Lung Cancer Screening

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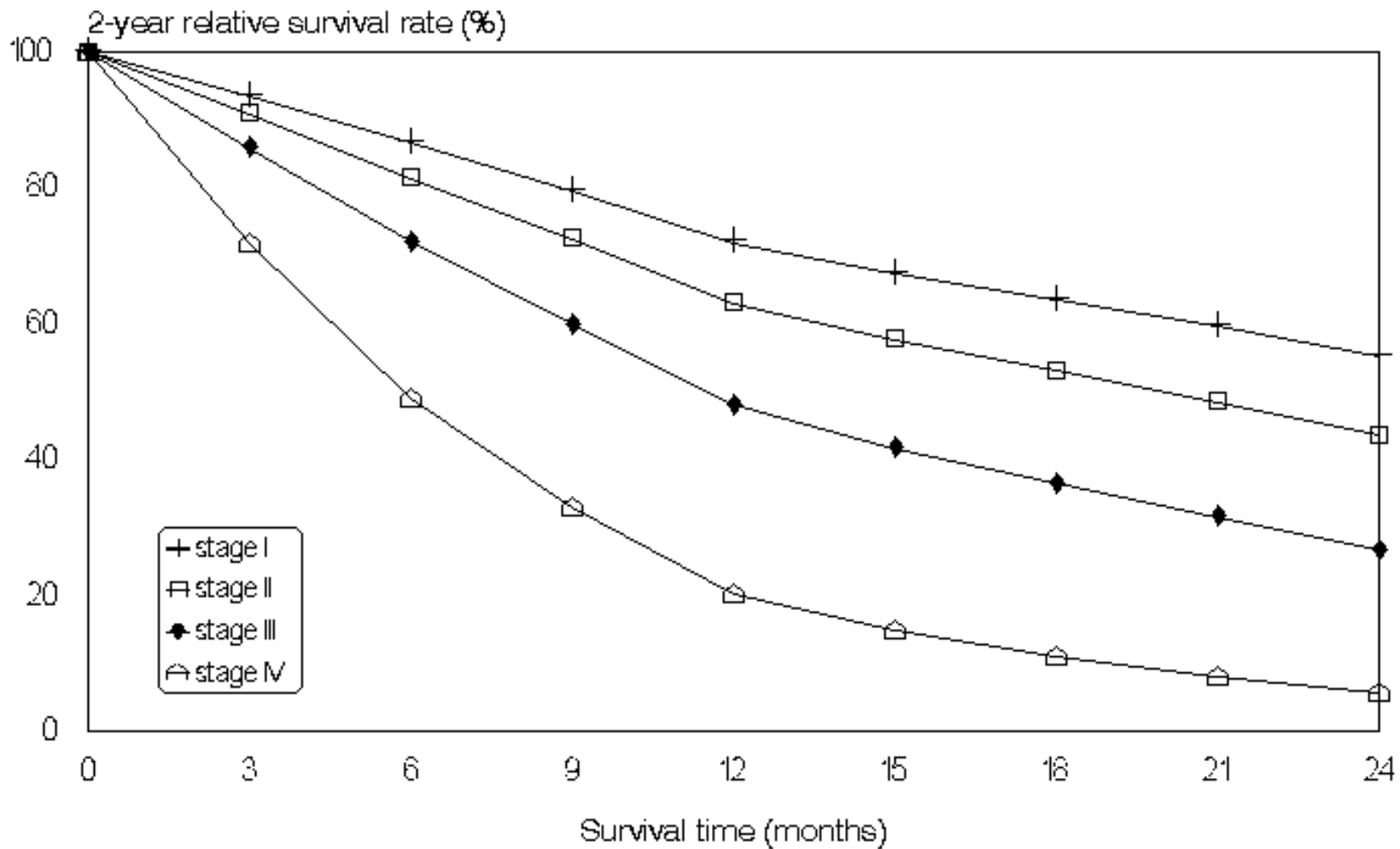Omaha, NE

No conflicts of interest to declare

Introduction

- Lung cancer - #1 cause of cancer-related deaths

- 2014 estimates
    1. 228,190 new cases
    2. 159,480 deaths

- 5-year survival - 16%

American Cancer Society. Facts and Figures

Zhang G. Public Health Agency of Canada

Rationale for screening

Ideal screening tool

- Major public health problem

- Clear understanding of the natural history

- Safe, acceptable, cost-effective method to detect latent disease

- Effective treatment for early disease

Wilson JM, Bol Oficina Sanit Panam 1968; 65: 281–393.

CT scan screening

- Rapid advances technology

- Improvement in image acquisition and analyses

- Low-resolution images of thorax - low radiation exposure, single breath-hold

CT screening studies

Institution		% Cancer	Mean/Median Size (mm)	% Stage I
Matsumoto Research Center, Japan	Prevalence	0.41	17/13.5	100
	Incidence	0.44	12/≈11	86
Cornell University	Prevalence	2.7	≈14/≤10	85
	Incidence	0.7	12/8	71
Mayo Clinic	Prevalence	1.9	14.7/14	67
	Incidence	2.1	14.6/8	60
National Cancer Center, Japan	Prevalence	0.86	20/20	79
	Incidence	2.8	15/20	82
Milan	Prevalence	1.06	21/NA	55
	Incidence	1.1	15/NA	100
Pittsburgh	Prevalence	1.45	NA	60
	Incidence	0.78	NA	53
I-ELCAP	Prevalence	1.28	NA	85
	Incidence	0.29	NA	

National Lung Screening Trial

- Randomized multicenter study

- Low-dose CT scans (n = 26,722) vs. chest X-rays (n = 26,732)

- Eligibility criteria

  - Age 55–74 years

  - ≥30 pack-year history of cigarette smoking

  - Former smokers must have quit smoking within the previous 15 years

- Low-dose CT or chest X-ray at baseline and two annual follow-up exams

- Primary endpoint - lung cancer mortality

- Secondary endpoints

  - All-cause mortality

  - Incidence of lung cancer

  - Lung cancer case survival

  - Lung cancer stage distribution

Test performance

|	Chest CT			CXR		
	T0	T1	T2	T0	T1	T2
Sensitivity (%)	93.8	94.4	93	73.5	59.6	63.9
Specificity (%)	73.4	72.6	83.9	91.3	94.1	95.3
Positive predictive value (%)	3.8	2.4	5.2	5.7	4.4	6.7
Negative predictive value (%)	99.9	99.9	99.9	99.7	99.8	99.8

NLST Team. N Engl J Med 2013; 368:1980-91.
Aberle DR. N Engl J Med 2013;369:920-31.

Incidence of lung cancer

- 645 cases per 100,000 person-years (1060 cancers) in the low-dose CT group

- 572 cases per 100,000 person-years (941 cancers) in the radiography group

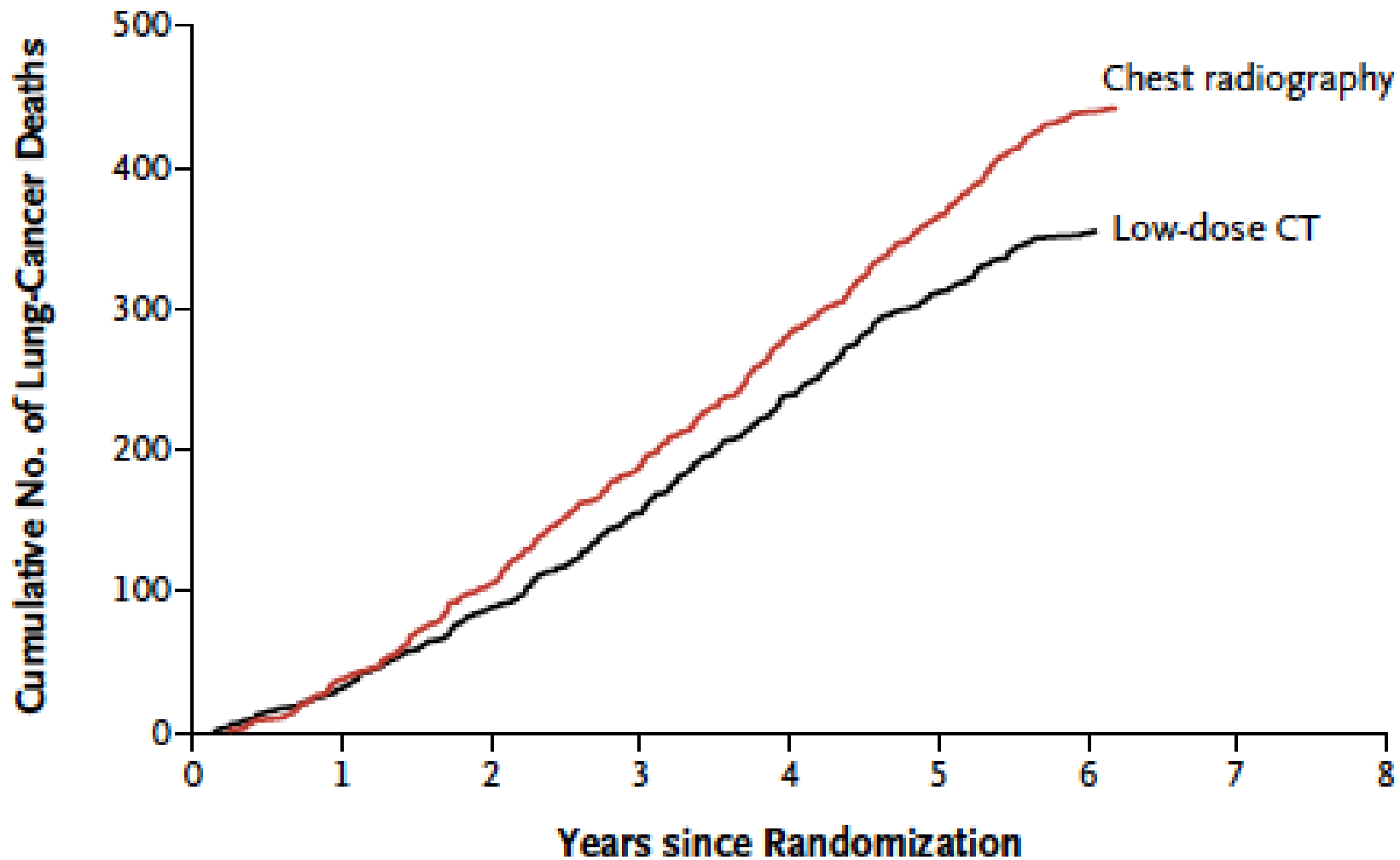- Rate ratio, 1.13 (95% CI, 1.03 to 1.23).

A Lung Cancer
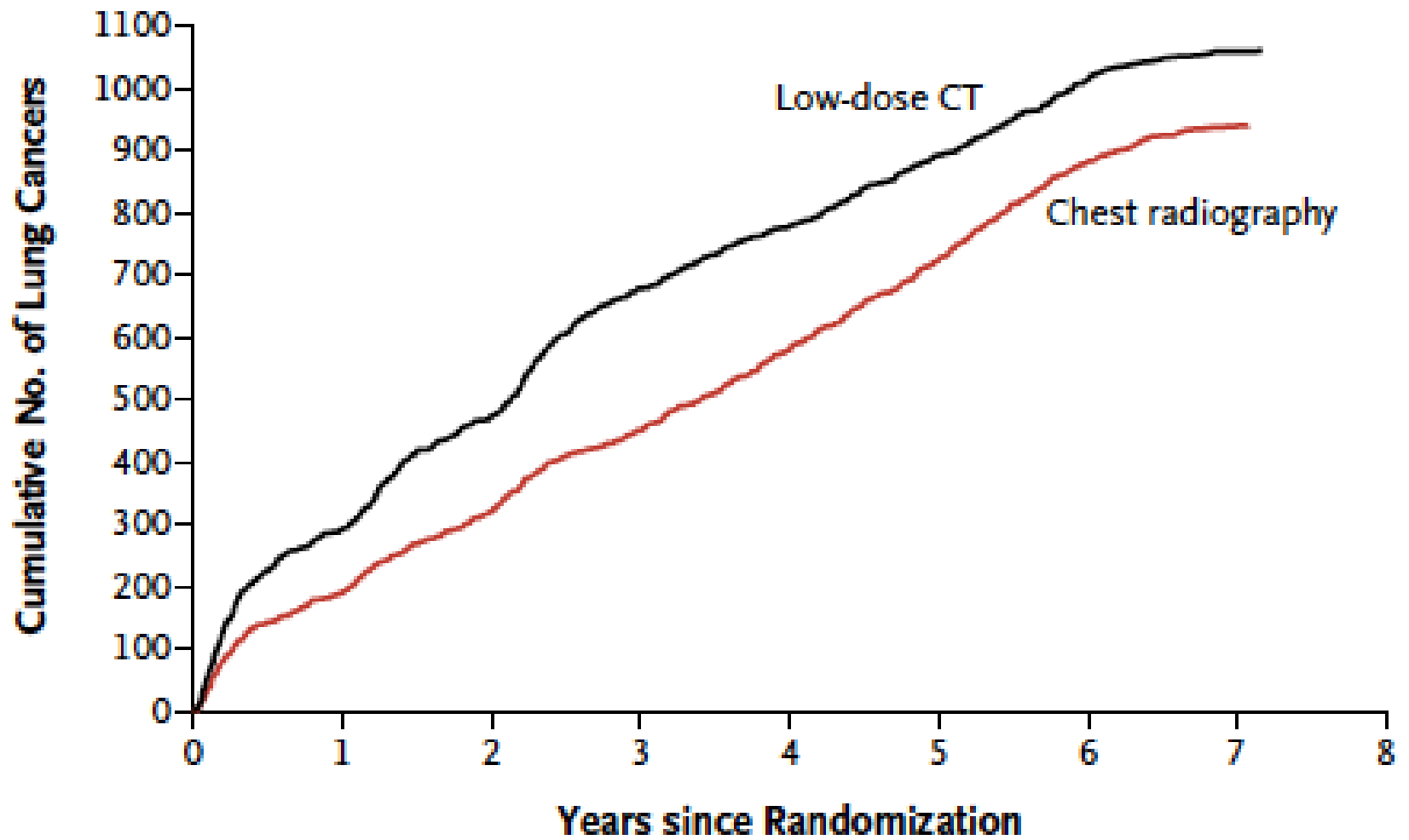
- **Lung cancer deaths**
  - 247/100,000 person-years in the low-dose CT group
  - 309/100,000 person-years in the CXR group
  - Relative reduction in lung cancer mortality with low-dose CT screening - 20.0% (95% CI, 6.8 to 26.7; P = 0.004).

N Engl J Med 2011;365:395-409.

B Death from Lung Cancer

N Engl J Med 2011;365:395-409.

- **All cause mortality**

  - 1877 deaths in the low-dose CT group vs. 2000 deaths in the CXR group

  - Reduction in mortality in the low-dose CT group - 6.7% (95% CI, 1.2 to 13.6; P = 0.02)

- **Lung cancer - 24.1% of all deaths**

  - 60.3% of excess deaths in the CXR group - due to lung cancer

Why not just screen everyone?

- High screening costs

- Uncertainty about overdiagnosis

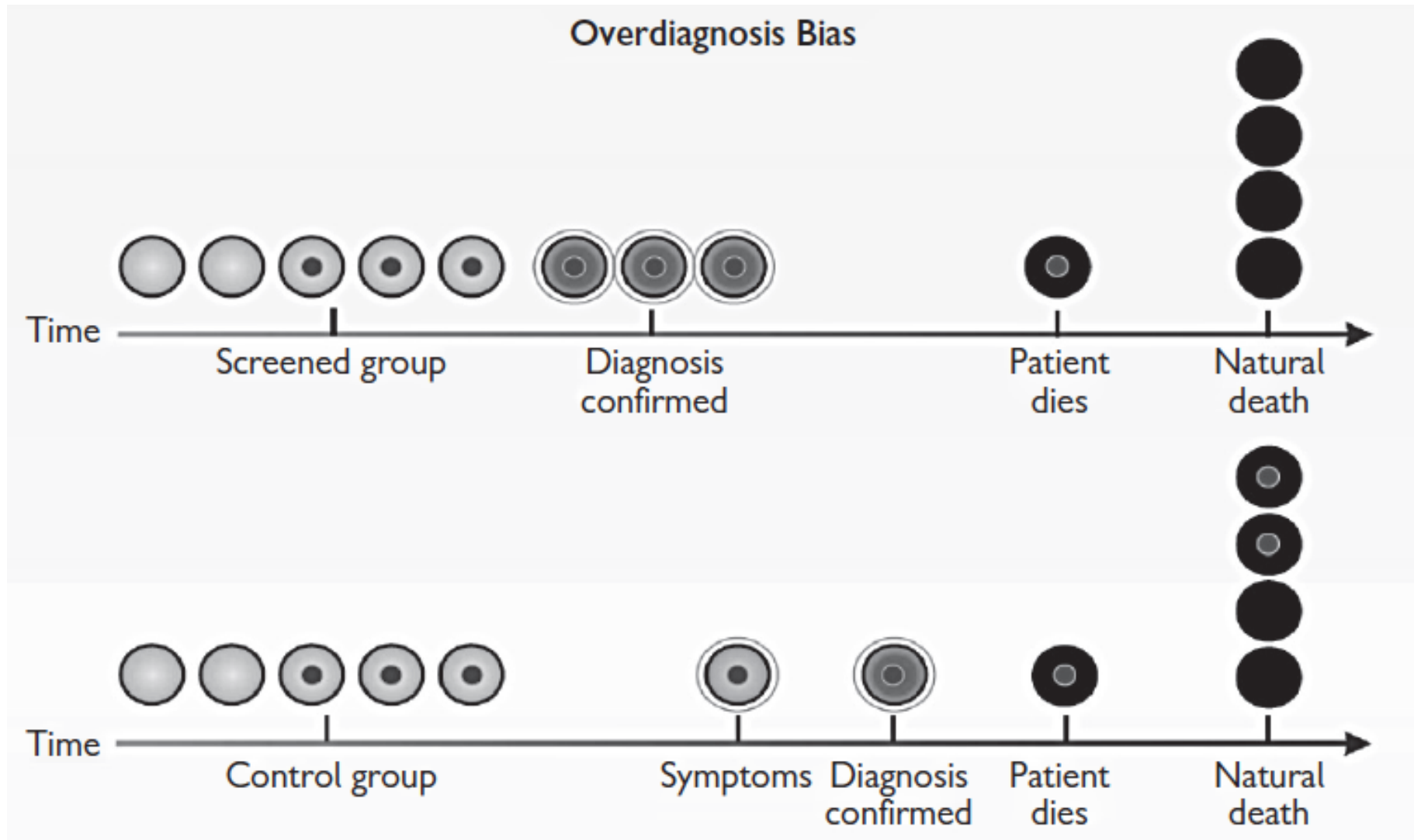- Harms associated with diagnosis and treatment

Overdiagnosis

- >80% of screen-detected tumors - stage I, but no stage shift

- No difference in advanced-stage disease between CT studies and CXR trials (~3/1,000 patients)

Swensen SJ. Radiology 2005;235:259–265.

Overdiagnosis Bias

- **Incidentally diagnosed lung cancers**

  1. Autopsy studies - 0.8%

  2. 1/123 patients - lung reduction surgery

- **Gene-expression profile: Screen-detected cancers ≈ symptomatic cancers**

False positives

- **Mayo Clinic**

  - 70% non-calcified lung nodules

    - Fraction needed invasive follow-up

- **NLST - ≈ 25%**

- **I-ELCAP - 23%**

- **COSMOS - 15%**

Swensen SJ. Radiology 2003;226:756–761.
Henschke CI. Nat Clin Pract Oncol. 2007;4:440-1.
Veronesi G. J Clin Oncol 2007;25:18S (Suppl): 7566

- **Peri-operative mortality**

  - Mayo Clinic - 1.7%

  - I-ELCAP - 0.5%

  - Widespread screening - more complications

Henschke CI. Radiology 2004;231:164–168.
Crestanello JA. J Thorac Cardiovasc Surg 2004;128:254–259.

Which nodules are likely to be malignant?

- Two cohorts

  1. Pan Canadian Early Detection of Lung Cancer Study (n=1871)

  2. British Columbia Cancer Agency (n=1090)

- Rates of cancer (individuals with nodules)

  - PanCan – 5.5%; BCCA – 3.7%

McWilliams A. N Engl J Med 2013;369:910-9.

Factors predicting for risk of malignancy

Variable	Odds Ratio	P-value
Sex (Female vs. male)	1.82 (1.12 – 2.97)	0.02
Nodule size*		<0.0001
Nodule location (upper lobe vs. middle or lower lobe)	1.93 (1.14 – 3.27)	0.02
Nodule count, per each additional nodule	0.92 (0.85 – 1.00)	0.049
Spiculation (Yes vs. No)	2.17 (1.16 – 4.05)	0.02

•Non-linear association

http://www.brocku.ca/lung-cancer-risk-calculator

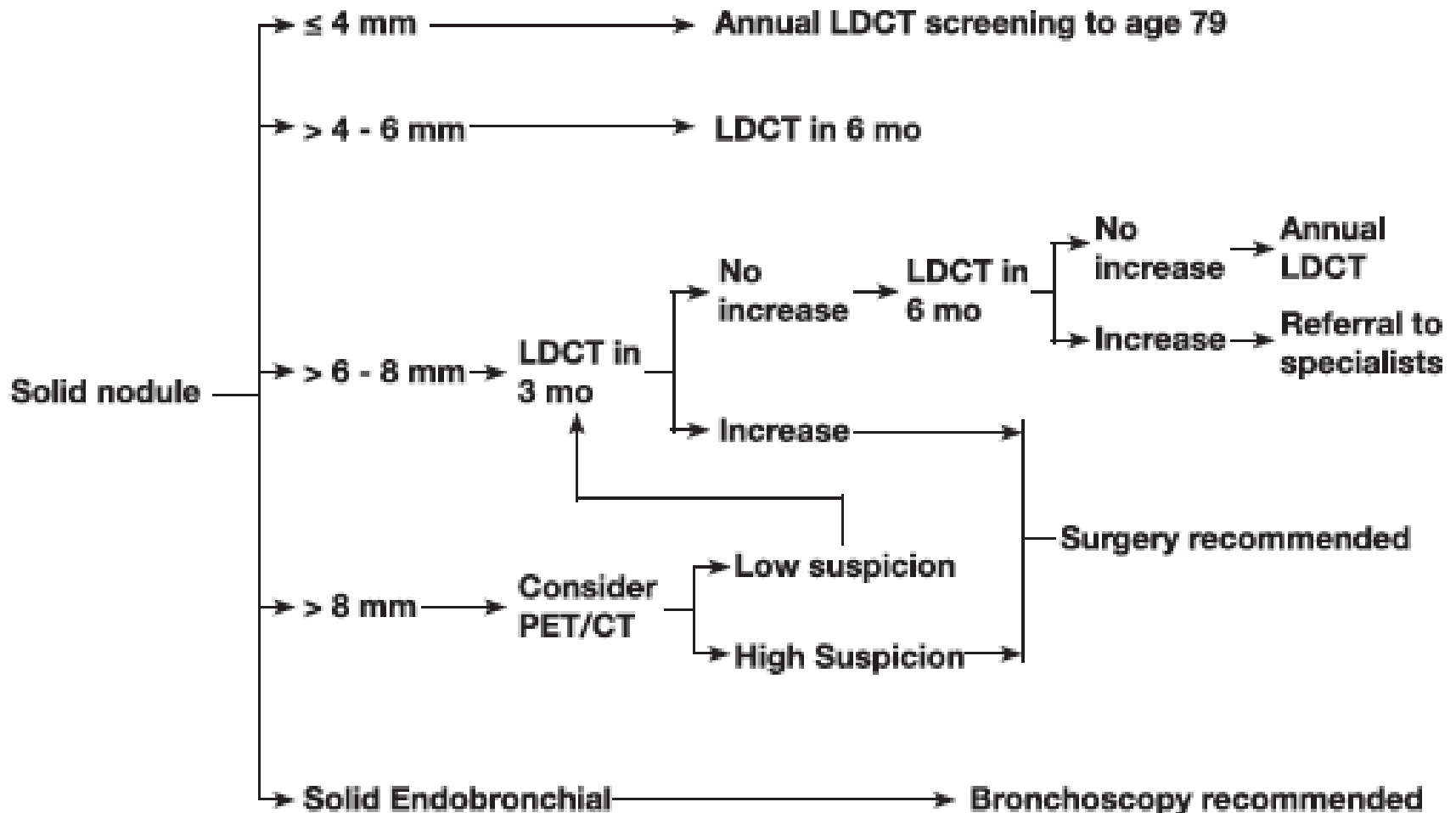# Incidental nodules

Algorithm based on

- Size

- Number

- Density

- Patient characteristics: age, gender, smoking, occupation, granulomatous disease

Libby DM. Chest 2004;125:1522–1529.

AATS guidelines

Jaklitsch MT, et al. J Thorac Cardiovasc Surg 2012;144:33-38.

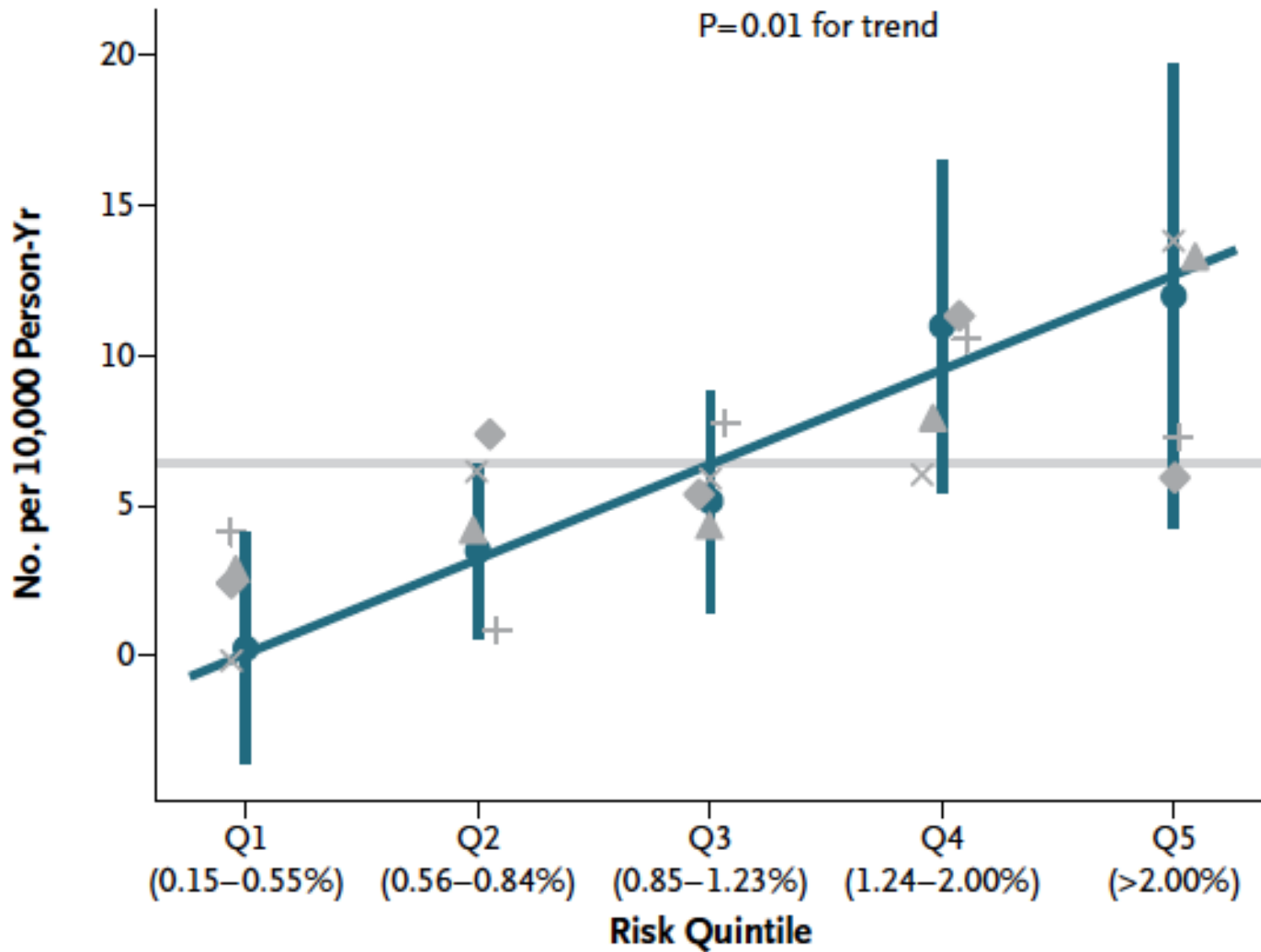# Prediction models for lung cancer death

Lung cancer deaths

- Age
- BMI
- Family history of lung cancer
- Pack-years of smoking
- Years since smoking cessation
- Emphysema diagnosis

Other causes of death

- Age
- Sex
- Race
- BMI
- Pack-years of smoking
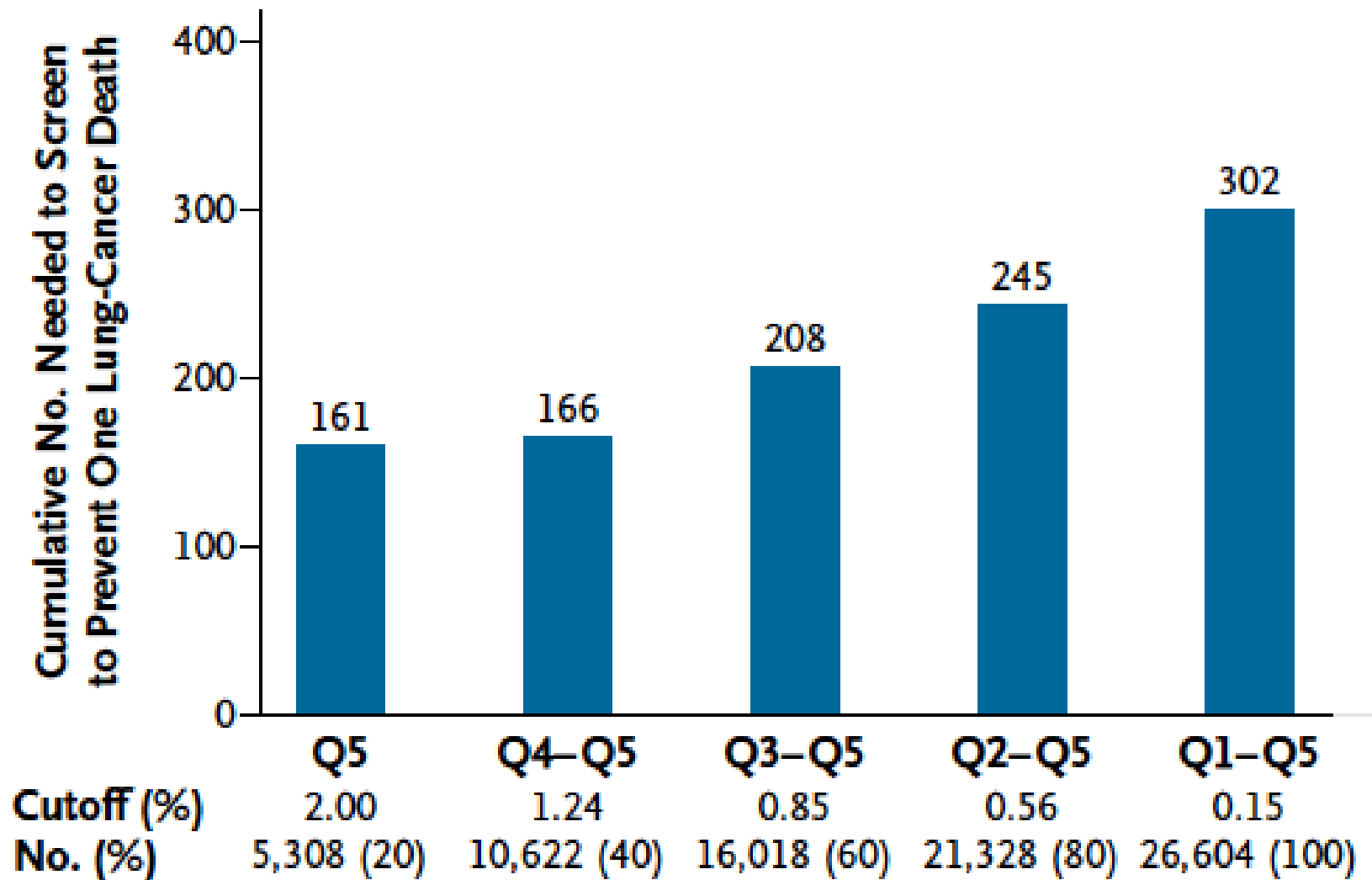- Years since smoking cessation
- Emphysema diagnosis

Kovalchik S et al. N Engl J Med 2013.369:245-254

B Lung-Cancer Deaths Prevented by Low-Dose CT

Kovalchik S et al. N Engl J Med 2013.369:245-254

B Number Needed to Screen

Kovalchik S et al. N Engl J Med 2013.369:245-254

- http://nomograms.mskcc.org/Lung/Screening.aspx

Radiation exposure

- If 50% of high-risk population screened annually (20-25 yrs) - 36,000 new cancers

- International Commission on Radiological Protection - 5 cancers/100,000 exams

- American Society of Radiation Technologists

  - http://www.xrayrisk.com/calculator/select_study.php?id=68

Brenner DJ. Radiology 2004;231:440–445.
Diederich S. Eur Radiol 2001;11:1916–1924.

Number needed to harm

- 55 year old male annual screening for 20 years – 0.2% additional risk

  1. Risk of lung cancer from screening - 1 in 567

- 55 year old female annual screening for 20 years – 0.22% additional risk

  - Risk of lung cancer from screening - 1 in 438

Scenario			Benefits		Harm		Screenings per death averted
Pack-yrs	Age of onset	Time since quit	Proportion of deaths averted	No. of deaths averted	No. of screenings	Deaths from radiation	
40	60	25	11%	410	171,924	17	419
40	55	25	12.3%	458	221,606	21	483
30	60	25	13.3%	495	253,095	21	511
30	55	15	14%	521	286,813	24	550
20	60	25	15.4%	573	327,024	25	583
30	55	25	15.8%	588	342,880	25	570
20	55	25	17.9%	664	455,381	31	685
10	55	25	19.4%	721	561,744	35	777

Cancer Intervention and Surveillance Modeling Network (CISNET). Source: USPSTF

USPSTF Recommendations

- "The USPSTF concludes with moderate certainty that annual screening for lung cancer with LDCT is of moderate net benefit in asymptomatic persons at high risk for lung cancer based on age, total cumulative exposure to tobacco smoke, and years since quitting"

- <u>Smoking cessation is the most important intervention to prevent NSCLC</u>

- Smoking cessation counseling is **the most effective way** to decrease the morbidity and mortality associated with lung cancer

- Lung cancer screening is only an adjunct to tobacco cessation interventions

A screening protocol should be conducted only in the setting of a comprehensive smoking cessation program

- NELSON - Dutch-Belgian trial

  - N = 15,600

  - Inclusion criteria

    - DOB: 1928 and 1956

    - Heavy smokers (≈15 pack years)

    - Quit < 10 years

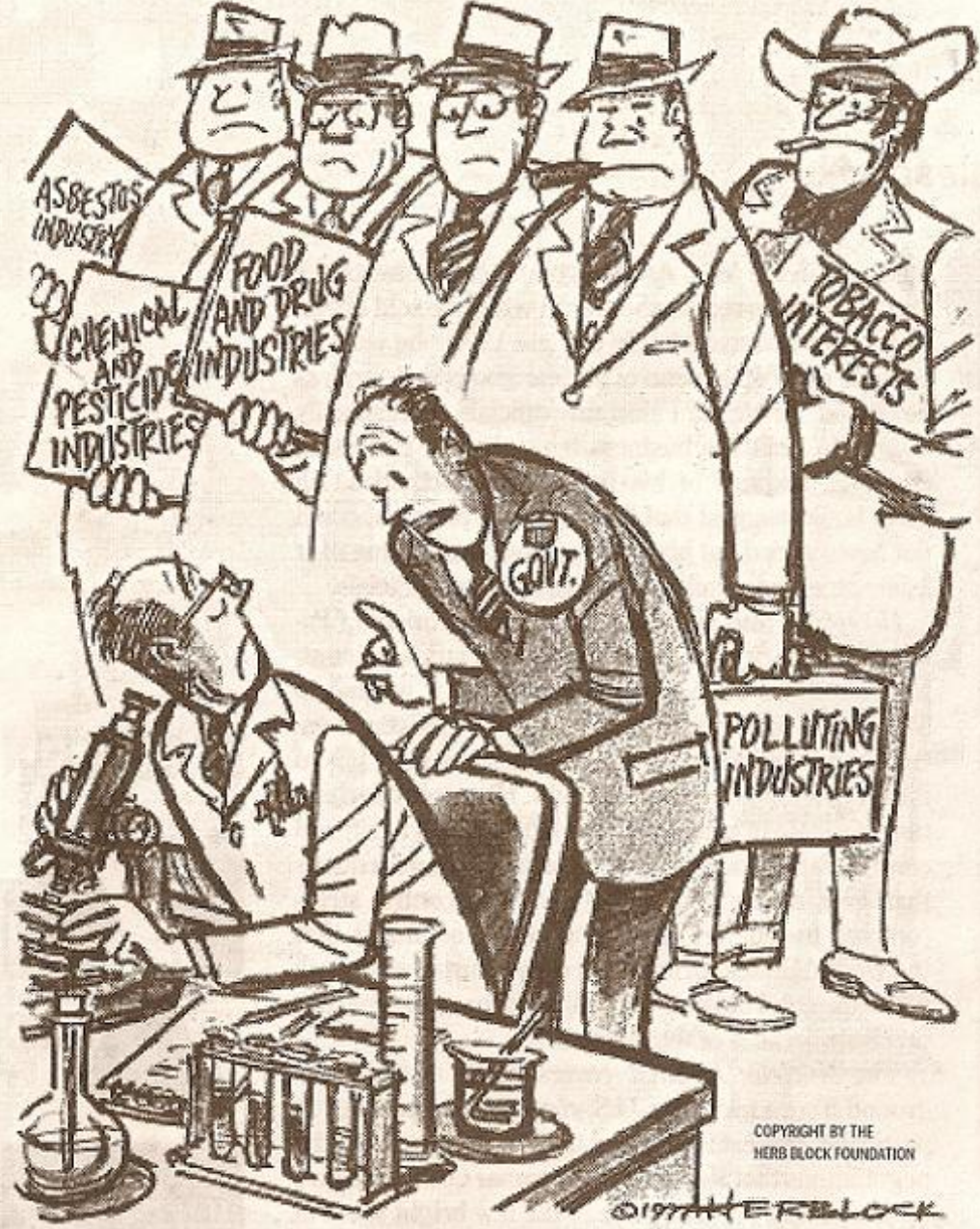 - Chest CT in years 1, 2, 4 + smoking cessation advice vs. smoking cessation advice

- Unresolved Issues

  - Defining optimal screening cohort

  - Evaluation of evolving computer-assisted diagnosis capabilities

  - Elucidating "best practice" for case management

  - Elucidating requisite frequency of screening and follow-up

Conclusions

- Lung cancer screening – major changes

- Decision to screen – individualized

  - Smoking cessation

  - Potential morbidity, mortality, and costs

  - "False positives" and "false negatives"

  - Expertise of the individual center in evaluating abnormalities