

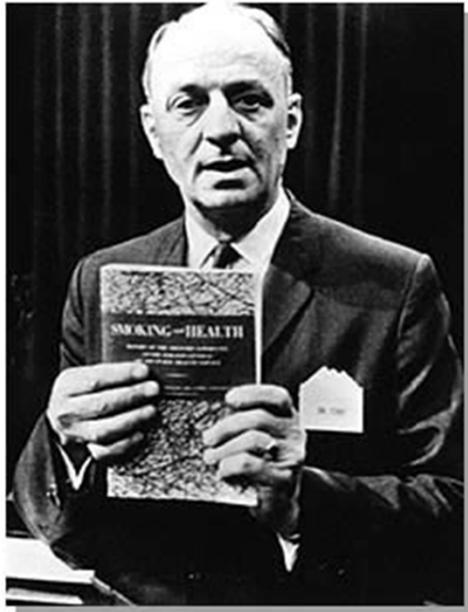
The Changing Risks of Bladder Cancer Related to Tobacco Smoking

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A Changing Epidemic and Response



1964 Surgeon General's Report
Dr Luther Terry



2011: New FDA warning labels

Tobacco: The Persistent Problem

- 20% of US adults smoke
- 24% of high school students currently use tobacco products
- 4,000 teenagers start to smoke every day
- Tobacco products and use are changing

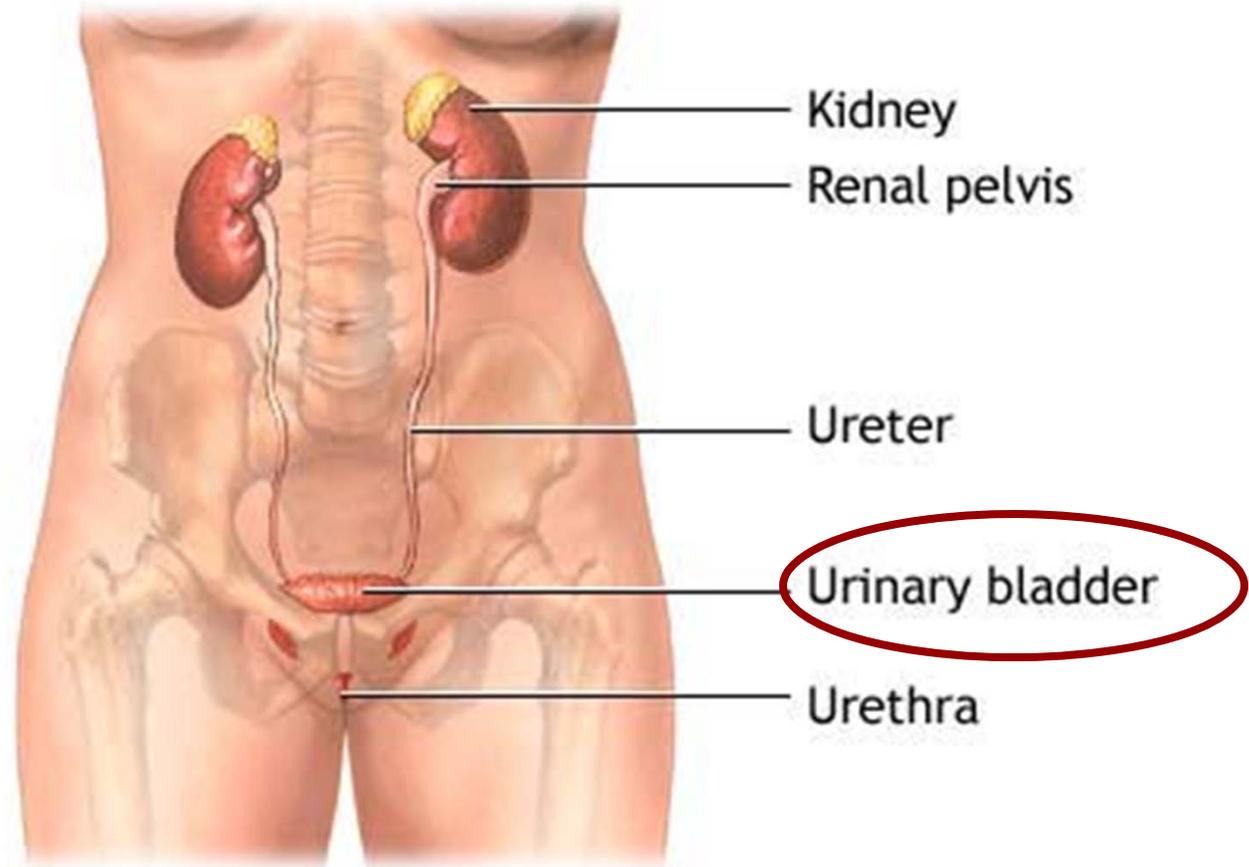
Tobacco Causes Cancer

- **Established associations**
 - Smokers, 20 times more likely to get lung cancer
 - More cigarettes per day = higher risk
 - More years of smoking = higher risk
 - Quitting reduces risk
- **But much has changed**
 - Men and women smoke similar amounts
 - Changes to cigarettes
 - Filters
 - Inhalation
 - New tobacco products

Cancers Caused by Tobacco Smoking

- **Bladder**
- Oral Cavity
- Pharynx
- Nasal Cavity
- Larynx
- Lung
- Esophagus
- Stomach
- Colorectum
- Liver
- Pancreas
- Uterine Cervix
- Ovary (mucinous)
- Kidney
- Ureter
- Myeloid Leukemia

Bladder is a Target of Tobacco Carcinogens

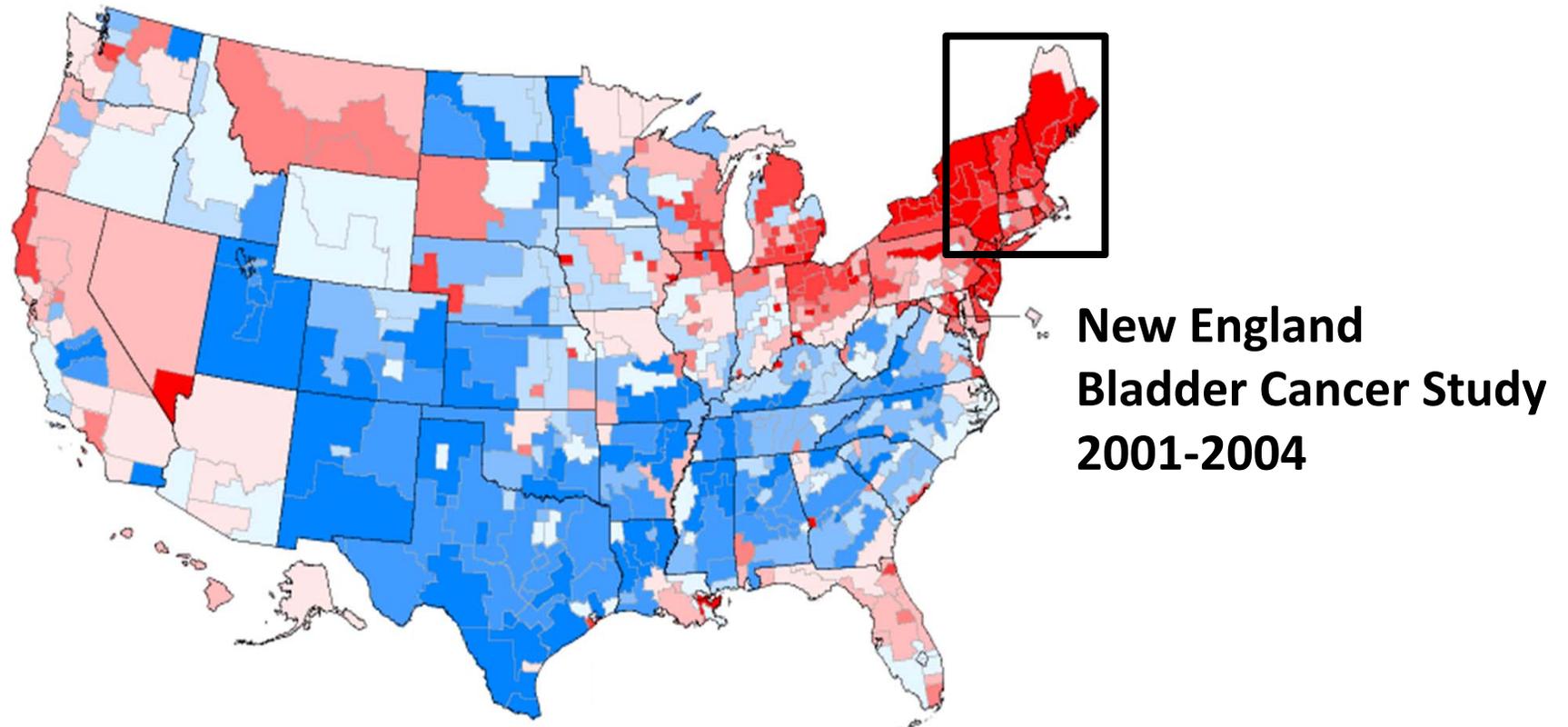


Bladder Cancer in Brief

- 70,000 cases per year in US
- 4 times more common in men
- Current smokers have 2-3 times higher risk*

*National Bladder Cancer Study, Hartge et al, JNCI 1987
Washington County MD Cohorts, Alberg et al, AJE 2007
US Veterans, McLaughlin et al, IJC 1995

NCI Atlas of Bladder Cancer Mortality in the US 1950-1994



New England Bladder Cancer Study: Unexpected Results for Smoking

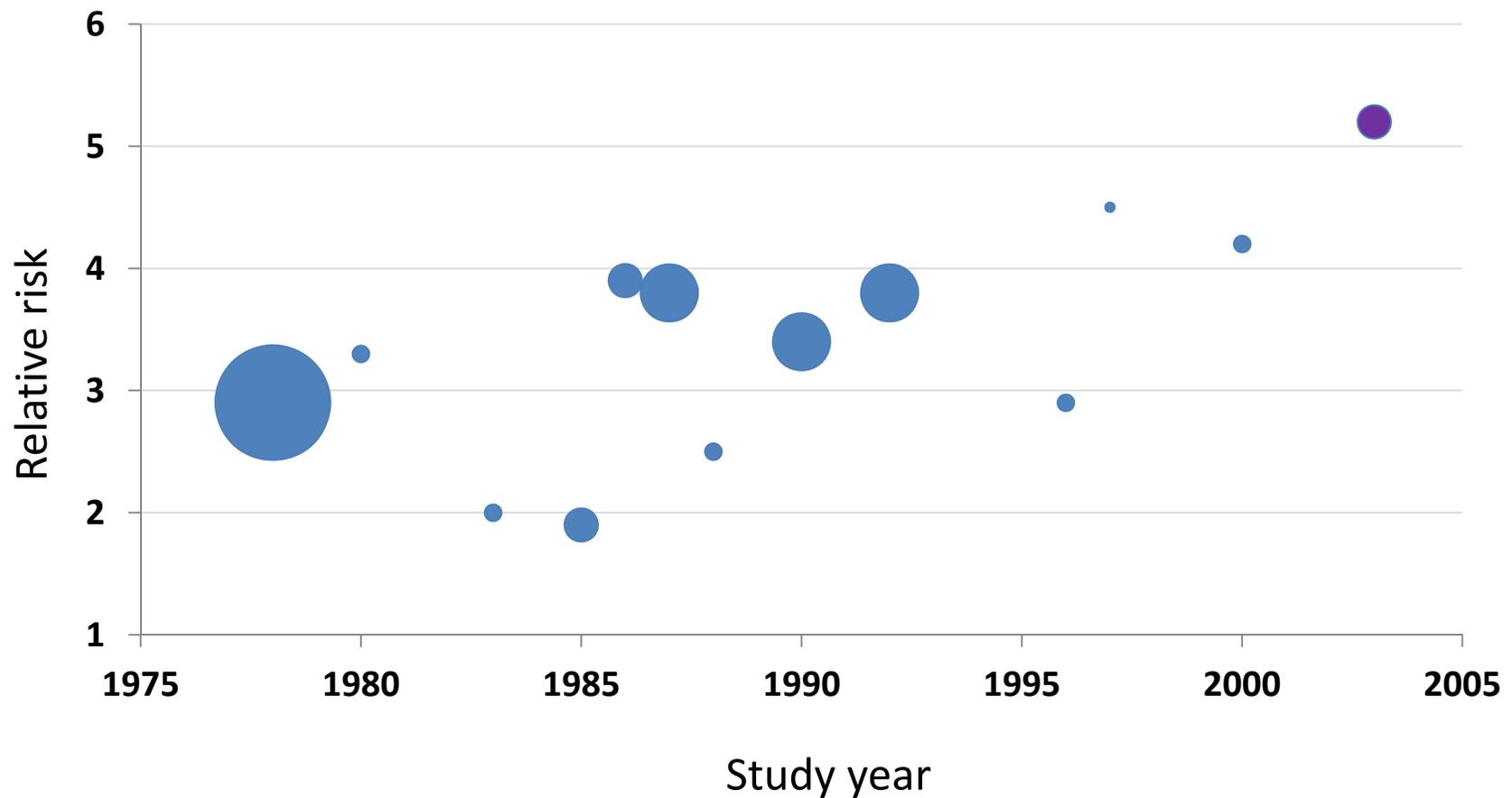
- 5 times higher risk for current smokers
 - Based on 1970s studies, expected risk 2-3 times
- Did they smoke more per day?
 - No
- Did they smoke for more years?
 - No

A Case–Control Study of Smoking and Bladder Cancer Risk: Emergent Patterns Over Time

Dalsu Baris, Margaret R. Karagas, Castine Verrill, Alison Johnson, Angeline S. Andrew, Carmen J. Marsit, Molly Schwenn, Joanne S. Colt, Sai Cherala, Claudine Samanic, Richard Waddell, Kenneth P. Cantor, Alan Schned, Nathaniel Rothman, Jay Lubin, Joseph F. Fraumeni Jr, Robert N. Hoover, Karl T. Kelsey, Debra T. Silverman

- Background** Cigarette smoking is a well-established risk factor for bladder cancer. The effects of smoking duration, intensity (cigarettes per day), and total exposure (pack-years); smoking cessation; exposure to environmental tobacco smoke; and changes in the composition of tobacco and cigarette design over time on risk of bladder cancer are unclear.
- Methods** We examined bladder cancer risk in relation to smoking practices based on interview data from a large, population-based case–control study conducted in Maine, New Hampshire, and Vermont from 2001 to 2004 (N = 1170 urothelial carcinoma case patients and 1413 control subjects). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. To examine changes in smoking-induced bladder cancer risk over time, we compared odds ratios from New Hampshire residents in this study (305 case patients and 335 control subjects) with those from two case–control studies conducted in New Hampshire in 1994–1998 and in 1998–2001 (843 case patients and 1183 control subjects).
- Results** Regular and current cigarette smokers had higher risks of bladder cancer than never-smokers (for regular smokers, OR = 3.0, 95% CI = 2.4 to 3.6; for current smokers, OR = 5.2, 95% CI = 4.0 to 6.6). In New Hampshire, there was a statistically significant increasing trend in smoking-related bladder cancer risk over three consecutive periods (1994–1998, 1998–2001, and 2002–2004) among former smokers (OR = 1.4, 95% CI = 1.0 to 2.0; OR = 2.0, 95% CI = 1.4 to 2.9; and OR = 2.6, 95% CI = 1.7 to 4.0, respectively) and current smokers (OR = 2.9, 95% CI = 2.0 to 4.2; OR = 4.2, 95% CI = 2.8 to 6.3; OR = 5.5, 95% CI = 3.5 to 8.9, respectively) (*P* for homogeneity of trends over time periods = .04). We also observed that within categories of intensity, odds ratios increased approximately linearly with increasing pack-years smoked, but the slope of the increasing trend declined with increasing intensity.
- Conclusions** Smoking-related risks of bladder cancer appear to have increased in New Hampshire since the mid-1990s. Based on our modeling of pack-years and intensity, smoking fewer cigarettes over a long time appears more harmful than smoking more cigarettes over a shorter time, for equal total pack-years of cigarettes smoked.

Bladder Cancer Risk in Current Smokers by Year: Case-Control Studies



NIH-AARP Diet and Health Study

- Prospective cohort
- 500,000 members of AARP (aged 50-71 years)
- Followed for 11 years, from 1995-2006
- 4,500 incident bladder cancers

Association Between Smoking and Risk of Bladder Cancer Among Men and Women

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Albert R. Hollenbeck, PhD

Arthur Schatzkin, MD, DrPH†

Christian C. Abnet, PhD, MPH

MORE THAN 350 000 individuals are diagnosed with incident bladder cancer per year worldwide,¹ including more than 70 000 per year in the United States.² In data from Surveillance, Epidemiology, and End Results Program, incidence rates in white individuals aged 50 years or more have remained stable during the past 30 years (1976-2006), from 123.8 per 100 000 person-years to 142.2 per 100 000 person-years in men and from 32.5 per 100 000 person-years to 33.2 per 100 000 person-years in women; similar patterns are observed in other ethnic and racial groups.³

Tobacco smoking is the best established risk factor for bladder cancer in both men and women.^{4,5} Although rates of bladder cancer have remained stable during the past 30 years, prevalence of cigarette smoking in the United States has substantially decreased during the

Context Previous studies indicate that the population attributable risk (PAR) of bladder cancer for tobacco smoking is 50% to 65% in men and 20% to 30% in women and that current cigarette smoking triples bladder cancer risk relative to never smoking. During the last 30 years, incidence rates have remained stable in the United States in men (123.8 per 100 000 person-years to 142.2 per 100 000 person-years) and women (32.5 per 100 000 person-years to 33.2 per 100 000 person-years); however, changing smoking prevalence and cigarette composition warrant revisiting risk estimates for smoking and bladder cancer.

Objective To evaluate the association between tobacco smoking and bladder cancer.

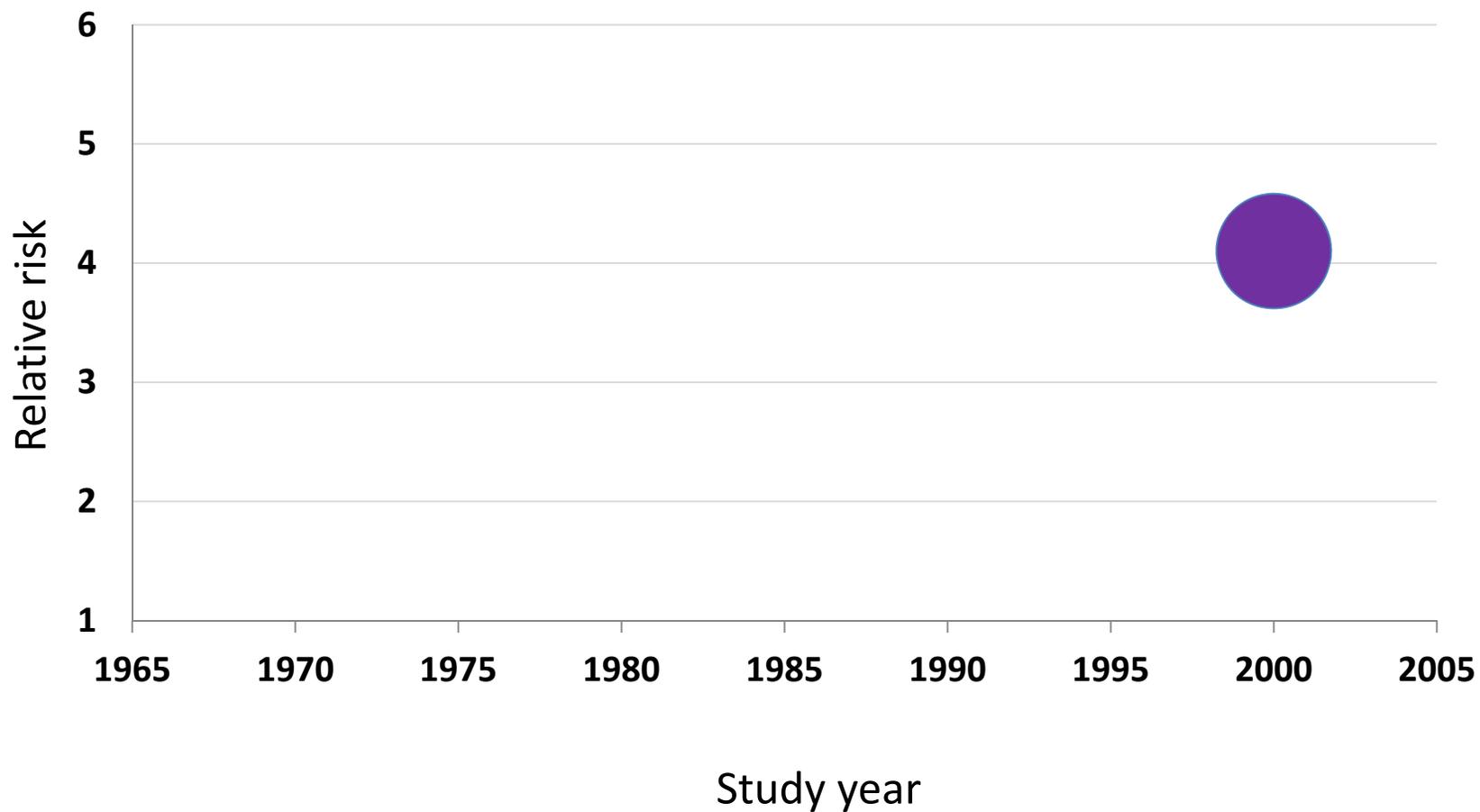
Design, Setting, and Participants Men (n=281 394) and women (n=186 134) of the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study cohort completed a lifestyle questionnaire and were followed up between October 25, 1995, and December 31, 2006. Previous prospective cohort studies of smoking and incident bladder cancer were identified by systematic review and relative risks were estimated from fixed-effects models with heterogeneity assessed by the I^2 statistic.

Main Outcome Measures Hazard ratios (HRs), PARs, and number needed to harm (NNH).

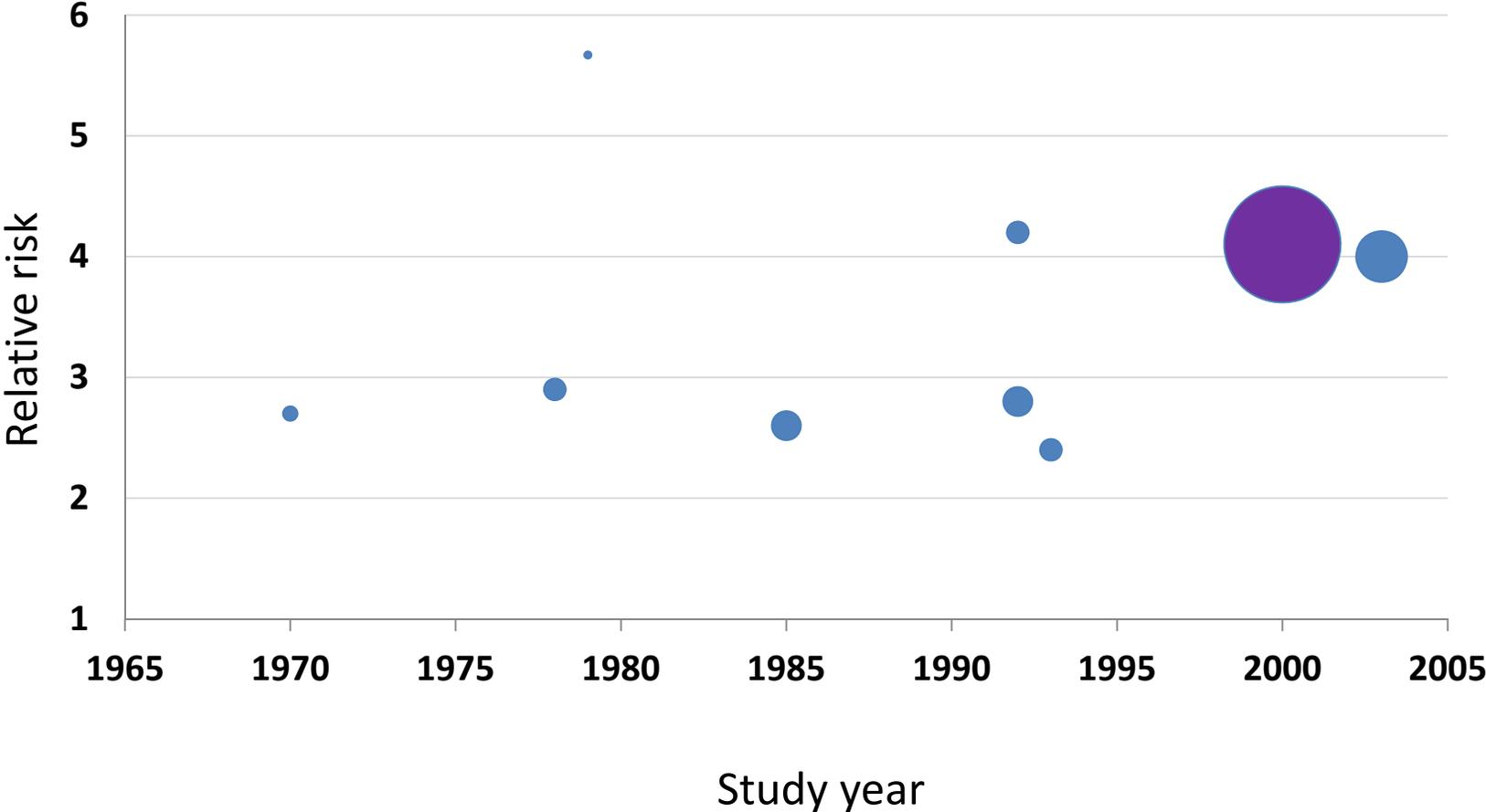
Results During 4 518 941 person-years of follow-up, incident bladder cancer occurred in 3896 men (144.0 per 100 000 person-years) and 627 women (34.5 per 100 000 person-years). Former smokers (119.8 per 100 000 person-years; HR, 2.22; 95% confidence interval [CI], 2.03-2.44; NNH, 1250) and current smokers (177.3 per 100 000 person-years; HR, 4.06; 95% CI, 3.66-4.50; NNH, 727) had higher risks of bladder cancer than never smokers (39.8 per 100 000 person-years). In contrast, the summary risk estimate for current smoking in 7 previous studies (initiated between 1963 and 1987) was 2.94 (95% CI, 2.45-3.54; $I^2=0.0\%$). The PAR for ever smoking in our study was 0.50 (95% CI, 0.45-0.54) in men and 0.52 (95% CI, 0.45-0.59) in women.

Conclusion Compared with a pooled estimate of US data from cohorts initiated between 1963 and 1987, relative risks for smoking in the more recent NIH-AARP Diet and Health Study cohort were higher, with PARs for women comparable with those for men.

Current Smokers in NIH-AARP: 4 Times Higher Risk of Bladder Cancer



Bladder Cancer Risk in Current Smokers by Year: Cohort Studies



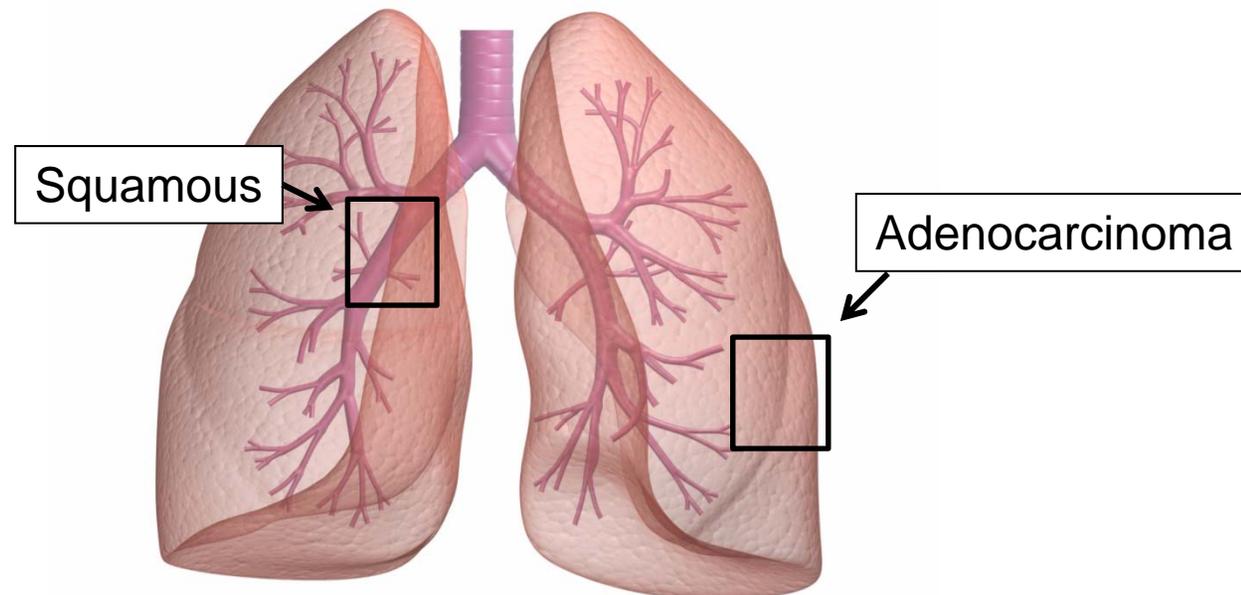
Hypotheses to Explain Changes Over Time

- More carcinogens in tobacco smoke?



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- More carcinogens in tobacco smoke?
- Unintended consequences of filters?
 - Lung: changes in subtype and location



Hypotheses to Explain Changes Over Time

- More carcinogens in tobacco smoke?
- Unintended consequences of filters?
 - Lung: changes in subtype and location
- Other exposures changing over time?
- Changes in intensity or duration of smoking?
- Better diagnosis?

Next Steps

- Investigate tobacco and bladder cancer in other populations
- Have associations with tobacco changed for other smoking-related cancers?
 - Mechanisms may differ by cancer type
- Larger context
 - Other diseases
 - Many other tobacco products

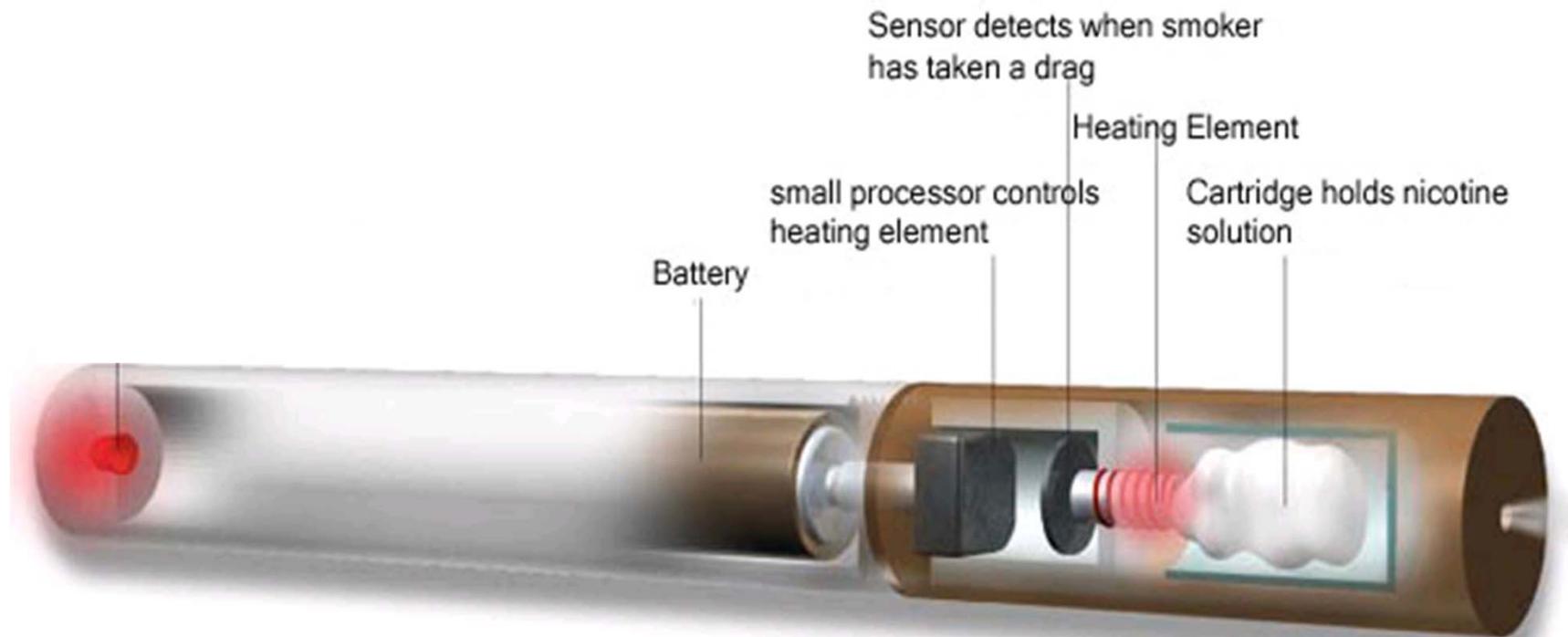
Smokeless Tobacco



Water Pipes



E-Cigarettes



Dissolvable Tobacco



2009: Family Smoking Prevention and Tobacco Control Act



NIH-FDA Partnership

- FDA has authority to regulate the **manufacture**, **distribution**, and **marketing** of tobacco products
- NIH and the FDA have formed an interagency partnership to foster research relevant to tobacco regulations
 - To generate relevant **findings and data** needed to inform the regulation of tobacco products

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New England Bladder Cancer Study:

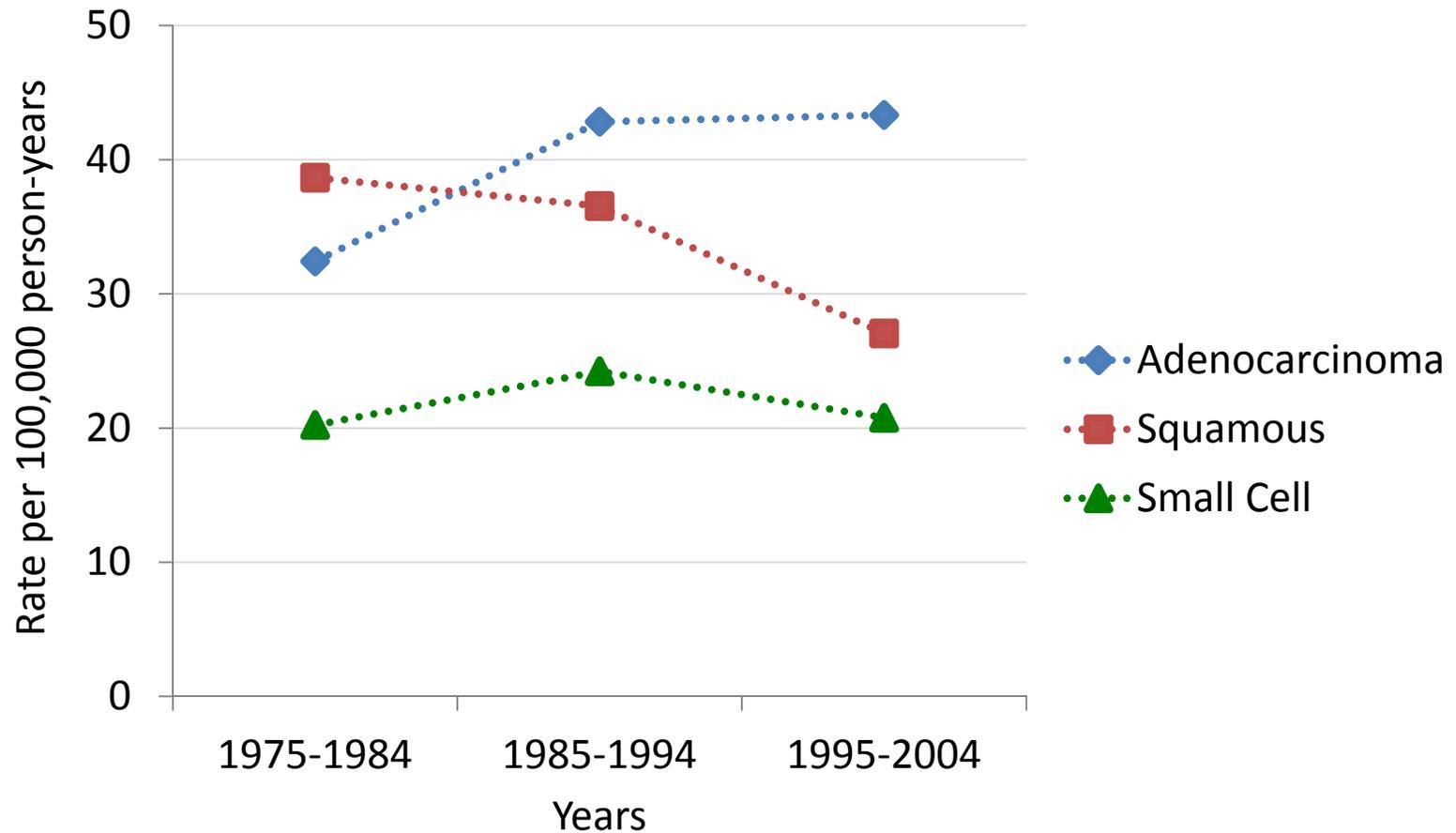
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Robert Hoover
Joseph Fraumeni, Jr

NCI DCCPS:

Michele Bloch

*In Memoriam

Changes in the Histologic Distribution of Lung Cancer



SEER-9 cancer registries, Cook et al, CEBP, 2009

Relative Risks for Bladder Cancer by Cigarette Pack-Years

Study	Hartge		Bruemmer		Quirk		Baris	
Year	1978		1988		1990		2002	
	Pack-years	RR	Pack-years	RR	Pack-years	RR	Pack-years	RR
					≤ 10	1.0		
	1-19	1.5			11-20	1.7	<20	1.7
	20-39	2.2			21-30	1.7	20-39	3.2
	40-59	2.7	≤ 48	3	31-40	2.3	40-49	4.9
	60-79	3.5	> 48	3.6	> 40	3.6	50-59	5.0
	80-89	2.4					≥ 60	4.2
	≥ 100	3.7						