II International Asbestos Seminar
I Health Surveillance Workshop
III Injured Families and Asbestos Victims´ Meeting

Asbestos and lung cancer: diagnostic and attribuition criteria

II Seminário Internacional de Amianto
Uma abordagem da Saúde dos Trabalhadores
15 a 18 de maio de 2018

Ubiratan Paula Santos
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16/05/2018

Asbestos Related Diseases

- **IARC. Mon 100c, 2012**
- **Guidotti TL et al. AJRCCM 2007**
- **ATS. AJRCCM 2004**
- **Helsinki 2014**

- Pleural effusion
- Diffuse pleural thickening
- Pleural plaques
- Round atelectasis
- Asbestosis
- COPD
- Retroperitoneal fibrosis
- Cancers
  - **Lung**, mesothelioma (pleura, peritoneum, pericardium, tunica vaginalis), ovary and larynx
  - Positive association, but insufficient evidence of causality: pharynx, stomach, **colorectal (?)**

Asbestos and Cancer

Descrição de 1º caso. Lynch KM & SMITH WA. Am J Cancer 1935

Primeiros estudos

Gloyne, S. R. (1951). *Lancet*, 1, 810.
Merewether, E. R. A. (1949). *Annual Report of the Chief Inspector of Factories for the Year 1947*. H.M.S.O., London.

MORTALITY FROM LUNG CANCER IN ASBESTOS WORKERS

BY

RICHARD DOLL

From the Statistical Research Unit, Medical Research Council, London

Brit. J. industr. Med., 1955, **12**, 81.

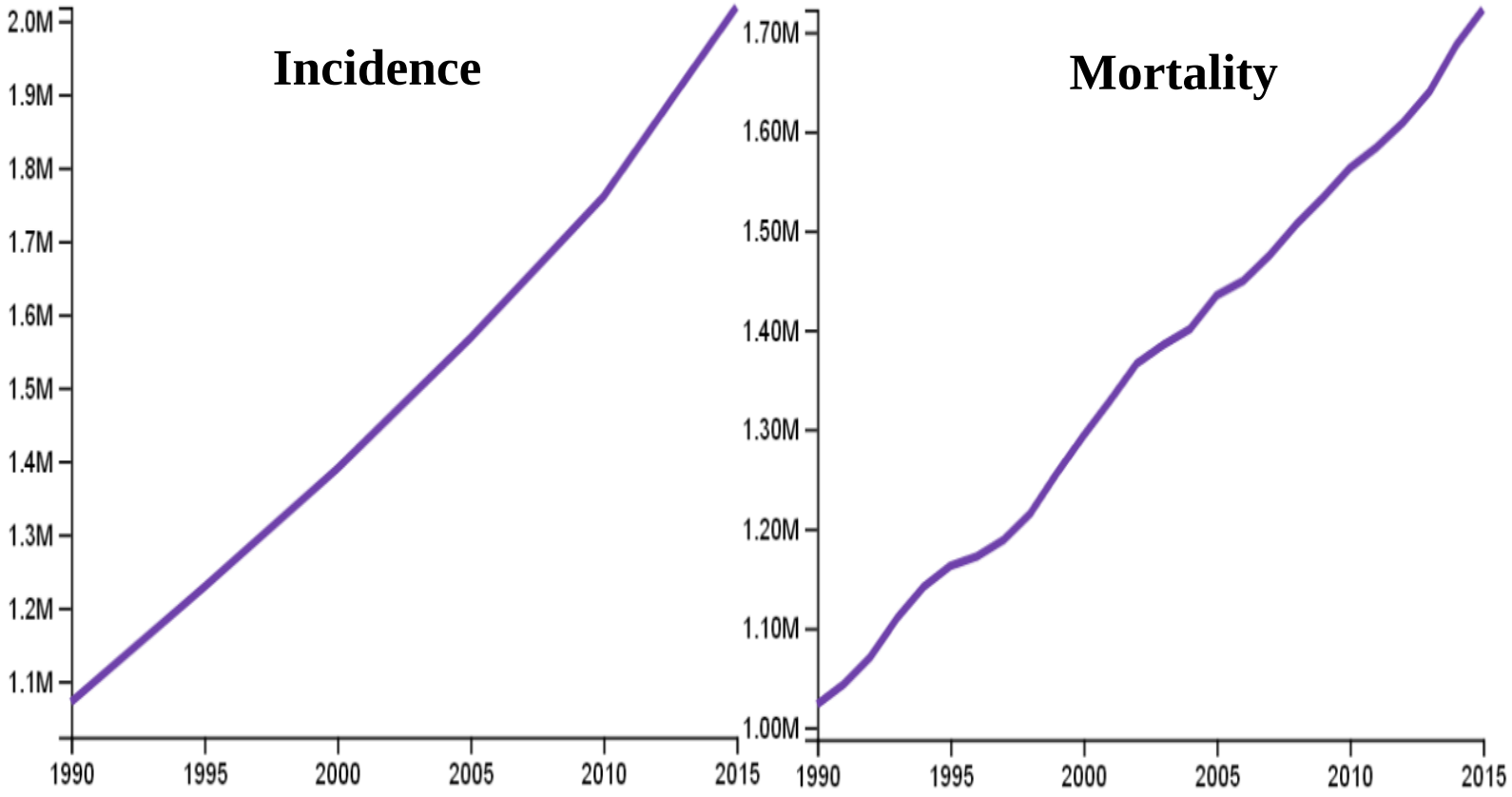
Global Impact – Asbestos exposure

Global Burden Disease 2016: Lancet 2017; 390: 1211-; Lancet 2017; 390: 1151-; Lancet 2017; 390: 1345-; Lancet 2017; 390: 1260-

Diseases	Incid X 1000 IC95%	Preval X 1000 IC95%	Total Deaths X 1000 IC95%	Asbestos Deaths X 1000 IC95%	Total DALYs X 1000 IC95%	Asbestos DALYs X 1000 IC95%
Asbestosis	12 (11-13)	152 (138-170)	3.5 (3.4-4.1)	3.5 (3.4;4.1)	84 (68 -97)	84 (68 -97)
Lung cancer	**2,01 1,96; 2,06**	**2,84 2,75;2,92**	**1,71 1,66;1.75**	**182 128;237**	**36,441 35,401;37,463**	**2,844 1,958;3,803**
Mesothe-liome	35 (32;36)	53 (49;56)	30.2 (28.3;32.0)	27.6 (25.6;29.3)	661 (619;701)	554 (507;598)
Larynx cancer	187 (184;191)	638 (627;653)	111 (108-115)	3.7 (2.0;5.5)	2,750 (2,661-2,846)	66 (35;99)
Ovary cancer	254 (242;260)	786 (743;809)	165 (157;173)	6.0 3.0;9.4)	4,258 (4,036;4,459)	93 (46;150)

Câncer de Pulmão: Incidence and Mortality

- **Didkowska et al. Ann Transl Med 2016**
- **GBD, *The Lancet*, Vol. 388, No. 10053, Oct 2016**



Lung Cancer in Brazil - 2015

- **Global Burden of Disease Cancer Collaboration. JAMA Oncol 2017**
- **Brasil/Instituto Nacional do Câncer/MS.**

- 4th most incident cancer- 31,270
- 3rd cancer in deaths - 24,500

IARC Conclusions

There is sufficient evidence in humans for the carcinogenicity of all forms os asbesto (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite).

They causes mesothelioma, cancer of larynx, lung and ovary. All forms of asbestos are carcinogenic to humans (Group 1).

Diario da Manha

CHAPEX
CONTÉM AMIANTO
USE ESTE LADO VIRADO PARA A CHAMA
ECONOMIZE ENERGIA
CHAPEX

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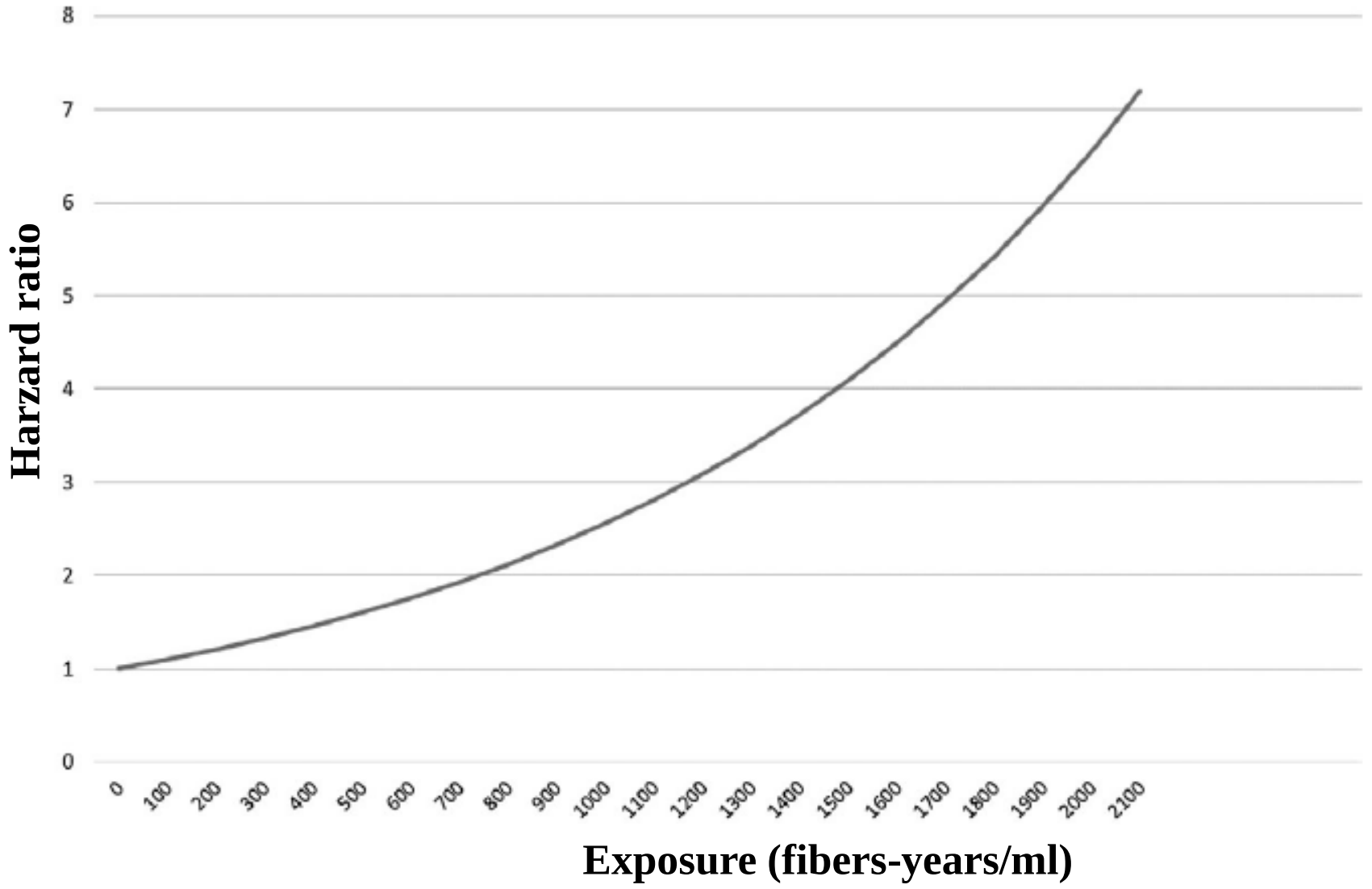
Lung cancer risk in exposed to asbestos

- **Selikoff, et al. JAMA 1968**
- **Balmes JR. AJRCCM 2013**
- **IARC. Mon 100 C. 2012**
- **Lenters V, et al. EHP 2011**
- **Markowitz SB, et al. AJRCCM 2013**

- Risk increases with cumulative exposure. ***Elliott L, et al. Occup Environ Med 2012***
- There is insufficient evidence of potency differences between chrysotile and amphiboles. ***IARC; Balmes***
- Fibers of all sizes are associated with risk; risk is greater for longer and thinner fibers. ***Loomis D, et al. OEM 2012***
- There is no safe exposure limit. ***Deng Q, et al. OEM 2012***
- Asbestosis increases risk
- Smoking increases and cessation decreases risk

Risk of lung cancer deaths and cumulative exposure to chrysotile - cohort 577 exposed, followed by 37 years (China)

Courtice MN, et al. AJIM 2016



Mortality in workers exposed to chrysotile- North Carolina / USA

Loomis D, e col. OEM 2009

- Cohort study with 5,770 workers (between 1950 and 1973)
- **Results** SMRs (CI95%)
  - Lung cancer 1.96 (1.7 – 2.2)
  - Mesotheliome 10.9 (3.0 – 28.0)
  - Pleural cancer 12.4 (3.4 – 31.8)
  - Asbestosis 3.5 (2.7 – 4.4)

- Standardised mortality ratios (SMRs) increased with cumulative exposure

Exposure to different fibers and lung cancer

McCormack V, e col. BrJ Cancer 2012

- Data analysis of 55 cohort studies
- Risk of lung cancer mortality
- **Results:**
  - For all fibers, the risk of death from Ca Lung was double

Tipo de asbesto	Razão de Mortalidade por CP padronizada
Crocidolite (6)	2.0 (1.6 – 2.7)
Chrysotile (16)	1.7 (1.4 - 2.0)
Amosite (4)	2.5 (1.4 - 4.3)

Cohort of the exposed to chrysotile (China)

Wang X, e col. Thorax 2012

Prospective cohort from 1972 to 2008 (37 years)

	Deaths	LC deaths	Resp diseases
• 577 exposed	259 (45%)	53	81
• 435 controls	76 (18%)	9	11

Exposed to asbestos x non exposed (Relative risk; CI 95%)

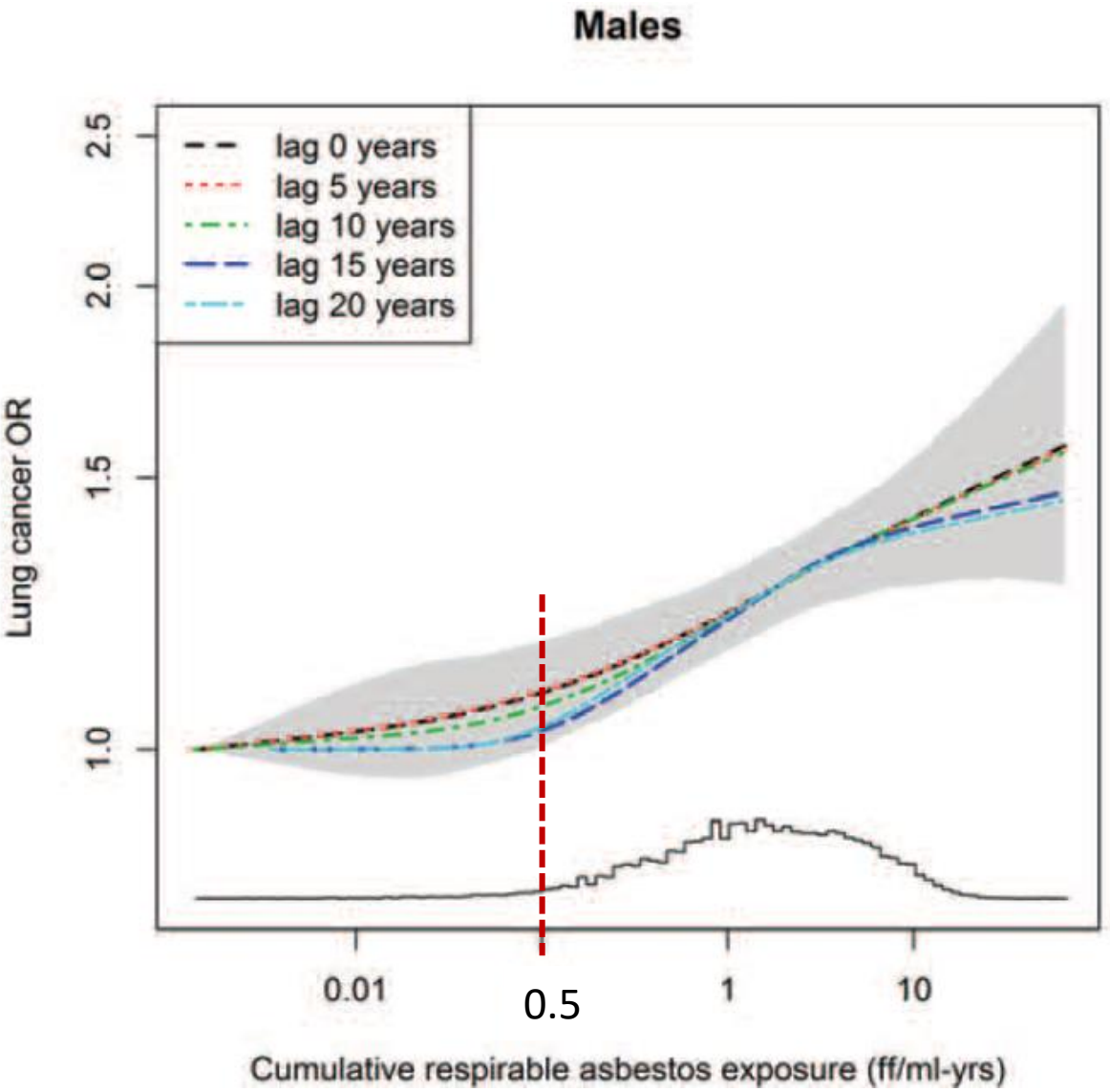
- Lung cancer deaths 3.3 (1.6 - 6.9)
- Respiratory diseases deaths NM*: 3.2 (1.7 - 6.2)

***NM: non malignants**

Lung cancer: Exposure-response to low cumulative exposure to asbestos

Olsson AC, et al. Epidemiology 2017

Pooled Analysis of 14 Case-Control Studies (cases:7,700; control: 21,800, on European countries and Canada (1985-2010). Figure - data adjusted for smoking, age. Median of cumulative exposure - 1.21 ff-year/ml and 0.57 ff –year/ml, for men and women, respectively.



Exposure to chrysotile, smoking and lung cancer deaths (cohort in China) - dose-response

Wang X, e col. Thorax 2012

	Non -smokers RR (IC 95%)	Smokers RR (IC 95%)
Control cohort	1.00	6.03 (0.75 - 48.21)
Asbestos cohort	7.5 (0.9 - 62.8)	17.4 (2.4 – 126.6)
Exposure level		
Low	2.1 (0.13 - 33.2)	10.7 (1.4 - 81.6)
Medium	6.4 (0.4 - 102.7)	18.4 (2.3 - 145.9)
High	26.2 (2.9 - 234.9)	28.6 (3.8 - 213.6)

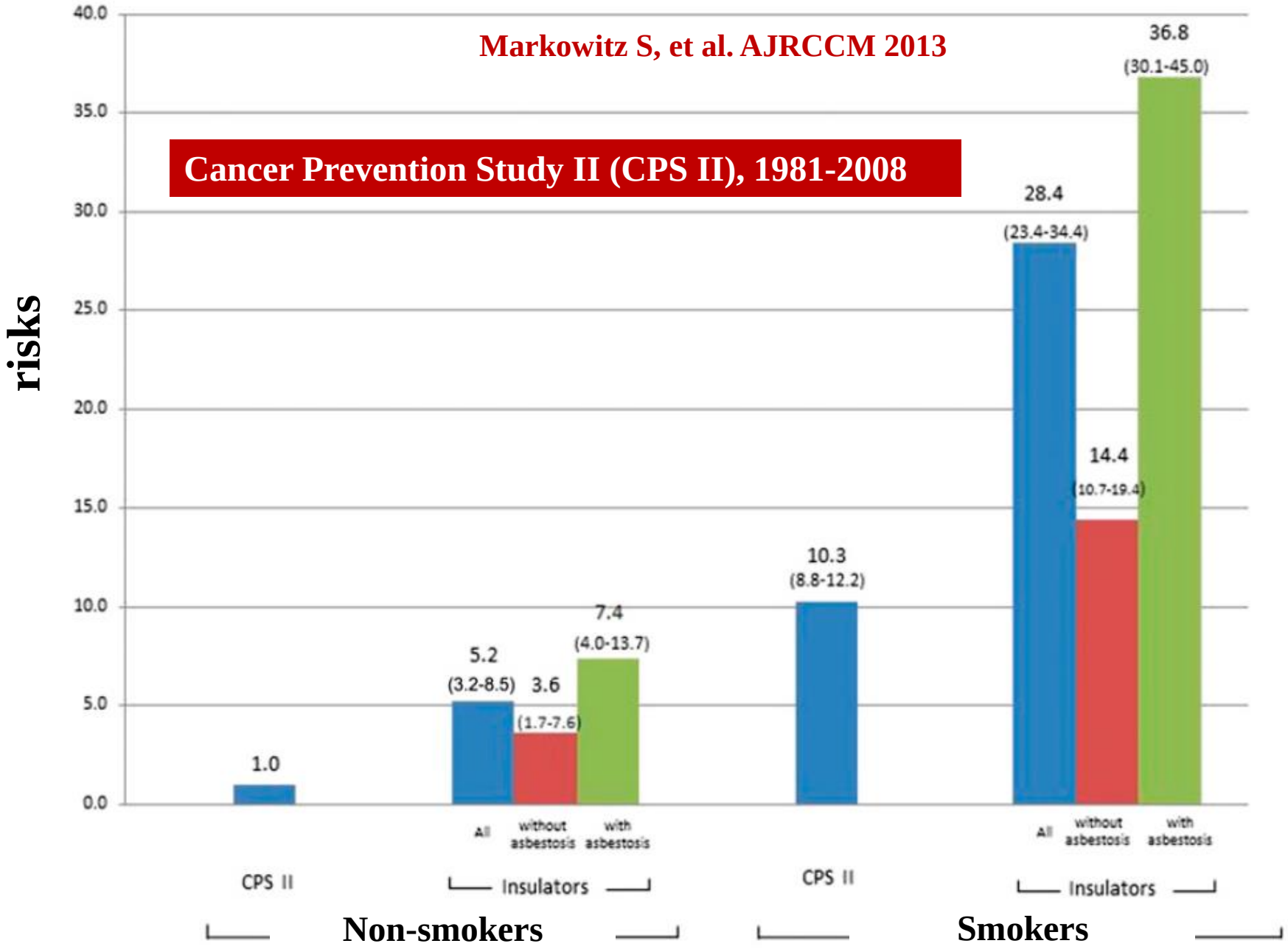
Lung cancer - USA cohort: 1981- 2008. Impact of exposure to asbestos and tobacco

Markowitz SB, et al. AJRCCM 2013

- 2,377 absestos exposed x 54,243 unexposed
- Lung cancer death risks

• Exposed no asbestosis and N-Smokers:	3.6 (IC95%: 1.7-7.6)
• Asbestosis and N-Smokers:	7.4 (IC95%: 4.0-13.7)
• Smokers, not exposed to asbestos:	10.3 (IC95%: 8.8-12.2)
• Smokers, exposed, no asbestosis:	14.4 (IC95%: 10.7-19.4)
• Smokers with asbestosis:	36.8 (IC95%: 30.1-45.0)

Asbestos, asbestosis, smoking and Lung cancer deaths



Asbestos and tobacco - parallel lives

- **Newman-Taylor A. OEM 2009**
- **OMS.Tobacco Atlas 2018**
- **IARC 2004, 2010**

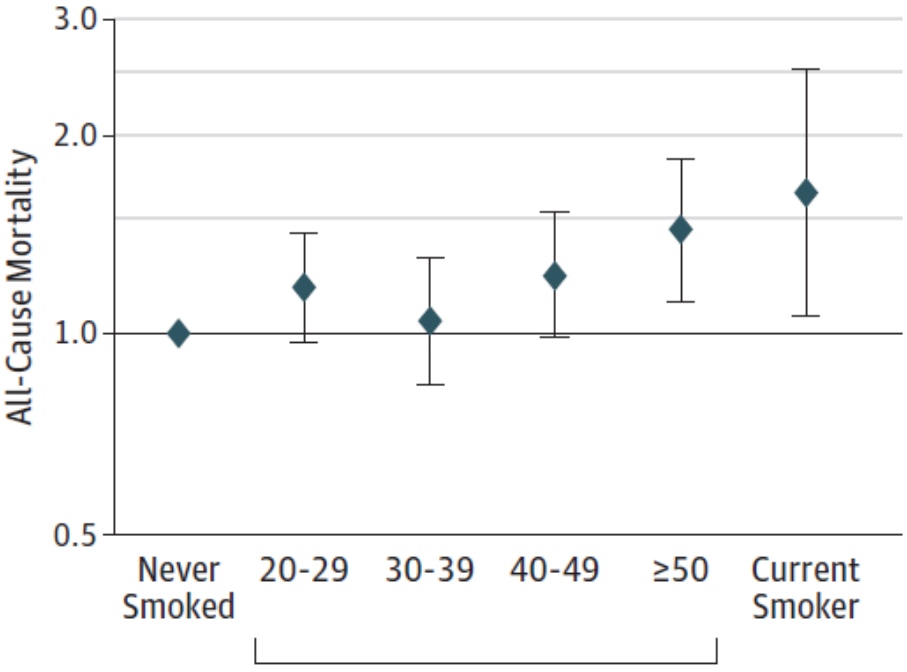
- **Epidemiological evidence**
  - Tobacco - 1950 **(Doll R)**
  - Asbestos - 1955 **(Doll R)**
- **Recognition by public powers/agencies of risk**
  - Tobacco – 1964 (EUA)
  - Asbestos- 1973 (England- 1ª regulation 1931- “controlled use”)
- **The fallacy of light cigarettes and "light" asbestos, safe limits**

Association between low intensity smoking (<1 cig / day and 1-10 cig/day) and cardiovascular risk

Inoue-Choi M, et al; JAMA 2016

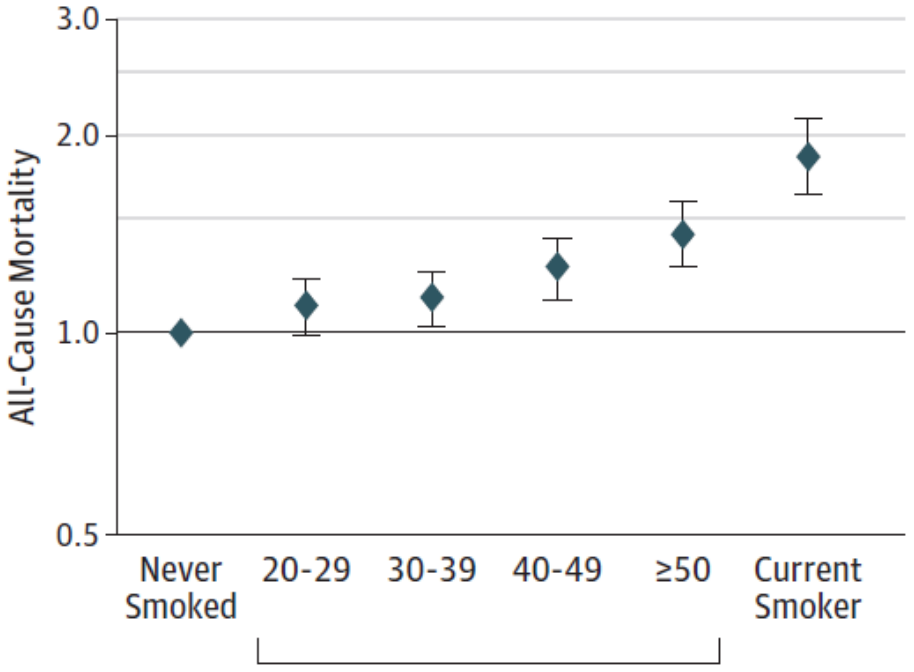
US-290,000 adult cohort: 59-82 years

A Smokers < 1 cig/d



former smokers, age cessation

B Smokers: 1-10 cig/d

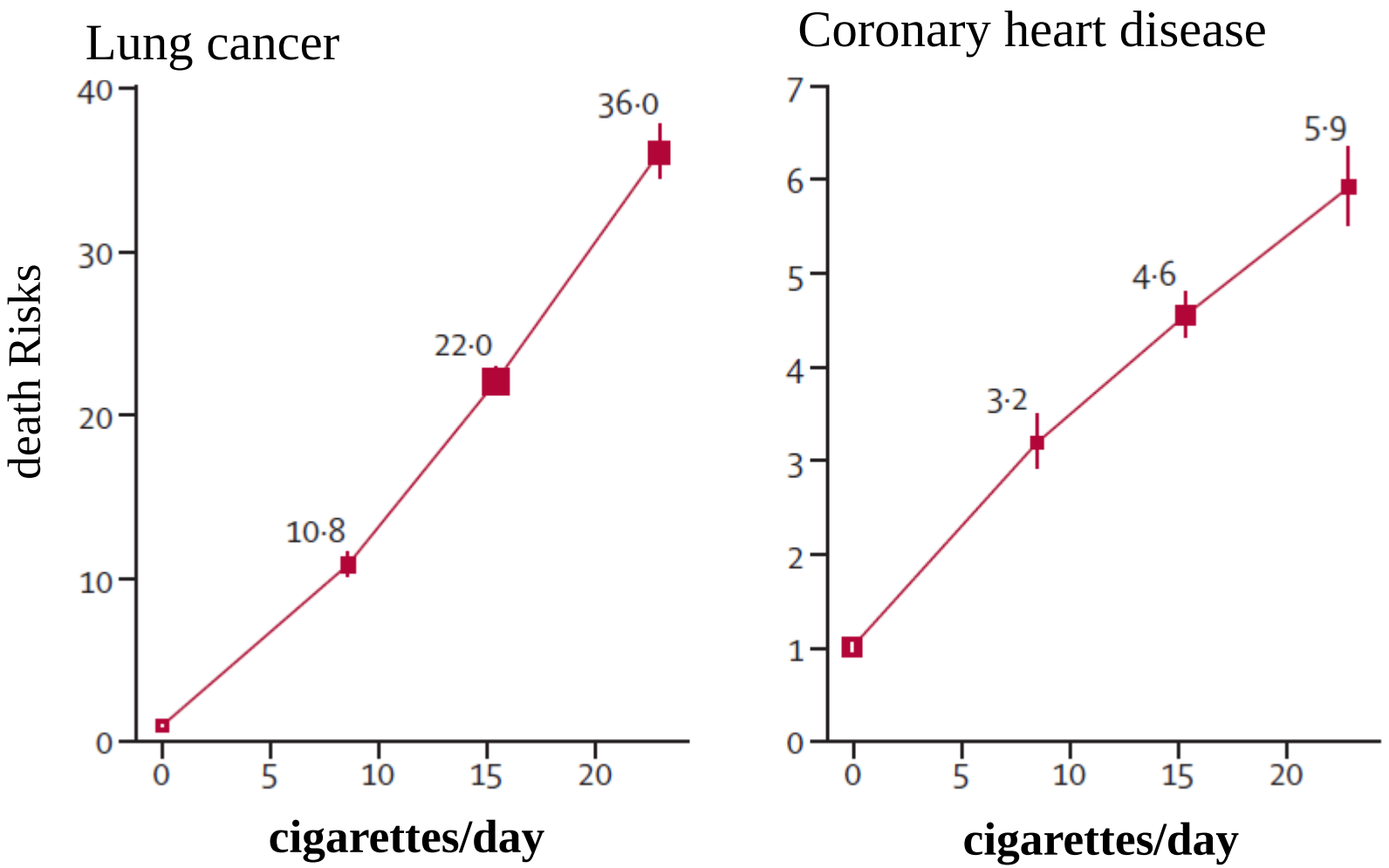


former smokers, age cessation

Smoking: Lung cancer and Coronary disease

Pirie K, et al. Lancet 2013

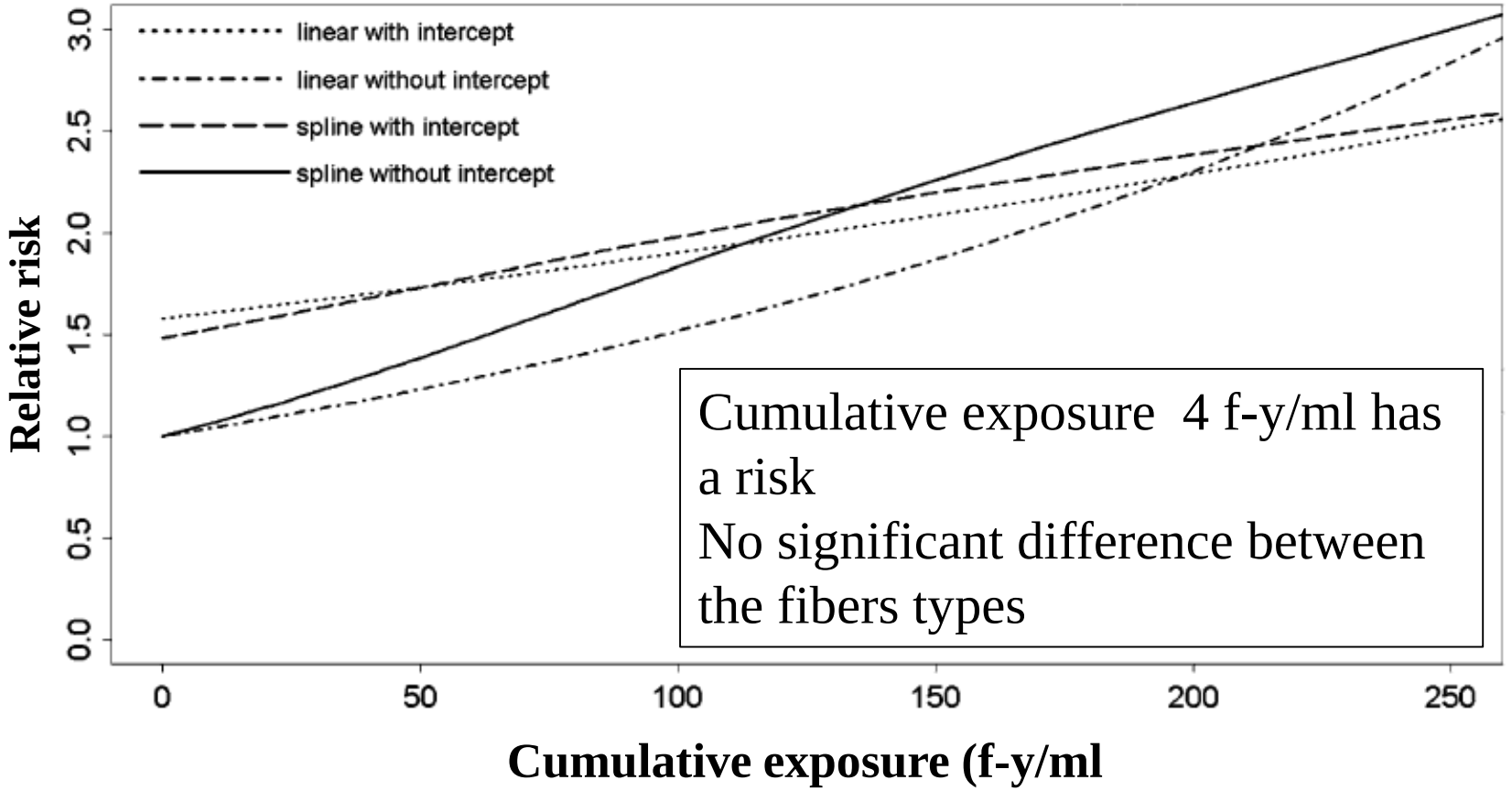
Coorte RU 1,2 milhão de mulheres, idade: 65 anos



Lung Cancer and low cumulative exposure to asbestos

Van der Bij S, et al. Cancer Causes Control 2013

19 studies with exposure between 0.11 to 4.71 fibers-year/ml



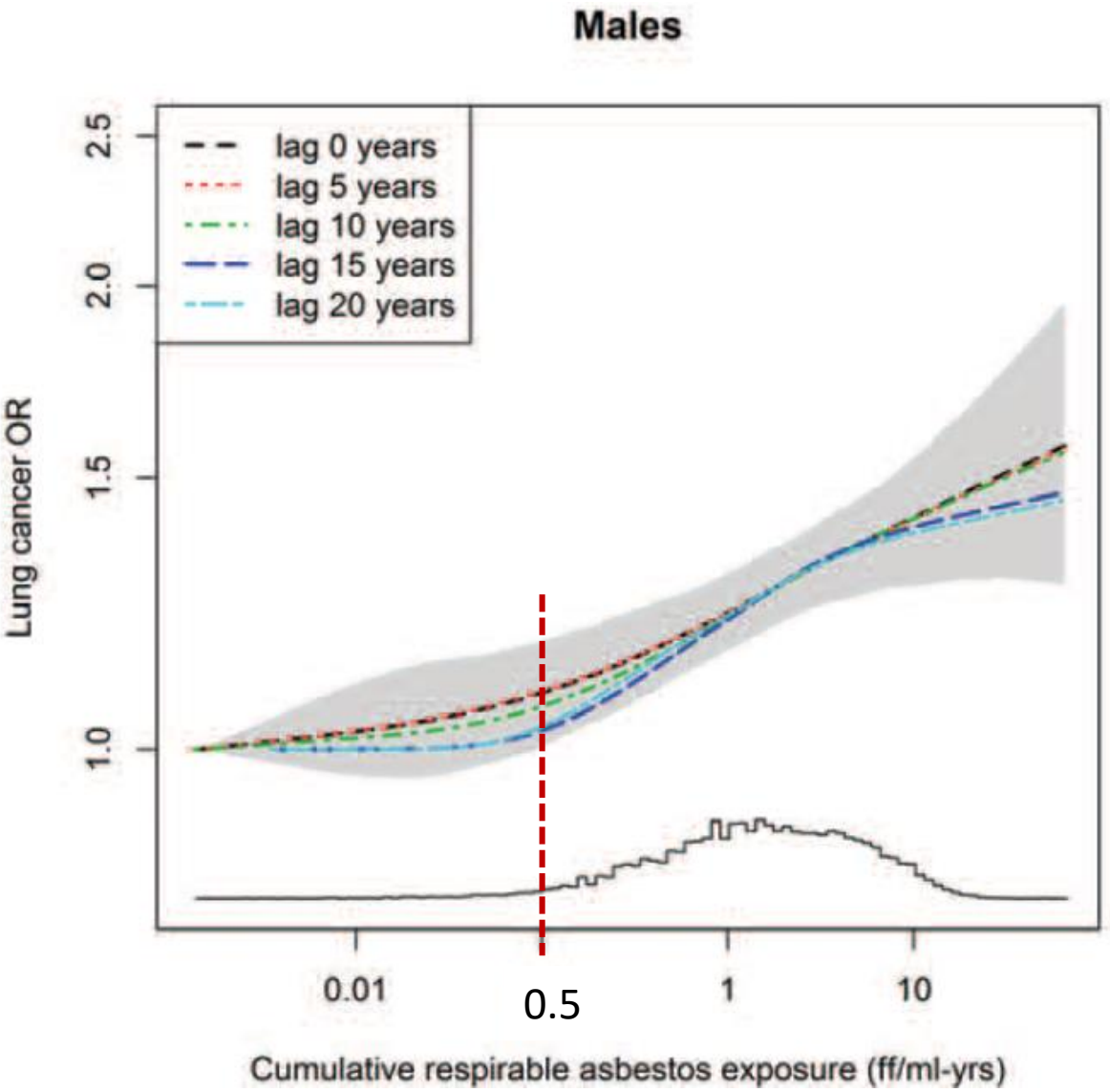
Cumulative exposure 4 f-y/ml has a risk

No significant difference between the fibers types

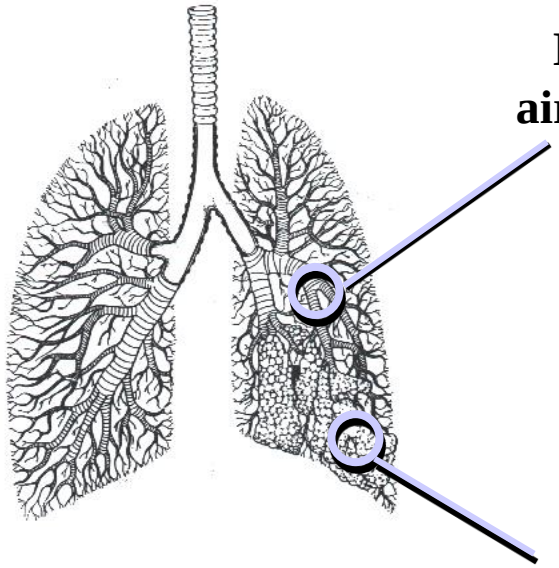
Lung cancer: Exposure-response to low cumulative exposure to asbestos

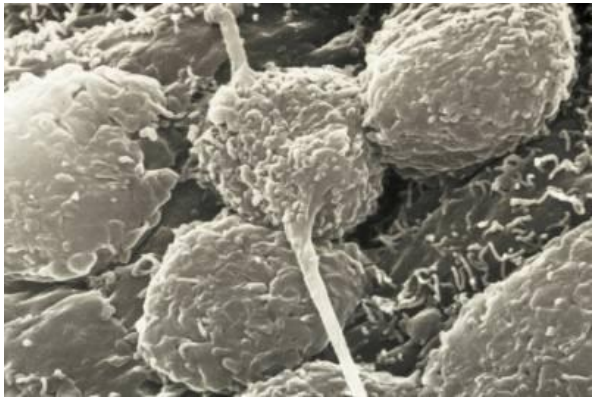
Olsson AC, et al. Epidemiology 2017

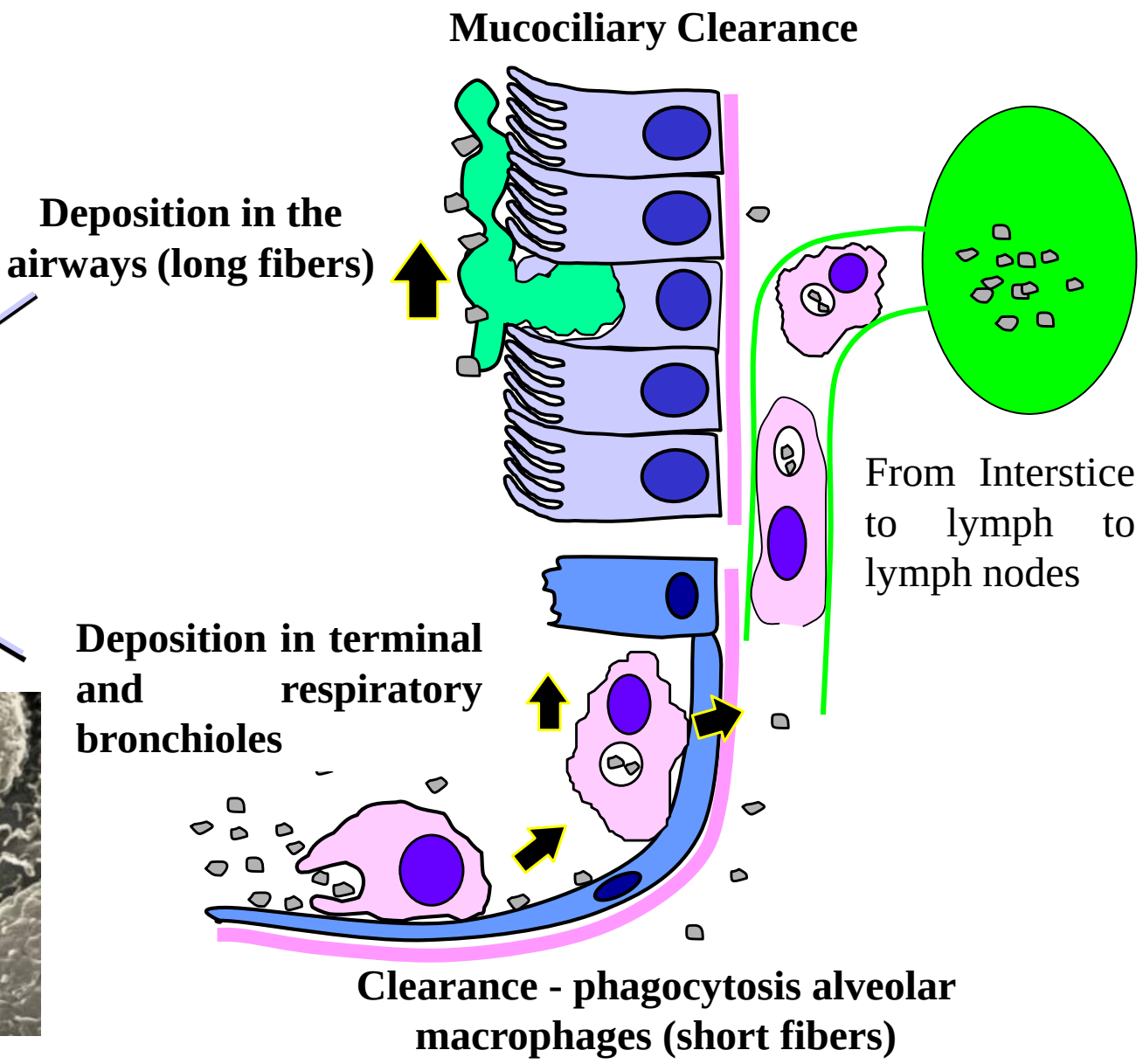
Pooled Analysis of 14 Case-Control Studies (cases:7,700; control: 21,800, on European countries and Canada (1985-2010). Figure - data adjusted for smoking, age. Median of cumulative exposure - 1.21 ff-year/ml and 0.57 ff –year/ml, for men and women, respectively.



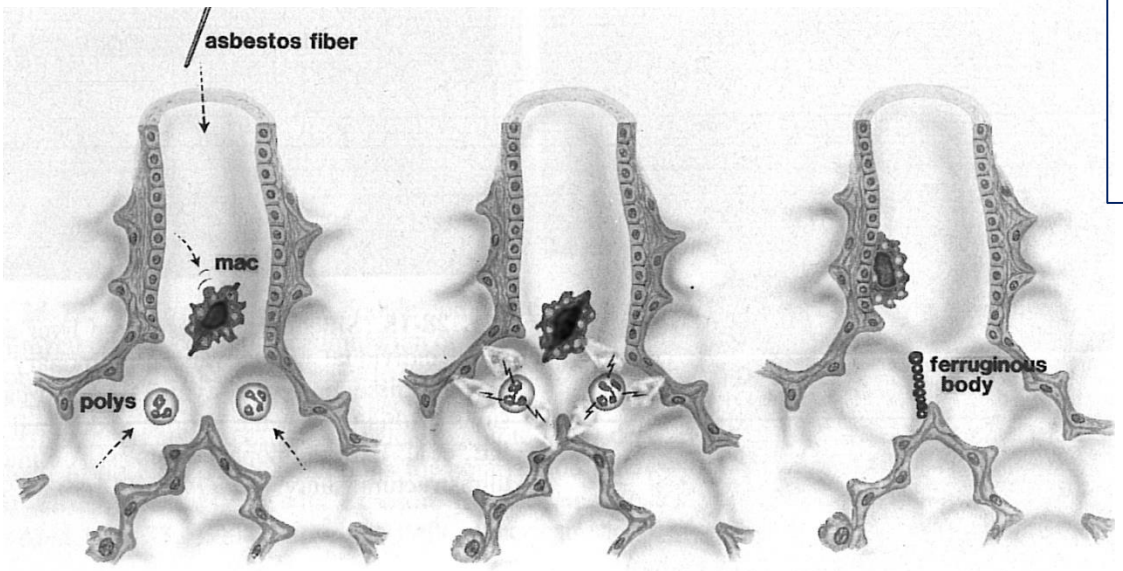
Exposure and defenses - fiber clearance





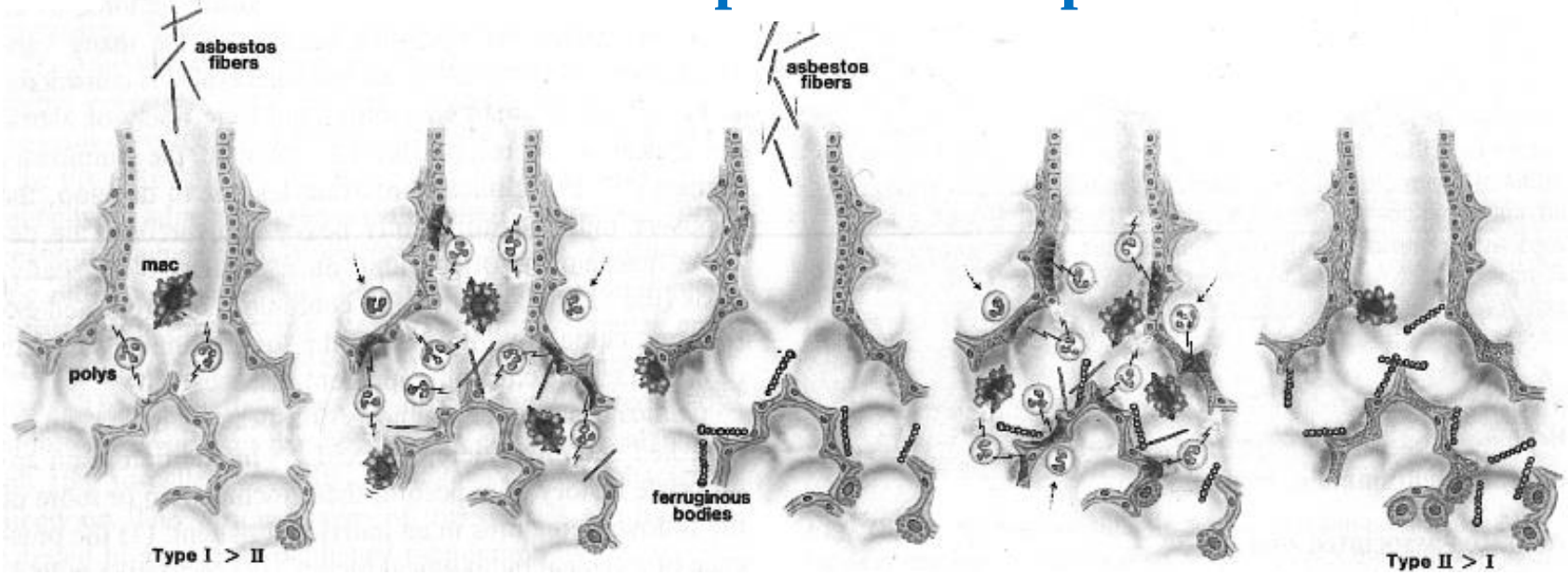


Light and transient exposure



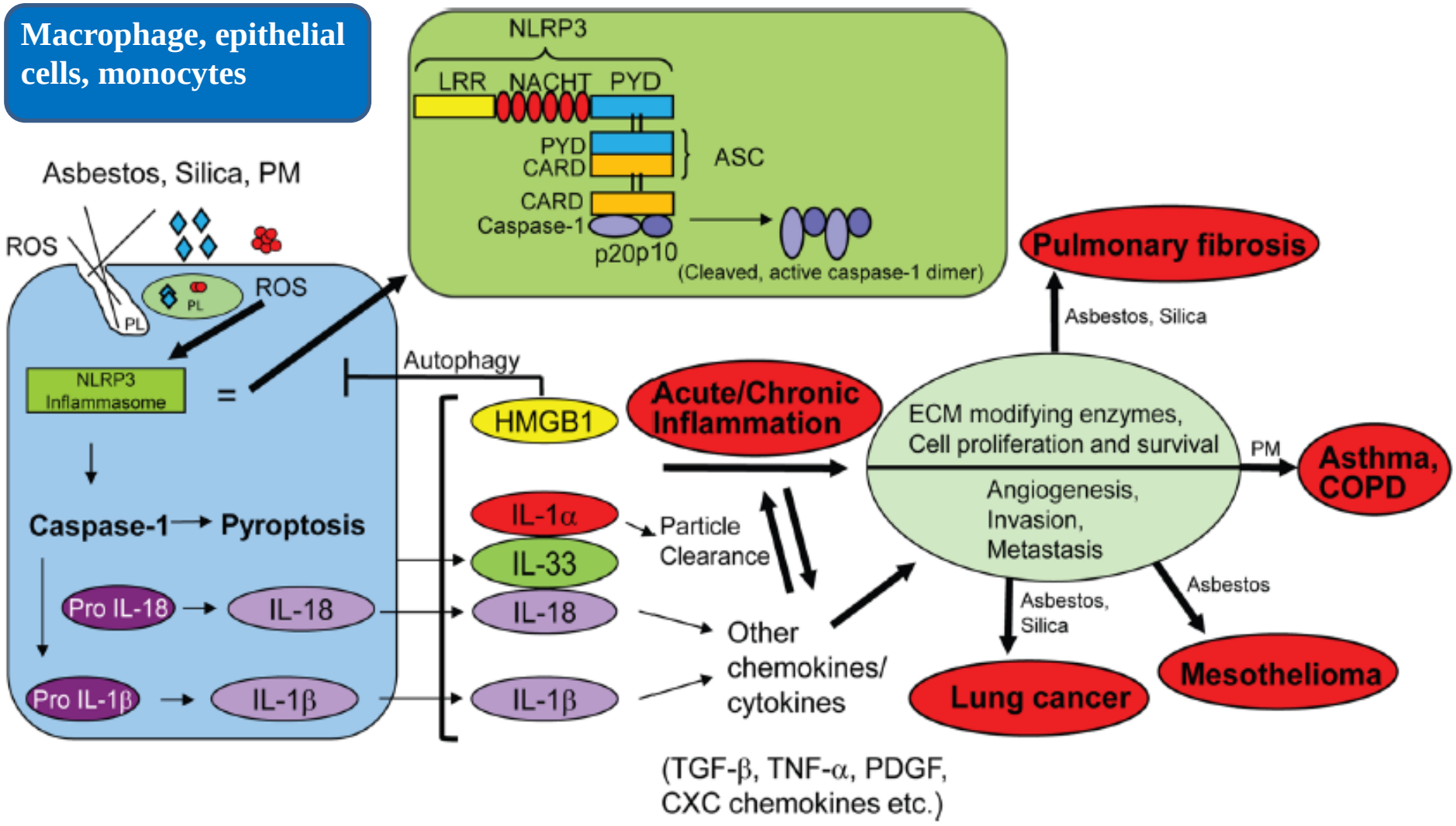
Craighead JE. Patho-logy of Environmen-tal and Occupational Disease. Mosby 1995

Intense and/or persistent exposure



Pathophysiology associated with particle exposure

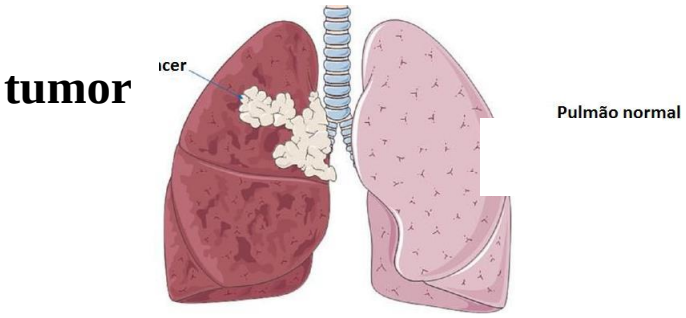
Sayan &Mossman. Particle and Fibers Toxicology 2016



Criteria for assigning lung cancer to asbestos

- Diagnosis of lung cancer
- History of occupational, environmental, or domestic exposure and / or
- Information on the working or living environment
  - Exposure time
  - Cumulative exposure quantitative/qualitative- exposure load
- Latency
- Asbestos exposure markers

Lung cancer - approach for diagnosis



- Image exams
- biopsy of lymphnodes: supraclavicular, cervical, axillary
- Bronchoscopy with BAL and endo and / or transbronchial biopsy or by EUS/EBUS
- Medistinoscopy
- Transthoracic biopsy guided by CT
- Biopsy open/video
- Histological examination
- Immunohistochemistry

Lung Cancer and Asbestos: Attribution Criteria-1

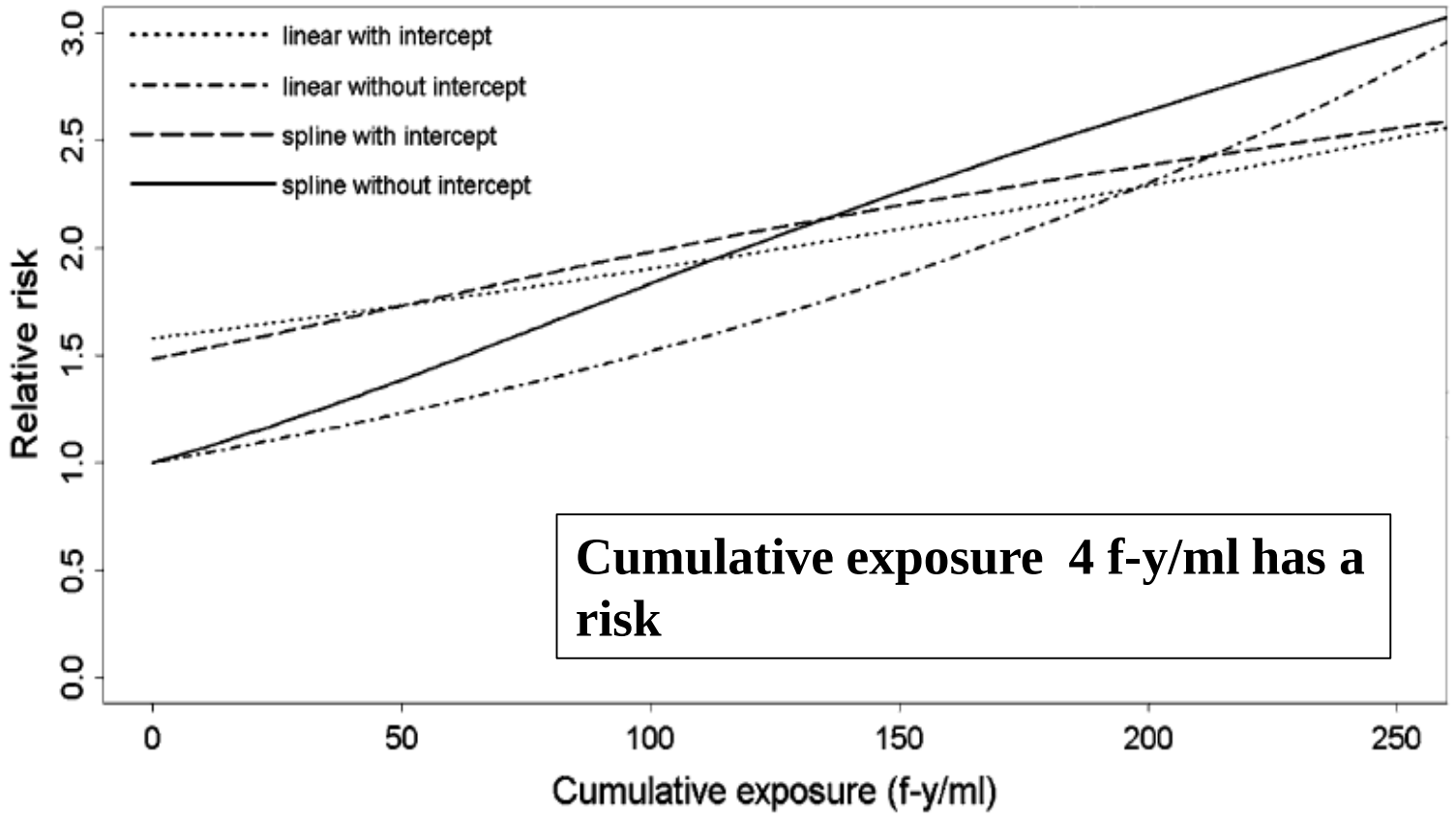
- **Wolff H, et al Helsinki Criteria 2014. Scand J Work Environ Health 2015**
- **IARC Mon 100 C 2012**

- All types: squamous, adenocarcinoma, small and large cells, sarcomatoid and adenosquamous carcinoma
- Histological type and location has no value for assignment
- Risk increases with exposure - dose response
- Cumulative exposure - main criterion for attribution
  - Risk increases from 0.5% to 4%/fiber/cm3/year (fiber years) of cumulative exposure
  - 25-year fiber exposure - risk increases twice, even without detectable asbestosis
  - Exposure <25 years-fiber, also increases risk, but is lower

Exposure

IARC. Mon 100 C. 2012; Van der Bij S, et al. Cancer Causes Control 2013[2]

- Occupational - proven evidence[1]
- Environmental- more controversial studies, but.[1,2]



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Attribution Criteria-2

- **Helsinki Criteria 1997/2014**
- **IARC mono 100C, 2012**

- Occupational history (fibers-years exposure) - best indicator for chrysotile
- Latency> 10 years
- 1 year or - of intense exposure = 5-10 years of moderate and increases the risk of lung cancer in 2 times
- Diffuse, bilateral pleural thickening → moderate / severe exposure is attribution criterion
- Pleural plaque is an exposure indicator
  - Mas individualmente não é suficiente para atribuição
- Asbestosis is not necessary, but contributes with additional risk

High probability of asbestos exposure

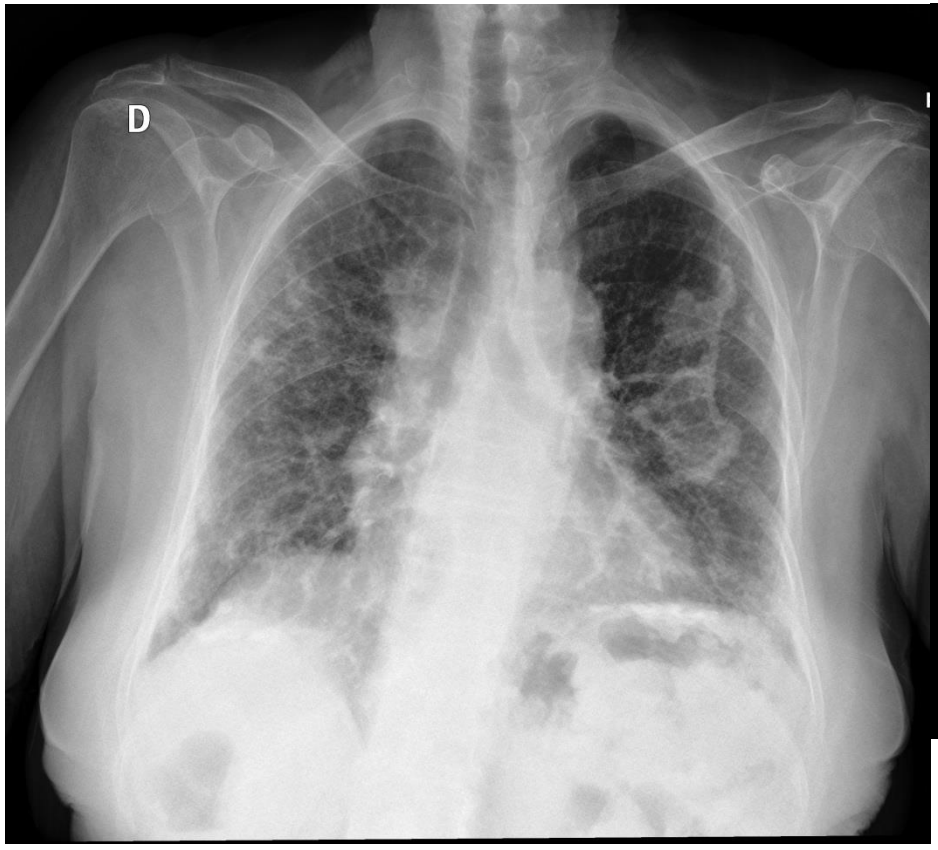
Helsinki Criteria 1997/2014

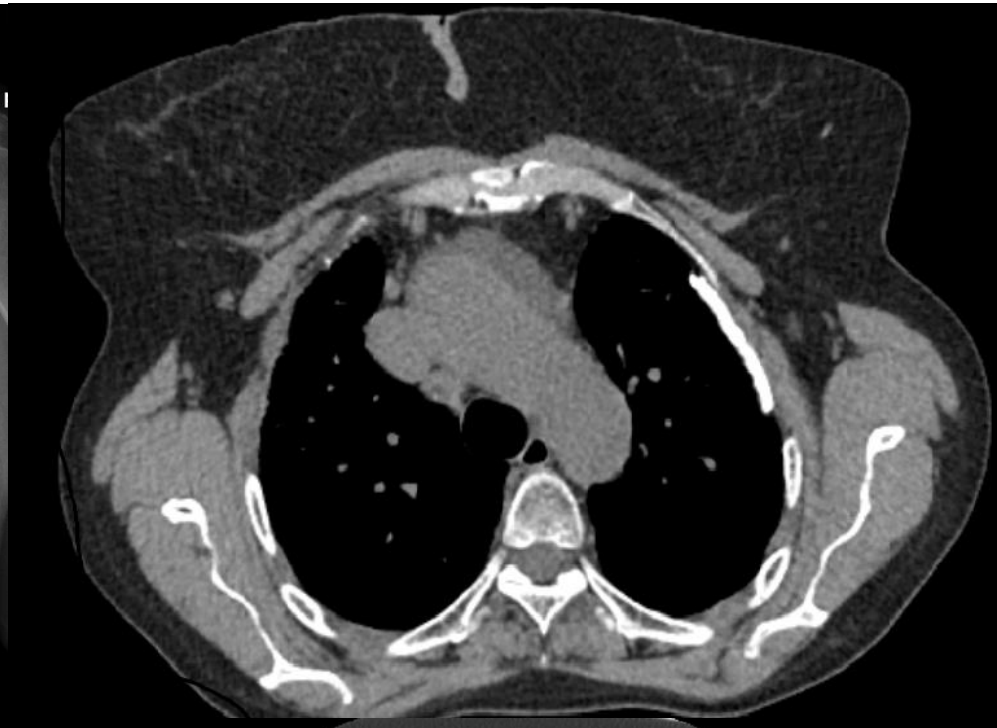
Complementary data to occupational history

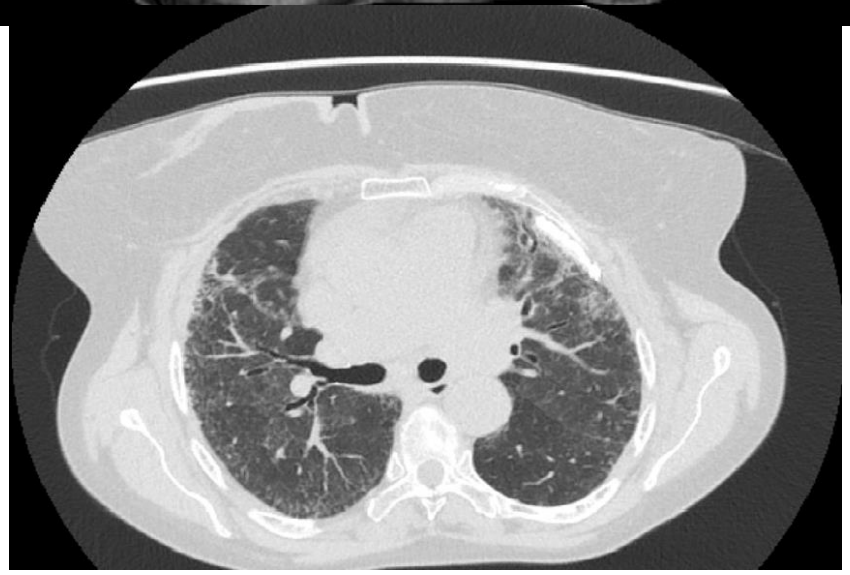
- Over 0.1 million amphibole fibers (>5 μm)/g of dry lung tissue, or
- Over 10^6 amphibole fibers (>1 μm)/g of dry lung tissue measured by EM, or
- Over 1000 asbestos bodies/g of dry lung tissue (100 asbestos bodies/g wet lung tissue), or
- Over 1 asbestos bodies/ ml de bronchoalveolar lavage fluid (BAL)
- Each laboratory should establish its own reference values

Asbestosis with diffuse thickening and pleural plaques

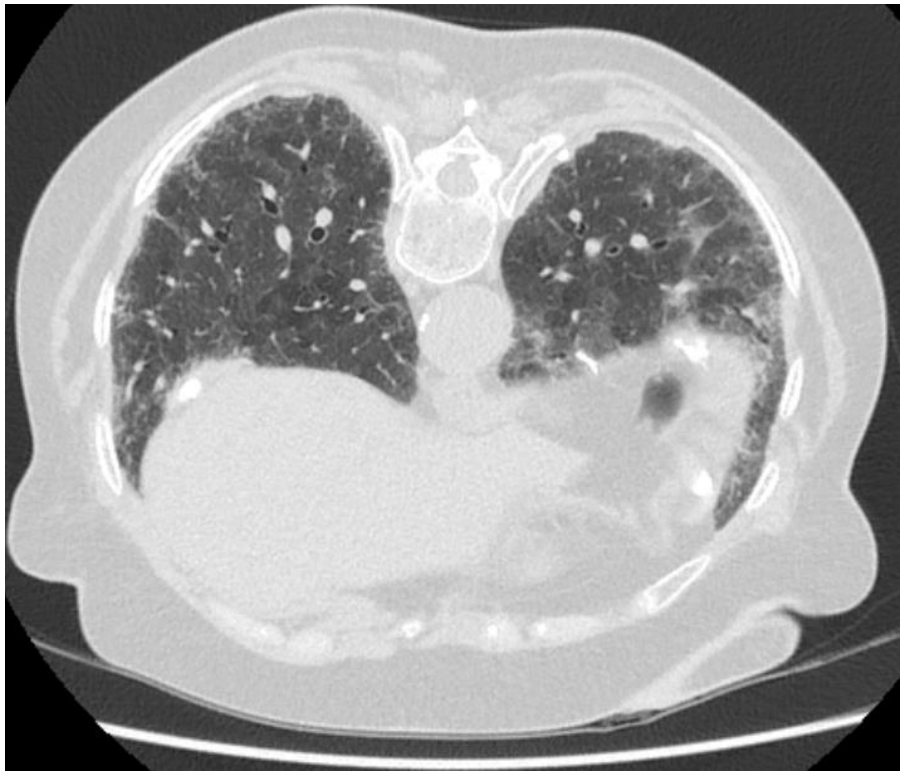
OMS, woman, 71 years old - soapstone handicraft



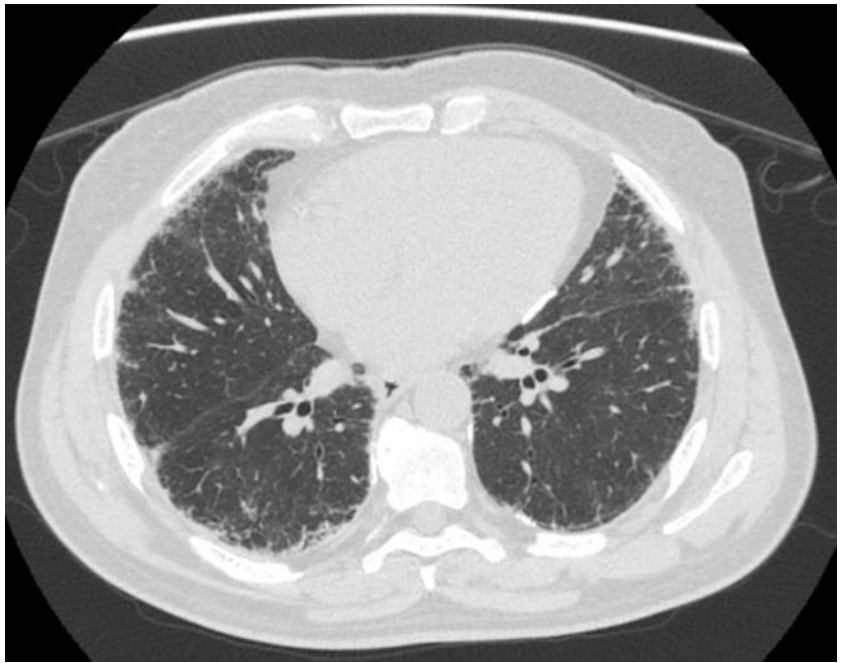


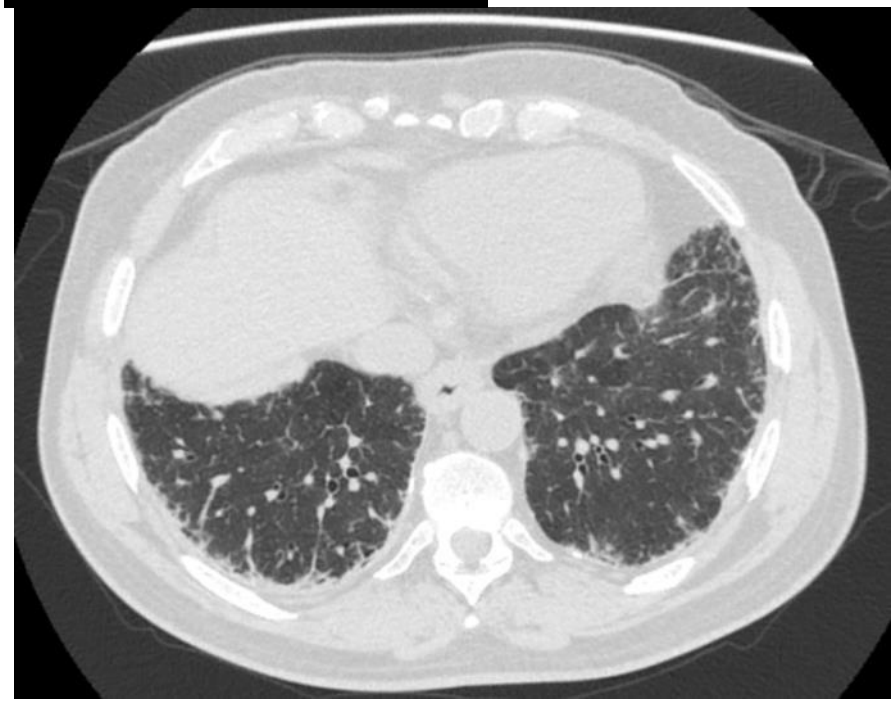


Woman, 65 years old, polishing/scraping of asbestos tiles, in the house, for over 20 years, latency 42 years

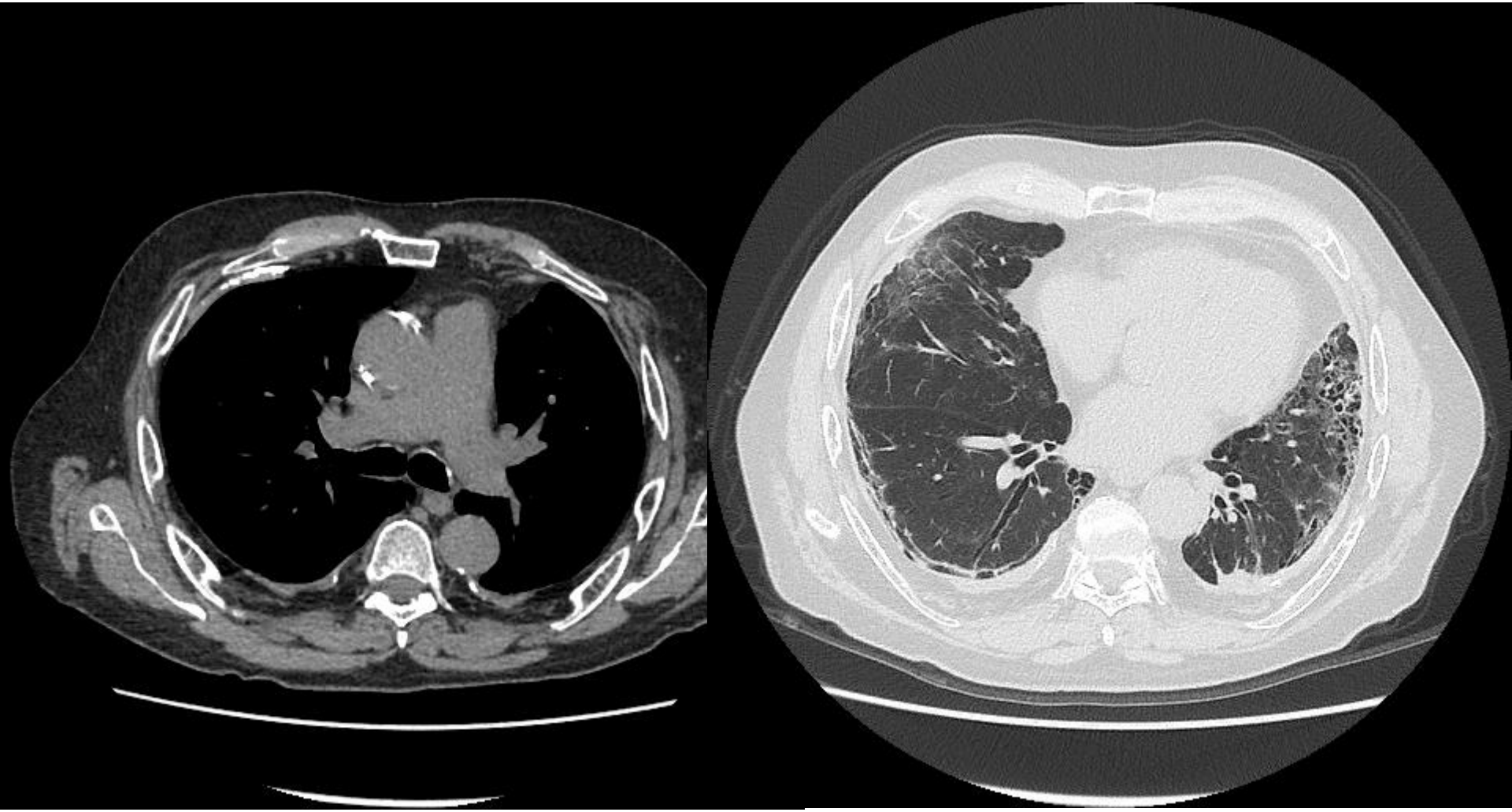


Worked at Brasilit from 1966-68

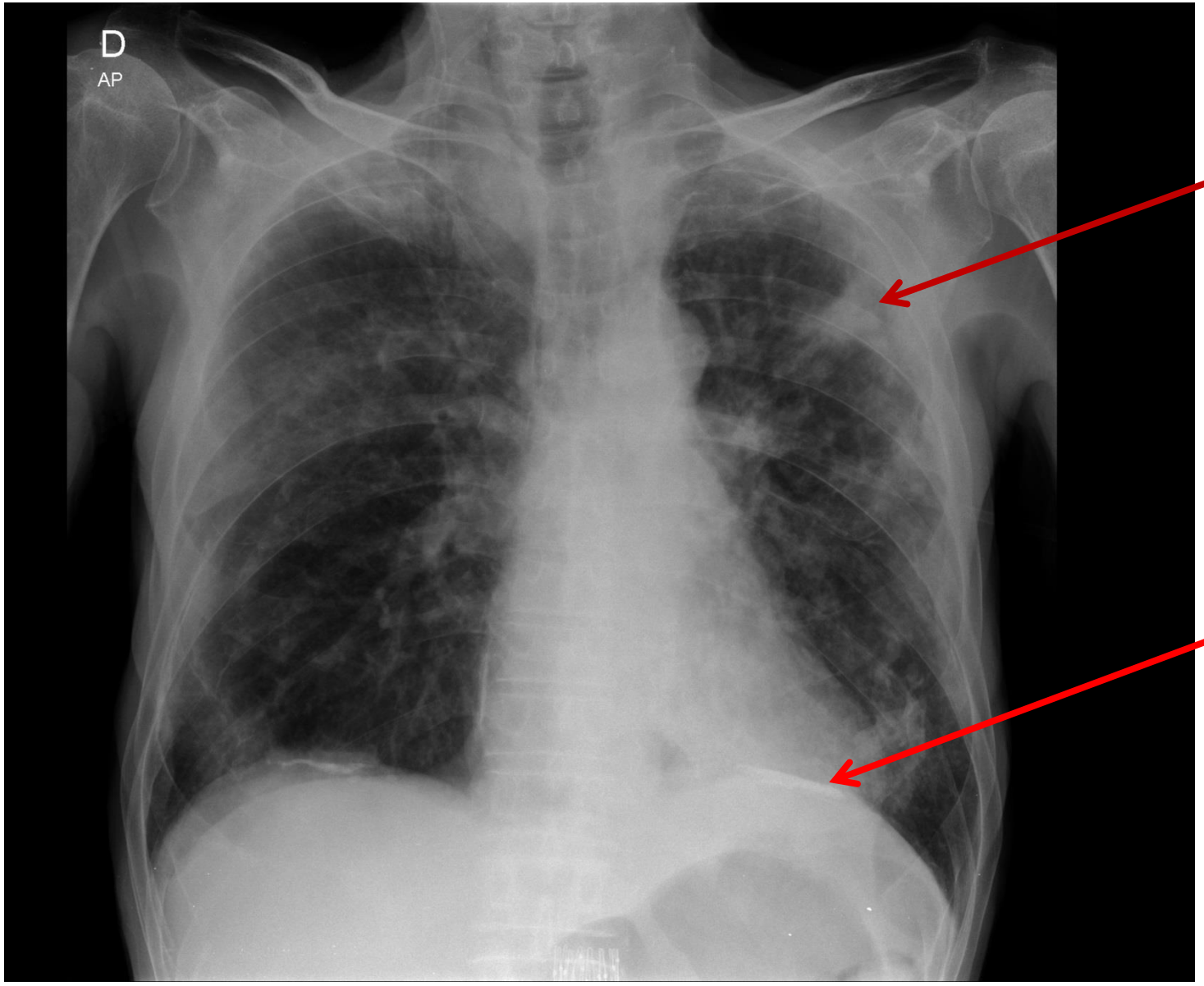




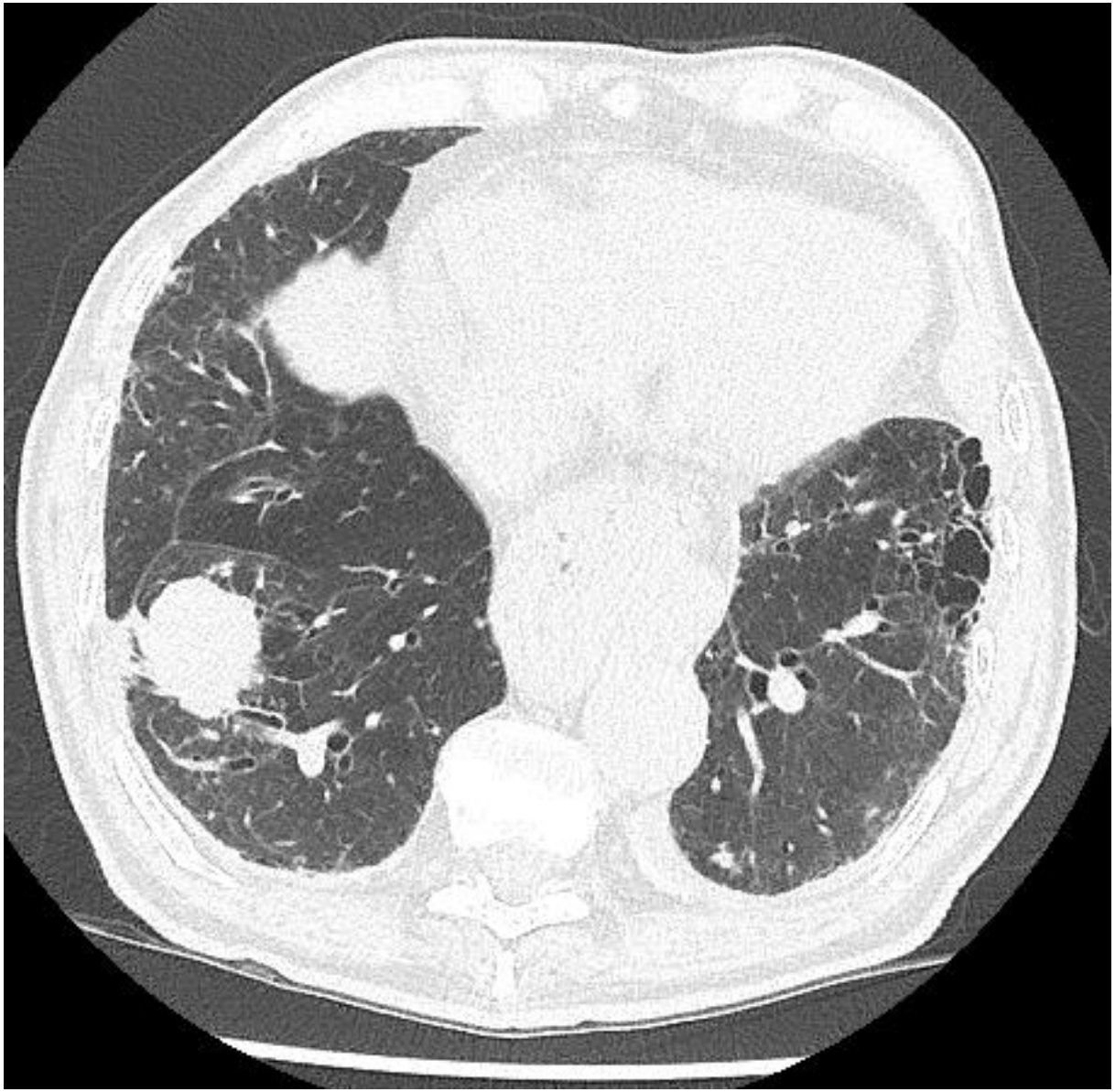
71 years old, worked 8 months manufacturing joints with asbestos. Latency 50 years



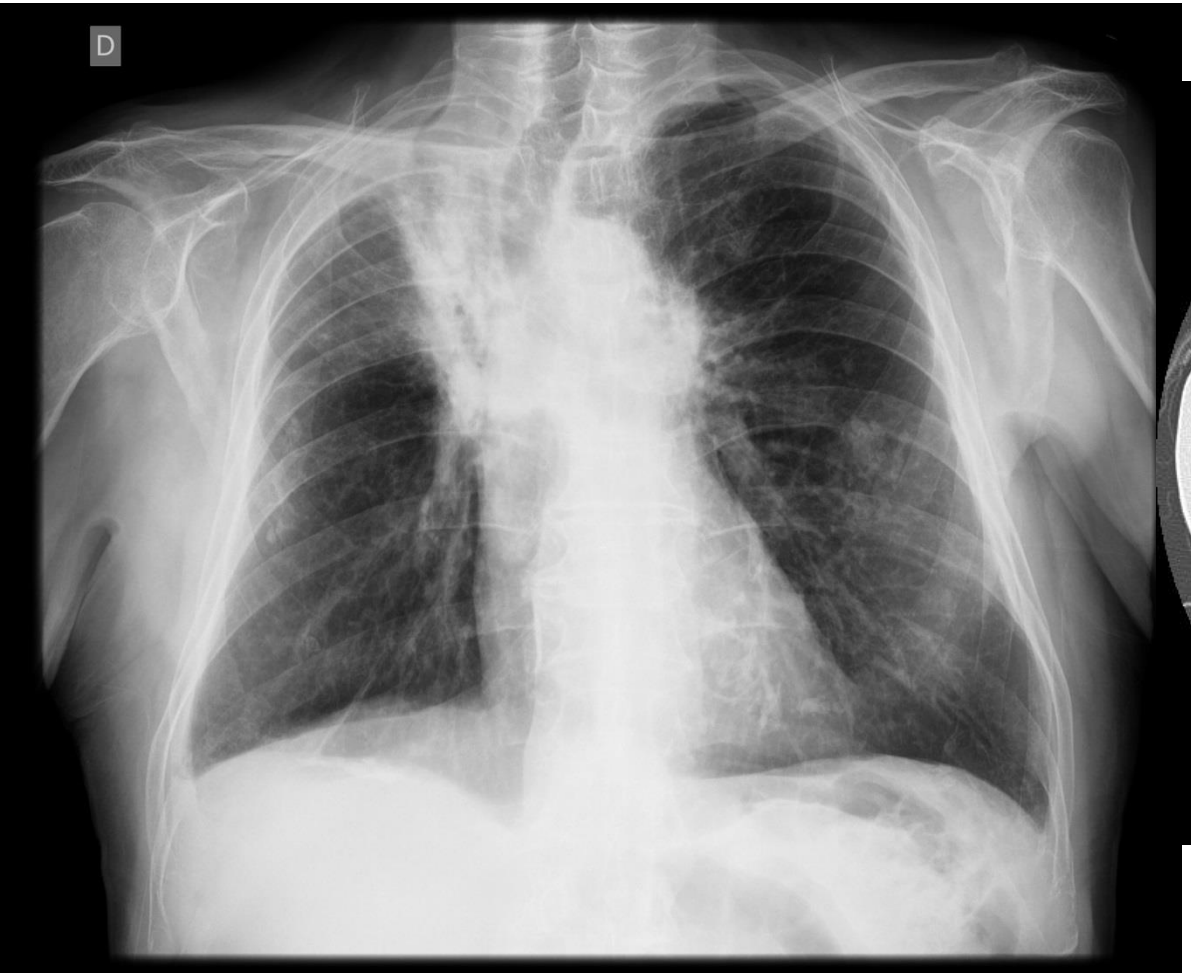
WS, 70 years old, smoker. He reported pain in HTD radiating to MSD. Worked at Cia. Metalúrgica Barbará (Saint-Gobain group).

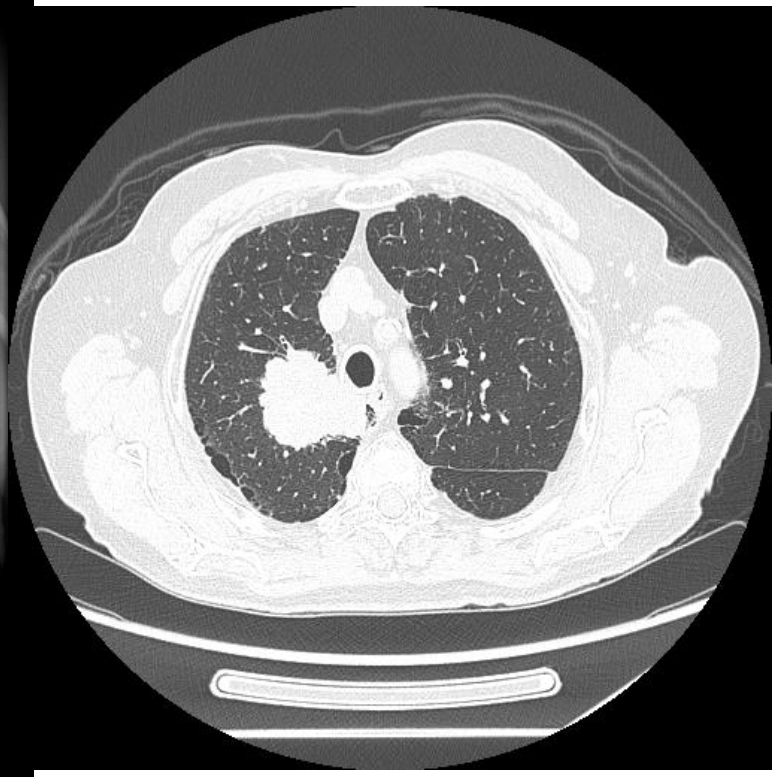


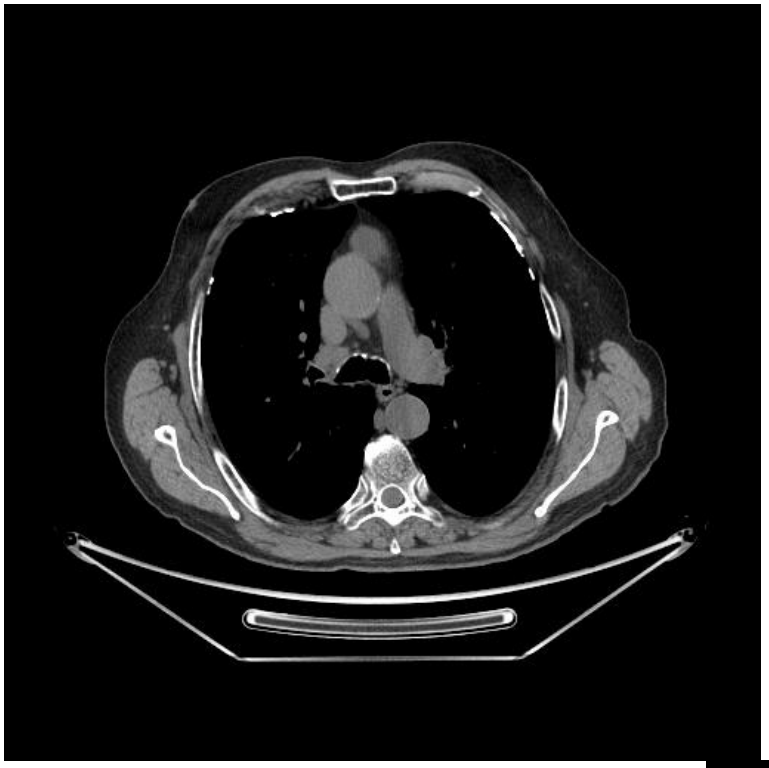
EVS - worked at Eternit from 1966 to 1980



JAF, 78 years old: Chronic cough and weight loss. Former smoker. Worked at Eternit from 1963 to 1985

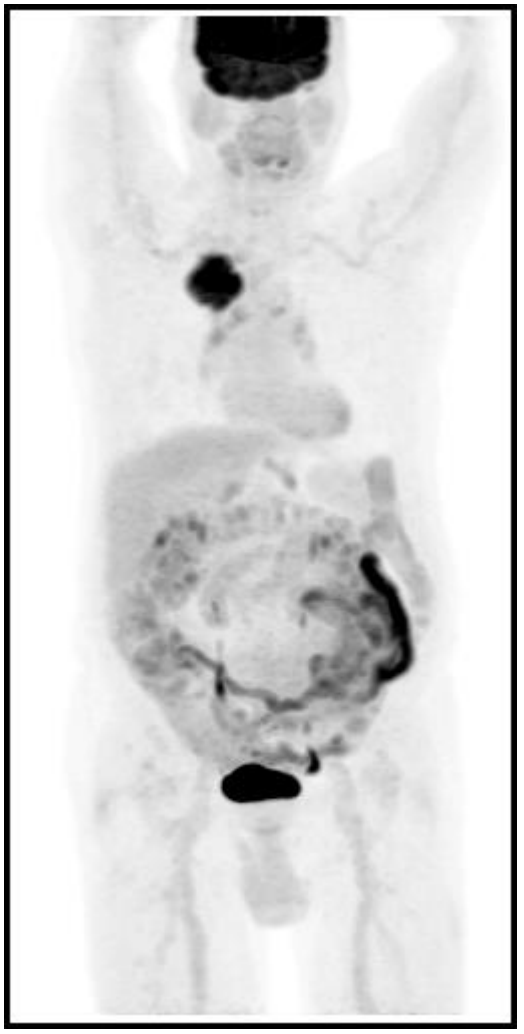


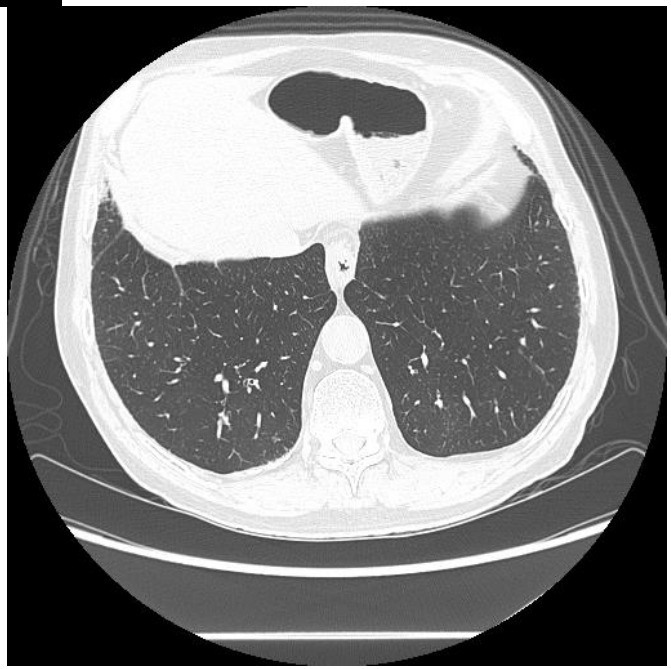




Adenocarcinoma

- Asbestos bodies in LBA
- Pleural plaques
- Latency: 49 years
- Without asbestosis





Worker - JAD

- Worked at Eternit from 1976 to 1991
- In 2001 (63 years old) : pulmonary nodule on chest CT
  - Adenocarcinoma
- Pneumonectomy due to pulmonary nodule in 2002
- Former smoker, he ceased at 37 years old
- Latency 25 years
- Without asbestosis and/or pleural alterations
- 2013: new pulmonary nodule

Worker JAD in 2016

Attribution Criteria-3

Helsinki Criteria 1997/2014

- Not all criteria need to be present for attribution, ex:
  - Significant exposure to chrysotile, low number of fibers, but long latency between end of exposure
- Presence of asbestos bodies or a high fiber count in the lung or BAL, with a history of uncertain or short-term exposure
  - should be considered for attribution
- Smoking does not decharacterizes asbestos cancer attribution

Some comments about the Helsinki Criteria

- **Landrighan PL. Annals of Global Health 2016**
- **Collegium Ramazzini. SJWEH/Industrial Health 2016**

1. Excessive confidence in the detection of "asbestos bodies" and in the count of fibers in the lung, as indicators of past exposure to asbestos.

2. Use of scanning electron microscope (SEM) with low magnification, as a tool for assessing asbestos-related diseases.

3. Failure to recognize that chrysotile is the predominant type of asbestos fiber found in pleural mesothelioma tissue.

4. Postulate the existence of a threshold for the development of lung cancer related to asbestos

5. Change in classification to consider asbestosis

CONCLUSIONS:

- The diagnosis should be based on a occupational history carefully obtained. A precise exposure history is a much more sensitive and specific indicator of asbestos exposure, than asbestos body count or lung fiber burden analysis
- Recommends review of pathology criteria proposed in the diagnostic by Helsinki criteria 2014

Structural alteration - Histology

Craighead JE. Arch Pathol Lab Med 1982
Green FHY, Attifield M. Scand J Work Environ Health 1983

- Open biopsy - only dubious situations
- Structural change
  - **Grade 0: No fibrosis associated with bronchioles**
  - Grade 1: Fibrosis involving the wall of at least one respiratory bronchiole with or without extension into the septa of the adjacent layer of alveoli
  - Grade 2: Grade 1 + involves alveolar ducts and / or two or more layers of adjacent alveoli
  - Grade 3: whole acinar structure is involved, between two or more respiratory bronchioles have thickened, fibrotic septa; some alveoli may be obliterated completely
  - Grade 4: honeycombing

Structural alteration - Histology

Rogli VL, et al. Arch Pathol Lab Med 2010

Table 3. Histologic Grading[a] Scheme for Asbestosis	
Grade	**Description**
Grade 0	No appreciable peribronchiolar fibrosis, or fibrosis confined to the bronchiolar walls
Grade 1[b]	Fibrosis confined to the walls of respiratory bronchioles and the first tier of adjacent alveoli
Grade 2[b]	Extension of fibrosis to involve alveolar ducts and/or ≥2 tiers of alveoli adjacent to the respiratory bronchiole, with sparing of at least some alveoli between adjacent bronchioles
Grade 3	Fibrotic thickening of the walls of all alveoli between ≥2 adjacent respiratory bronchioles
Grade 4	Honeycomb changes

More Comments

- Companies or the State have not and / or do not provide records of exposure levels throughout their working life
- They claim that workers may not be able to accurately recall asbestos exposures. And tend to overestimate to get insurance. **Gibbs A et al. Arch Pathol Lab Med 2007**
- So, the only valid criterion would be asbestosis. **Gibbs A et al. Arch Pathol Lab Med 2007**
- Or, in the doubt about the exposure, to make count of fibers in the tissue - necessity of biopsy (iatrogeny) - **Helsinki 2014**
- For chrysotile it is better the exposure in fiber-year, than tissue analysis- **Helsinki 2014**
  - ***Who measures and supplies data to workers?***
- Occupational history is the gold standard. **Bégin R &Christiman JW. AJRCCM 2001; Landrighan/2016; C Ramazzini/2016; Sartorelli E, 1980**

Conclusions

- Occupational history and/or environmental data on exposure should be the main attribution factor
- Exposure time and latency should be considered
- Exposure markers - plaques, diffuse thickening, asbestos bodies in the BAL
- If responsibles for exposure (companies) and surveillance (State) do not have information on exposure, validated
  - It does not make sense the worker to demonstrate, through submission to a surgical procedure, that has been exposed enough