OCCUPATIONAL LUNG CANCER

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INTRODUCTION

“Occupational cancer is a workplace dangerous problems“

How much is caused by work?

“Studies worldwide suggest the occupational contribution to the cancer total is between 8 and 16 per cent.”


WHAT’S KILLING YOU AT WORK?

Causes of work-related deaths worldwide.

1. Cancers: 32%
2. Circulatory disease: 26%
3. Work accidents: 17%

Source:
International Metal Workers Federation 2007
“Occupational cancer is the forgotten epidemic”

ILO

“...It estimates occupational cancers make up almost one-third of all work-related deaths.”

Source:
International Metal Workers Federation 2007

Why work cancers get missed

- **Common cancers** Dusty jobs in general have a higher lung cancer rate, but because lung cancer is common and is often caused by smoking, the link to work is usually missed.

- **Inadequate studies** Most of what we know about occupational cancer is based on big studies in industrial workplaces. These miss many jobs dominated by women, for example, or workers in small firms.

- **New factors** New substances or processes can present new risks. By the time cancers emerge, the substance, process and even the workplace may be long gone.

- **Unexpected exposures** Hairdressers have developed asbestos cancers, caused by asbestos used in hairdryers. Teachers, nurses and doctors have developed the same cancers caused by asbestos used in their workplaces.

- **Paying the price** Industry financed studies and lobbying ensure evidence of risks posed by some jobs is suppressed or played down.
How about occupational lung cancer?

There are three main ways workers are exposed to workplace cancer risk – they can touch it, breathe it or swallow it.

- Skin exposure – either by touching the substance or being exposed by other means, for example skin exposure to sunlight or radiation.
- Ingestion – swallowing hazardous substances, perhaps contaminating food, drink or skin.
- Inhalation – breathing in gases, fumes or vapours.

A World Health Organisation (WHO) study concluded 20-30 per cent of males and 5-20 per cent of females in the working-age population could have been exposed to an occupational lung cancer risk during their working lives.

“**Inhalation is a most causes**“

**Occupational lung cancer**

“**one of a big problem in occupational cancer**“

Source: International Metal Workers Federation 2007
Occupational lung cancer

Etiology of Lung Cancer

Smoking is the most environmental cause in communities

American Lung Association
Lung disease data in Culturally Diverse Communities : 2005
EPIDEMIOLOGY

• USA data
  1. Approximately 6-10% cancers were attributable to occupational exposure → 5% is a lung cancer
  2. Estimated 9000-10,000 men and 900-1,900 women develop lung cancer annually as a result of occupational exposure
  3. Estimated 3-17% of male lung cancer were attributable to occupational exposure
Increased risk of lung cancer induced by occupational exposure:

- Sweden (proportion 9.5%)
- Germany
- England (1800 death lung cancer causes by asbestos)
- China (67 occupational lung cancer in 1997)
The Global disease burden from occupational carcinogens

Legend:


Subregions: AFR = Africa; AMR = Americas; EMR = Eastern Mediterranean; EUR = Europe; SEAR = South-East Asia; WPR = Western Pacific; A: Very low child, very low adult mortality; B: Low child, low adult mortality; C: Low child, high adult mortality; D: High child, high adult mortality; E: High child, very high adult mortality.
Epidemiology of histological types occupational lung cancer

- Travis et al
  Reported analyses of Surveillance, Epidemiology, and End Results (SEER) → period 1973-1987.
  - The percentage of lung cancers that were adenocarcinoma in all race-sex groups combined increased to 32 percent, surpassing squamous cell carcinoma as the most frequently occurring histologic type.
  - Squamous cell carcinoma, however, continues to constitute a large proportion (29 percent) of lung tumors.
## Table 19.1  IARC classification of the carcinogenicity of substances

<table>
<thead>
<tr>
<th>Group</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The agent is carcinogenic to humans</td>
</tr>
<tr>
<td>2A</td>
<td>The agent is probably carcinogenic to humans</td>
</tr>
<tr>
<td>2B</td>
<td>The agent is possibly carcinogenic to humans</td>
</tr>
<tr>
<td>3</td>
<td>The agent is not classifiable as to its carcinogenicity to humans</td>
</tr>
<tr>
<td>4</td>
<td>The agent is probably not carcinogenic to humans</td>
</tr>
</tbody>
</table>
Almost 150 carcinogen or probable carcinogen in workplace (IARC)

Until now there is:
- 21 agents to be carcinogenic for the human lung
- 5 agents as probable human lung carcinogen
- 4 agents to be possible human lung carcinogen

The single most important occupational "chemical" cause is asbestos
→ blue asbestos → 60% as a causes occ lung cancer
Agents/processes to be carcinogen for the human lung (IARC)

- Arsenic/arsenic compounds
- Asbestos
- Chromium/chromium compounds
- Mustard gas
- Underground hematite mining
- Coal gasification
- Coke production
- Iron and steel founding
- Talc containing asbestiform fibers
- Alumunium production
- Soot
- Radon
- Sulfuric acid mist
- Bis (chloromethyl) ether and chloromethyl methyl ether
- Cadmium/cadmium compounds
- Nickel
- Spray painting
- 2,3,7,8-tetrachlorodibenzo-paredioxin
- Berrylium/berrylium compounds
- Paint manufacturing/painting
- Chrystalline silica

International Agency for Research on Cancer (IARC)
Agents/processes to be probable human lung carcinogens (IARC)

<table>
<thead>
<tr>
<th>Substance or process</th>
<th>Year of first report</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epichlorohydrin</td>
<td>1976</td>
</tr>
<tr>
<td>Non-arsenical pesticides (spraying)</td>
<td>1979</td>
</tr>
<tr>
<td>(\alpha)-Chlorinated toluenes and benzoyl chlorides</td>
<td>1982</td>
</tr>
<tr>
<td>Diesel particulate</td>
<td>1983</td>
</tr>
<tr>
<td>Glass manufacture</td>
<td>1987</td>
</tr>
</tbody>
</table>
**Agents/processes to be possible human lung carcinogens (IARC)**

<table>
<thead>
<tr>
<th>Agent/Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde</td>
</tr>
<tr>
<td>Acrylonitrile</td>
</tr>
<tr>
<td>Very fine vitreous fibers</td>
</tr>
<tr>
<td>Welding fumes</td>
</tr>
</tbody>
</table>

*International Agency for Research on Cancer (IARC)*
### Table. Occupational lung carcinogen (IARC)

<table>
<thead>
<tr>
<th>Site</th>
<th>Strength of evidence</th>
<th>High-risk substance or circumstance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Strong</td>
<td>Aluminum production; arsenic and arsanic compounds; asbestos; beryllium; cadmium and cadmium compounds; chromium compounds, hexavalent; coal gasification; coke production; hematite mining, underground, with radon exposure; involuntary (passive) smoking; ionizing radiation; iron and steel founding; selected nickel compounds, including combinations of nickel oxides and sulfides in the nickel refining industry; painters; silica, crystalline soots; talc containing asbestiform fibers</td>
</tr>
<tr>
<td>Lung (oat cell)</td>
<td>Suggestive</td>
<td>Benz[a]anthracene; benzo[a]pyrene; α-chlorinated toluenes; coal tars and pitches; dibenz[a,h]anthracene; diesel engine exhaust; epichlorhydrin; hairdressers and barbers; inorganic acid mists containing sulfuric acid; isopropanol manufacture (strong acid process); mineral oils (untreated and mildly treated); nonarsenical insecticides; mustard gas; production of art glass, glass containers, and pressed ware; rubber industry; TCDD</td>
</tr>
</tbody>
</table>

*Health perspective 2004; 112: 1447-59.*
Relative risk

- Relative risk for lung cancer caused by occupational carcinogen exposure (exclude radon) approximately 1.6
  
  WHO report 2002

- Tobacco and many workplace carcinogens
  → “Multiplicative risk”
  → Increasing the reported incidences 10 – 100 fold
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk$^a$</th>
<th>95% CI$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lung carcinogens</em>$^c$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic</td>
<td>3.69</td>
<td>3.06–4.46</td>
</tr>
<tr>
<td>Asbestos</td>
<td>2.00</td>
<td>1.90–2.11</td>
</tr>
<tr>
<td>Beryllium</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>1.49</td>
<td>0.96–2.22</td>
</tr>
<tr>
<td>Chromium</td>
<td>2.78</td>
<td>2.47–3.52</td>
</tr>
<tr>
<td>Diesel exhaust</td>
<td>1.31</td>
<td>1.13–1.44</td>
</tr>
<tr>
<td>Nickel</td>
<td>1.56</td>
<td>1.41–1.73</td>
</tr>
<tr>
<td>Silica</td>
<td>1.33</td>
<td>1.21–1.45</td>
</tr>
</tbody>
</table>
Table III—Relative risks of lung cancer due to smoking and occupational hazards

<table>
<thead>
<tr>
<th>Hazard and study</th>
<th>Occupational exposure</th>
<th></th>
<th>Relative risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmoker</td>
<td>Smoker</td>
<td>Unknown</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hammond^27</td>
<td>1</td>
<td>14.7</td>
<td>–</td>
</tr>
<tr>
<td>Minerals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meurman et al^28</td>
<td>1</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>Berry et al^29</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Selikoff^30</td>
<td>1</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Arsenic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ott et al^31</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Lee et al^32</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Chromates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>International Agency for Research on</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer^33</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Nickel</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mastromatteo^34</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Chemicals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloromethyl ethers</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Figueroa et al^35</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Coal tar distillates</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Redmond et al^36</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Environmental Protection Agency^37</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Mustard gas</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Wada et al^38</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uranium mines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archer et al^39</td>
<td>1</td>
<td>4</td>
<td>–</td>
</tr>
<tr>
<td>Fluorspar mines</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
</tbody>
</table>

*Estimated ratios of the incidence in those exposed to a hazard to the incidence in those not exposed.
Is histological types of lung cancer associated with specific agent?

- No study has unequivocally demonstrated any one lung cancer cell type to be uniquely associated with a specific agent.

- Many studies have attempted to identify differences in distribution of histologic types:
  - Arsenic exposure → adenocarcinomas
  - (bis) chloromethyl ether or to uranium/radon → Small cell carcinomas
- Nickel \[\rightarrow\] small cell carcinomas and epidermoid
- Vinyl chloride \[\rightarrow\] large cell cancers
- Mustard gas \[\rightarrow\] Squamous cells carcinoma or undifferentiated lung carcinoma
- Silica \[\rightarrow\] bronchogenic carcinoma or undifferentiated lung carcinoma

- Asbestos
  - All histologic type of lung cancer maybe seen
  - Some studies have shown a preponderance of adenocarcinoma
Pathogenesis

- Mechanism occupational agent induced lung cancer, almost still unclear
- Arsenic
  - “Induced chromosom malformation in mammalian cells also in perifer lymphocyte worker who exposed arsenic “
- Radon
  - “Induced epitelial break and genetic mutation epitelial cells of airways”
Asbestos induced lung cancer

- Mechanism are not well understood
- Some possible mechanism:
  1. DNA damaged by reactive oxygen species induced by fiber
  2. Direct DNA damaged by physical interactions between fibres and target cells
  3. Enhancement of cells proliferation by fiber
  4. Fibre-provoked chronic inflammatory cytokines and growth factors
  5. Actions by fibre as co-carcinogens or carrier of chemical carcinogens to the target tissue
Pathogenesis smoking induced lung cancer and interaction with occupational lung carcinogen

Asbestos
Chloromethyl ethers
Mustard gas
Radioactive
other

Synergistic effect

Nicotine addiction → Cigarette smoking → PAH, NNK and other carcinogens → Metabolic activation → DNA adducts → Persistence, Miscoding, Repair → Mutations and other changes: RAS, MYC, P53, p16, RB, FHIT, and other critical genes → Lung cancer

Excretion → Normal DNA → Apoptosis
ASBESTOS AND LUNG CANCER

- Asbestos is the most occupational agent induced lung cancer with relative risk 2.0

  WHO report 2002

- Approximately 6% lung cancer cases in men and 1% in women caused by asbestos exposure

- Asbestos caused lung cancer independent or synergistically with cigarettes smoking
Epidemiology asbestos induced lung cancer

- USA
  In 1990 → approximately 1200 cases lung cancer /years

- Europe:
  → 11.6% lung cancer cases in Nederland
  → 18.3% cases in Italy

- Asia
  China → in 1993 there was 67 cases lung cancer caused by asbestos exposure
FIGURE 7. Frequency distribution of the number of lung cancer cases by time since asbestos exposure began among a cohort of asbestos insulation workers. Adapted from Selikoff.221
### Table 19.8 Multiplicative risk of smoking and asbestos exposure

<table>
<thead>
<tr>
<th>Smoking</th>
<th>No asbestos</th>
<th>Heavy asbestos</th>
<th>Increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light</td>
<td>2.9</td>
<td>11.9</td>
<td>×4.1</td>
</tr>
<tr>
<td>Heavy</td>
<td>90.3</td>
<td>370.2</td>
<td>×4.1</td>
</tr>
<tr>
<td>Increased risk</td>
<td>×31</td>
<td>×31</td>
<td></td>
</tr>
</tbody>
</table>

*Given that the risk associated with no smoking and no asbestos exposure is 1.*
RELATIVE RISK OF DYING OF LUNG CANCER FOR SMOKING AND NONSMOKING ASBESTOS WORKERS

Asbestos

Serpentine

Chrysotile (White)
$\text{Mg}_3\text{Si}_2\text{O}_5(\text{OH})$

Amphiboles

Crocidolite (Blue)
$\text{Na}_2(\text{Fe}^{2+})_3(\text{Fe}^{3+})_2\text{Si}_8\text{O}_{22}(\text{OH})_2$

Actinolite
$\text{Ca}_2(\text{Mg,Fe})_5\text{Si}_8\text{O}_{22}(\text{OH})_2$

Amosite (Brown)
$(\text{Fe,Mg})_3\text{Si}_8\text{O}_{22}(\text{OH})_2$

Anthophyllite (Mg,Fe)$_7$Si$_8$O$_{22}$(OH)$_2$

Tremolite
$\text{Ca}_4\text{Mg}_5\text{Si}_8\text{O}_{22}(\text{OH})_2$
AMPHIBOLE

- High carcinogenicity
- High carcinogenicity *amphibole* maybe caused by several factors:
  - long biopersistence
  - \( \text{Fe}^+ \) in fibers could catalysis product reactive oxigen radicals \((\text{H}_2\text{O}_2 \text{ and OH}^-)\)
The Biopersistence of Amphibole Fibers

Number of Fibers L>20 µm in the Lung

Time since cessation of exposure (days)
IARC (Monograph 81, 2002)

“...characteristic, known as **high biopersistence**, is correlated with the high carcinogenic potency of asbestos fibres. Some of these newer materials have now been tested for carcinogenicity and most are found to be non-carcinogenic, or to cause tumours in experimental animals only under very restricted conditions of exposure.”
CHRYSOTILE

- Carcinogenicity still debate & controversy

Some study:

- *Chrysotile* still carcinogen, but less compare *amphibole*.
- One of reason, there is no asbestos that 100% *chrysotile* and free *amphibole*
Other study:

- New study showed *chrysotile* there is no carcinogen effect or low carcinogenicity

- Hodgson et al.
  - *chrysotile* exposure low risk caused cancer
  - 1:100:500 for *chrysotile, amosite* and *crocidolite*
Bernstein et al

- Study in rat showed that biopersistence and clearance chrysotile better than amphibole.
- *Chrysotile* fibers had clearance fast in lung (short retention in lung).

LOW CARCINOGEN
DIAGNOSIS & MANAGEMENT

• Diagnosis and management occupationally induced lung cancer is not any differently from lung cancer generally

Anamnesis:

• Full occupational and environmental histories should be considered
• History of smoking → a significant cause
• A latency period → 12 – 40 years
• Symptoms
Investigation

- Imaging (Thorax X-ray dan CT)
- Sputum cytology
- Biopsy
- Bronchoscopy

- **Mineralogic analysis**
  
  To evaluate relevance of occupational exposures to the development of lung cancer
  
  - Bronchoalveolar fluid $\rightarrow$ BAL
  - Peripheral blood lymphocyte transformation response to beryllium
  - There are no another reliable cellular and serologic test
Primary prevention is important to prevent occupational lung cancer.
Worker selection

- Preemployement recruitment → low risk
- There are no guideline for worker selection regarding lung cancer except identifying smokers
  → Nonsmokers, if exposed asbestos

Exposure control

- Limiting occupational exposure
- Not fully protect, maybe minimalized risk for lung cancer

Smoking cessation policy

- Most of the agents synergistic relationship with tobacco exposure
- Smoking cessation in and out work place → lower overall risk of lung cancer

National regulatory

- Focus on elimination (or minimization)
- Substitute with a less hazardous materials
- Minimize exposure through engineering modification
- Personal protective
ILO Convention to prevent occupational cancer

The International Labour Organisation (ILO) convention on occupational cancer makes clear, commonsense recommendations which could and should be followed everywhere. There’s good reason for occupational cancer to be an ILO priority – it says it is the top cause of work-related deaths worldwide, killing one person every 52 seconds.

The convention, C139, requires ratifying countries to:

- Periodically determine the carcinogenic substances and agents to which occupational exposure shall be prohibited or made subject of authorisation and control.
- Make every effort to replace carcinogenic substances and agents with non-carcinogenic and less harmful alternatives.
- Take measures to reduce to the minimum the number of workers exposed to carcinogenic substances, and the duration and degree of exposure and to establish an appropriate system of records.
- Ensure that workers who have been, are, or are likely to be exposed to carcinogens, are provided with information on dangers and relevant preventive measures.
- Organise medical surveillance of workers at risk, during and after employment.
CONCLUSION

- The was estimated increased risk of lung cancer induced by occupational exposure
- Exposure occupational agent and cigarettes smoking had multiplicative risk for lung cancer
- A single most important occupational "chemical" cause of lung cancer is blue asbestos or amphibole
- Diagnosis and management occupationally induced lung cancer is not any differently from lung cancer generally
- Primary prevention is most important act to prevent occupational lung cancer
Thank you