LUCIA

LUng Cancer-related risk factors and their Impact Assessment

HORIZON-MISS-2021-CANCER-02

LUCIA Workshop – Understanding Lung Cancer

San Sebastian, Sept. 5th, 2023

Speaker: Clara Frick

PI: Prof. Dr. Hermann Brenner
German Cancer Research Center (DKFZ)

European Commission

Epidemiology and Lung Cancer Risk Factors

Speaker: Clara Frick
PI: Prof. Dr. Hermann Brenner

German Cancer Research Center,
Division of Clinical Epidemiology and Aging Research

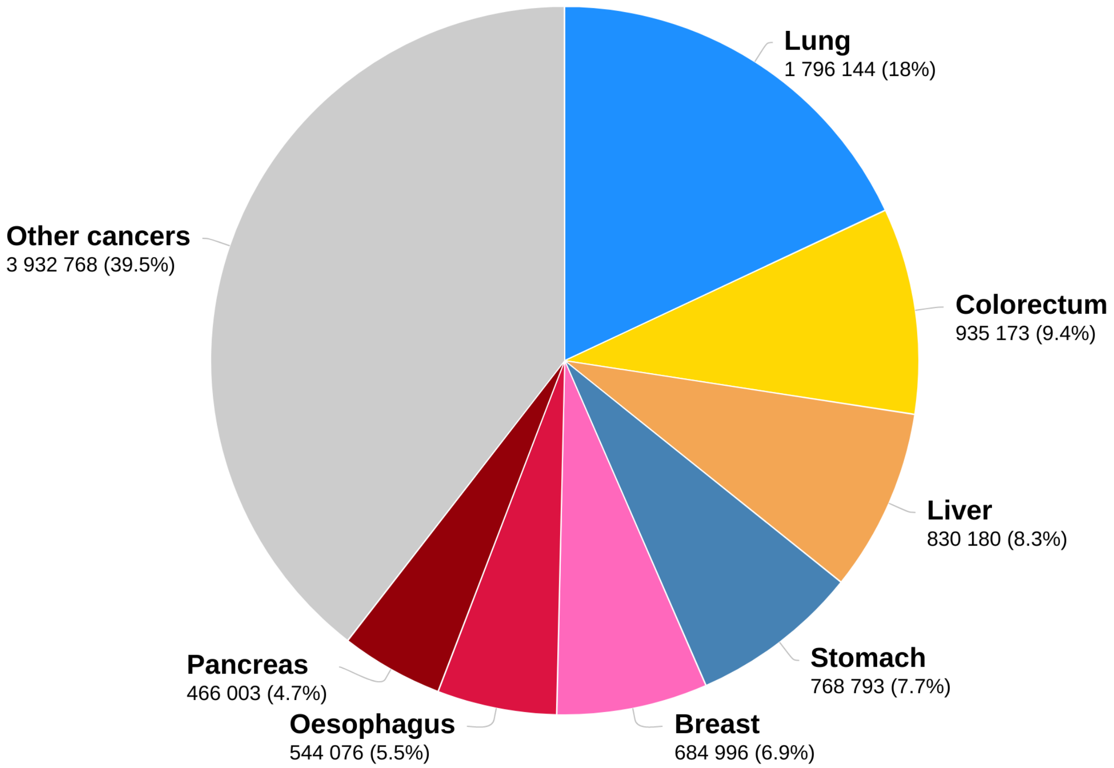
GERMAN
CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

Research for a Life without Cancer

Outline:

- Epidemiology of lung cancer
- Risk factors: smoking and environmental / occupational exposures
- Regional variability
- Risk-based screening:
    - Criteria-based LDCT-based screening → risk prediction models
    - Blood-based biomarkers

Estimated number of deaths in 2020, World, both sexes, all ages



Total : 9 958 133

Data source: Globocan 2020
Graph production: Global Cancer Observatory (http://gco.iarc.fr)

International Agency for Research on Cancer
World Health Organization

- Stage of diagnosis heavily influences treatment outcomes
  - Five-year survival decreases from 55% to 4% when diagnosed in stage IV (versus stage I)

(Cronin et al, *Cancer*. 2018; 124(13):2785-2800)

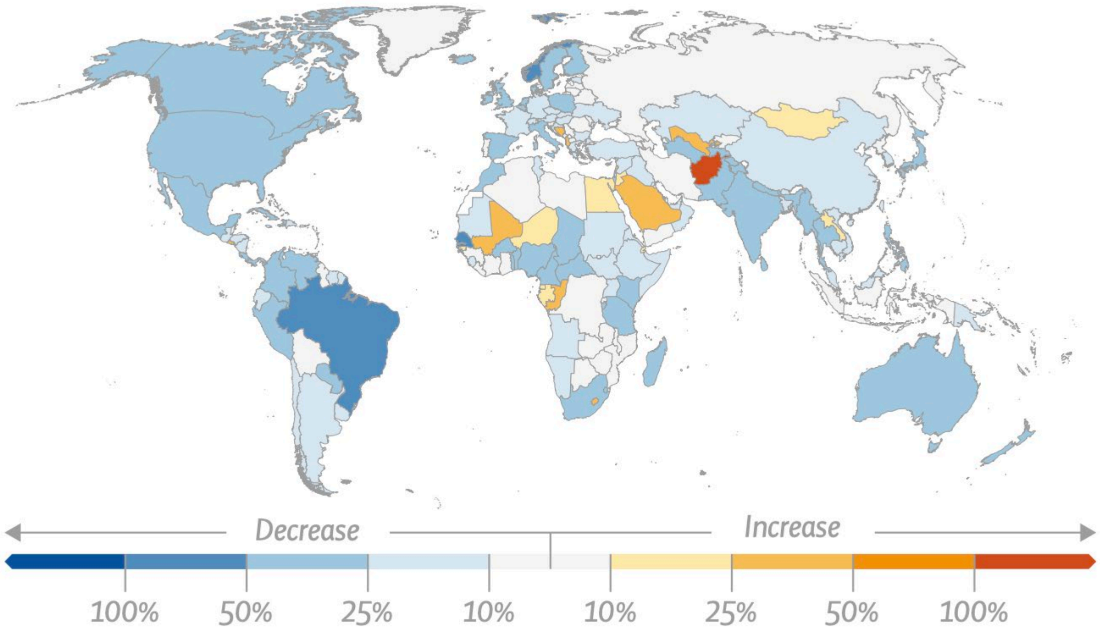
- Opportunity to reduce mortality by improving primary and secondary prevention (i.e. risk factor reduction, screening and early diagnosis)

Tobacco smoking

- **80-90%** of lung cancer cases attributable to smoking
- Increases risk by **15** to **30** times
- **Intensity**, **duration** and **time since cessation** impact risk
- About **20%** of smokers develop lung cancer
- Second-hand smoke increases risk by **20-30%**

CDC 2006, IARC 2004

Change in prevalence by country, 1990–2019



Retrieved from: https://www.thelancet.com/pb/assets/raw/Lancet/infographics/tobacco/Tobacco_infographics_global.pdf

Globally, prevalence of tobacco smoking is estimated at **22%**

- Regions with the highest prevalence: South-East Asia, Western Pacific, Europe (estimated prevalence of 25%-30%)

- In Europe:
  - Men (estimated prevalence of 33%), Women (estimated prevalence of 18%)
  - Slower decline in cigarette smoking in women than in men

E-cigarettes use has increased among adolescents and young adults

WHO global report tobacco, 2019

Other risk factors for lung cancer

Environmental and **occupational** exposures:

- Unprocessed biomass fuels
- Arsenic
- Radon
- Asbestos
- Diesel exhaust

Family history and other **diseases**:

- Genetic variants
- Previous chronic lung diseases
- HIV / HPV infection

Lifestyle factors:

- Diet and metabolic factors

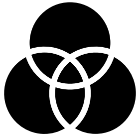
Leiter et al, Nature Reviews 2023, 20:9, 624–639

Incidence and mortality trends vary according to:

- National human development index (HDI):
  - Mortality rate in very high HDI (22.8 ASR per 100,000 py) versus low HDI settings (3.2 ASR per 100,000 py)
- World region:
  - Eastern Asia, Western Europe and Northern America had among the highest incidence rates (32.6-34.4 ASR per 100,000 py)
- Sex:
  - Trends in incidence and mortality were decreasing among men in most countries
  - In European countries, trends increased in women

Zhou et al eBioMedicine 2022, 78:103951

- Regional variation in lung cancer incidence and mortality linked to
  - **Differences** in smoking patterns



  - **Environmental** exposures
  - Frequency of somatic **mutations** (such as (EGFR) alterations)
  - Lung cancer **subtypes**

Leiter et al, Nature Reviews 2023, 20:9, 624–639

- Existing predictive models for risk stratification:

Supplementary Table 1: Covariates included in the established LC risk prediction models

		Model [reference]							
		Bach Model [14]	**Spitz Model** [15]	**LLP Model** [16]	**Hoggart Model** [17]	**PLCO$_{M2012}$** [18]/ **PLCO$_{all2014}$** [19] **Models**	**Pittsburgh Predictor**[21]	**LLPi** [20]/ **LLPv3** [23] **Models**	**LCRAT** [22]/ **LCDRAT**[22]
Country/Region		USA	USA	UK	EU	USA	USA	UK	USA
Target population, smoking status		Ever smokers	Never, former & current smokers	Individuals aged	Ever smokers	Ever Smokers/ General population	Ever smokers	Individuals aged	Ever smokers
Target population, age range (years)		44-75	≥ 18	20-80	40-65	55-74/ 55-80	55-74	45-79/ 50-79	55-74/ 55-74
Cumulative risk prediction (year/s)		5	1	5	1	6/ 6	6	8.7/ 5	5/ 5
Covariates included	Demographics								
	Age	X	X	X	X	X	X	X	X
	Gender	X	X	X				X	X
	Race/ethnicity#					X			X
	BMI					X			X
	Education					X			X
	Smoking								
	Smoking status		X		X	X	X		
	Years/age quit smoking	X	X		X	X			X
	Years smoked	X		X	X	X	X	X	X
	Cigarettes per day	X			X	X	X		X
	Pack-years		X						X
	Comorbidities								
	Lung disease (COPD/Emphysema)		X			X		X	X
	Prior cancer			X		X		X	
	Pneumonia			X					
	Hayfever		X						
	Occupational exposures								
	Asbestos exposure	X	X	X					
	Dust exposure		X						
	Family history								
	Any FDR with cancer		X						
	Any FDR with smoking related cancer		X						
	Any FDR with LC			X		X		X	X
	Num. FDR with LC								X
	Early onset FDR with LC			X				X	

Bhardwaj et al
Lung Cancer 2022, 174:83-90

ESTHER Study cohort (9,940 participants)

Saarland, Germany:

N = 4812 Ever smokers aged 50-75 years (with no previous LC diagnoses)

17 year FU

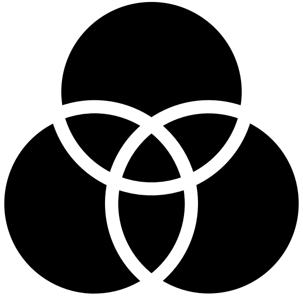
262 Incident LC, 4450 No LC

Bhardwaj et al
Lung Cancer 2022, 174:83-90

Table 2
Performances of different **LC risk prediction models** for incident cases identified during 6, 11 and 17 years of follow-ups among **ever smoking participants** of the ESTHER-study.

Model, country [reference]	Time horizon (n total = 4812) 0–6 years (n iLC = 102)	0–11 years (n iLC = 179)	0–17 years (n iLC = 262)
	AUC (95% CI)		
Bach model, USA [14]	0.782 (0.739–0.824)	0.774 (0.742–0.805)	0.766 (0.740–0.792)
Spitz model, USA [15]	0.725 (0.677–0.774)	0.688 (0.648–0.728)	0.638 (0.604–0.672)
LLP model, UK [16]	0.744 (0.698–0.790)	0.717 (0.679–0.756)	0.676 (0.641–0.710)
Hoggart model, Europe [17]	0.705 (0.649–0.761)	0.708 (0.667–0.749)	0.712 (0.678–0.745)
$PLCO_{M2012}$, USA [18]	0.751 (0.699–0.803)	0.742 (0.703–0.781)	0.739 (0.707–0.771)
$PLCO_{all2014}$ model, USA [19]	0.749 (0.698–0.800)	0.741 (0.702–0.779)	0.742 (0.711–0.774)
LLPi model, UK [20]	0.773 (0.731–0.815)	0.753 (0.720–0.787)	0.725 (0.697–0.754)
Pittsburgh Predictor, USA [21]	0.778 (0.737–0.820)	0.763 (0.730–0.797)	0.766 (0.739–0.792)
LCRAT, USA [22]	0.786 (0.745–0.827)	0.771 (0.739–0.804)	0.771 (0.745–0.797)
LCDRAT, USA [22]	0.787 (0.746–0.828)	0.770 (0.738–0.802)	0.765 (0.739–0.792)
LLPv3 model, UK [23]	0.773 (0.731–0.815)	0.753 (0.720–0.787)	0.725 (0.697–0.754)

Improvements of risk models with blood-based biomarkers



miRNA-Score → increase in AUCs of risk models of 0.041 and 0.096

TABLE 1 Performance of LC models* [7] individually and in combination with the miR-score for LC risk prediction among ever-smokers ($n_{cases/controls}$ = 206/ 101) in prospective set participants

LC model	AUC (95% CI) LC model only	LC model + miR-score apparent#	LC model + miR-score .632+$	*P*-value for improvement in AUC
LLPi	0.712 (0.651-0.774)	0.765 (0.708-0.821)	0.762	0.019
Pittsburgh Predictor	0.717 (0.656-0.779)	0.764 (0.707-0.821)	0.762	0.042
Bach	0.716 (0.654-0.778)	0.760 (0.703-0.817)	0.758	0.034
$PLCO_{M2012}$	0.694 (0.632-0.755)	0.757 (0.700-0.814)	0.754	0.008
LLP	0.669 (0.606-0.732)	0.750 (0.693-0.808)	0.747	0.003
Hoggart	0.655 (0.591-0.719)	0.738 (0.679-0.797)	0.734	0.004
Spitz	0.623 (557- 0.689)	0.723 (0.665-0.781)	0.719	0.001
LCRAT	0.721 (0.658-0.783)	0.765 (0.707-0.822)	0.762	0.061

Yu et al Cancer Communications 2022, 42(11), 1222–1225

Inflammatory plasma protein biomarker score → increase in AUCs of risk models up to 0.07

Ever smoking participants from ESTHER study, incl. 172 incident LC cases and 285 randomly selected participants free of LC

92 inflammation protein biomarkers were measured

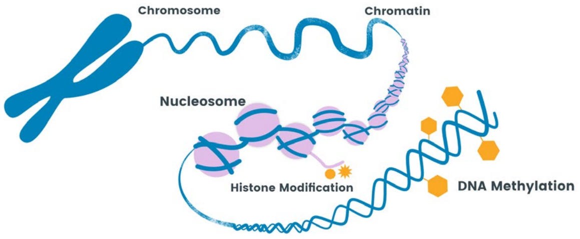
0.632+ bootstrap applied for correction of overoptimism

Bhardwaj et al Cancers 2022, 14(9):2146

DNA Methylation analyses in **ESTHER** Dataset

N = 162 ever-smoking cases,

N = 721 ever-smoking randomly selected controls



AHRR (cg05575921) methylation

- Adding to LC risk models, increase in AUCs from 0.036 to 0.133 (P < 0.05 for all 10 risk models)

F2RL3 (cg03636183) methylation

- Adding to LC risk models, increase in AUCs from 0.041 to 0.129 (P < 0.05 for all 10 risk models)

Future epidemiological work within LUCIA

- Analyses in ESTHER dataset
  - Complete genotyping
  - Methylation arrays for all lung cancer cases and controls
  - microRNA analyses
  - OLINK proteomics analyses

Conclusions:

- Globally lung cancer is the leading cause of cancer deaths, with geographical variability in incidence and mortality
- Regional variability is largely reflected by trends in tobacco smoking and other risk factors
- Risk models for selecting high-risk individuals for screeningare promising, especially in combination with biological signatures

References

Bhardwaj M, Schöttker B, Holleczek B, Brenner H. Comparison of discrimination performance of 11 lung cancer risk models for predicting lung cancer in a prospective cohort of screening-age adults from Germany followed over 17 years. Lung Cancer. 2022 Dec;174:83-90. doi: 10.1016/j.lungcan.2022.10.011. Epub 2022 Oct 30. PMID: 36356492.

Bhardwaj M, Schöttker B, Holleczek B, Benner A, Schrotz-King P, Brenner H. Potential of Inflammatory Protein Signatures for Enhanced Selection of People for Lung Cancer Screening. Cancers. 2022; 14(9):2146. https://doi.org/10.3390/cancers14092146

Bhardwaj M, Schöttker B, Holleczek B, Brenner H. Enhanced selection of people for lung cancer screening using AHRR (cg05575921) or F2RL3 (cg03636183) methylation as biological markers of smoking exposure. Cancer Commun (Lond). 2023 Aug;43(8):956-959. doi: 10.1002/cac2.12450. Epub 2023 Jun 6. PMID: 37278142; PMCID: PMC10397557.

Cronin KA, Lake AJ, Scott S, *et al.* Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. *Cancer* 2018; **124**: 2785–800.

Centers for Disease Control and Prevention. (2023). What Are the Risk Factors for Lung Cancer? CDC. https://www.cdc.gov/cancer/lung/basic_info/risk_factors.htm

Centers for Disease Control and Prevention (US), & U.S. Department of Health and Human Services. (2006). The Health Consequences of Involuntary Exposure to Tobacco Smoke. Publications and Reports of the Surgeon General. https://www.ncbi.nlm.nih.gov/books/NBK44324/

de Koning HJ, van der Aalst CM, de Jong PA, *et al.* Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. *New England Journal of Medicine* 2020; **382**: 503–13.

Huang, Z., Sun, S., Lee, M. et al. Single-cell analysis of somatic mutations in human bronchial epithelial cells in relation to aging and smoking. Nat Genet 54, 492–498 (2022). https://doi.org/10.1038/s41588-022-01035-w

IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Tobacco smoke and involuntary smoking. IARC Monogr Eval Carcinog Risks Hum. 2004;83:1-1438. PMID: 15285078; PMCID: PMC4781536.

Leiter, A., Veluswamy, R. R., & Wisnivesky, J. P. (2023). The global burden of lung cancer: current status and future trends. Nature Reviews Clinical Oncology 2023 20:9, 20(9), 624–639. https://doi.org/10.1038/s41571-023-00798-3

National Lung Screening Trial Research Team, Aberle DR, Adams AM, *et al.* Reduced Lung-Cancer Mortality with Low-Dose Computed Tomographic Screening. *New England Journal of Medicine* 2011; **365**: 395–409.

Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209–49.

World Health Organization. Regional office for Europe. European tobacco use. trend. Available from: http://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2019/european-tobacco-use-trends-report-2019- 2019.

WHO global report on trends in prevalence of tobacco use 2000–2025, third edition. Geneva: World Health Organization; 2019.

Yu, H., Raut, J. R., Bhardwaj, M., Zhang, Y., Sandner, E., Schöttker, B., Holleczek, B., Schrotz-King, P., & Brenner, H. (2022). A serum microRNA signature for enhanced selection of people for lung cancer screening. Cancer Communications, 42(11), 1222–1225. https://doi.org/10.1002/CAC2.12346

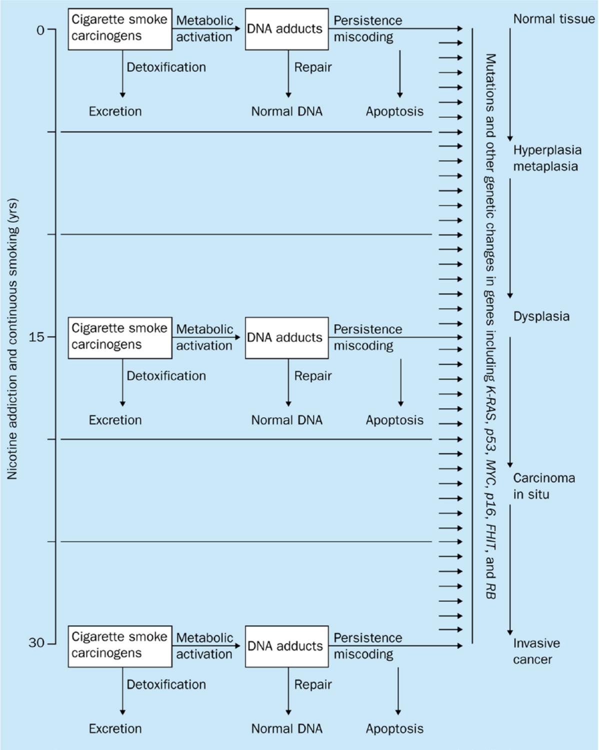
Zhou B, Zang R, Zhang M, et al. Worldwide burden and epidemiological trends of tracheal, bronchus, and lung cancer: A population-based study. EBioMedicine 2022; 78. DOI:10.1016/j.ebiom.2022.103951.

Evidence from LDCT-based screening program trials:

US National Lung Screening Trial (NLST) (US) and NELSON (EU)

- Enrollment criteria-based (age, history of smoking, and time since smoking cessation)
- 20% reduction in mortality but still substantial number of false-negative and false-positive results → need for optimized selection for screening
- Slow uptake when compared with other cancer screening programs

- **Lung cancer risk factor tobacco smoking**
  - Impact of smoking on lung cancer affected by intensity, duration and time since cessation
  - Less than 20% of smokers develop lung cancer (IARC, 2004) – many factors determine individual susceptibility



Huang et al. 2022, Nature genetics