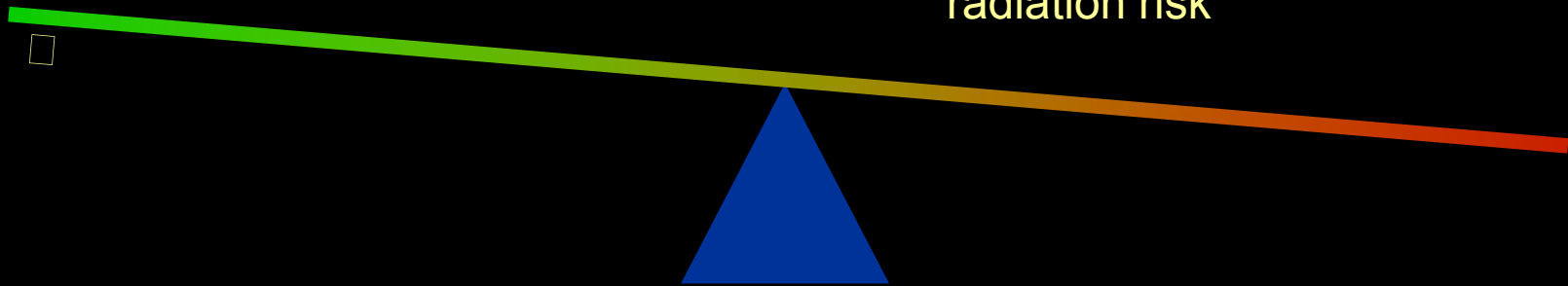
evidence
unproven benefit
survival



Does CT screening reduce mortality?

evidence
unproven benefit
survival

lead time bias
length time bias
overdiagnosis
risk of morbidity (harms) from
invasive dx procedures
surgery
for benign lesions
radiation risk



Reducing Mortality

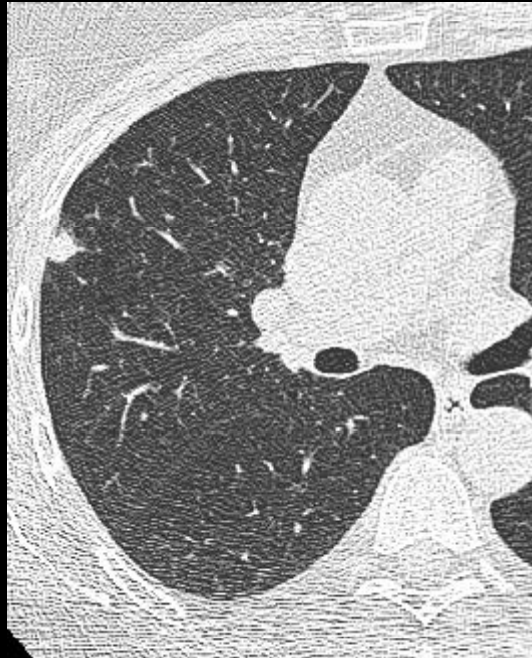
Length time bias

- prevent the treatment of slow-growing cancers
- individual biological potential?
 - size
 - growth rate
 - angiogenic and metastatic potential
 - mitotic rate
 - mutation rate
 - immunological host response
- simplest biological profile to date is growth rate

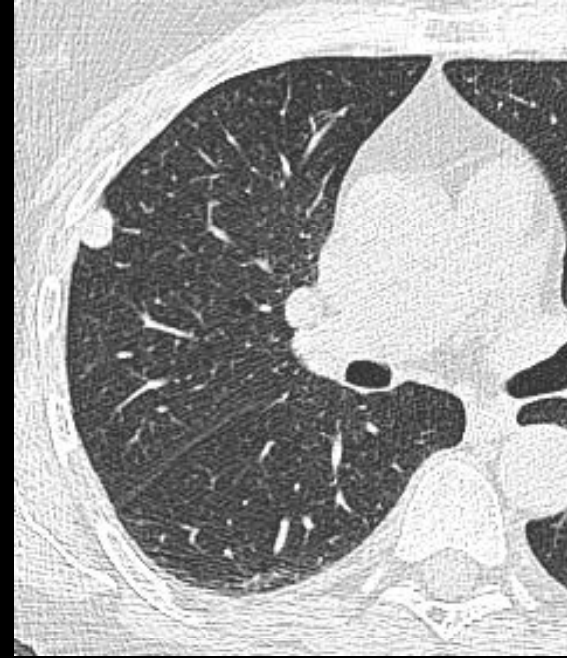
Growth rate

- growth rate
 - common rule: 2 years stable = benign
 - doubling time < 30 days & > 500 days benign





3 months



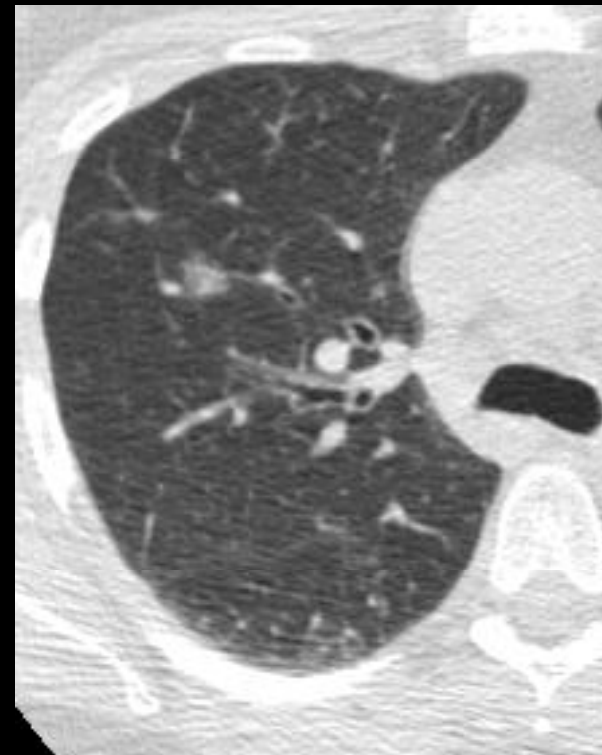
doubling time 72 days

combined small cell-large cell neuroendocrine carcinoma

Overdiagnosis?



3 months



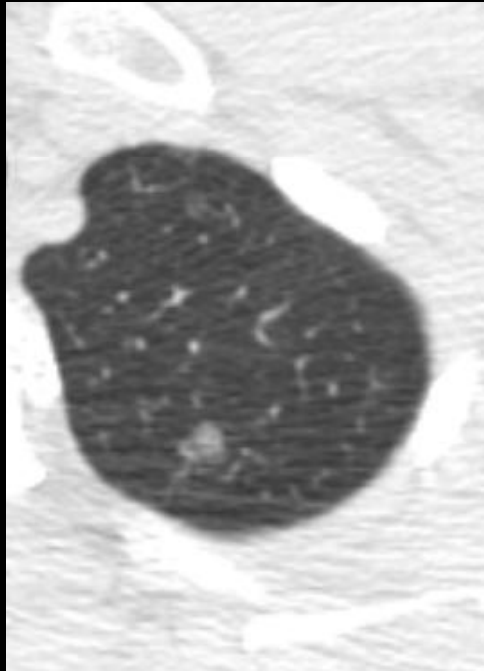
no growth

biopsy: malignant cells

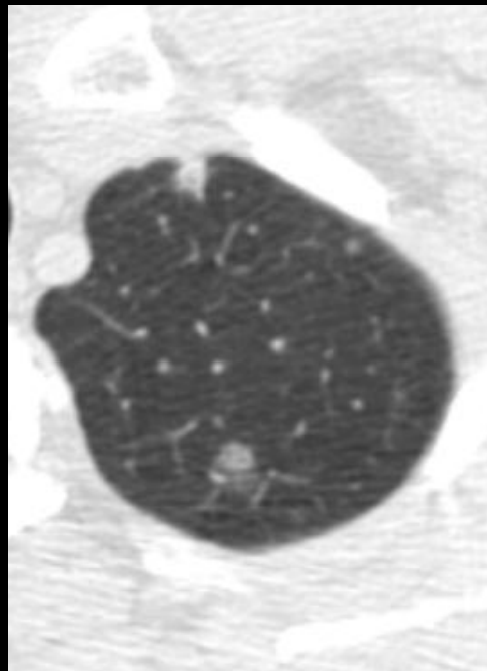
surgical resection

1.1 cm bronchioloalveolar carcinoma

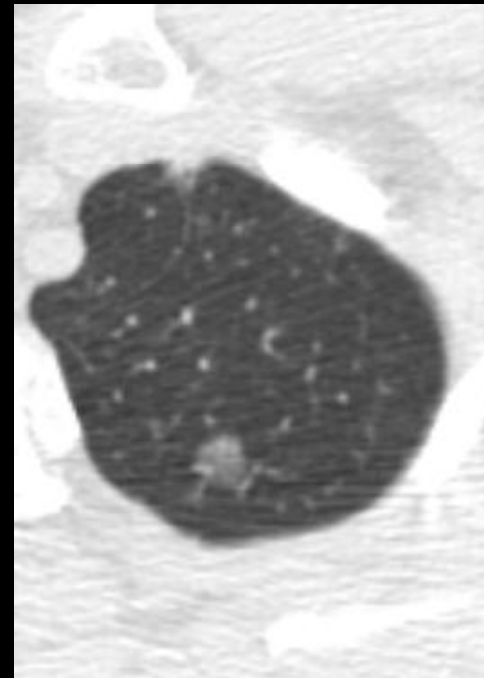
no invasion



July 2007



March 2008



July 2008

growth rate ~380 days



3 months

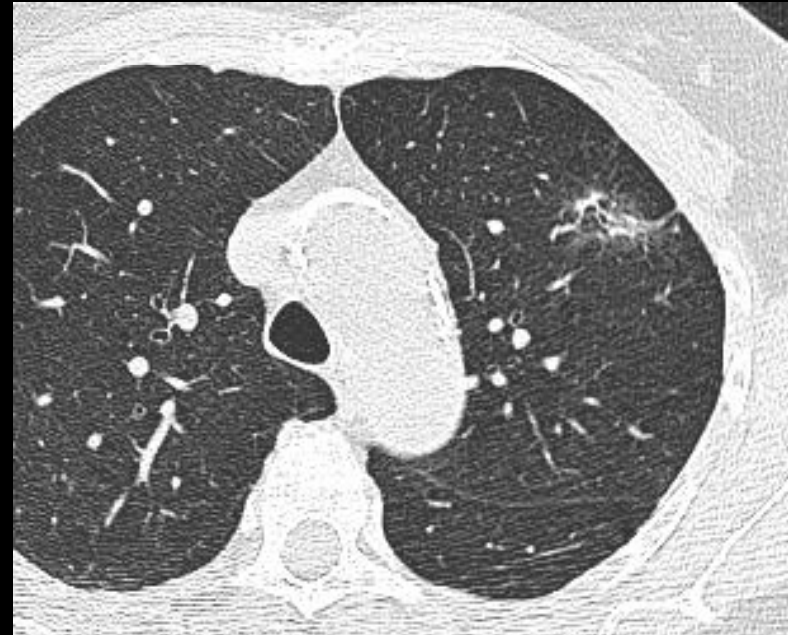


same size, higher density

adenocarcinoma



3 months



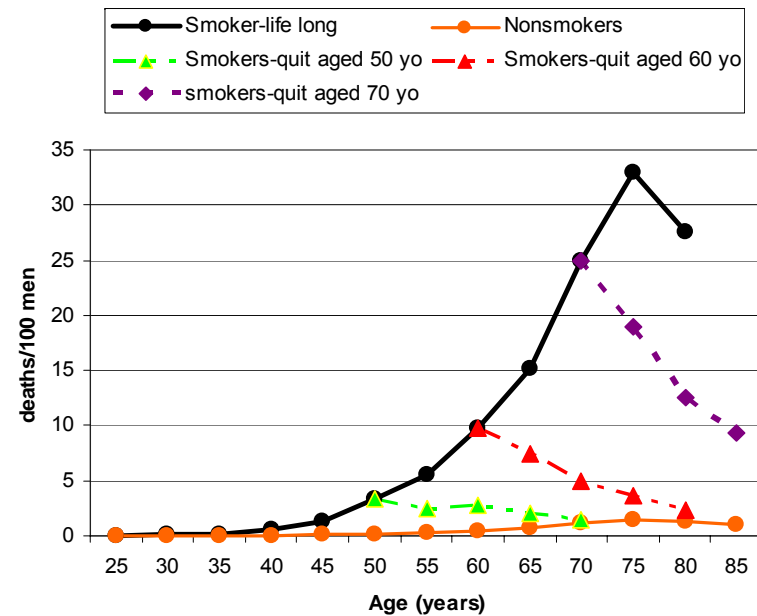
measurement?
adenocarcinoma

Reducing Mortality

Overdiagnosis

- non-lethal, indolent cancer
- aggressive cancer that is overtaken by lethal competing morbidities

10 year mortality for lung cancer by smoking status



Reducing Mortality

Overdiagnosis

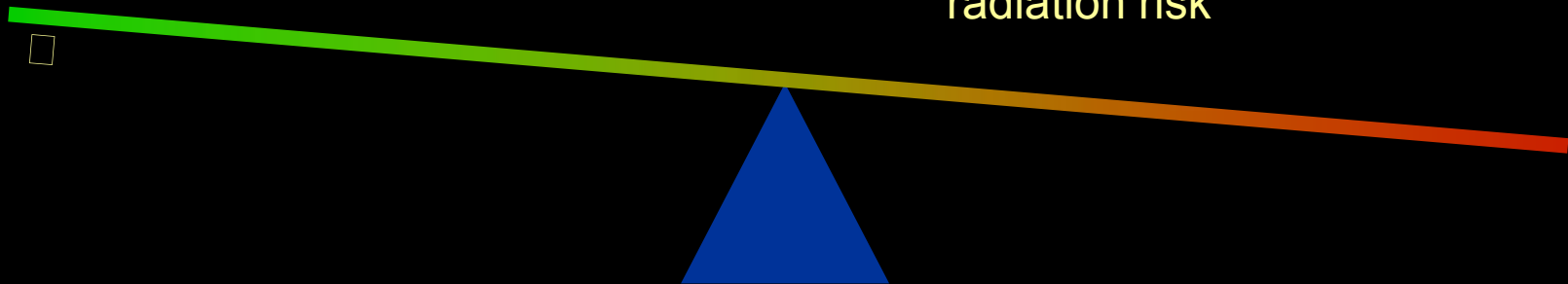
- non-lethal, indolent cancer
- aggressive cancer that is overtaken by lethal competing morbidities

decrease risk
of comorbidities

Does CT screening reduce mortality?

evidence
unproven benefit
survival

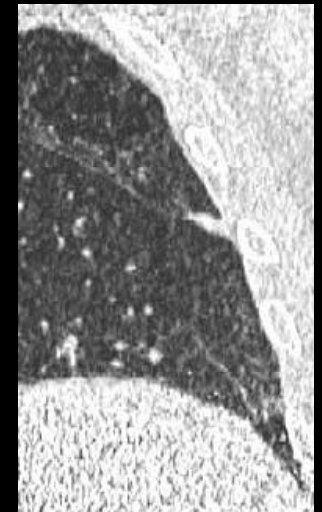
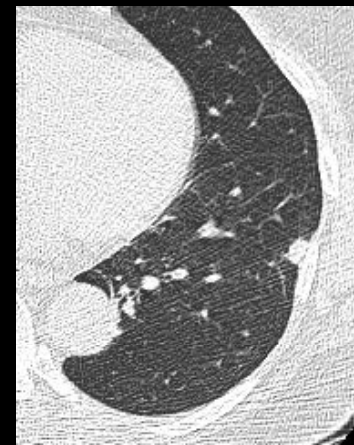
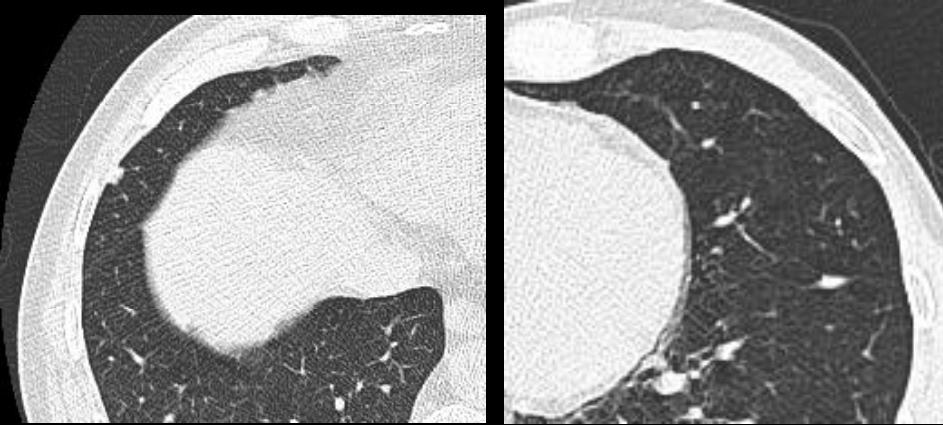
lead time bias
length time bias
overdiagnosis
risk of morbidity (harms) from
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surgery
for benign lesions
radiation risk



Reducing Mortality

Harms from diagnostic interventions for benign lesions
(false positives)

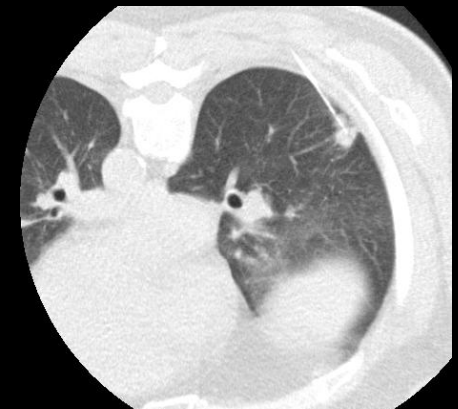
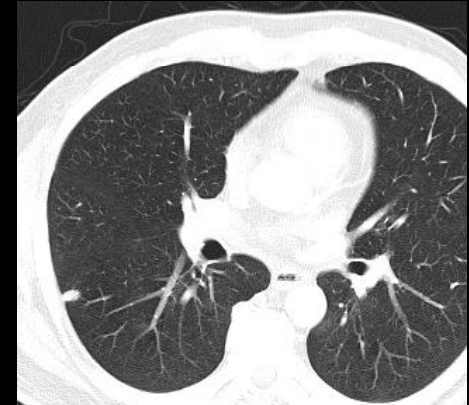
- positive baseline: I-ELCAP 15% Toronto first 1,000 26%



Reducing Mortality

Harms from interventions for benign lesions

- diagnostic interventions
- CT-guided biopsies
 - ≤ 10 mm
 - 45.5% adequate for diagnosis
 - sensitivity for malignancy 67.7%
 - accuracy 78.8%
 - pneumothorax 52.7%, chest tube 9.1%



Reducing Mortality

Radiation risk

- low-dose
- how long screen?
- how often screen?

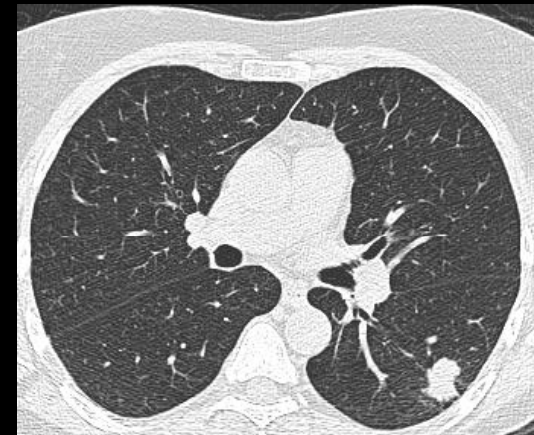
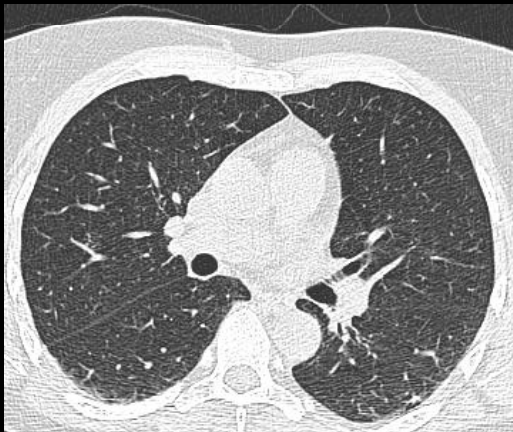
baseline



annual
(no change)



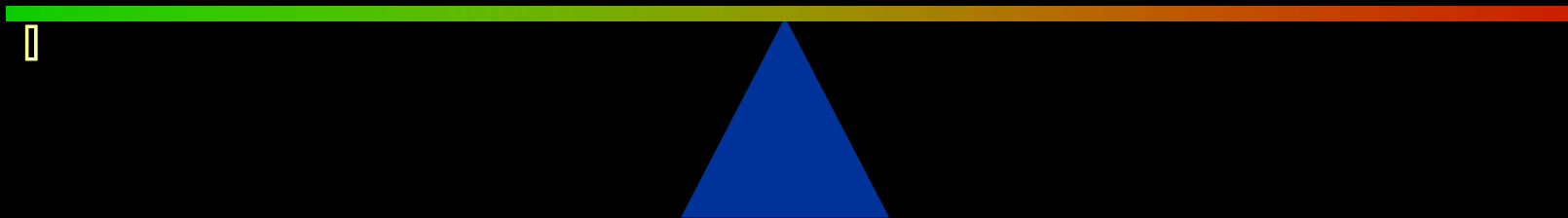
biennial



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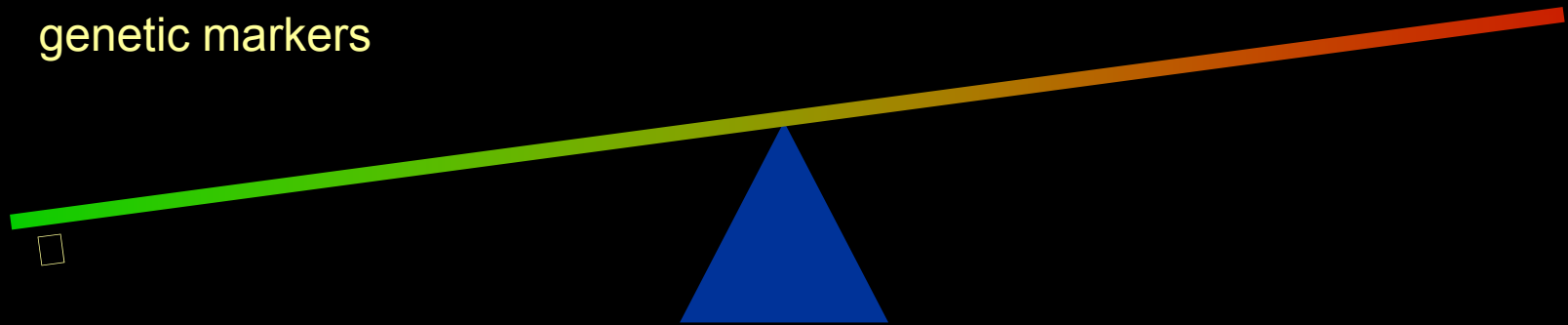


Does CT screening reduce mortality?

evidence
unproven benefit
survival

false negatives
biomarker
genetic markers

lead time bias
length time bias
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Reducing Mortality

False negatives



Reducing Mortality

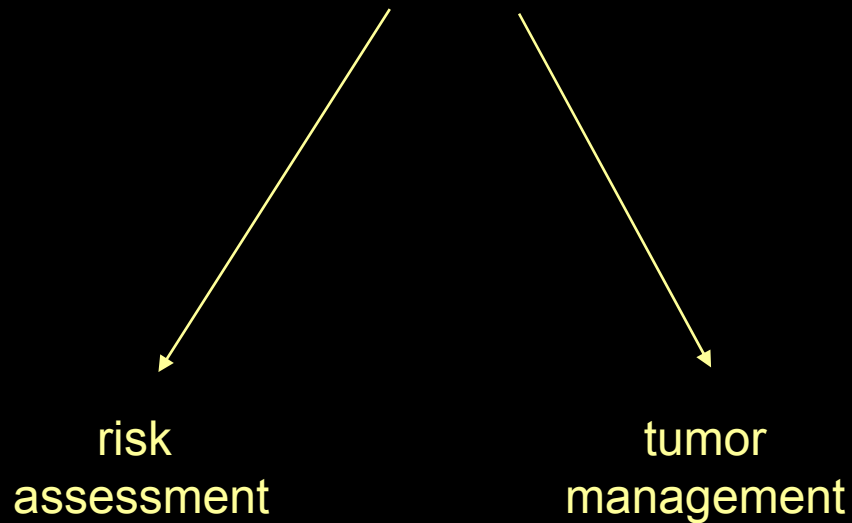
False negatives

- combining LDCT with autofluorescence bronchoscopy
- Pan-Canadian Screening study
 - 7 centers in Canada – including PMH
 - 2500 participants
 - funded by the Terry Fox Research Institute / Canadian Partnership Against Cancer
 - launched Sep 2008

Reducing Mortality

Individual profile

- combining LDCT with
 - sputum analysis
 - blood analysis (biomarkers)



Does Screening Reduce Mortality?

- mortality benefit directly addressed in randomized trials
- dynamic process
- factors influencing morbidity can be minimized
- depending on the setting