Epidemiology of Lung Cancer: Implications for screening and prevention
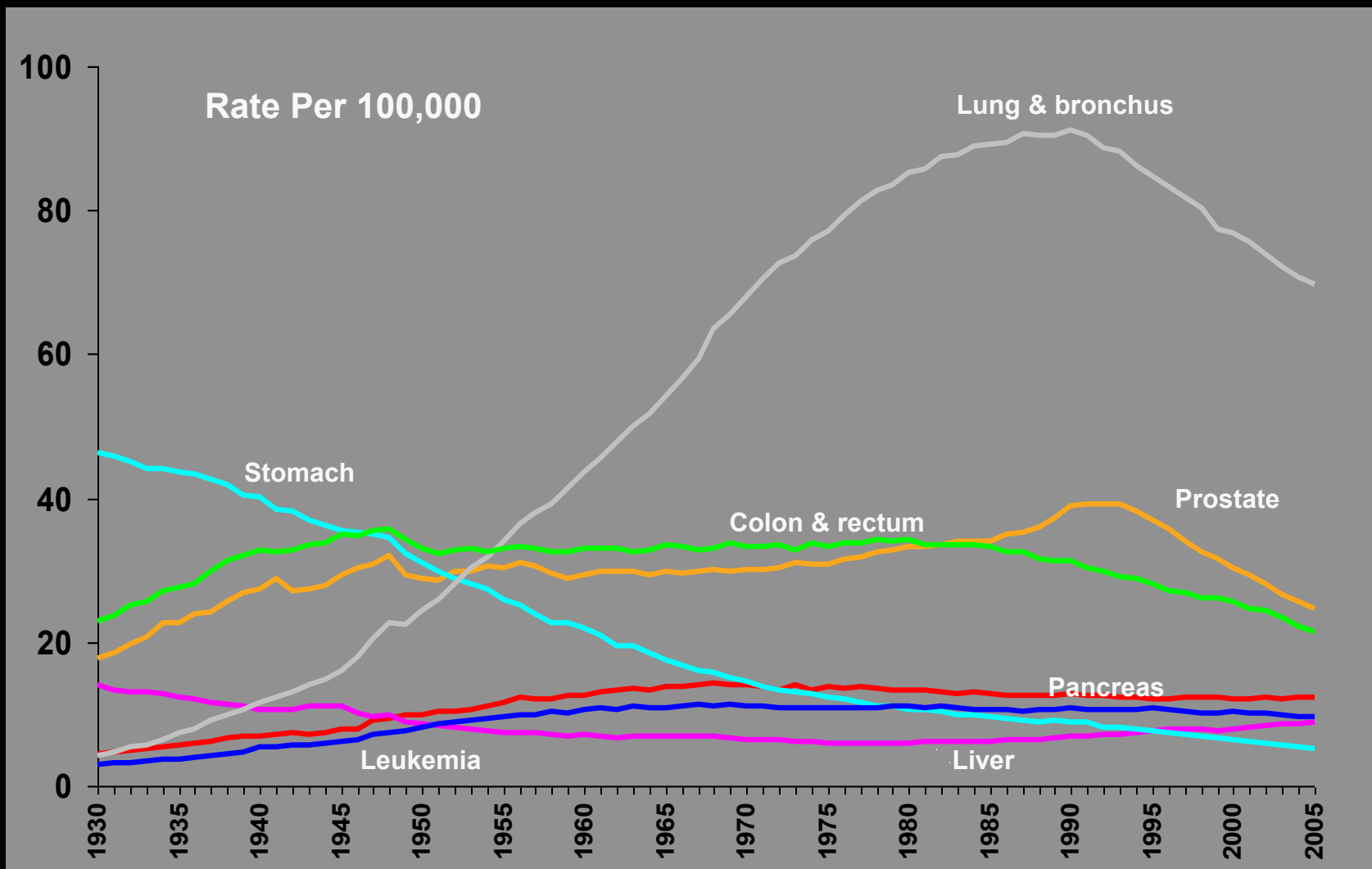
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I thank my DCEG colleagues Neil Caporaso and Neal Freedman for sharing slides with me

Cancer Death Rates* Among Men, US, 1930-2005

Rate Per 100,000

Lung & bronchus

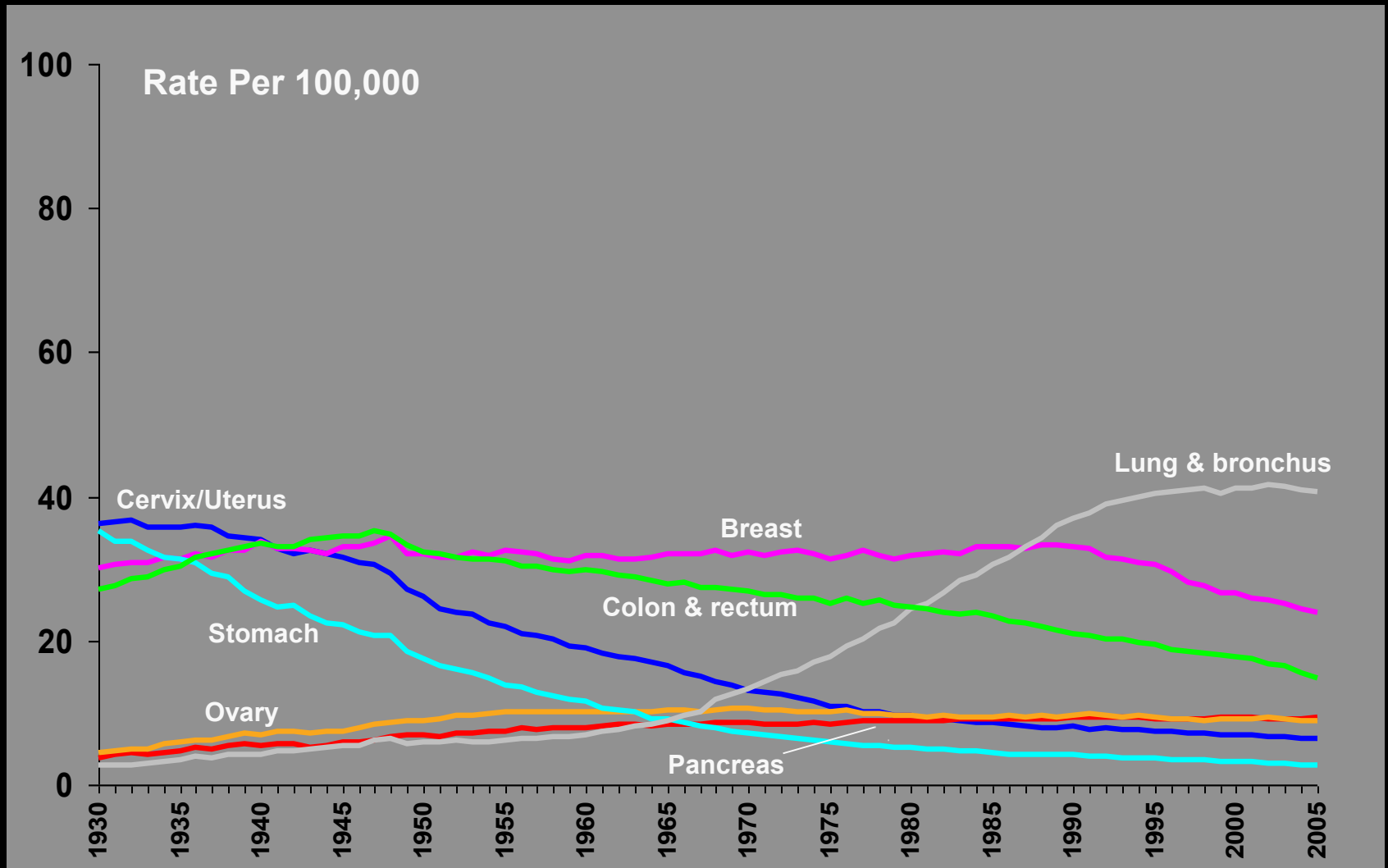Stomach

Prostate

Colon & rectum

Pancreas

Leukemia

Liver

*Age-adjusted to the 2000 US standard population.
Source: US Mortality Data 1960-2005, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2008.
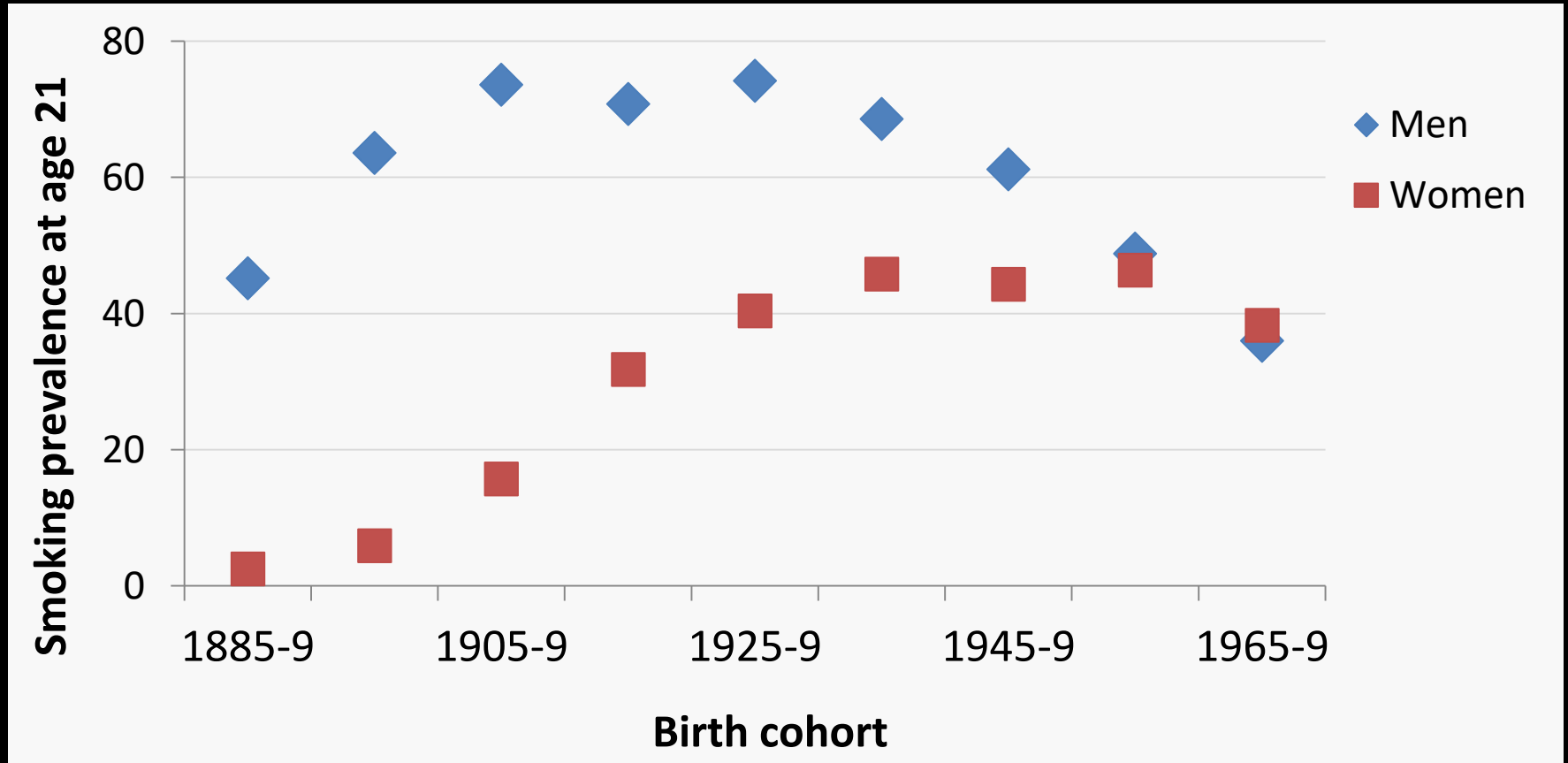
Cancer Death Rates* Among Women, US,1930-2005

*Age-adjusted to the 2000 US standard population.
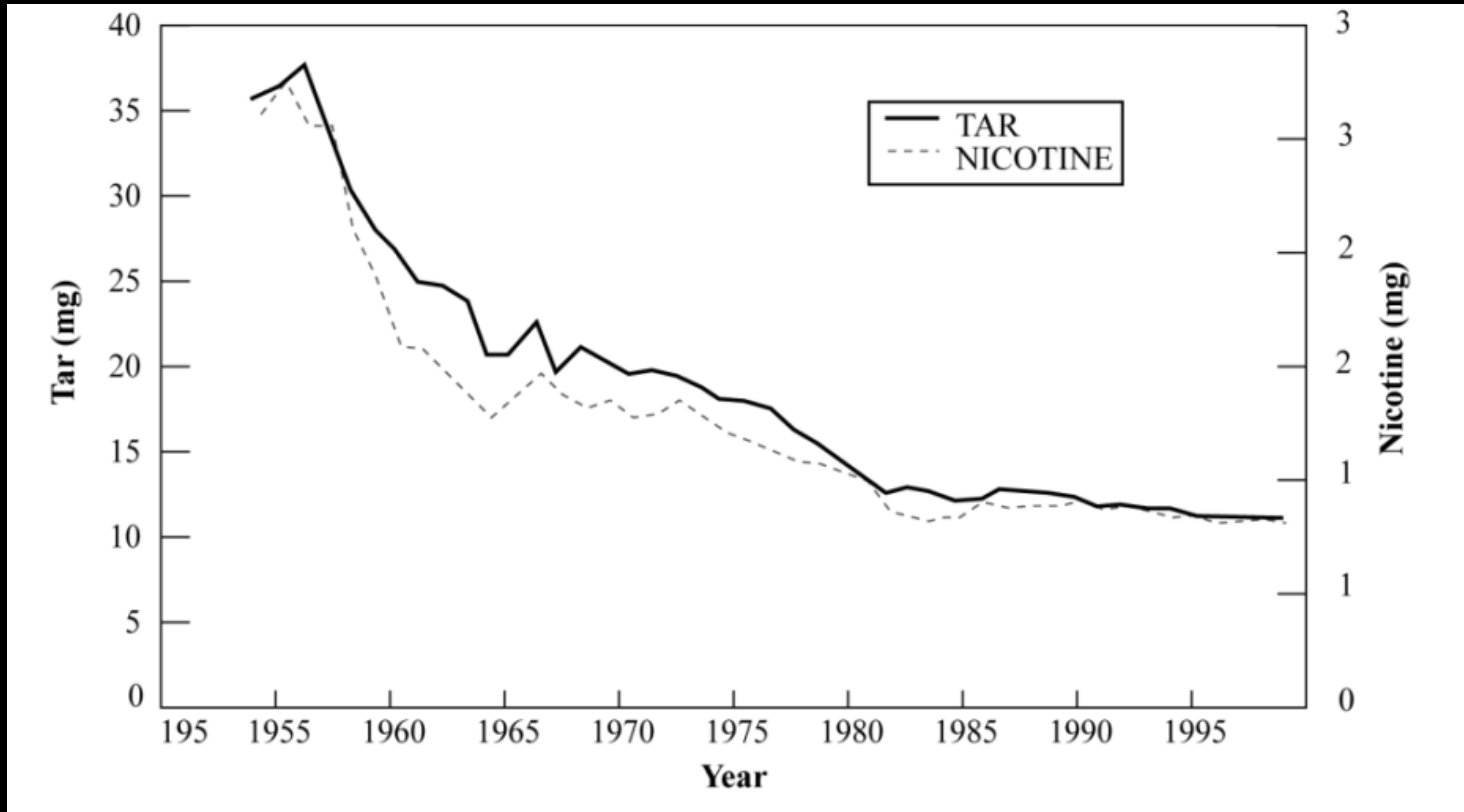Source: US Mortality Data 1960-2005, US Mortality Volumes 1930-1959,
National Center for Health Statistics, Centers for Disease Control and Prevention, 2008.

Smoking prevalence in US men and women

Burns et al, NCI Smoking and Tobacco Control Monograph No. 8, 1997

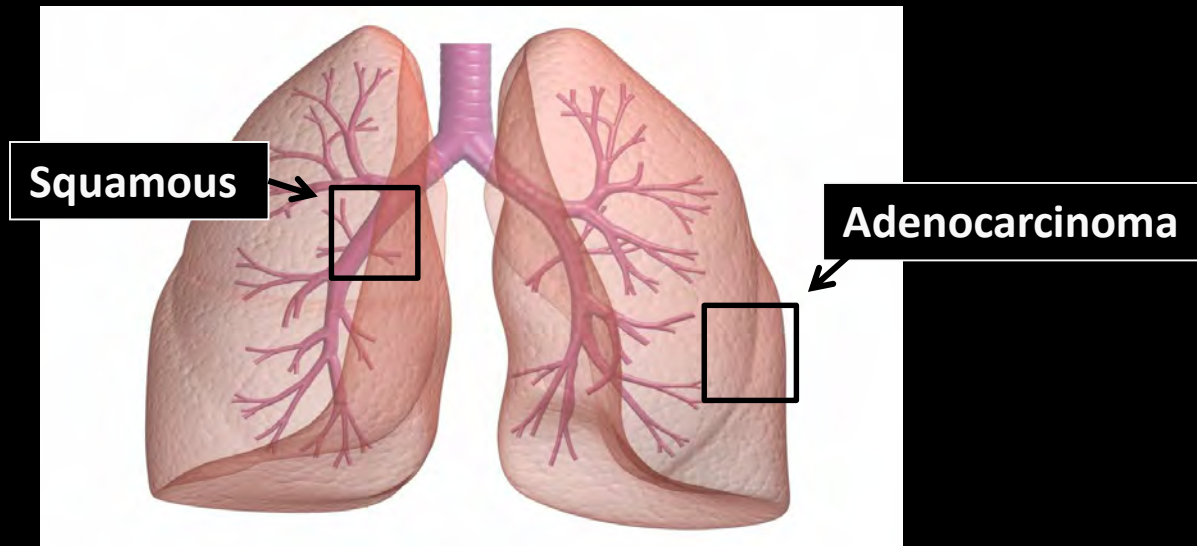# Haven't cigarettes gotten safer?

Burns, Benowitz, et al, NCI Smoking and Tobacco Control Monograph No. 13, 2001

People changed the way they smoke

- **Increased number of puffs**

- **Increased puff volume**

- **Increased inhalation depth**

Changing distribution of lung cancer histologic types over time

SEER-9 cancer registries, Cook M et al, CEBP, 2009
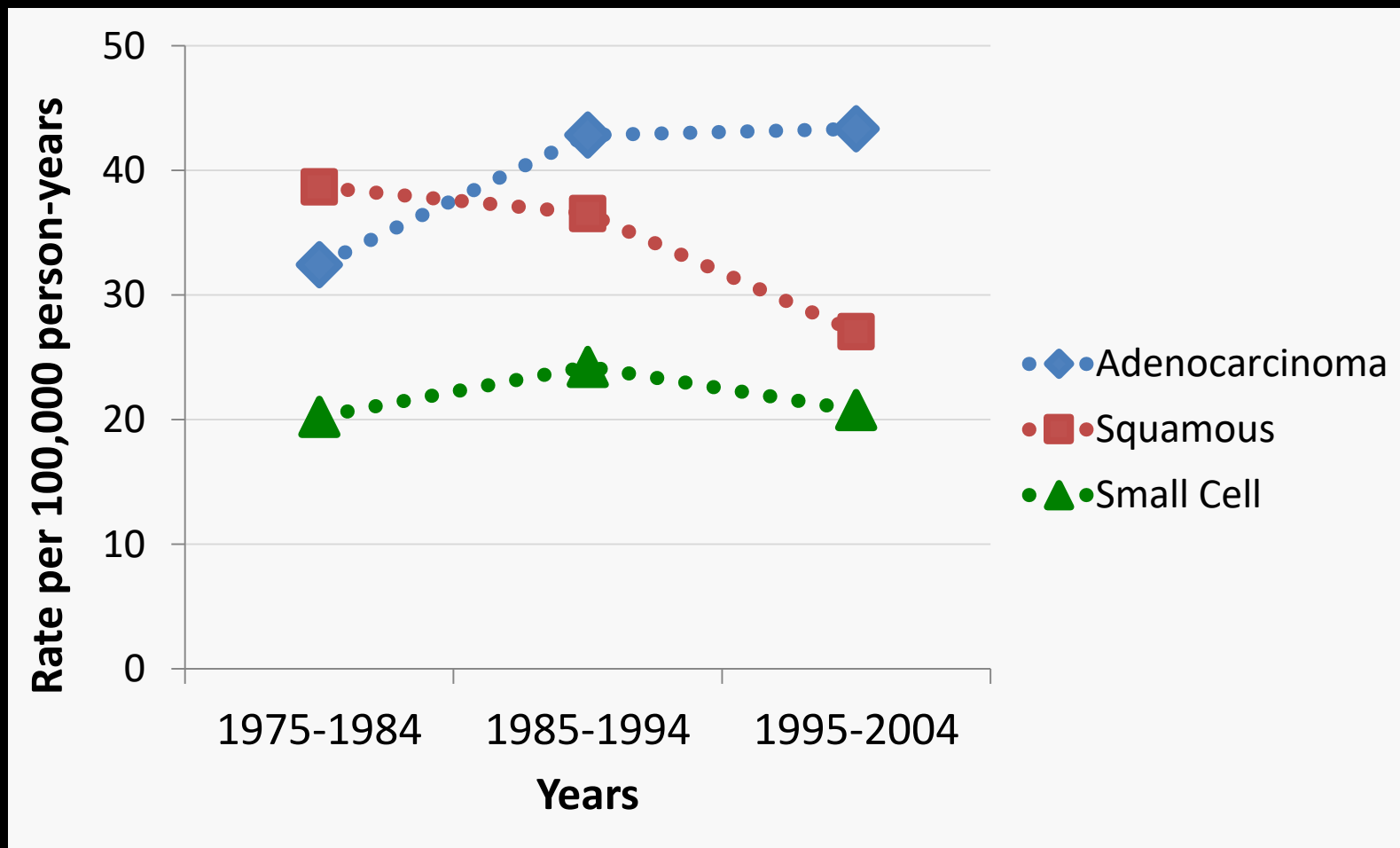
New and emerging tobacco products

TEENS MORE LIKELY TO USE MARIJUANA THAN CIGARETTES

Daily use among 12th graders

1997
24.6%

1992
1.9%

Marijuana
5.9%

Cigarettes
4.2%

25%
20%
15%
10%
5%

1992   1997   2002   2007   2012   2017

National Institute on Drug Abuse

DRUGABUSE.GOV

Lung cancer <u>relative risk</u> drops after quitting smoking, but …

Relative Risks of Lung Cancer According to Years Since Quitting Smoking among Males in Three Cohort Studies of Smokers

Relative Risk vs. Years Since Quitting Smoking

Legend: British Physicians, U.S. Veterans, American Cancer Society
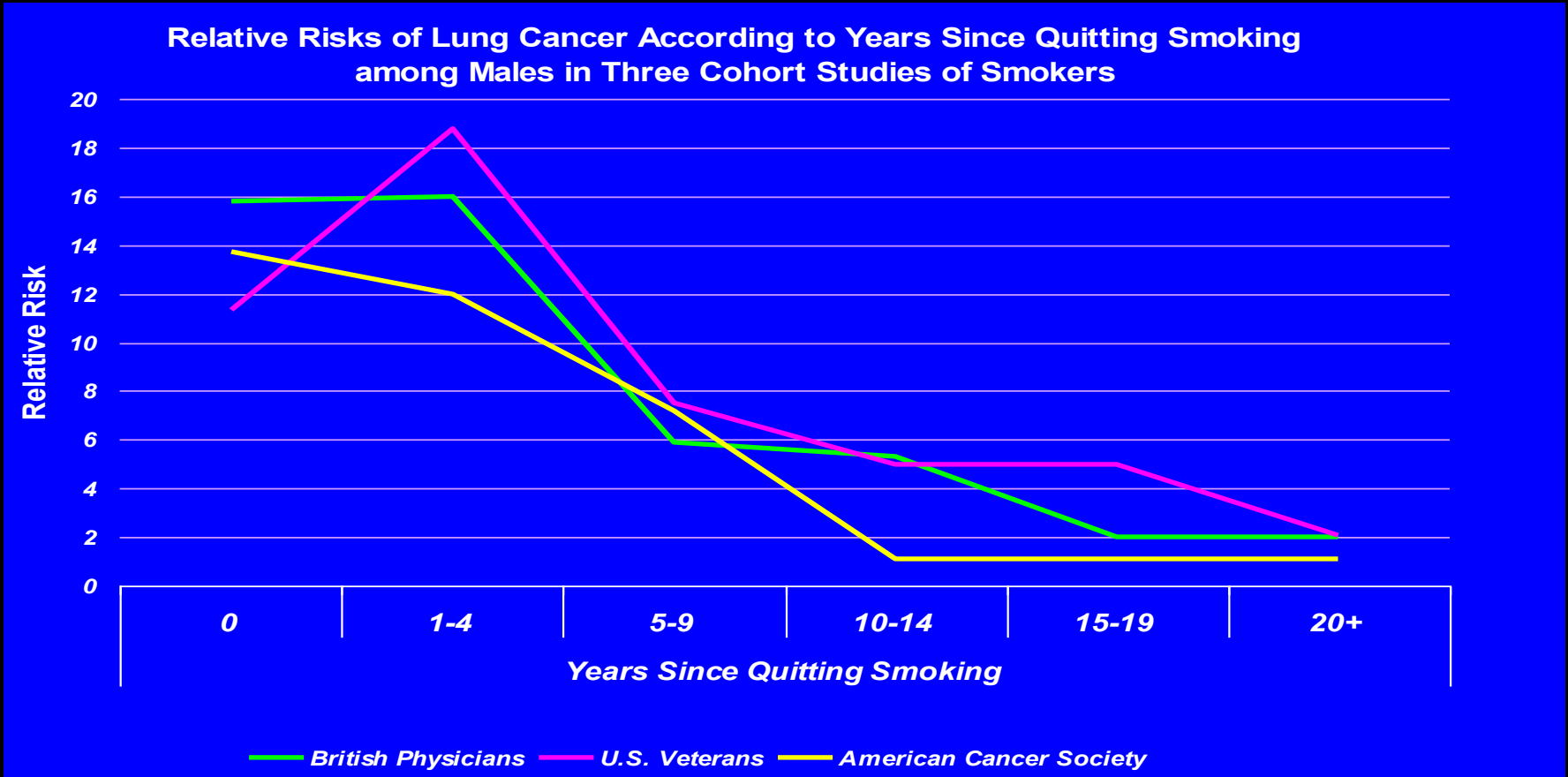
20+ year quitters still have double the lung-cancer risk of non-smokers

Lung-cancer death risk plateaus after quitting smoking
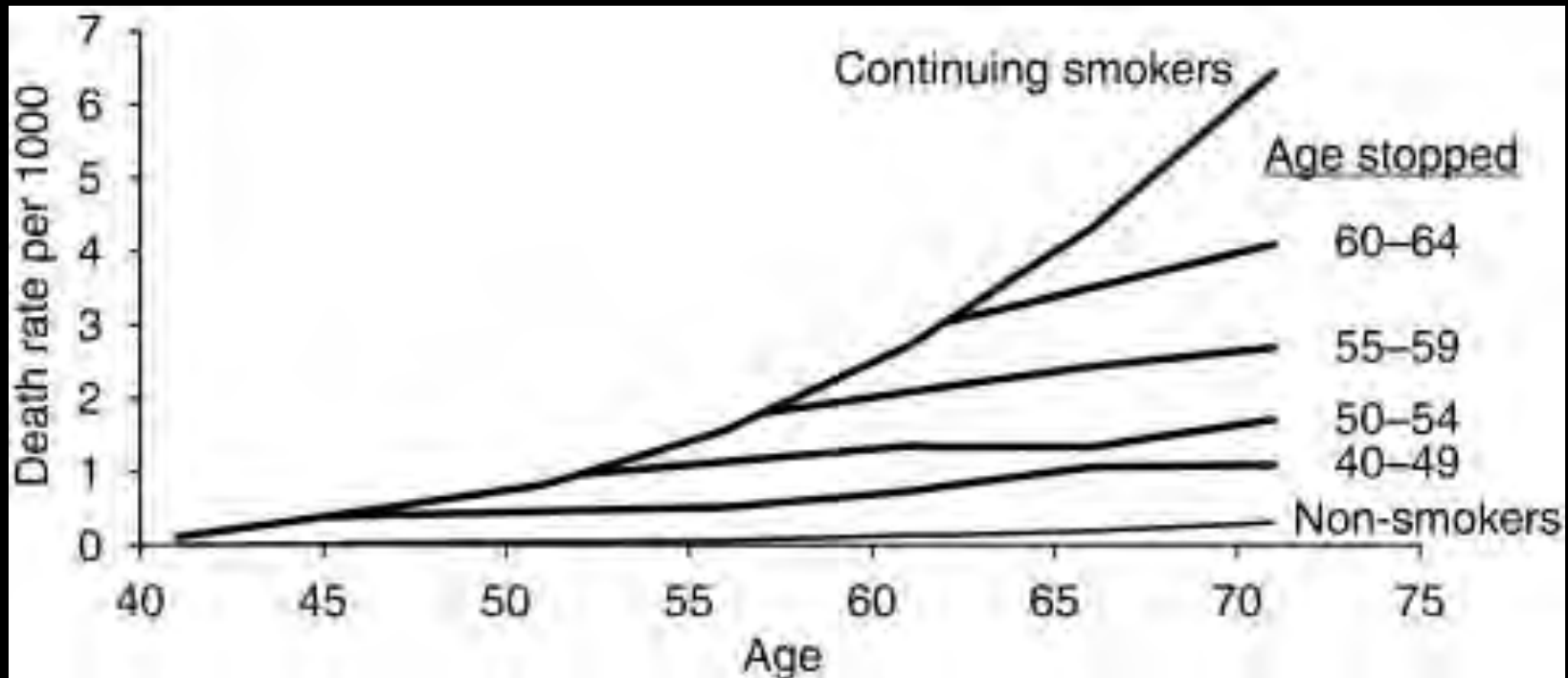
- **Don't just quit, quit <u>AS YOUNG AS POSSIBLE</u>**

- **Most lung cancer in the US is in former smokers!**

Halperin, JNCI, 1993; Peto J, Br J Cancer 2011

Slightly more quitting among those with major abnormalities found by CT lung screening?

Background
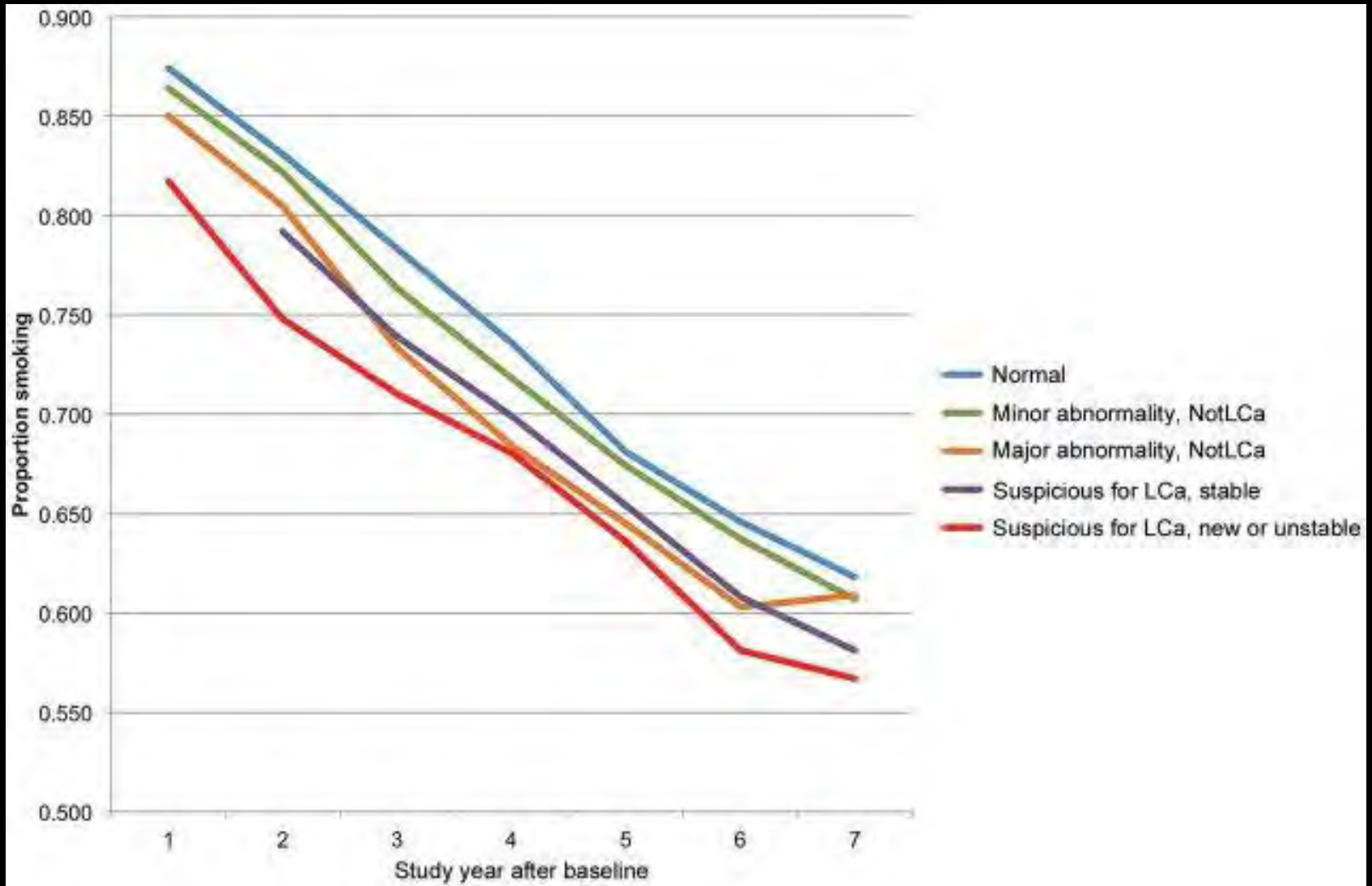## National Lung Screening Trial (NLST)

B Death from Lung Cancer

(Graph: Cumulative No. of Lung-Cancer Deaths vs. Years since Randomization, comparing Chest radiography and Low-dose CT)
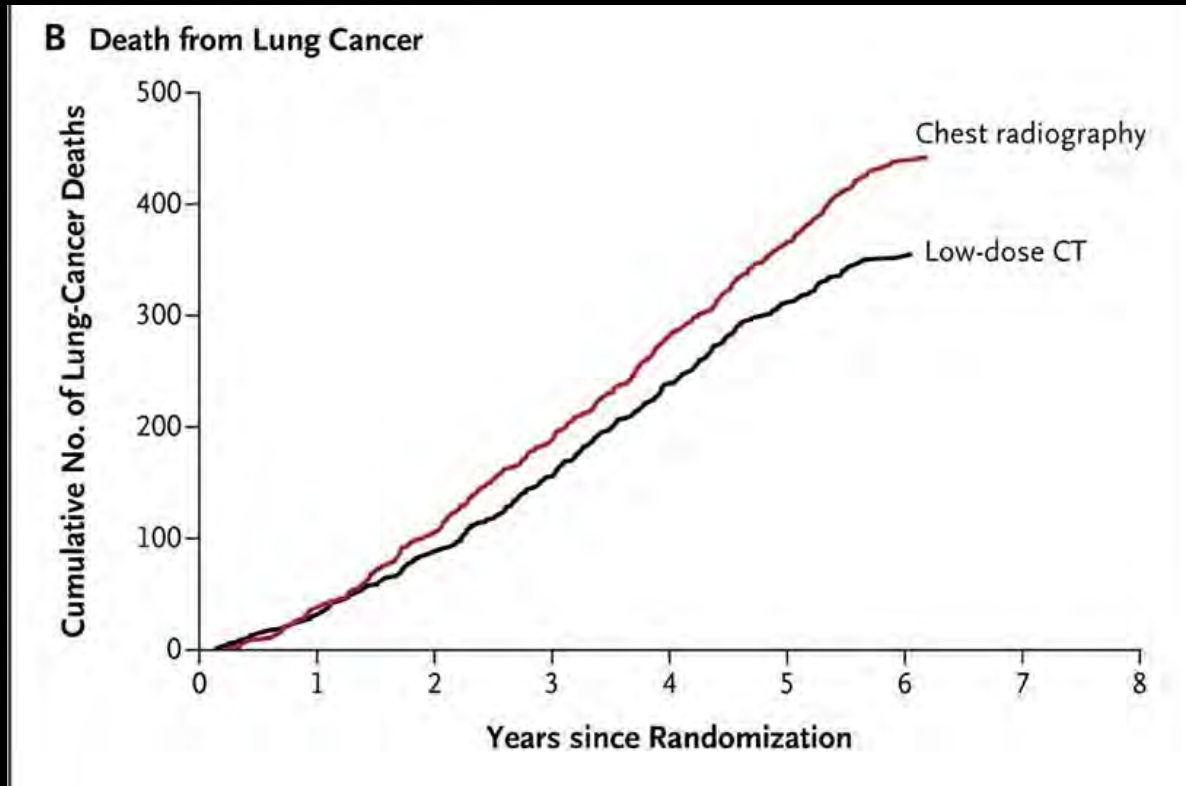
- **NLST participants: ages 55-74, ≥30 pack-years, ≤15 quit-years**
- **3 CT screens reduced lung cancer death by 20%**

Background: USPSTF and CMS
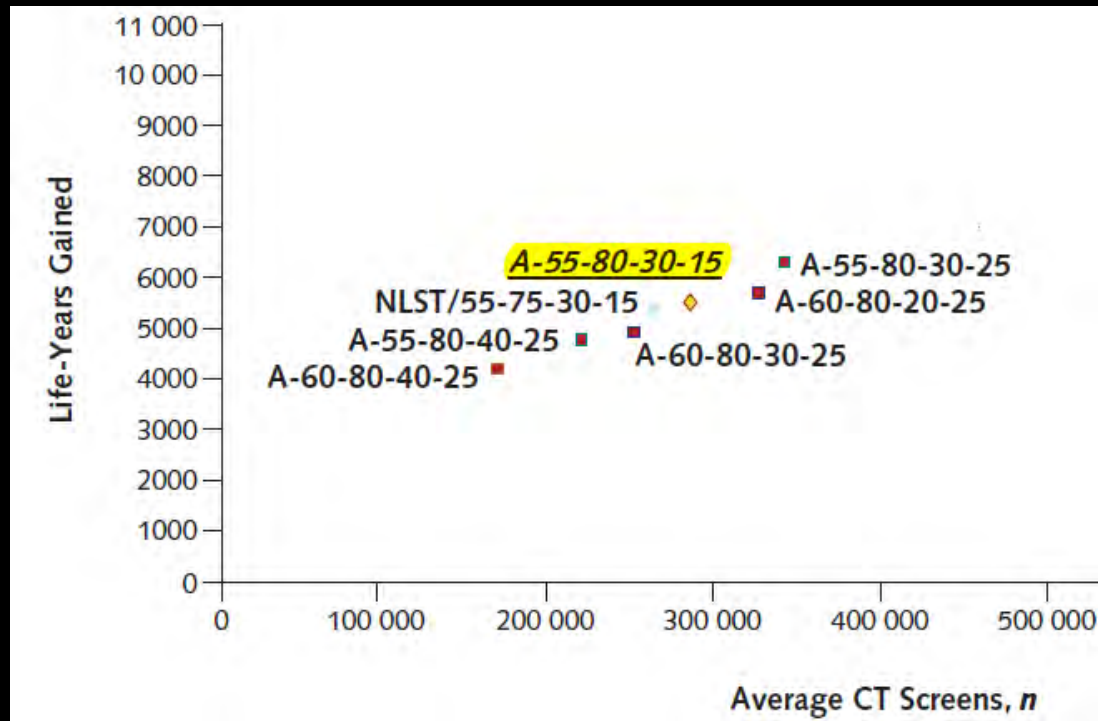
- **USPSTF guidelines**
  - ages 55-<u>80</u>, ≥30 pack-years, ≤15 quit-years

- **CMS reimbursement guideline**
  - ages 55-<u>77</u>, ≥30 pack-years, ≤15 quit-years

de Koning et al, *Ann Int Med*, 2014

No one is getting lung screening

- **Sadly, <u>less than 4%</u> of eligible US ever-smokers have received a lung-cancer screen.**

- **CT lung screening has Grade B from USPSTF, so plans must offer screening.**

- **We need a public campaign to energize eligible ever-smokers to ask their doctors about the lung screening they are entitled to**

Jemal, et. al., *JAMA Oncol*, 2017

Lung screening has false-positives and is expensive: Example of the VA

- **The VA conducted a demonstration project for CT lung screening**
  - **58% of baseline screens were false-positive**
  - **Estimated cost to implement screening: $100 million**
  - **VA has declined to implement screening**

- **However, as observed in the NLST, the ratio of false-positives per prevented death was dramatically lower <u>for those at highest risk</u>**
  - **2749 vs. 363 comparing lowest to highest risk quintiles**

Kinsinger et. al., *JAMA Intern Med*, 2017
Caverly et. al., *JAMA Intern Med*, 2018
Kovalchik et.al., *N Engl J Med*, 2013

USPSTF calls for improved risk assessment tools for screening

- **In response to public comments that lung screening be restricted to those at highest risk, the USPSTF stated:**

  "The USPSTF acknowledges the importance of accurately identifying persons who are at highest risk to maximize the benefits and minimize the harms of screening and calls for <u>more research to improve risk assessment tools</u>."

Lung cancer death model
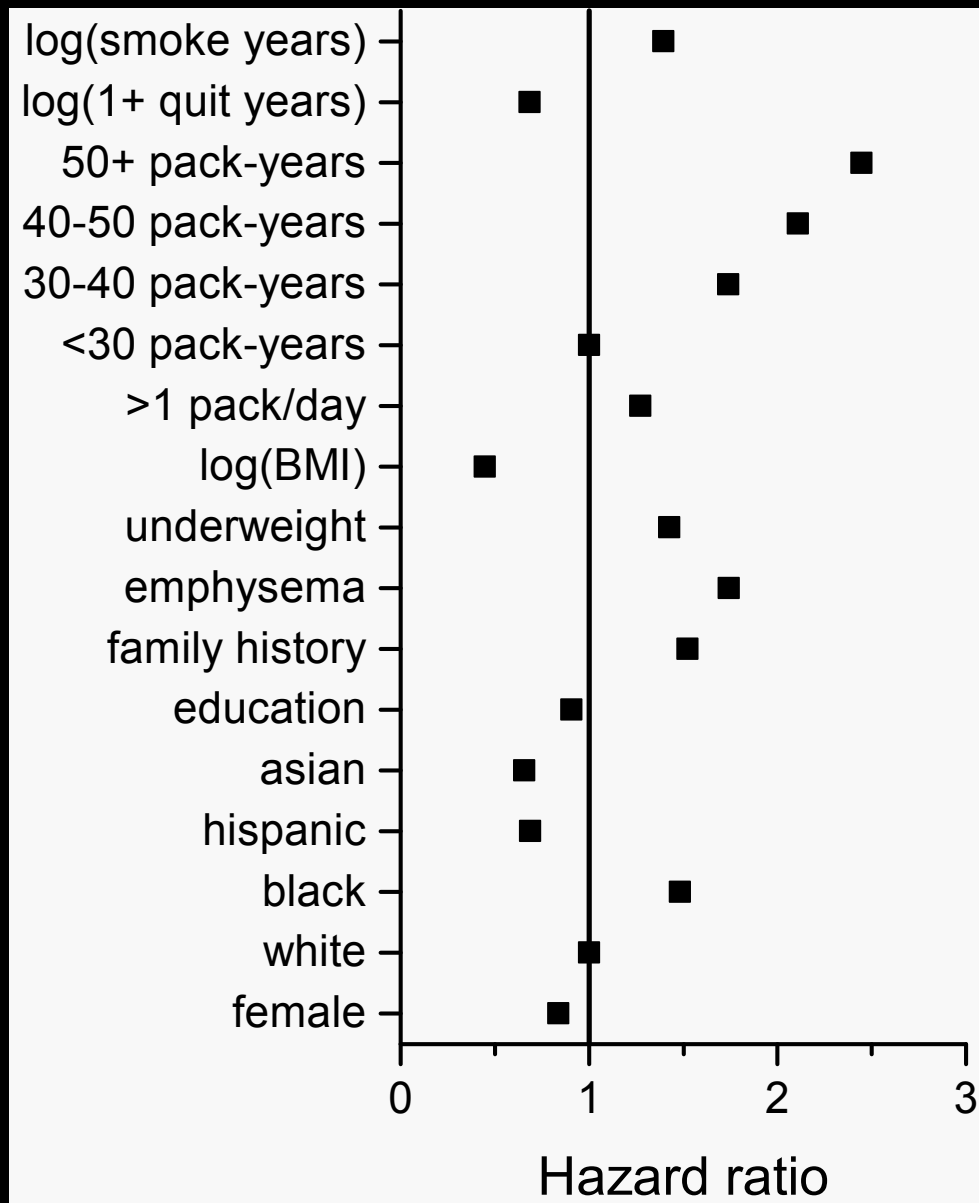
- **Risk factors**
  - **self-reported**
  - **well-known**

- **Log(age): HR=431**

- **Continuous**
  - **Age**
  - **Smoke years**
  - **Quit years**
  - **BMI**

Katki, … Chaturvedi, *JAMA*, 2016

Risk-based selection may be more effective and efficient than current guidelines
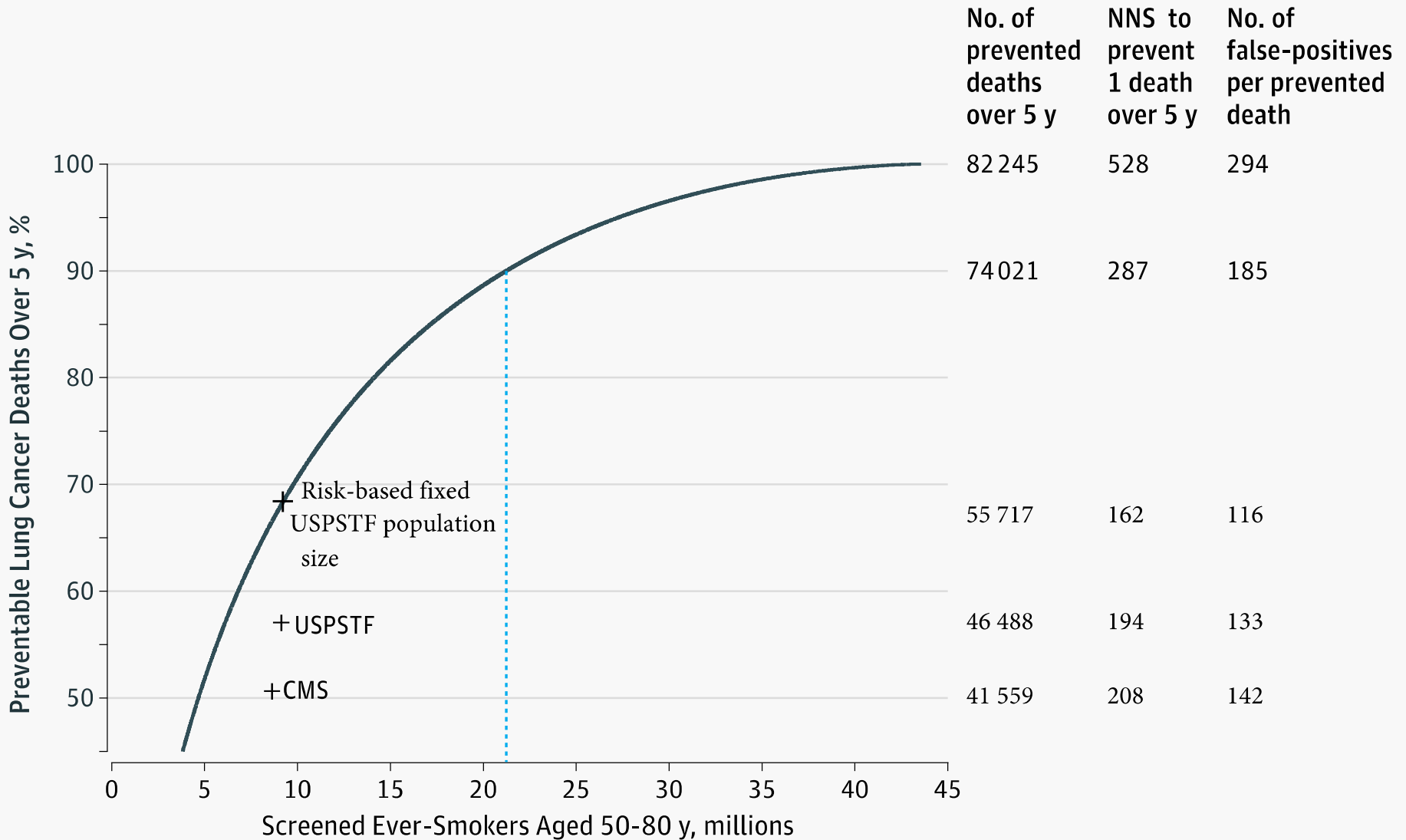
	USPSTF-eligible smokers	Risk-based: Fixed-USPSTF population size	% gain
Number of eligible smokers (% ever-smokers screened)	9,018,130 (21%)	9,018,693 (21%)	
5-year lung-cancer risk threshold	-	1.9%	
Number of preventable lung-cancer deaths (% of preventable lung-cancer deaths)	46,488 (57%)	55,717 (68%)	20%
Effectiveness: Number needed to screen (NNS) to prevent 1 lung-cancer death	194	162	17%
Efficiency: # of false-positive screens per prevented lung-cancer death	133	116	13%

Katki, … Chaturvedi, *JAMA*, 2016

Projected outcomes from risk-based CT lung cancer screening

Risk-based strategies replace the lowest-risk USPTF-eligible smokers with higher-risk USPSTF-_in_eligible smokers.

- **Replacements have**
  - Much higher 5-year lung cancer risk (3.2% vs. 1.3%)
  - Much lower NNS to prevent 1 death (226 vs. 647)

- **Risk-based selection preferentially selects**
  - Older (ages 70-80)
  - African-Americans
  - Current smokers
  - Low-intensity long-term current-smokers
    - 61% of whom smoke less than _half_ a pack per day
    - 67% are female; 25% are African-American
  - High-intensity former-smokers who have quit for more than 15 years

1a. U.S. smokers selected for screening
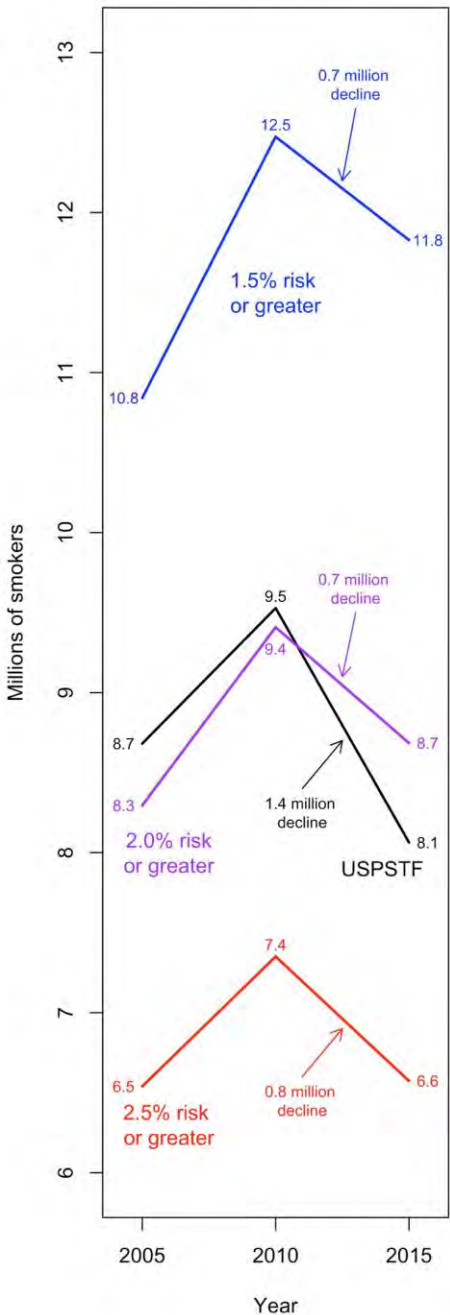
Declining # of high-risk US ever-smokers: 2010-2015

- # of USPSTF-eligible US ever-smokers declined by <u>1.4 million</u> (9.5M to 8.1M) from 2010-2015

- However, # of US ever-smokers with 5-year risk >2.0% declined by <u>only 0.7 million</u> (9.4M to 8.7M).
  - Declines in # with 30+ pack-years mitigated by increases in # with 20-29 pack-years

- Current USPSTF criteria will do an increasingly worse job of identifying high-risk smokers

- Guidelines need to adopt risk-based screening over current USPSF criteria, <u>as soon as possible</u>

Jemal, et. al., *JAMA Oncol*, 2017
Cheung, et. al., *Ann Intern Med,* 2018

Unforgiving Math of Screening

- 20% reduction in death applies only to
  - Ever-smokers (~85% of lung cancer deaths)
  - 57% of US lung cancer deaths in ever-smokers from current USPSTF screening guidelines
  - Might increase to 68% under risk-based screening

- <u>Only 10-12% of US lung-cancer deaths are realistically preventable by CT screening</u>
  - However, this would roughly equal eliminating all US stomach cancer deaths

Achilles Heel of Precision Prevention:

Dissemination and implementation of risk-based precision prevention

How can risk-based screening happen in real-life?

- **Some doubts**
  - **How will we collect the information?**
  - **What is the right risk threshold to qualify for screening?**
  - **What happens to those who don't qualify but get cancer?**
  - **Will I get sued?**

- **Validated shared decision-making process**
  - **Validated and appropriate risk tools and quantitative decision aids**
  - **Validated process that accurately conveys information and leads to appropriate decision-making in light of a patient's values**
  - **http://www.shouldiscreen.com/lung-cancer-risk-calculator**

- **How will this be explained?**
  - **Doctors, public health professionals, a trained cadre of "medical counselors"? "Screening Navigators?"**

Risk Tool

The task force does not recommend that you get screened if you are not between the ages of 55 and 80, or if you are a non smoker, or if you are a current smoker with less than 30 pack-year of smoking or if you are a former smoker who quitted for more than 15 years.

Age	66
Gender	Male
Type of Smoker?	Current Smoker
What age did you start smoking?	23
How many cigarettes per day do you smoke on average?	36
Race or Ethnic Group:	White
Lung disease?	None
Family history of lung cancer?	No parent
Units?	US
Height?	6 Feet 1 Inch(es)
Weight?	176 Pound(s)
Education?	Vocation/technical scl

Calculate   **Reset**

Your Results

White male of 66 years of age with BMI = 23.22

Risk of dying from lung cancer within 5 years in the absence of screening: 4.29%

Explanation: text

<u>Click here</u> to learn more about your results.

5-year lung cancer death risk reduction due to lung cancer screening: 0.87%

The chance of lung cancer diagnosis within 5 years in the absence of screening: 6.02%

The chance of lung cancer diagnosis within 5 years with screening: 6.77%

The chance of having a false positive result after 3 screens: 0.42%

Print   **Download Results**

Further Information

Learning about lung cancer and its treatment can help you prepare for your appointments, understand different types of treatment, and prevent and manage any side effects.

https://analysistools.nci.nih.gov/lungCancerScreening/

Lung cancer screening as a template:

Principles of precision prevention

Template for precision prevention?

- **Screening general populations is hard**
  - Most people at low disease risk, thus at high risk of false-positives
  - Clinical trials of screening in general populations has mixed results: low power

- **Shift question from "Does screening work?" to "_For whom_ does screening work?"**

- **CT lung screening model**
  - When introducing a new screening program, select only those at highest risk (NLST)
  - Increased statistical power for trials (88 prevented deaths)
  - Focus on high-risk smokers has resolved an acrimonious decades-long debate about whether lung screening works

Rule-Out/Rule-In Screening: "for *whom* does screening work?"

- **Rule-out everyone *not* at high risk**
  - **Immediately**
    - **Lung screening**
  - **Rule-out for a long time based on tests (single or sequence)**
    - **Cervix screening, prostate screening (?)**
  - **Base rule-out on: *low*-risk of untreatable cancer or death**

- **Rule-in based on triage test**
  - **Even HPV needs Pap and biopsy triage**
  - **Base rule-in on: *high*-risk of finding treatable disease (early stage cancer or precancer)**
  - **Can consider extending to those at moderate risk, *if an excellent triage test exists***