Ospedale
"Sacro Cuore - Don Calabria"

Incontri
di aggiornamento
del Dipartimento
Oncologico

Responsabile Scientifico:
Dott.ssa Stefania Gori

10 marzo
5 maggio - 11 maggio
2016

SEDE
CENTRO FORMAZIONE
Ospedale "Sacro Cuore - Don Calabria"
Via Don Angelo Sempreboni, 5 - 37024 Negrar (Verona)
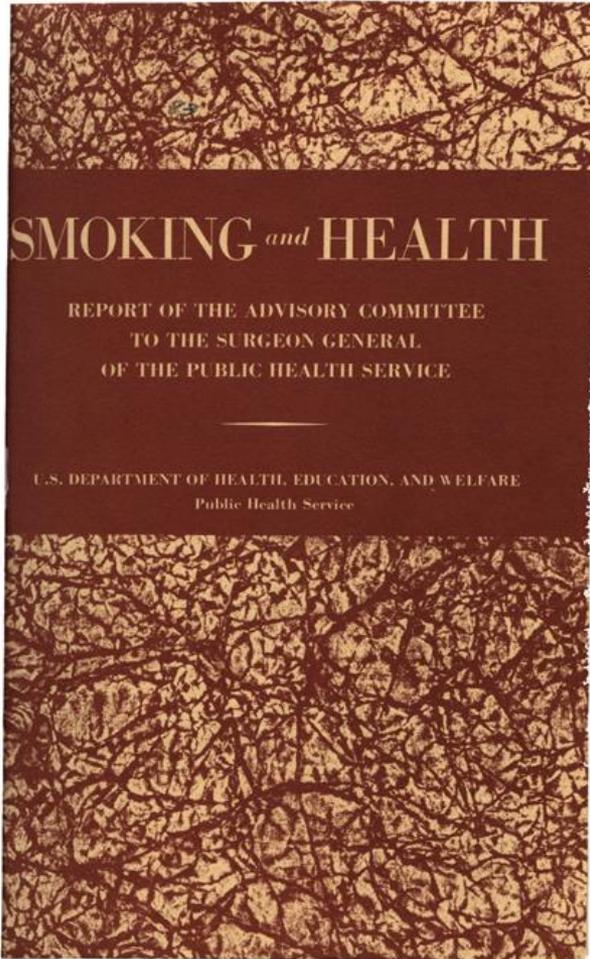
Fattori di rischio

Alessandro Inno

Oncologia Medica
Ospedale Sacro Cuore Don Calabria
Negrar - Verona

Cigarette smoking and lung cancer

Expected and observed deaths for smokers of cigarettes and mortality ratios in 7 prospective studies (1,123,000 men)

Underlying cause of death	Expected deaths	Observed deaths	Mortality ratio
Cancer of the lung	170.3	1833	10.8
Bronchitis and emphysema	89.5	546	6.1
Cancer of larynx	14.0	75	5.4
Oral cancer	37.0	152	4.1
Cancer of esophagus	33.7	113	3.4
Stomach and duodenal ulcers	105.1	294	2.8
Other circulatory diseases	254.0	649	2.6
Cirrhosis of liver	169.2	379	2.2
Cancer of bladder	111.6	216	1.9
Coronary artery disease	6430.7	11177	1.7
Other heart diseases	526.0	868	1.7
Hypertensive heart	409.2	631	1.5
General arteriosclerosis	210.7	310	1.5
Cancer of kidney	79.0	620	1.5
All causes	**15635.9**	**23223**	**1.68**

Smoking and Health: Report of the Advisory Committee of the Surgeon General of the Public Health Service , 1964
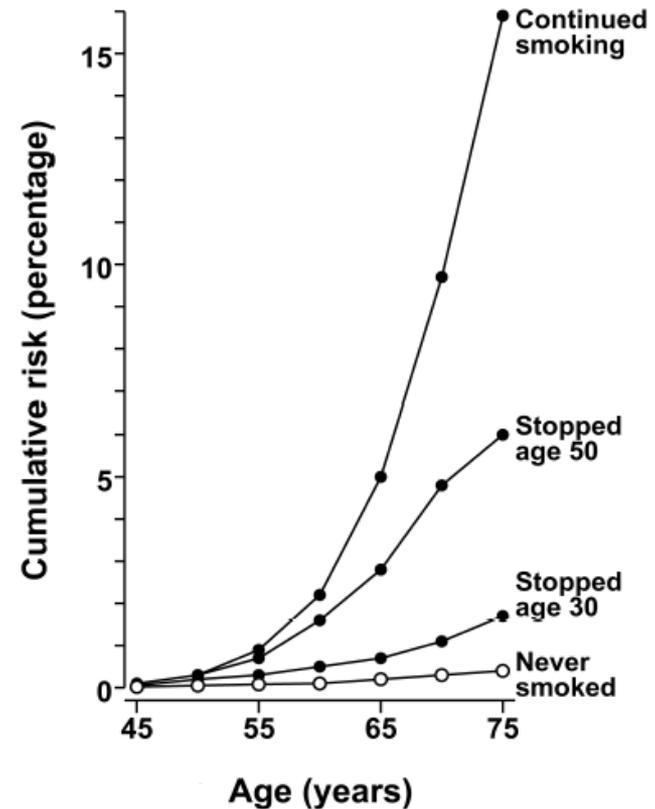
Duration of cigarette smoking and lung cancer

Relationship between age at starting regular cigarette smoking and lung cancer death rates at age 55–64 years in US men

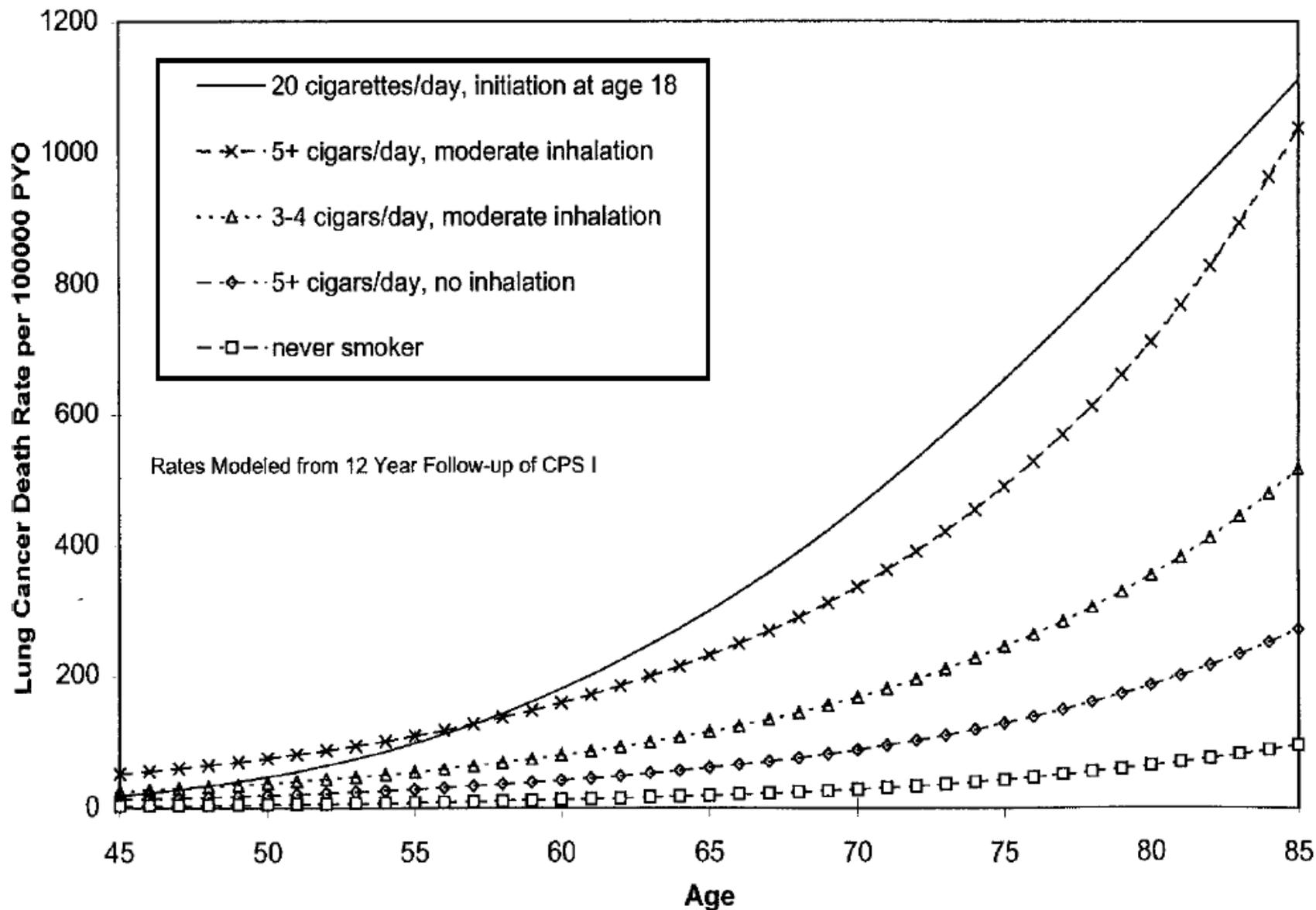
Doll R, Peto R. J Natl Cancer Inst. 1981;66:1191-1308
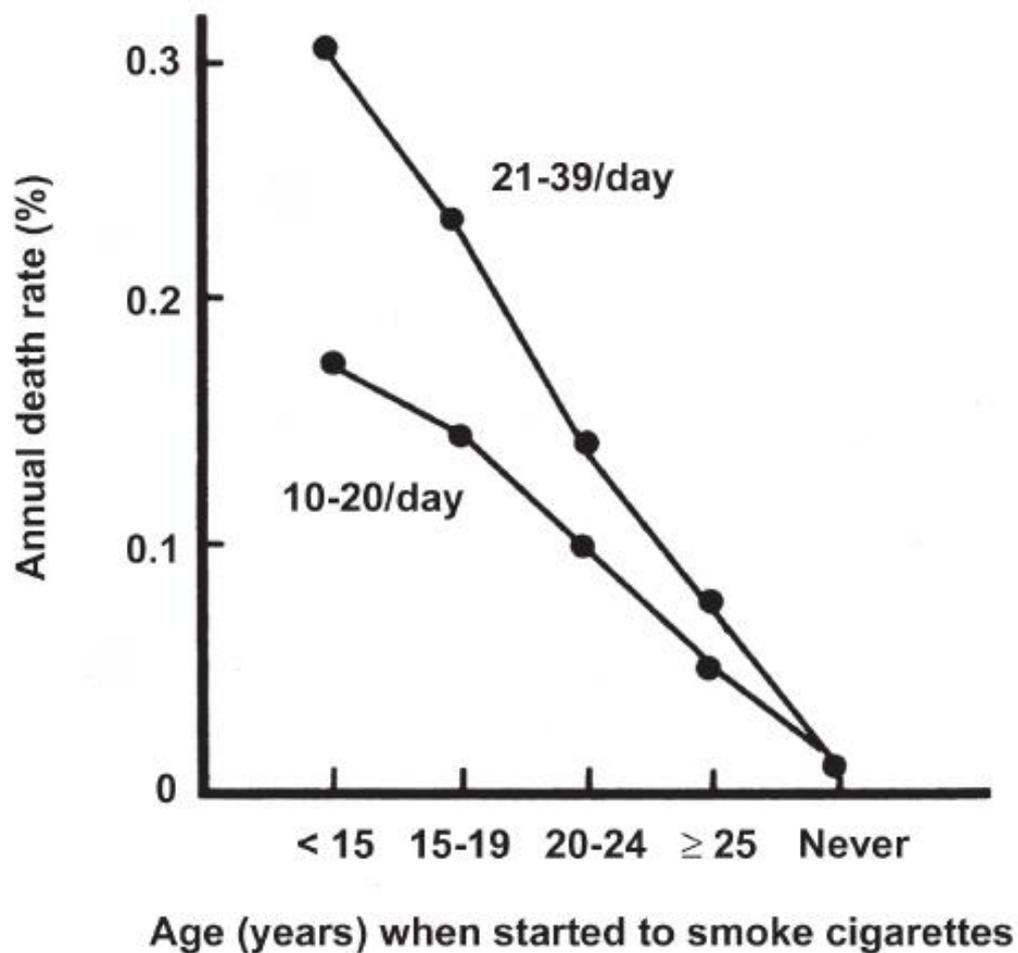
Continuing vs quitting smoking and lung cancer
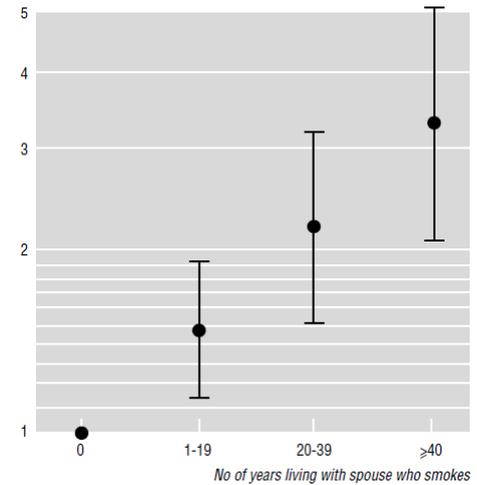
Cumulative lung cancer risk by smoking status and age at quitting smoking in men in the United Kingdom

Peto R et al. BMJ. 2000;321:323-329

Lung cancer death rates for cigar smokers

Cigars: Health effects and trends. NIH monograph n. 9, 1998

Secondhand smoking and risk of lung cancer

Hackshaw AK et al. BMJ. 1997;315:980-988
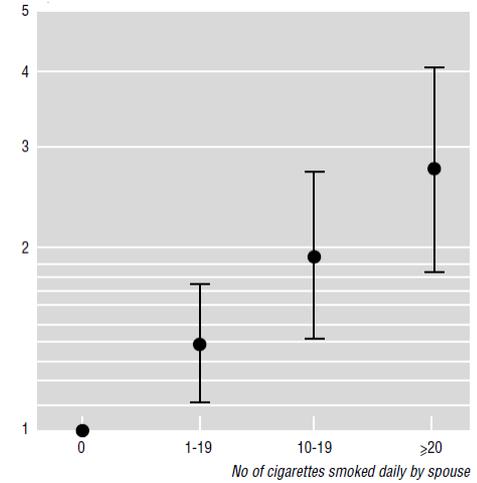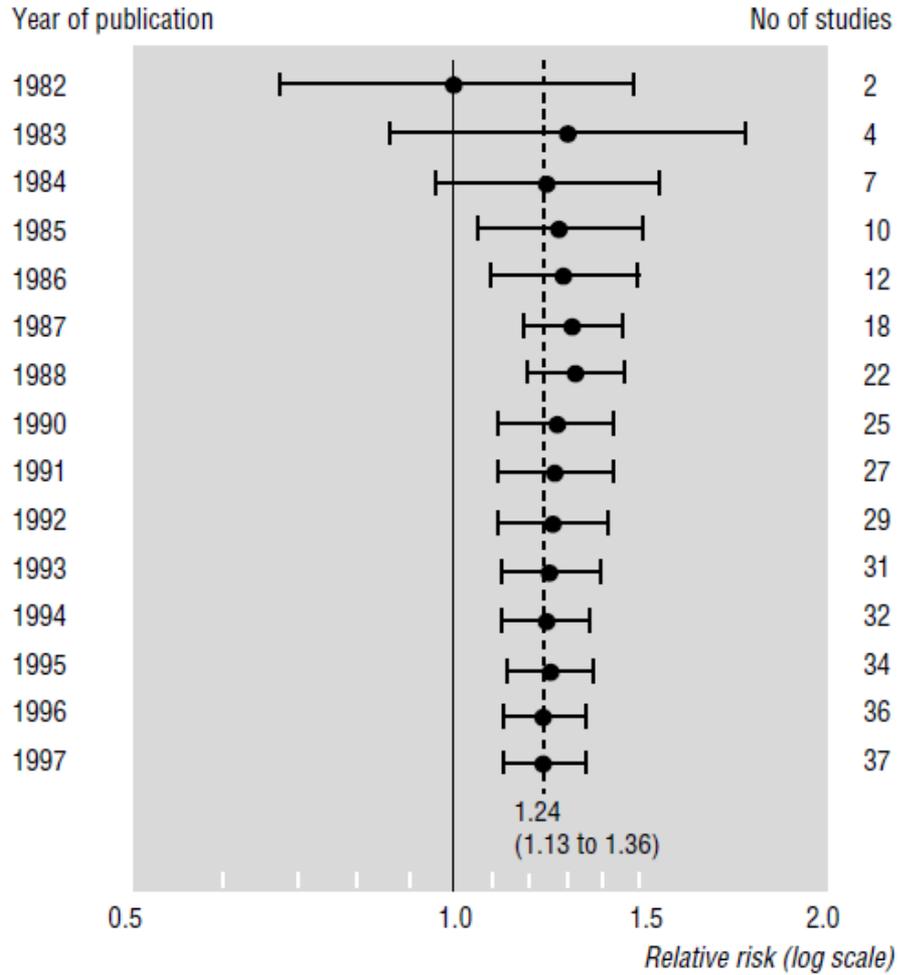
Pathway for causation of cancer by carcinogens in cigarette smoke

- There are more than 4000 chemicals in cigarette smoke
- There are at least **50 carcinogens** in cigarette smoke
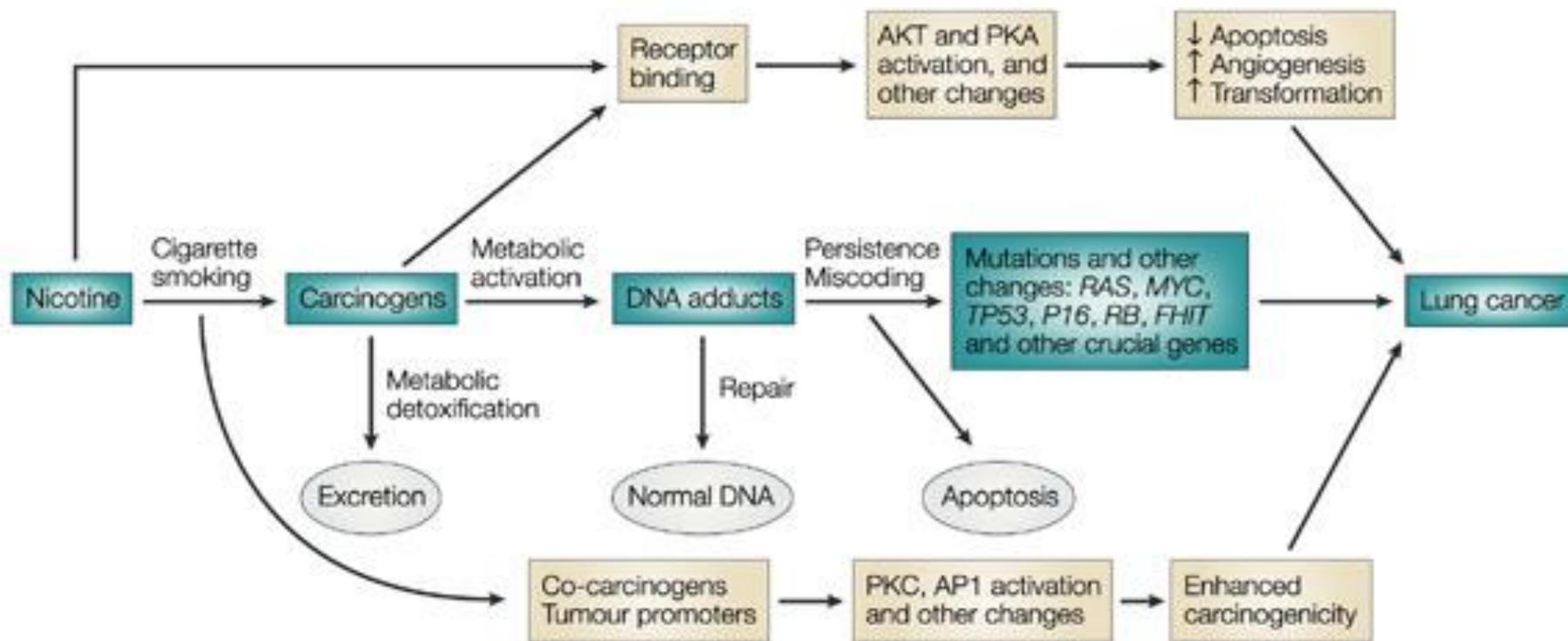
Nature Reviews | Cancer

Smith CJ et al. Food Chem Toxicol 2000;38:371-383
Hecht SS. Nat Rev Cancer. 2003;3:733-744

Occupational carcinogens linked to lung cancer

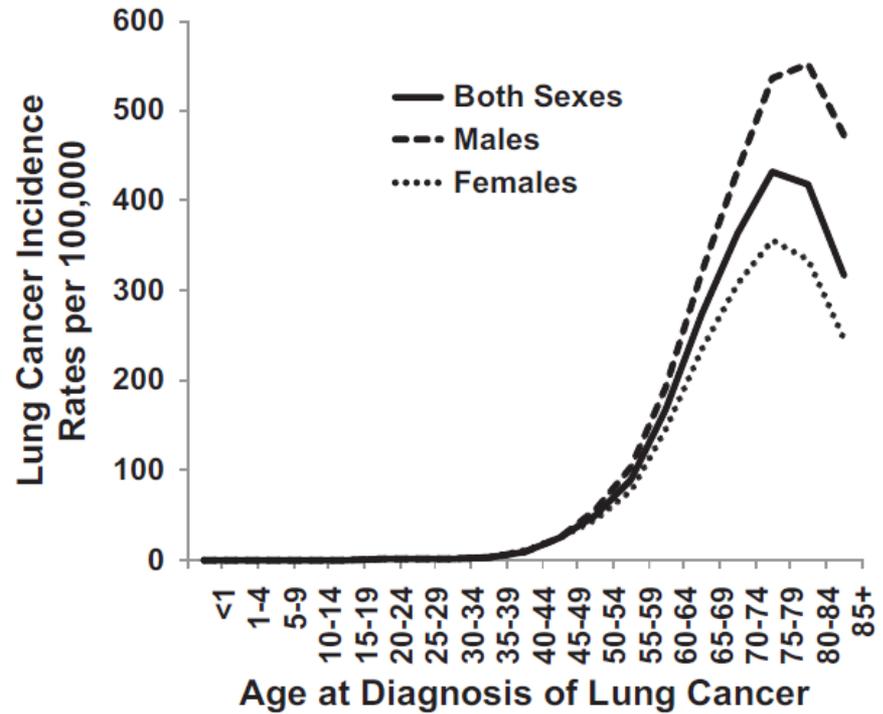| Known Carcinogen	Occupational Exposure
Arsenic	Copper, lead, or zinc ore smelting Manufacture of insecticides Mining
Asbestos	Asbestos mining Asbestos textile production Brake lining work Cement production Construction work Insulation work Shipyard work
Beryllium	Ceramic manufacture Electronic and aerospace equipment manufacture Mining
Chloromethyl ethers	Chemical manufacturing
Chromium	Chromate production Chromium electroplating Leather tanning Pigment production
Nickel	Nickel mining, refining, electroplating Production of stainless and heat-resistant steel Polycyclic aromatics Aluminum production Hydrocarbon compounds Coke production Ferrochromium alloy production Nickel-containing ore smelting Roofing
Radon	Mining
Silica	Ceramics and glass industry Foundry industry Granite industry Metal ore smelting Mining and quarrying

Dela Cruz CS et al. Clin Chest Med. 2011;32:605-644

Air pollution

Adjusted Mortality Relative Risk (RR) Associated With a 10-μg/m^3 Change in Fine Particles Measuring Less Than 2.5 μm in Diameter

Cause of Mortality	Adjusted RR (95% CI)*		
	1979-1983	1999-2000	Average
All-cause	1.04 (1.01-1.08)	1.06 (1.02-1.10)	1.06 (1.02-1.11)
Cardiopulmonary	1.06 (1.02-1.10)	1.08 (1.02-1.14)	1.09 (1.03-1.16)
Lung cancer	1.08 (1.01-1.16)	1.13 (1.04-1.22)	1.14 (1.04-1.23)
All other cause	1.01 (0.97-1.05)	1.01 (0.97-1.06)	1.01 (0.95-1.06)

*Estimated and adjusted based on the baseline random-effects Cox proportional hazards model, controlling for age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure, and diet. CI indicates confidence interval.

Pope CA et al. JAMA. 2002;287:1132-1141.

Age and lung cancer risk

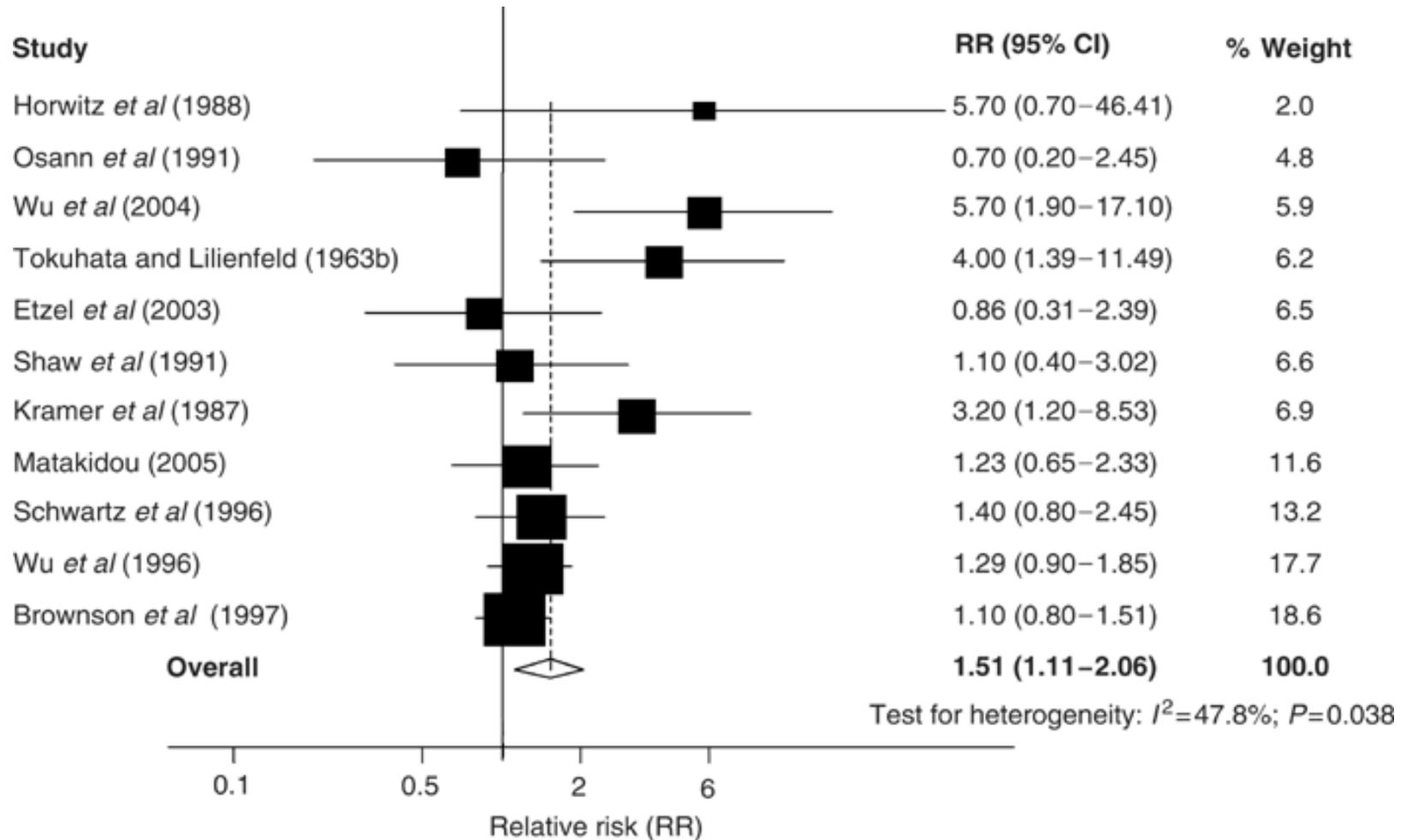Dela Cruz CS et al. Clin Chest Med. 2011;32:605-644
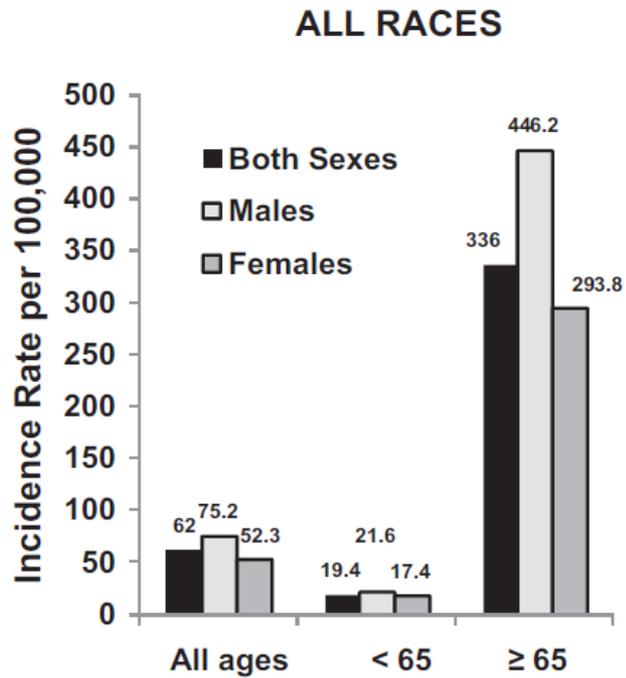
Gender and lung cancer risk

- **Lung cancer seems more common in nonsmoking women** than in nonsmoking men[1]

- **Controversial data for smoking women:**
  - ACS Cancer Prevention Study II: Overall Risk for women smokers was 11.94 vs 22.36 for male smokers[2]
  - American Health Foundation data found odds ratio consistently higher for women than for men at every level of exposure of cigarette smoke[3]

- **Gender-related differences in metabolic activation or detoxification** of lung carcinogens[4]

- **Hormonal factors** (use of hormonal therapies associated with an increased risk for lung cancer in women,[5] early meonopause associated with a decreased risk of adenocarcinoma)[6]

1. Wynder EL et al. J Am Med Assoc. 1950;143:329-336. 2. Halpern MT et al. J Natl Cancer Inst. 1993;85:457-464. 3. Zang EA et al. J Natl Cancer Inst. 1996;88:183-192. 4. Ryberg D et al. Cancer Res. 1994;54:5801-5803. 5. Slatore CG et al. J Clin Oncol. 2010; 28:1540-1546. 6. Taioli E et al. J Natl Cancer Inst. 1994;86:869-870.

Family history and lung cancer risk

Forrest plot of familial lung cancer risks in never-smokers

Study	RR (95% CI)	% Weight
Horwitz et al (1988)	5.70 (0.70–46.41)	2.0
Osann et al (1991)	0.70 (0.20–2.45)	4.8
Wu et al (2004)	5.70 (1.90–17.10)	5.9
Tokuhata and Lilienfeld (1963b)	4.00 (1.39–11.49)	6.2
Etzel et al (2003)	0.86 (0.31–2.39)	6.5
Shaw et al (1991)	1.10 (0.40–3.02)	6.6
Kramer et al (1987)	3.20 (1.20–8.53)	6.9
Matakidou (2005)	1.23 (0.65–2.33)	11.6
Schwartz et al (1996)	1.40 (0.80–2.45)	13.2
Wu et al (1996)	1.29 (0.90–1.85)	17.7
Brownson et al (1997)	1.10 (0.80–1.51)	18.6
Overall	**1.51 (1.11–2.06)**	**100.0**

Test for heterogeneity: I^2=47.8%; P=0.038

Relative risk (RR)

Matakidou A et al. Br J Cancer. 2005;93:825-833

Genetic susceptibility

- Genetic polymorphysms encoding **enzymes involved in the activation and conjugation of tobacco smoke compounds** (CYP1A1, GST, MPO, NQO1, EPHX1)

- Genetic polymorpysms encoding **DNA repair enzymes** (XRCC1, OGG1, ERCC1)

- Genes encoding **proteins involved in chonic inflammation** (IL-1, IL-6, IL-8, COX-2, MMP-1, MMP-2, MMP-3, MMP12)

- **Despite many genetic association studies, the specifica genes responisble for the enhanced risk for lung cancer remain poorly understood**

COPD and lung cancer

TABLE 2. RELATION OF LUNG CANCER MORTALITY TO CHRONIC OBSTRUCTIVE PULMONARY DISEASE AMONG NEVER SMOKERS IN THE CANCER PREVENTION STUDY II COHORT, UNITED STATES, 1982–2002

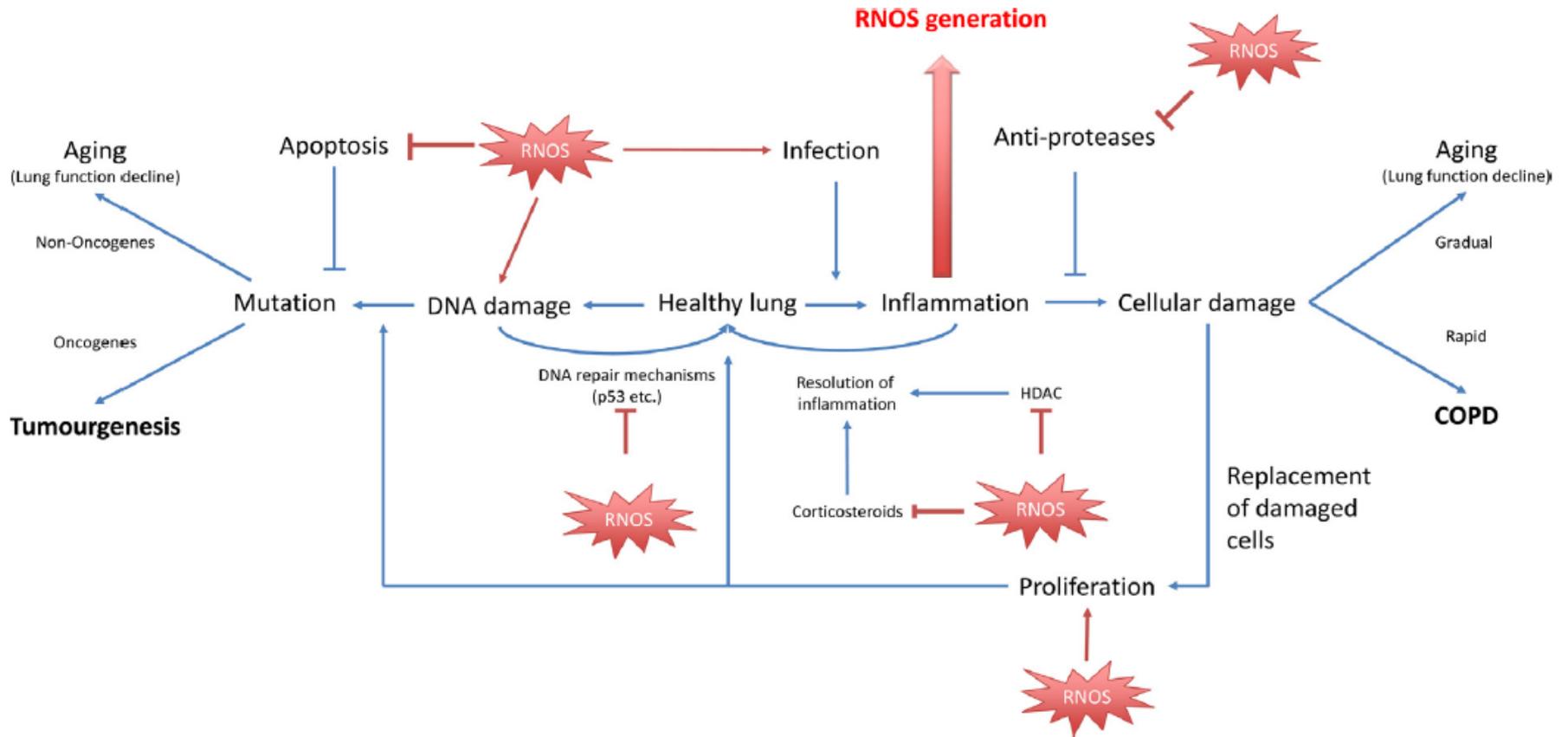| Previous Lung Disease	No. of Lung Cancer Deaths	Person-Years	Death Rate*	Minimally Adjusted Hazard Ratio[†] (95% CI)	Fully Adjusted Hazard Ratio[‡] (95% CI)
Chronic bronchitis					
Yes	48	210,569	19.0	0.96 (0.72, 1.28)	0.96 (0.72, 1.28)
No	1,711	7,932,210	21.1	1.00	1.00
Emphysema					
Yes	20	35,418	42.0	1.71 (1.10, 2.66)	1.66 (1.06, 2.59)
No	1,739	8,107,361	21.0	1.00	1.00
Chronic bronchitis and emphysema					
Yes	8	10,585	52.6	2.50 (1.24, 5.02)	2.44 (1.22, 4.90)
No	1,751	7,907,377	21.1	1.00	1.00

Definition of abbreviation: CI = confidence interval.

* Per 100,000 person-years, age-standardized to the age distribution of the entire Cancer Prevention Study II cohort.

[†] Age, sex, and race stratified.

[‡] Age, sex, and race stratified, and adjusted for education, marital status, body mass index, occupational exposures, beer, wine, and liquor consumption, vegetable/fruit/fiber intake, fat intake, and passive smoking.

Turner MC et al. Am J Respir Crit Care Med. 2007;176:285-290.

Link between COPD and Lung Cancer

Durham AL et al. Lung Cancer. 2015;90:121-127.

Other lung diseases

- **Alfa1-antitripsin deficiency** carriers have a higher risk for lung cancer (approximately 2-fold risk)[1]

- Patients with **idiopathic pulmonary fibrosis** have increased risk for lung cancer (OR 8.25 compared with control subjects)[2]

1. Yang P et al. Arch Intern Med. 2008;168:1097-1103.
2. Hubbard R et al. Am J Respir Crit Care Med. 2000;161:5-8.

Infections

- **HPV DNA** detected within some squamous cell carcinoma lung cancer tissues, but data are not conclusive[1]

- *Chlamidia pneumoniae* might be involved in lung carcinogenesis (through inflammation and ROS)[2]

- Some studies have reported association of **pulmonary tuberculosis** and lung cancer[3]

- Some evidence suggest an increased risk for lung cancer in **HIV**-infected patients after controlling for smoking status[4]

1. Chen YC et al. Cancer. 2004;101:1428-1436.
2. Littman AJ et al. Cancer Epidemiol Biomarkers Prev. 2005;14:773-778.
3. Yu YH et al. J Thorac Oncol. 2011;6:32-37.
4. Kirk GD et al. Clin Infect Dis. 2007;45:103-110.

Clinical models of risk prediction

First Author	Bach	Spitz	Cassidy	Tammemegi	Hogart
Source	Caret	MDA (Case-Control)	LLP (Case-Control)	PLCO	EPIC
Subjects	18,172, 10-60 cpd x 25-55 yrs	3,852 n/f/c smokers	1,736 n/f/c smokers	115,185 healthy population	169,035 ever smokers
Ages	50-75	20-80	20-80	55-74	35-65
Variables	**Age** Gender Asbestos **Smoking**	**Age** Gender Dust **Smoking** Fam hx Emphysema	**Age** Gender Asbestos **Smoking** Fam hx Pneumonia Prior ca	**Age** Education BMI **Smoking** Fam hx Hx of cancer COPD	**Age** **Smoking**

Web-based tools for risk prediction

http://lungcancerrisk.s3-website-us-east-1.amazonaws.com/

Basic Info

Gender
Male | Female

Education
Some college ▾

X-rays in past 3 years
0 | 1 | ≥2

1° relative with lung cancer
None ▾

0 — 60 y/o — 90 y/o
Age

0 — 22 kg/m² — 40 kg/m²
BMI

Smoking History

0 — 30 y/o — 60 y/o — 90 y/o
Smoking Ages
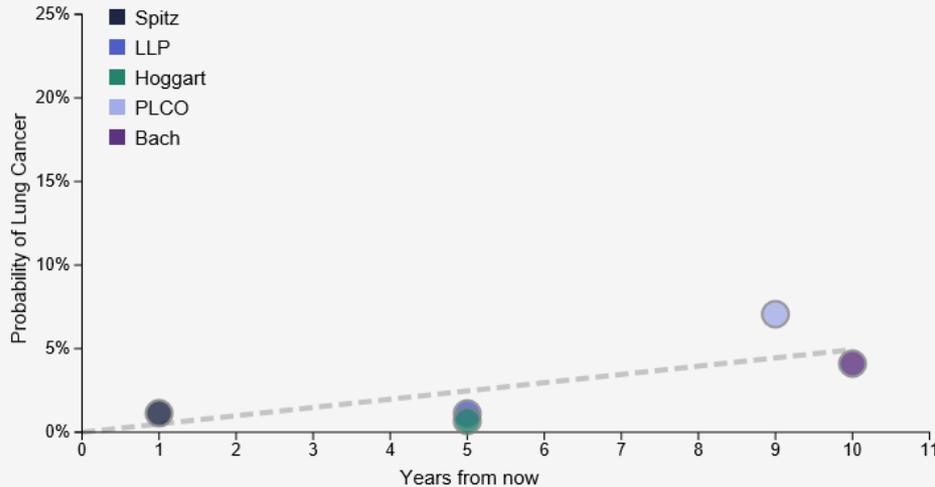
0 — 40 cpd — 80 cpd
Smoking Intensity

Exposures and Other

Hay fever | COPD | Emphysema | Pneumonia | Asbestos | Dust | Prior Malignant Tumor
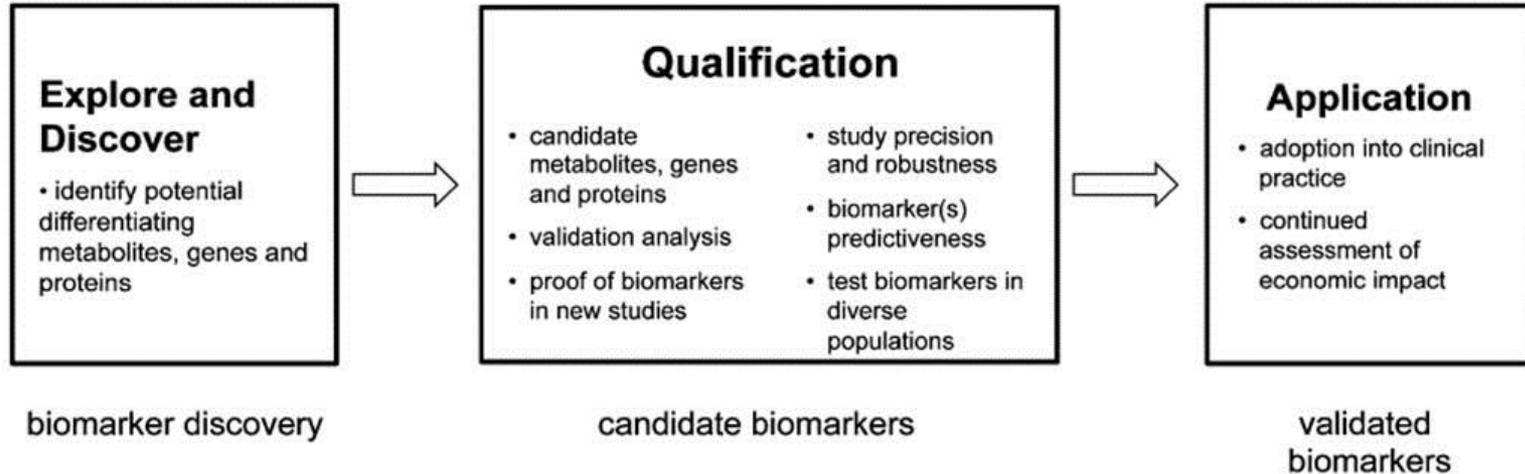

Probability of Lung Cancer Diagnosis by Risk Model
60 y/o male current smoker at 40 cigarettes per day for 30 years (60 pack-years)

■ Spitz
■ LLP
■ Hoggart
■ PLCO
■ Bach

Spitz	LLP	Hoggart	PLCO	Bach
VALID	VALID	VALID	VALID	VALID
1.1%	1.1%	0.7%	7.1%	4.1%
over 1 year(s)	over 5 year(s)	over 5 year(s)	over 9 year(s)	over 10 year(s)

Future perspectives

Serkova, Am J Resp Crit Care Med 2011.

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GRAZIE

PER L'ATTENZIONE