



LUNG CANCER EXPOSOME & PRECISION MEDICINE

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Dr. Mezquita

- **Lectures and educational activities:**
 - AstraZeneca, Roche, Takeda, J&J, MSD, Pfizer, BeOne, Regeneron
- **Consulting, advisory role:**
 - Roche, Takeda, J&J, MSD, Pfizer, Lilly, Regeneron
- **Research Grants:**
 - Gilead, Tempus
- **Travel, Accommodations, Expenses:**
 - Bristol-Myers Squibb, Roche, Takeda, AstraZeneca, J&J, Regeneron, Pfizer

1. Risk factors & Exposome Approach
2. Lung Cancer Exposome & Precision Medicine (ICAPEM)
3. Preliminary Data
4. Challenges & Future Directions
5. Take-Home Messages

- 1. Risk factors & Exposome Approach**
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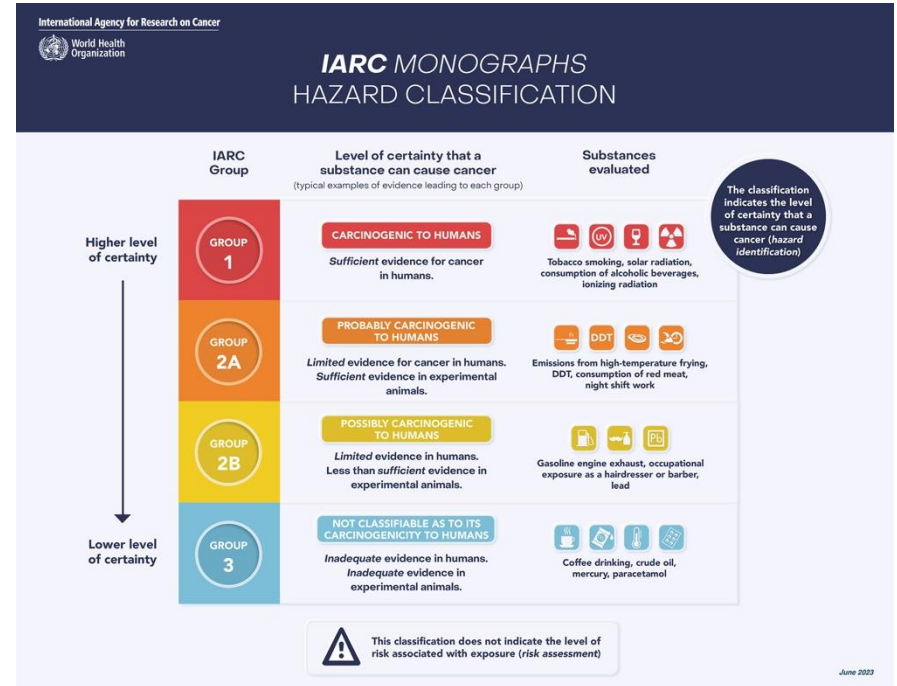
LUNG CANCER: Multifactorial disease



- 135 agents as Group 1 carcinogens according to International Agency for Research on Cancer (IARC) classification, with sufficient evidence for cancer in humans

→ More than 30 risk factors for lung cancer, including:

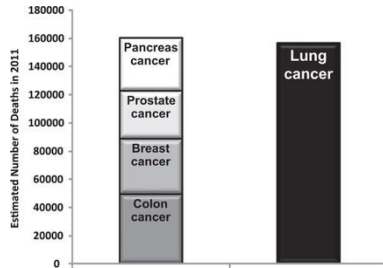
- tobacco smoke
- environmental factors
- occupational exposures



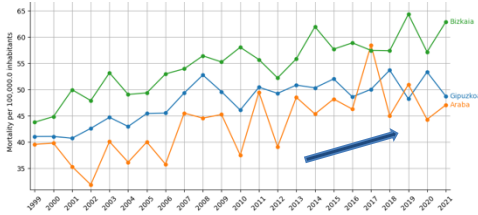
LUNG CANCER in 2026

MORTALITY

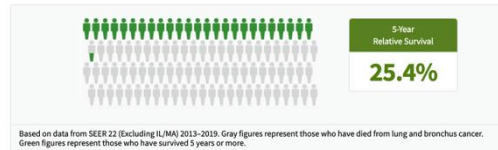
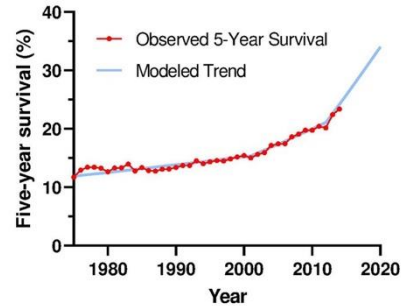
1st cause of mortality in cancer



Mortality, Basque Country, 1999-2021

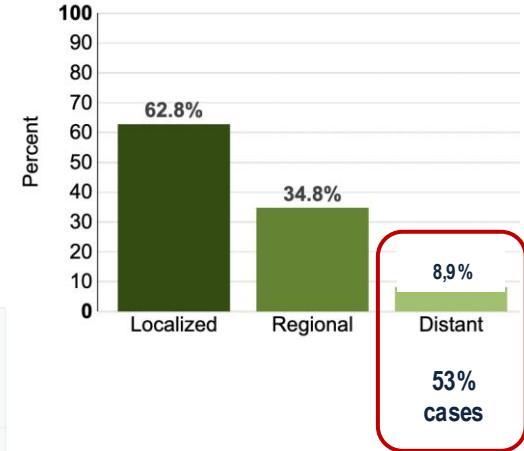


PROGNOSIS – 5yrs rate Survival

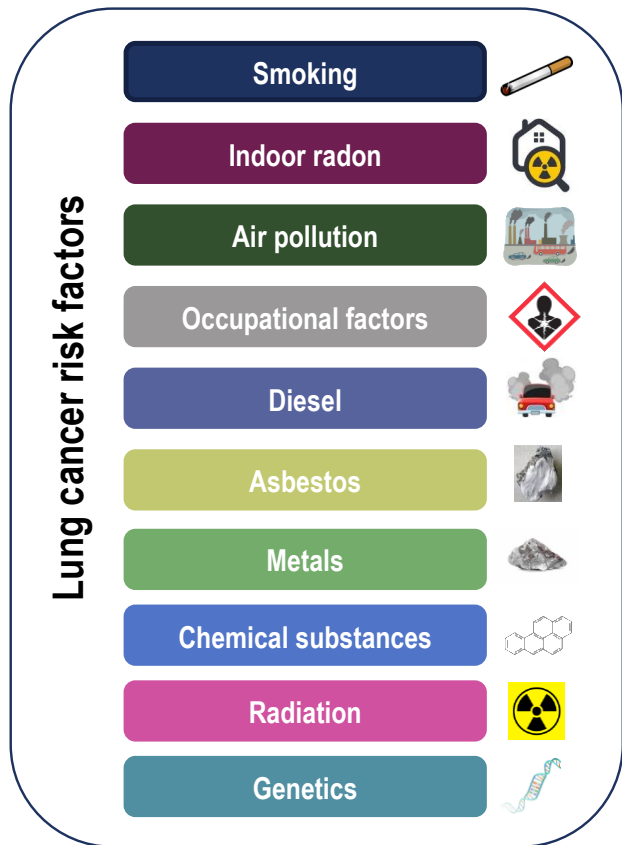


Based on data from SEER 22 (Excluding IL/MA) 2013–2019. Gray figures represent those who have died from lung and bronchus cancer. Green figures represent those who have survived 5 years or more.

5-Year Relative Survival



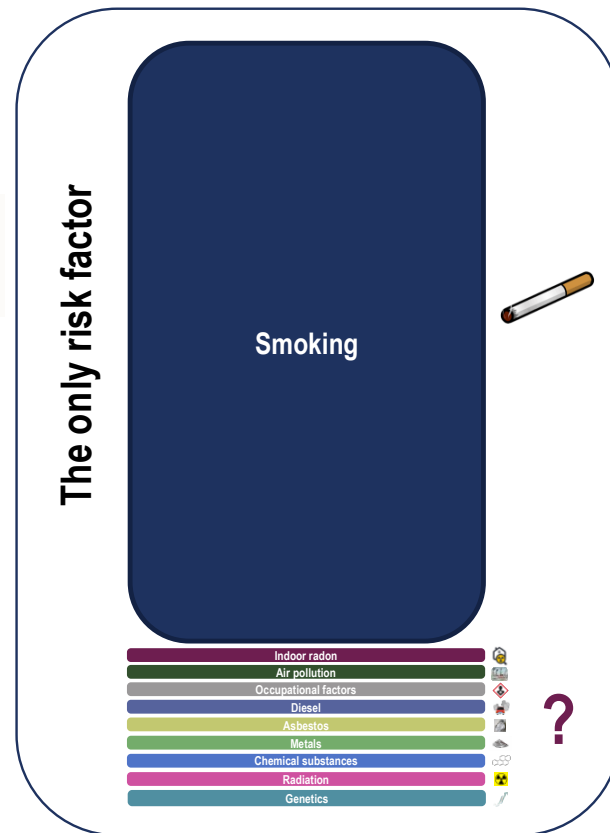
LUNG CANCER: Multifactorial disease



**REALITY =
misperception**



**TOBACCO Stigma
minimizes the others**



EXPOSOME: Lack of Knowledge in Clinics

“What is not studied is not reported,
what is not reported does not exist &
what does not exist is not prevented”

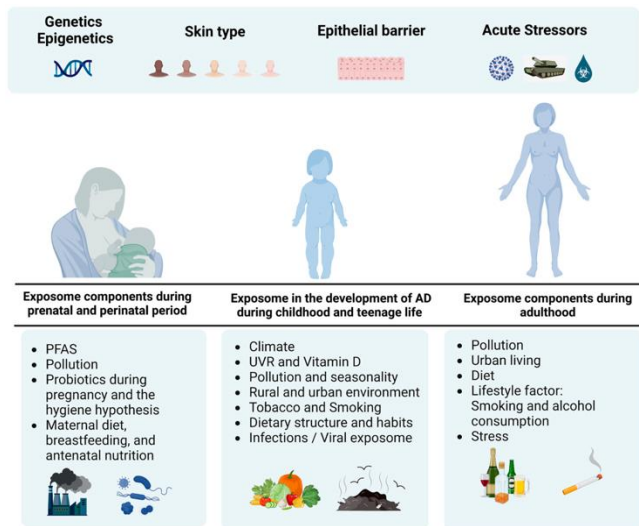


G E

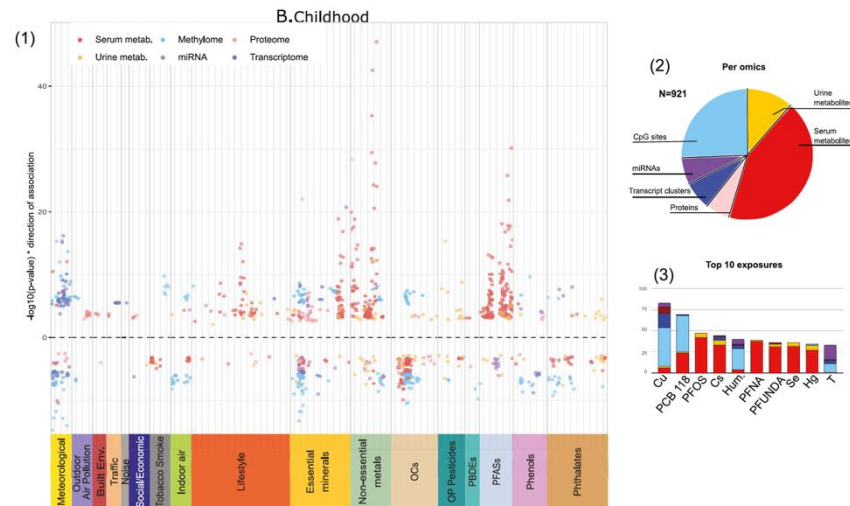
Recognizing the disparity in current knowledge between genes and environmental exposures, Chris Wild (2005) defined the “exposome” representing *all environmental exposures (including those from diet, lifestyle, and endogenous sources) from conception onwards*, as a quantity of critical interest to disease etiology.

Lifespan Studies

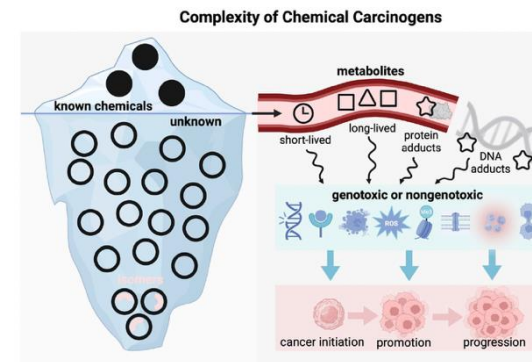
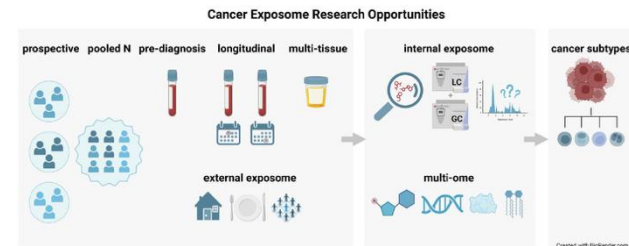
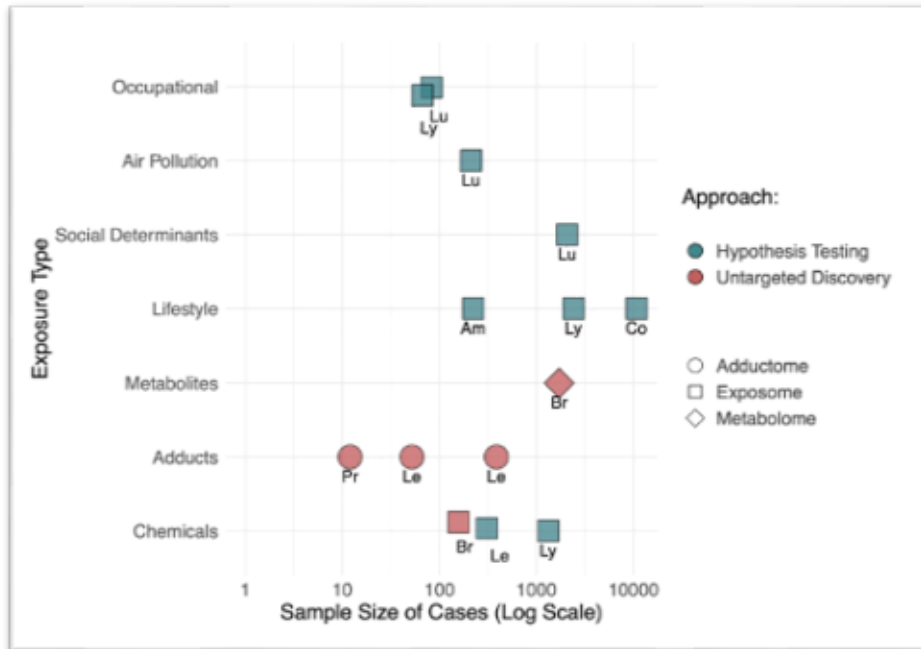
Atopic Dermatitis



Pregnancy & Childhood



EXPOSOME in Cancer: Limited data



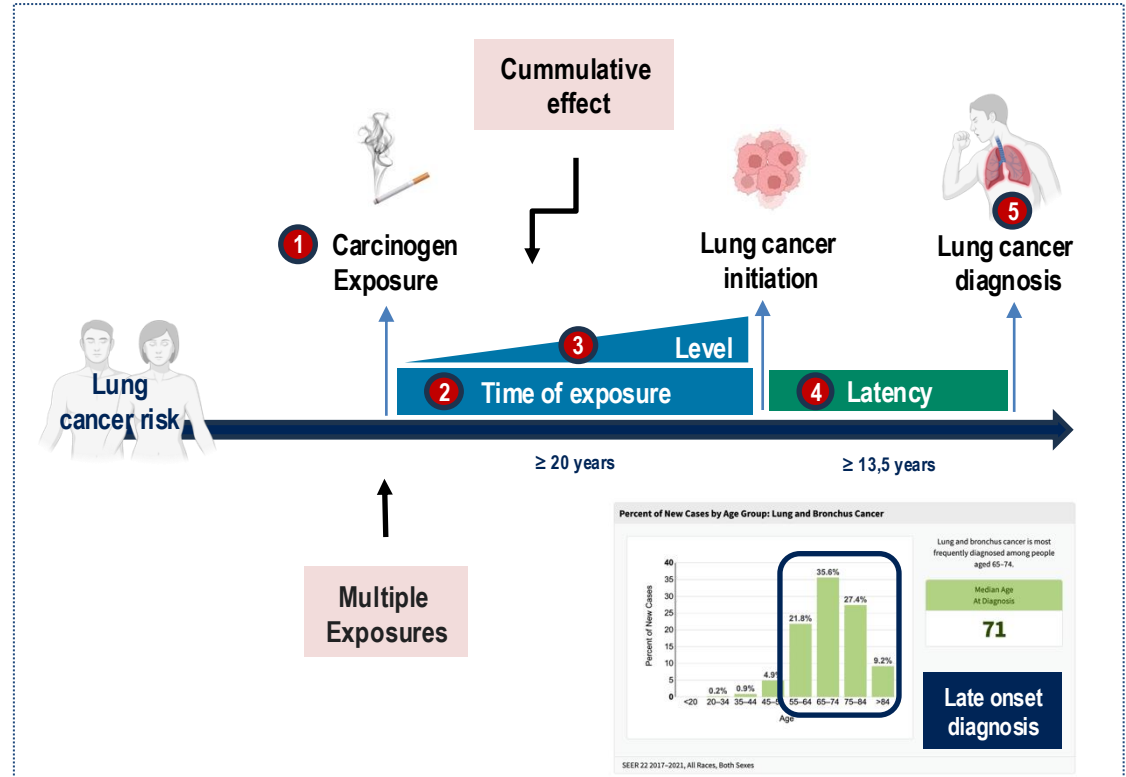
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EXPOSOME & LUNG CANCER

- **Environmental exposures** that an individual encounters throughout life, and how these exposures **impact biology & health**
- External factors
- Internal factors
- *Chemical, physical, biological, & social factors*

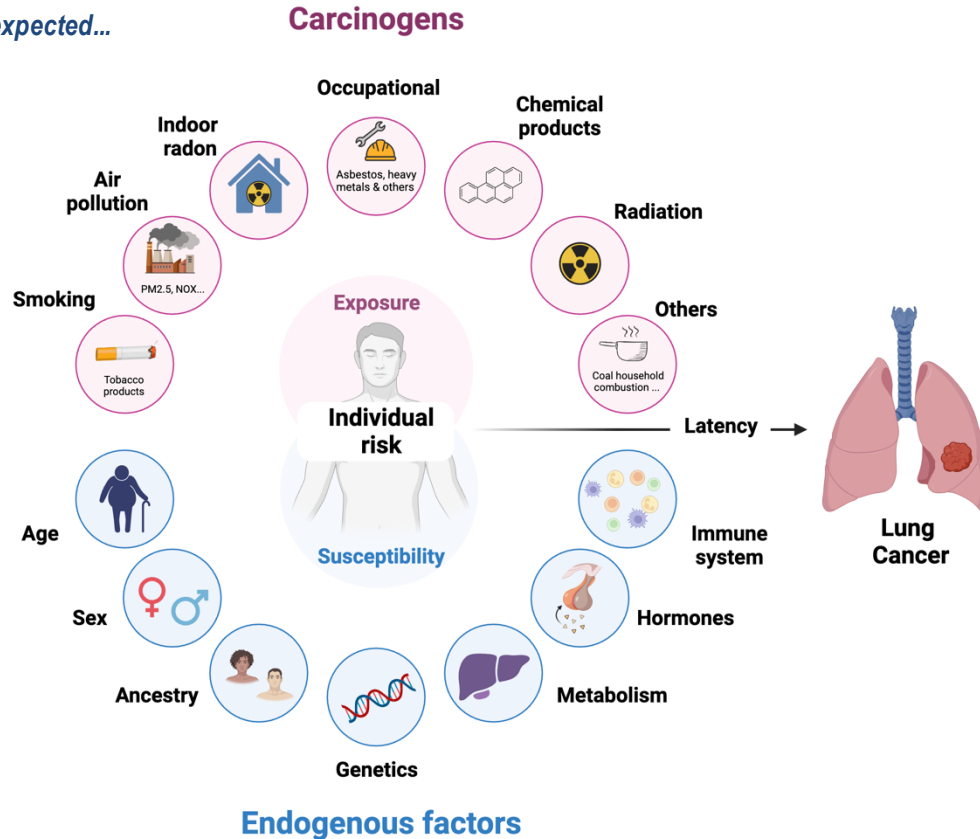
APPLICATIONS

- Interplay - genetics & environment
- Accurate risk assessment



Lung Cancer Exposome

More complex than expected...



2 questions arising ...



Is this relevant
for patients with lung cancer?



Is this relevant
for oncologist?





PEOPLE
WITH
LUNG
CANCER

- ✓ MAIN INTEREST: CANCER CARE (priority)
- ✓ ~~Cancer risk~~
- ✓ Cancer prevention (families)



Patients appreciate that their doctors inform them about risk factors, but with information tailored to their context

EXPOSOME: Impact on cancer care?

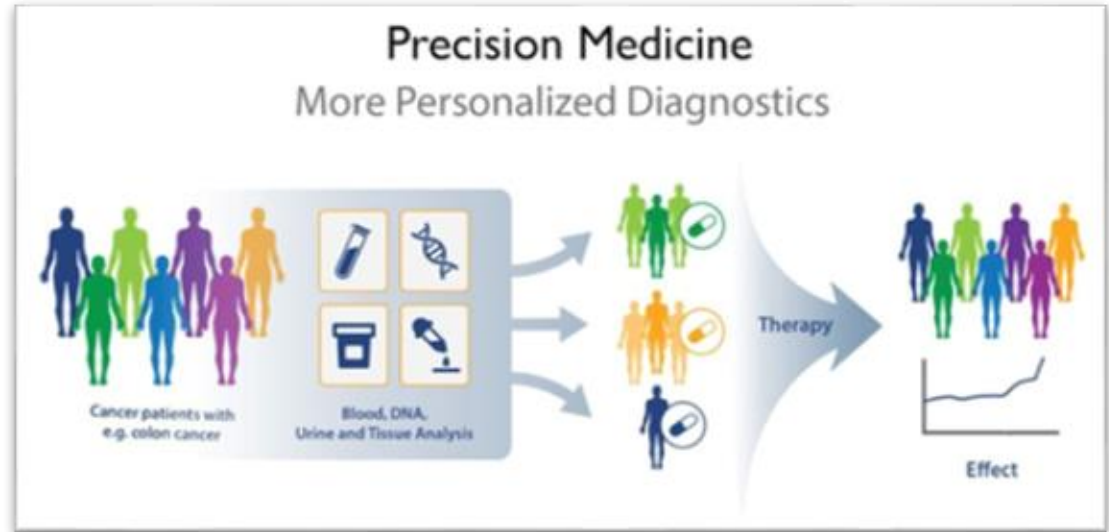


EXPOSOME:

- ↑ cancer risk
- Influence the **mechanism?**
- Influence the **profile?**
- Influence the **outcomes?**



More awareness
More dedicated research!

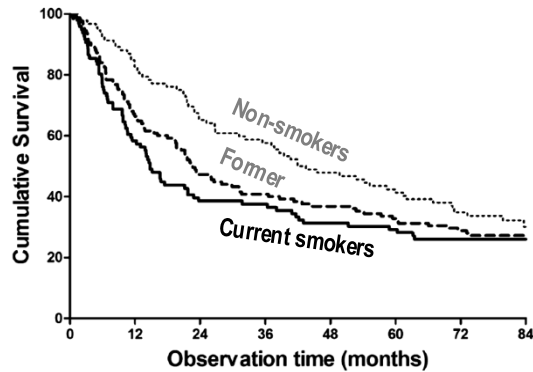


Identification of **vulnerabilities** related to each exposome pattern

One exposure (Smoking): Lung Cancer Outcomes

PROGNOSTIC factor

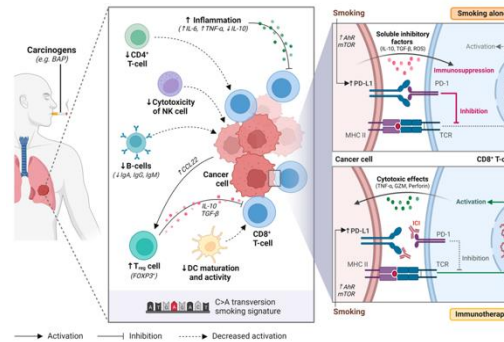
Smoking - **Mortality**
Patients with NSCLC
POOR outcomes



Lee SJ et al, Thorac Cancer 2014

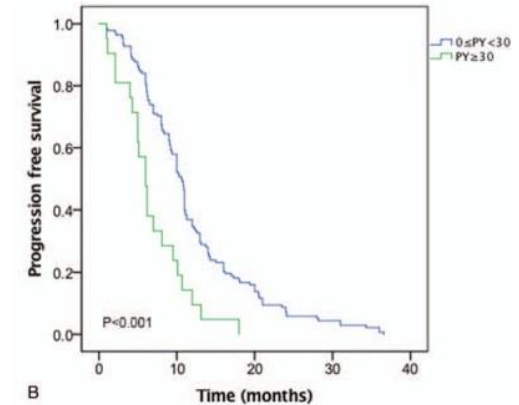
PREDICTIVE factor of RESPONSE

Smoking - **Immunotherapy**
Patients with NSCLC
BETTER outcomes



Corke LK, Current Oncol 2022

Smoking - **Targeted therapy**
Patients with NSCLC
POOR outcomes

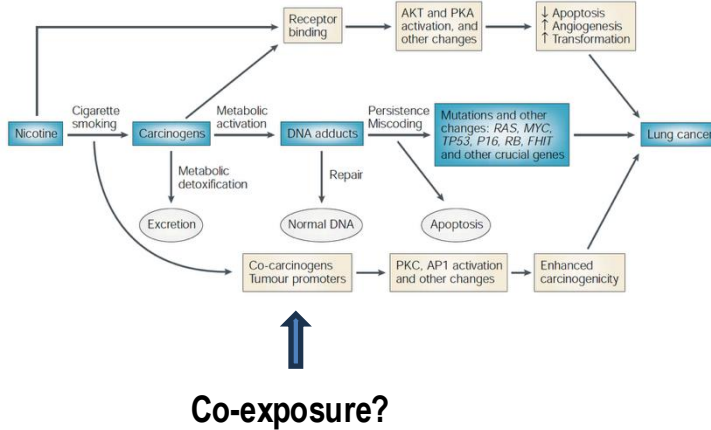


Zhang P, Medicine 2018

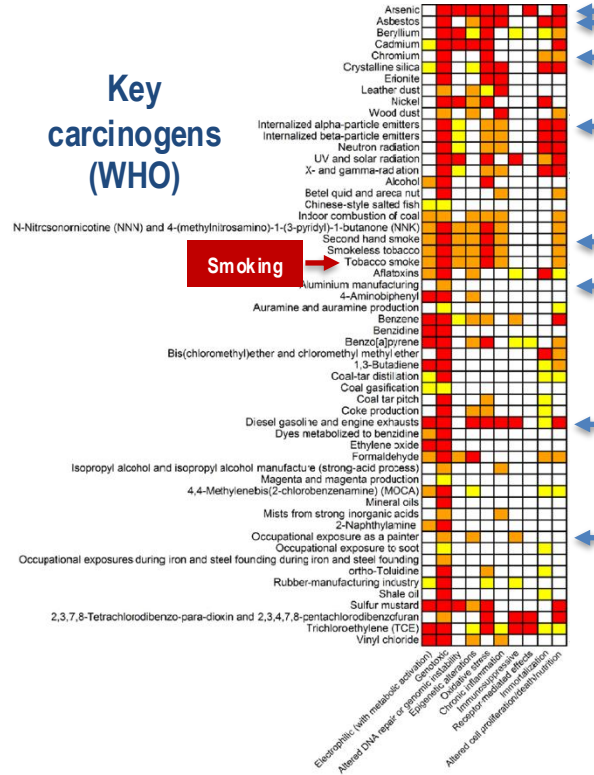
What is the impact of OTHER risk factors?

CARCINOGENESIS: “~~one risk factor, one disease~~”

Tobacco smoking - Carcinogenesis



Key carcinogens (WHO)



Co-carcinogens

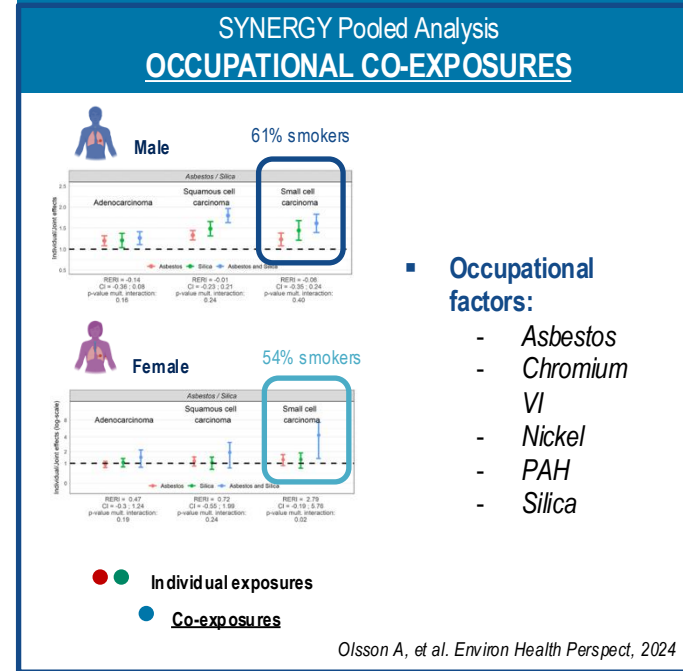
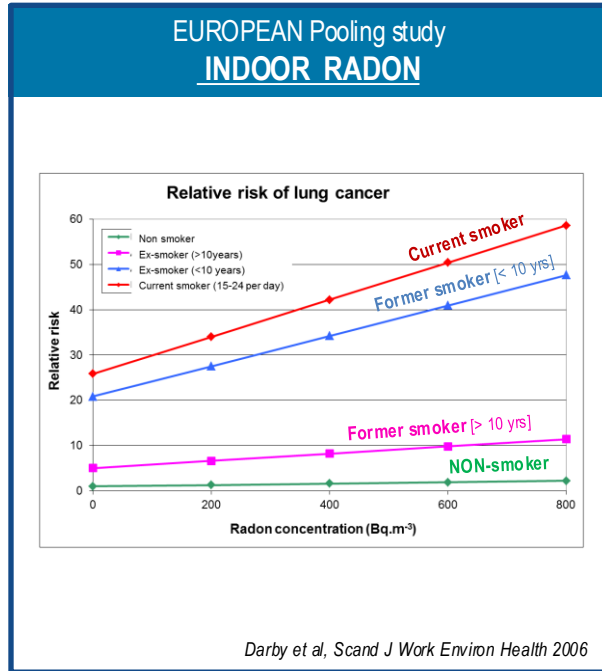


Shared Mechanisms

- ✓ Metabolic activation
- ✓ Genotoxic
- ✓ Altered DNA repair
- ✓ Genomic instability
- ✓ Oxidative stress
- ✓ Chronic inflammation
- ✓ Among others

Co-exposures (Smoking + others): Lung Cancer

Synergism

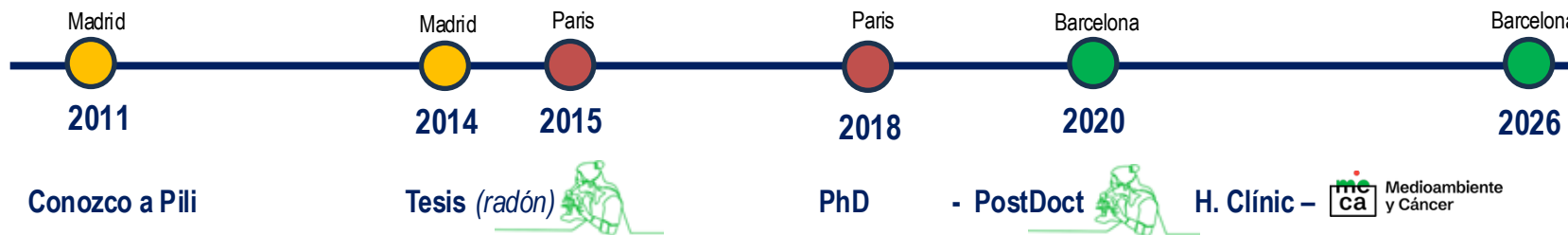


Perspective: Research – firstly in Radon

Pili

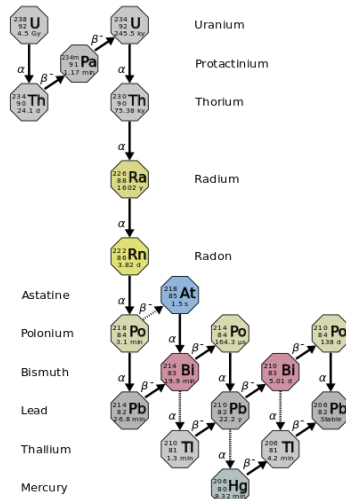


- Mujer 42 años, **no fumadora**
- Adenocarcinoma de pulmón
- Perfil molecular: EGFR mutación

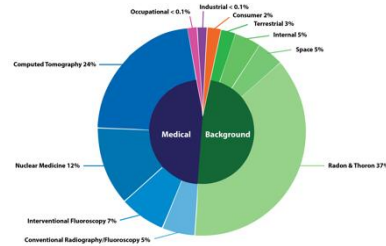


Radon gas – one of the leading causes of lung cancer

- Radon is an odorless, colorless, tasteless **radioactive gas** (Uranium decay chain)



- Most important source of **natural radiation**
- ++ frequent in rocky areas (**granite**, volcanic)

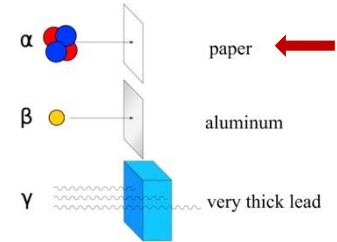


Risk: Indoor accumulation

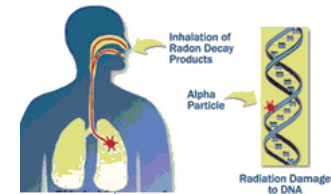


alpha-track detector

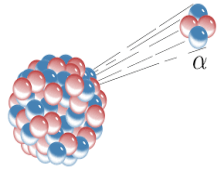
- Type of radioactivity: **alpha-particles**



↓ penentrance, ↑ transfer of energy



Understanding the radiation action mechanisms

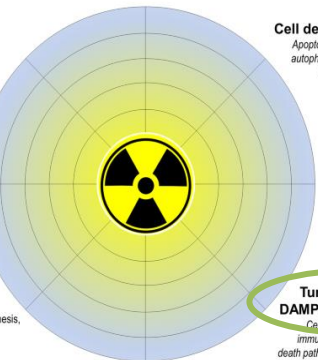


DNA damage
DNA strand breaks, DNA-DNA crosslinks, DNA-protein crosslinks, modification of deoxyribose rings & bases, homologous & non-homologous recombination

Soluble Factors
Cytokines, chemokines, growth factors, growth-inhibitory factors, coagulation factors, ECM proteins

Immune cell response
Immune cell recruitment, immunity, recruitment, activation, polarisation, antigen presentation

Hypoxia
Reduced angiogenesis, vasculogenesis, lymphangiogenesis, ceramide-induced apoptosis



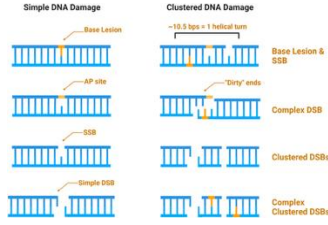
Bystander & abscopal effects
Micronucleation, apoptosis, cell-cell-communication, soluble factors

Cell death & senescence
Apoptosis, mitotic catastrophe, autophagy, bystander-induced, senescence-like

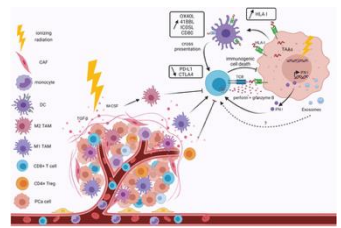
Cellular stress
ROS/RNS, ER stress, Inflammasome, antioxidant enzymes

Tumour antigens, DAMPs, & neo-antigens
Cell adhesion molecules, immunoregulatory molecules, death pathway & apoptosis associated, miscellaneous molecules

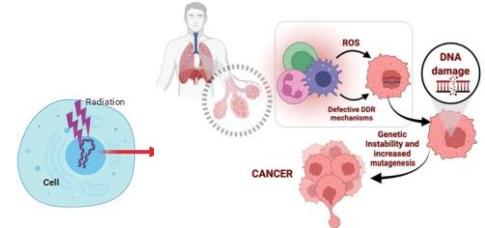
Molecular mechanisms



Immune mechanisms



Other mechanisms?

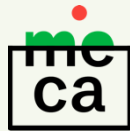


Lung cancer profile?

MECA: Medioambiente y Cáncer



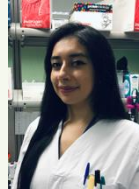
L Mezquita
MECA Leader



Nuestro Grupo



A. Arcocha
Project Manager



J Mena
Study coordinator



J Bakkali
Data manager



M Bustamante
Research Support T.



L Alcolea
Adm. Support



C. Teixidó
Senior Biologist



Maxime
Senior Postdoc



M Ferriol
Postdoc AI scientist



M Jimenez
Bioinformatician



M Marini
Visiting Scientist



JC Laguna
Pre-doc Fellow
Genetics



T Gorria
Pre-doc Fellow
Radon/Immuno



D Anguita
Pre-doc Fellow
Sex perspective



A Montes
Pre-doc Fellow
Occupations



M. Rota
Pre-doc Fellow
Exposome



M. Meazza
Pre-doc Fellow
Exposome

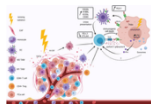
<https://www.meca-lab.org/>

EXPOSOME (radon): Impact on cancer care?

MIRROR



N= 806 patients



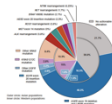
Dr. Garcia
Research fellow

16 centers - Spain

BIORADON



N= 975 patients



Dr. Gorria
PhD student

36 centers – 5 European Countries

SCAN



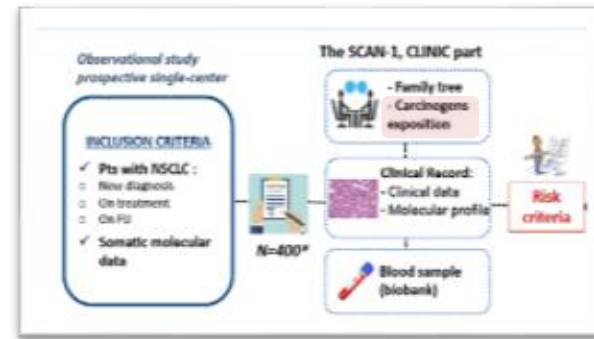
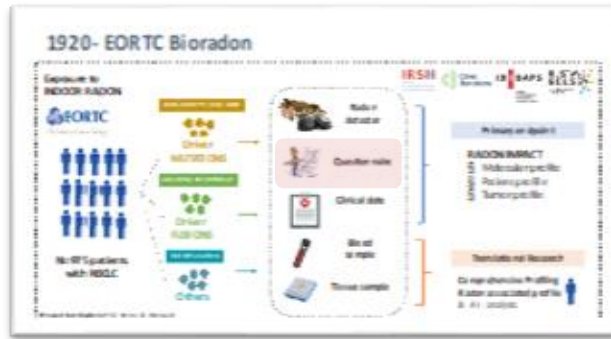
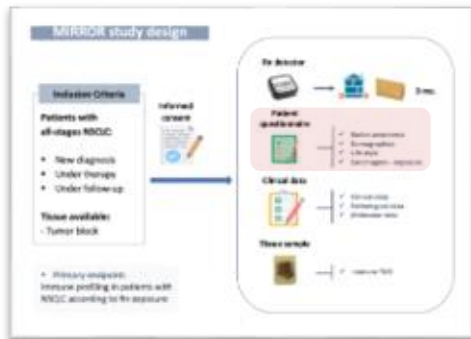
N= 380 patients



Single center - Spain



JC Laguna
PhD student



1st step - Precision Medicine Consultation

Generation of knowledge

Patients – Oncologist Collaboration



Hospital Clinic (2021-2024)



2nd step - Lung Cancer EXPOSOME & Precision Medicine

Generation of knowledge

Multicenter prospective study

INCLUSION CRITERIA

- ✓ Patients with lung tumor **all-histologies, all-stages:**
 - New diagnosed
 - Under treatment
 - Under FU
- ✓ Good PS (PS <2)
- ✓ Referral by the oncologist/ICAPEM network

Consultation
assessment



N=1,000

360°



Clinical data



Carcinogens



Questionnaire



Blood sample



Tumor sample

EXPOSOME
MTB



Are you interested?
imezquita@clinic.cat



- ✓ EXPOSOME patterns
- ✓ Lung cancer profiling
- ✓ Genetic predisposition

Activation: Sep 2024

1. Risk factors & Exposome Approach
2. Lung Cancer Exposome & Precision Medicine (ICAPEM)
3. **Preliminary Data**
4. Challenges & Future Directions
5. Take-Home Messages

EXPOSOME & Precision Medicine in Lung Cancer

Update – Mar 2026



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Challenge N#1: Endogenous factors

INHERITY STUDY

Prospective study

10% of patients with NSCLC - carriers

14 patients (88%) didn't met criteria for study in a GCU

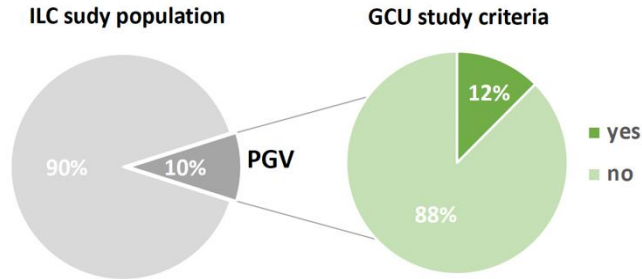


Figure 4. Proportion of patients with PGV with GCU study criteria.

Cancer prevention in families

- In 10 families (63%) genetic cascade study was recommended performing germline testing in 27 healthy relatives.
- Of them, in 12 individuals a PGV was detected

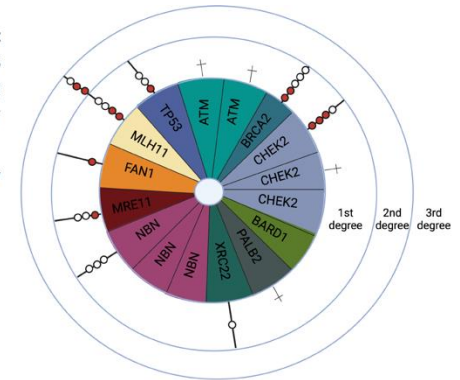
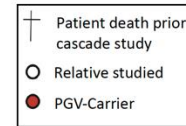
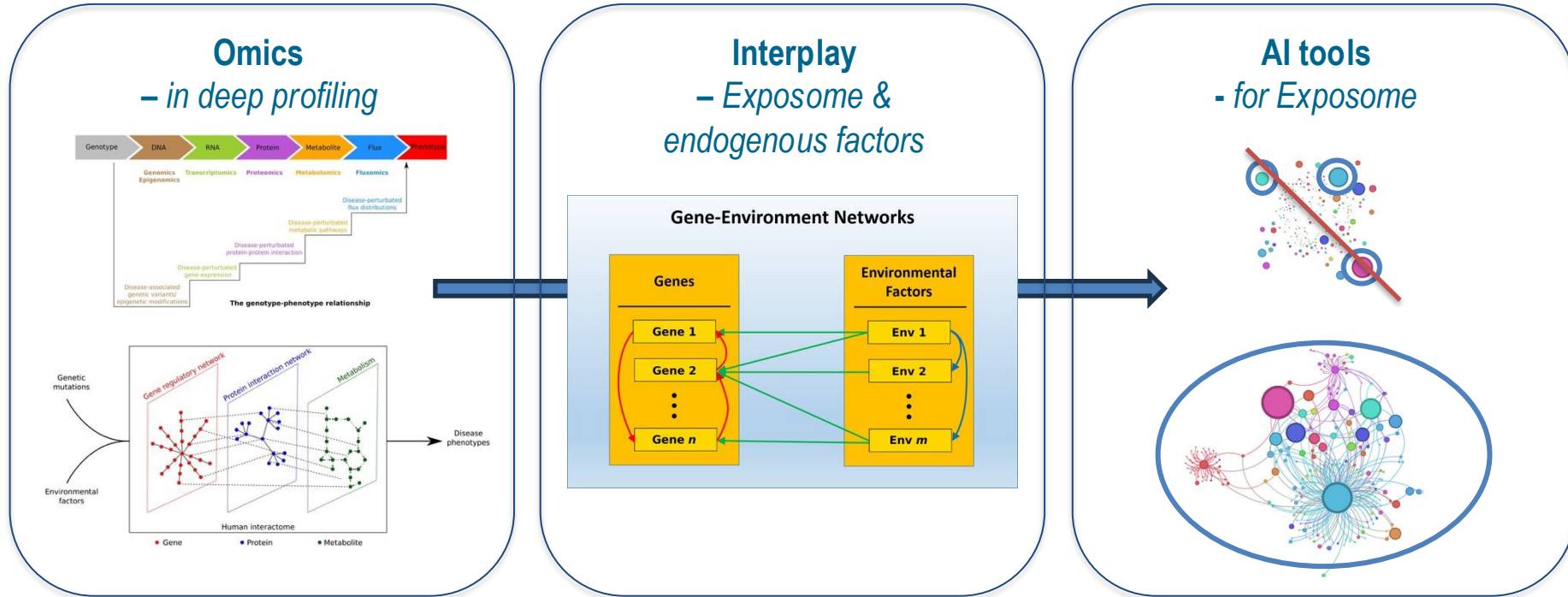


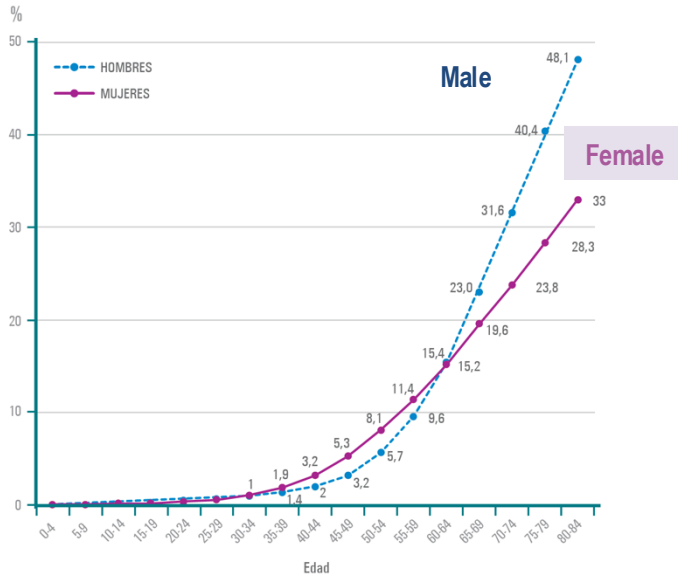
Figure 6. Cascade study in PGV-carriers. Relatives studied are represented by degree relationship.

Challenge n#2: In-deep characterization

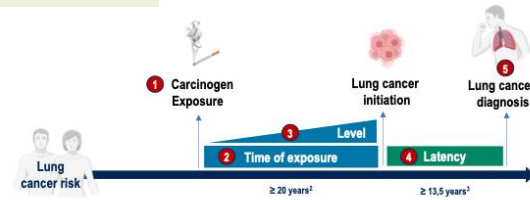


Challenge n#3: Data in understudied pop

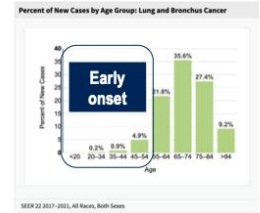
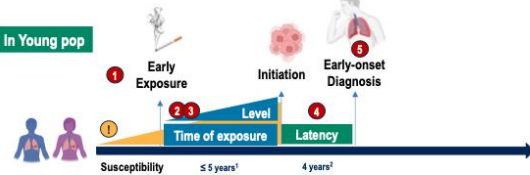
% of developing cancer by sex in Spain, 2025



Young pop



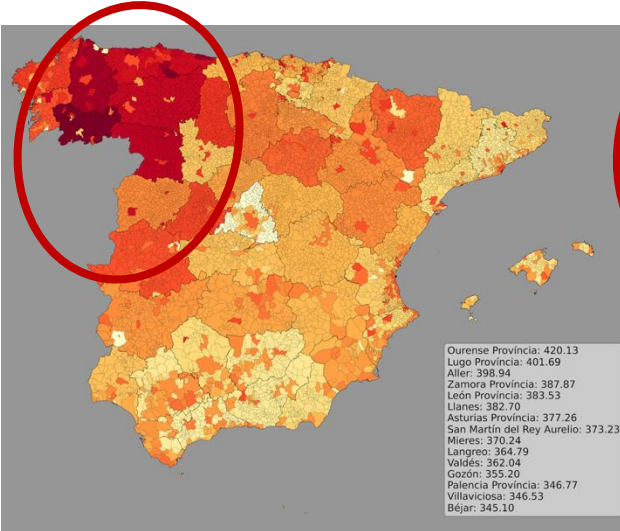
In Young pop



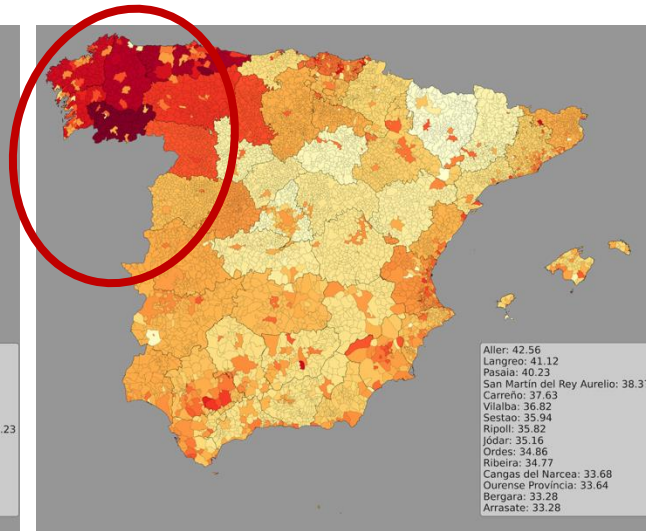
- ① Susceptibility (genetics)
- ① Early exposure (childhood)
- ②-③ Potent carcinogens (↑ period)
- ④ Shorter latency
- ⑤ Lung cancer diagnosis

Geographical differences: *Exposome* & Cancer Data

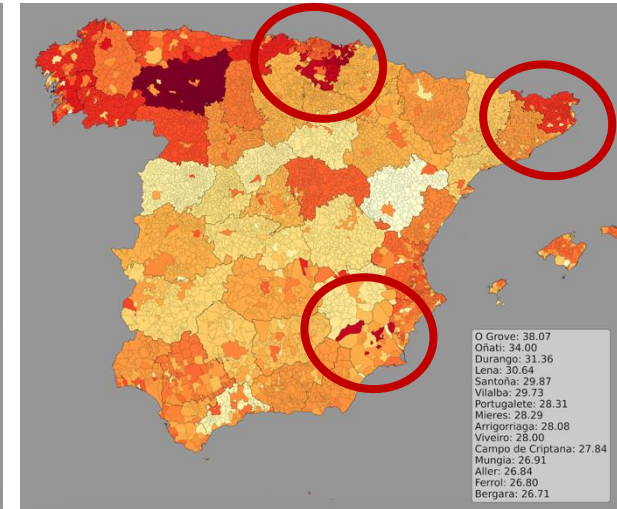
Overall



Male (<50 yrs)



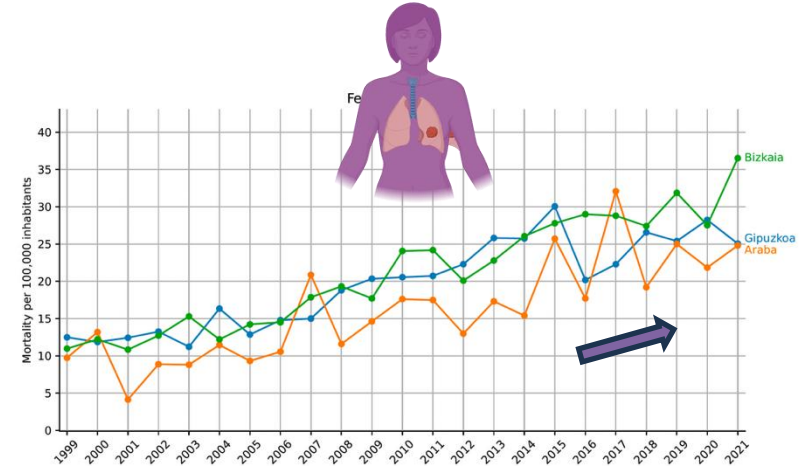
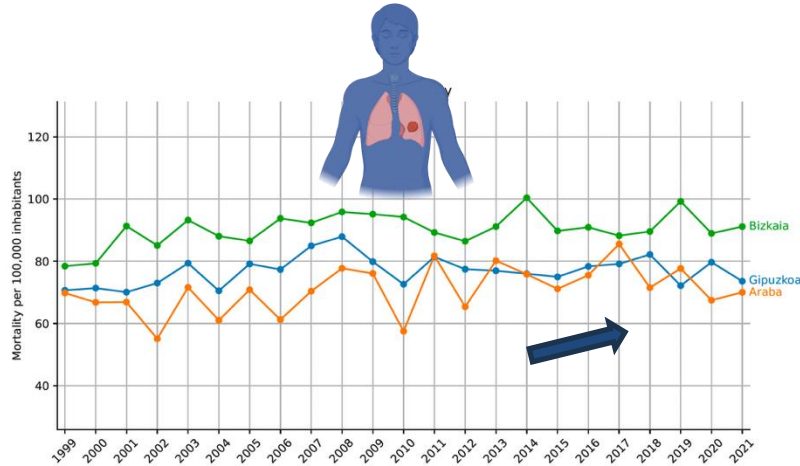
Female (<50 yrs)



SEX & AGE perspective

Geographical differences: *Sex perspective*

Example: Basque Country, Lung Cancer Mortality, 1999-2021

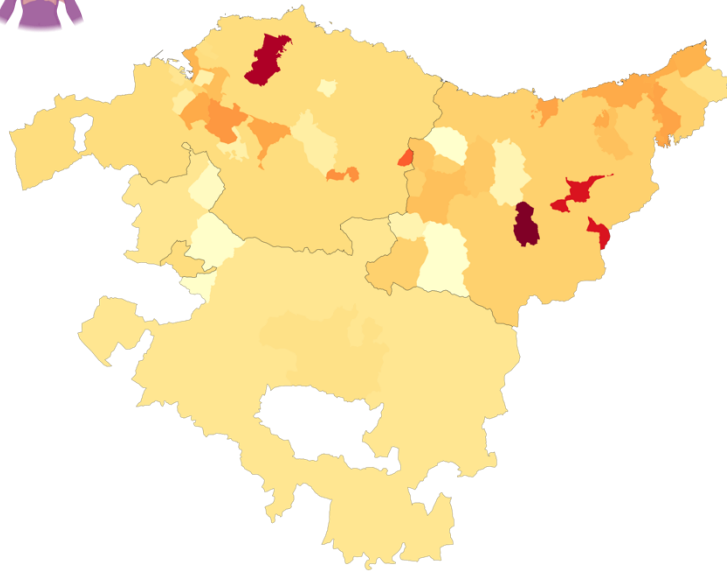


Geographical differences: *Prevention by Risk Areas*

Granularity



≤ 50 Female



Beasain:	8.72
Mungia:	8.00
Tolosa:	7.09
Ermua:	5.68
Durango:	4.86
Bilbao:	4.68
Zarautz:	4.40
Errenteria:	4.39
Galdakao:	4.31
Barakaldo:	4.21
Donostia:	4.21
Pasaia:	4.14
Hondarribia:	4.01
Getxo:	3.94
Erandio:	3.76

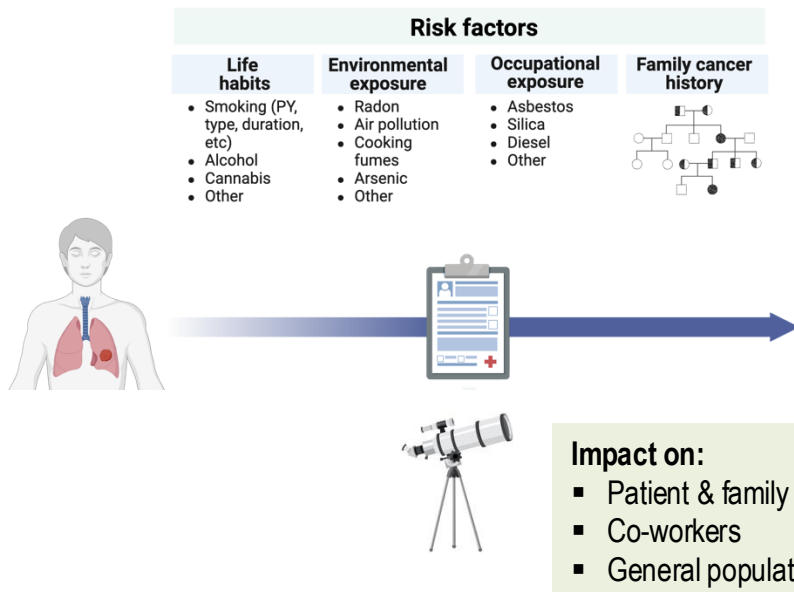


TO EXPLORE
THESE AREAS?

**“HOTSPOT
AREAS”**

TO PRIORITIZE
SPECIFIC
PREVENTION
ACTIONS

Future: How can we (MD) help?



My advice to you

5' extra minutes during the 1st consultation

1. Demographic data
2. Environmental history
3. Occupational history
4. Family history of cancer

Future: EXPOSOME – Preventive strategies

Primary prevention



EUROPEAN CODE AGAINST CANCER

12 ways to reduce your cancer risk

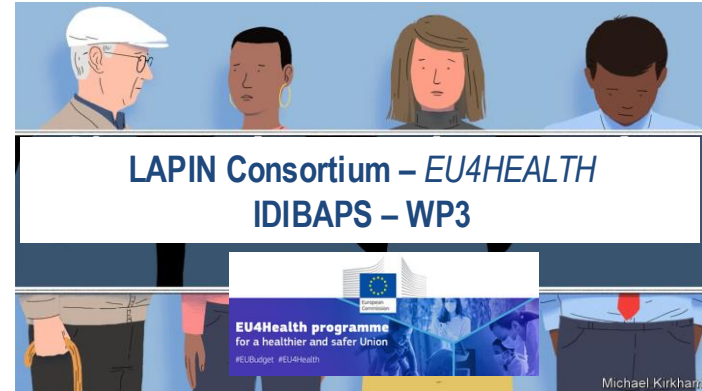


SHS →
Lifestyle →
Workplace →
Indoor Radon →

- 1 Do not smoke. Do not use any form of tobacco.
- 2 Make your home smoke free. Support smoke-free policies in your workplace.
- 3 Take action to be a healthy body weight.
- 4 Be physically active in everyday life. Limit the time you spend sitting.
- 5 Have a healthy diet
 - Eat plenty of whole grains, pulses, vegetables and fruits.
 - Limit high-calorie foods (foods high in sugar or fat) and avoid sugary drinks.
 - Avoid processed meat; limit red meat and foods high in salt.
- 6 If you drink alcohol of any type, limit your intake. Not drinking alcohol is better for cancer prevention.
- 7 Avoid too much sun, especially for children. Use sun protection. Do not use sunbeds.
- 8 In the workplace, protect yourself against cancer-causing substances by following health and safety instructions.
- 9 Find out if you are exposed to radiation from naturally high radon levels in your home. Take action to reduce high radon levels.
- 10 For women:
 - Breastfeeding reduces the mother's cancer risk. If you can, breastfeed your baby.
 - Hormone replacement therapy (HRT) increases the risk of certain cancers. Limit use of HRT.
- 11 Ensure your children take part in vaccination programmes for:
 - Hepatitis B (for new-borns)
 - Human papillomavirus (HPV) (for girls).
- 12 Take part in organized cancer screening programmes for:
 - Bowel cancer (men and women)
 - Breast cancer (women)
 - Cervical cancer (women).

The European Code Against Cancer focuses on actions that individual citizens can take to help prevent cancer. Successful cancer prevention requires these individual actions to be supported by governmental policies and actions.
Find out more about the European Code Against Cancer at: <http://cancer-code-europe.iarc.fr>

Cancer Screening



The Economist

Michael Kirkham

Redefining eligibility criteria?

1. Risk factors & Exposome approach
2. Lung Cancer Exposome & Precision Medicine (ICAPEM)
3. Examples
4. Challenges & future directions
5. **Take-home messages**



Lung Cancer is a **multifactorial** disease



Exposome:

- Environmental exposures
- Co-exposures; cumulative exposure; interplay with genetic factors



Patients:

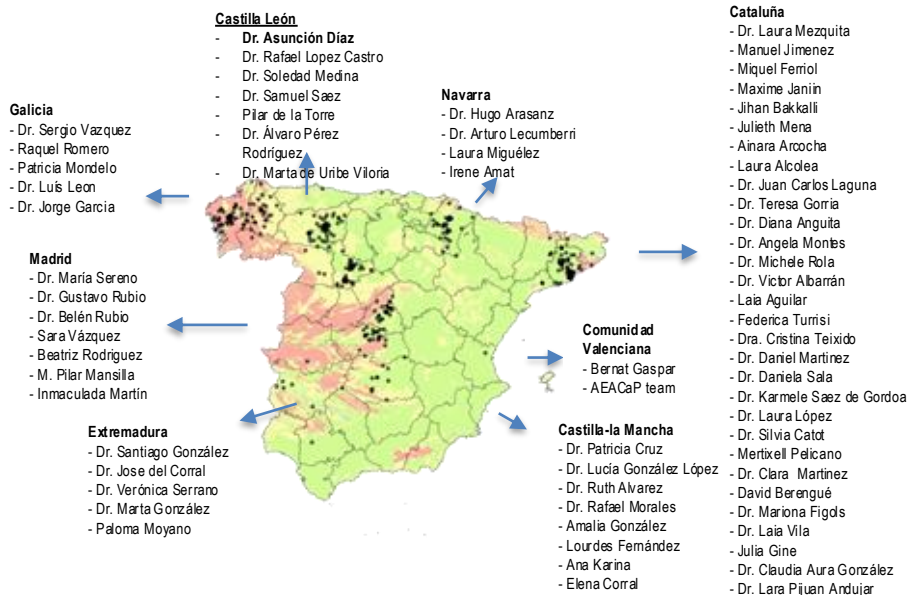
- Exposome – clinical & translational research
- Better understanding of the impact (Precision Medicine)



Challenges & future: Multidisciplinary Research for Prevention & Lung Cancer Care

THANKS!

- **PATIENTS & FAMILIES**
- **MECA Group & collaborating Groups**
- **All the researchers & centers participating in EXPOSOME studies**



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Funding Organisms:

