Design of prospective follow up of chrysotile asbestos miners and production workers in Asbest

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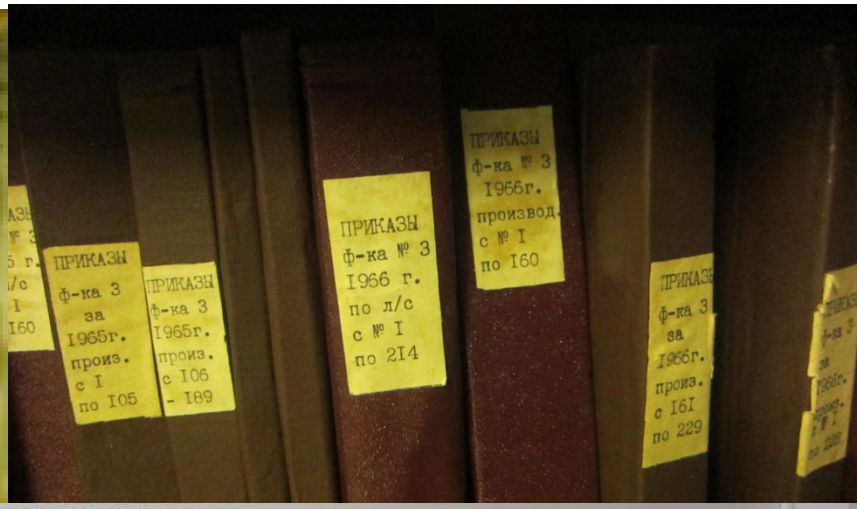


Cohort

A group of people who share <u>a common characteristic</u>

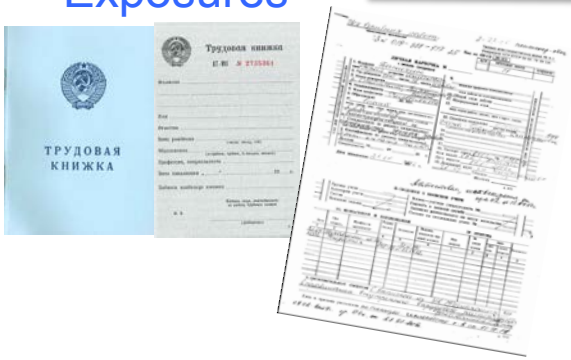
If the exposed group has a higher frequency of the outcome → may be an association between an exposure and outcome

Aim

- To **prospectively** follow up cancer incidence and causes of death in chrysotile exposed workers, extending an ongoing **retrospective** cohort study.

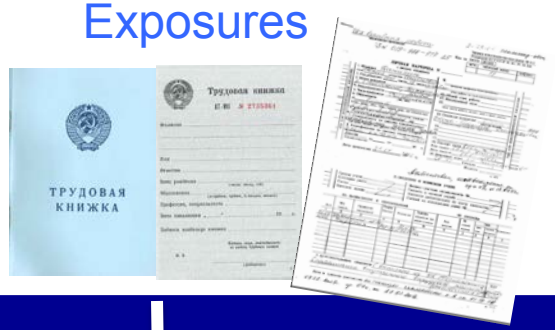
Retrospective cohort design

Exposures → Outcomes



Prospective cohort design

Lifetime Exposures → Outcomes → Outcomes



Past | Present | Future

Prospective design

Advantages

- **Temporal sequence is clear**

- **Outcome rate** can be calculated

Incidence (new case rate)

↓

онкологический диспансер (Свердловский областной)

Mortality (death rate)

↓

Óрганы зáписи áктов граждáнского состоя́ния (Свердлóвская óбласть)

$$IR = \frac{\text{Number of new cases of the disease that occur in a population observed for a period of time}}{\text{The sum of all person-time of observation of those at risk (free of the disease) during that period of time}}$$

- Can examine **multiple outcomes** after the exposure

Prospective design

Challenges

- Long wait for outcomes to occur
- Expensive
- Subjects enrolled can drop out of study
- Difficult to trace people

Retrospective design

Workers ≥ 1 year employment

(1 Jan 1975 -- 28 Feb 2016)

↓

> 54 000 work records found (37 000 eligible workers expected)

↓

Óрганы зáписи áктов граждáнского состоя́ния (Свердлóвская óбласть)

↓

Vital status and causes of death (full birth name and birth date)

Retrospective design

15 800 records matched

Death certificates

1 Direct cause

2 Related to direct

3 Underlying

4 Intent (external)

5 Co-morbidities

Primary cause of death ⟷ **Agreement evaluation**

International Classification of Disease codes

International Classification of diseases, version 10 (ICD-10)

- Systematic and standardized registration on disease
- Work was coordinated by the World Health Organization (WHO), with the participation of centers collaborating with WHO
- Disease classes I – XXII
  - Examples:
    - II : Neoplasms
    - IX: Diseases of circulatory system
    - X: Diseases of respiratory system
    - Etc…

Etiology
(Humerus Fracture)

Laterality
(Right Arm)

S 4 2 . 3 2 1 A

Category
(Displaced Transverse Fracture)

Location
(Shaft of Humerus)

Extension
(Initial Encounter
for Closed Fracture)

Unique to our design

Exposure can be assessed prospectively by collecting more data

- Biological samples
- Questionnaires for co-factors (smoking)

Prospective design

- Smoking is a **confounder**, related both to asbestos exposure and death outcomes
  - Survey has been conducted in Uralasbest (January-June 2017)
  - 8,090 respondents, both active and former workers
  - Question: What is the relationship between smoking duration and intensity with asbestos exposure?

Biological samples

- Mechanistic studies on tumors and matching normal tissues
- Using massively parallel (deep) sequencing

AIM: to identify specific **genome-wide effects of asbestos** on DNA and cancer development

IARC partners

- J. Zavadil, M. Korenjak, specialists in Molecular Mechanisms of Disease

Mechanistic prospective studies

1. Investigate **previously unrecognized links** between asbestos exposure and non-lung cancer types

Target sites: ***Stomach, esophagus, colorectum, ovary, bladder***
Sample types for deep sequencing: Fresh frozen tumor tissue and/or paraffin blocks

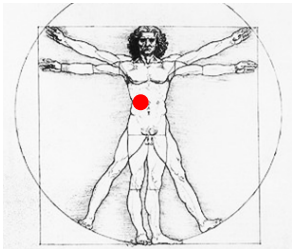
Sample power estimate per study/per target site:
At least N=25 tumors + 25 matched non-tumor controls to have over 80% power

2. Association of **asbestos exposure with lung cancer in female non-smoker patients**

Possible design:
Starting at 25 exposed with matched normal tissue vs. 25 unexposed non-smoker women cases with matched normal tissue control

- Asbestos-specific genomic signatures in mutually cross-validating systems
- Whole-exome and whole-genome analyses

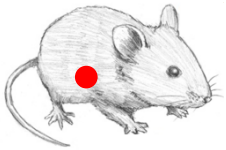
Effects of chrysotile exposure in cell immortalization assay



Centre Léon Bérard
LYON ET RHÔNE-ALPES

Asbestos associated ovarian tumors

Mouse tumors induced by chrysotile exposure



Public cancer genomics data

National Toxicology Program
U.S. Department of Health and Human Services

ICGC COSMIC
Catalogue of somatic mutations in cancer
The Cancer Genome Atlas
PCAWG
PanCancer Analysis OF WHOLE GENOMES

Conclusions

- This cohort has unique features
  - Long enrolment period with complete work history
  - Large case number
    - Risk calculation for rare outcomes and subgroups
  - Large proportion of working women
  - Detailed asbestos exposure data
    - Regular dust measurements at the workplace for different units, job titles, and across different time periods

Three methodological advantages

- One of the largest and best quality cohorts of miners and millers in place
  - Biological data collection
  - Long-term follow-up and lifetime exposures
    - Dose-response calculations
  - Incidence rate calculation

This is one of the most informative on-going studies on worker health, and with a special relevance to Russian Federation

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Thanks.