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

International Agency for Research on Cancer
Lyon, France

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Cohort

A group of people who share a common characteristic

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 за́писи áктов гражда́нского состоя́ния (Свердло́вская о́бласть)

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

\[\text{Асбест (asbestos)} \rightarrow \text{рак легких (lung cancer)} \rightarrow \text{рак яичников (ovarian cancer)} \rightarrow \text{рак желудка (stomach cancer)} \rightarrow \text{рак гортани (laryngeal cancer)} \rightarrow \text{и другие заболевания (And more…)}\]
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)

О́рганы за́писи а́ктов гражда́нского состоя́ния
(Свердло́вская обла́сть)

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 )

Category
( Displaced Transverse Fracture )

Location
( Shaft of Humerus )

Extension
( Initial Encounter for Closed Fracture )
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

Mouse tumors induced by chrysotile exposure

Asbestos associated ovarian tumors

Public cancer genomics data

International Agency for Research on Cancer
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 ongoing studies on worker health, and with a special relevance to Russian Federation.
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