BE.104 Spring
Evaluating Environmental Causes of Mesothelioma
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Outline: 1) Toxicological mechanisms and causation evaluations
2) An environetics case: Asbestos and Mesothelioma

Toxicological Mechanisms
-processes by which toxin cause toxicity

-chemical, molecular, macromolecular, cellular, histological, organ-based, organismal

Knowledge of toxicological mechanisms informs environetic causation analyses by:

1) Limiting the number of possible explanations
2) Providing possible signatures of cause

Consider the question of whether the proverbial "lady tasting tea" could actual tell the order of addition.

How would you think about and approach this problem if you knew that, when a large volume of hot tea was poured into a small volume of cool cream, a chemical reaction occurred that did not occur when a small amount of cool cream was poured into a large volume of hot tea?

Asbestos

What is it? - Naturally occurring

Silicate mineral crystal in fiber form

Serpentine <curly>- chrysotile- >90% of world's production

amphiboles	crocidolite*	
↑	anthrophyllite	
associate w/ MM	amosite	} rod-like forms
5-10% of the world's	actinolite	
production	tremolite	

Most commercial asbestos is a mixture
*crocidolite is a common contaminant of chrysotile

Mine and milled for insulating & fireproofing properties

Uses-
electrical insulation
high pressure sprays to coat outer surfaces of major construction
brake linings
floor tiles
transmissions

First uses in 1913

1940's World War II shipbuilding

Late 1960's use soared-
rocket engines for US space program, paper & cement products, pipe wrapping, ceiling tiles, gaskets, hair dryers, textiles, and potholders

1913 to 1973 world consumption increased from 30,000 tons to 4 million tons per year!

Epidemiology

Three major disease effects associated with exposure:

1) Asbestosis- fibrosis of lung alveoli

2) Bronchogenic lung cancers

3) Malignant Mesothelioma (MM)-
cancer of pleura-lung lining
cancer of the peritoneum- lining of the abdominal cavity

No effective treatment, no cure

Average survival @ Dx is < 1 yr.

Asbestos-related disease hierarchy

Epidemiology History

1920's- Miners were known to get asbestosis

1960's- Fist evidence- Miners in South Africa show high rates of a new form of cancer, MM

MM was unknown prior to 1950

Questions: 1) Does MM have a long latency after chronic exposure 20-40 yrs?
2) Is it related to another environmental change, e.g. cigarette smoking?

1976- 19,000 asbestos insulation workers in Canada, U.S., & Ireland

182 MM deaths ⇒ 958 per 100,000

Compare 1976 lung cancer for men who smoke:
[79 per 100,000] x 85% attribute risk for smoking =

67 per 100,000

14x! greater incidence for MM associated with asbestos

(in 2000 ≈ 92-96 lung cancer deaths in men = 76 x 85% = 65 per 100,000)

1978- Blot et al.
Shipyard workers from World War II
(>30 yrs. Since exposure for <5 yrs.)
continued to be at risk for MM

⇒Latent disease

1981- South-Central Turkey
Endemic MM & lung cancer
Naturally occurring airborne mineral fibers (zeolite)

What is the association with smoking?

1991 Muscat & Winder

1) Bronchogenic lung cancer is more common in asbestos-exposed, **if they smoke**
2) But no association between smoking and MM

1992 Sandin et al

4,000 shipyard workers
7-15 years after exposure to asbestos

1) Bronchogenic lung cancer rate decreases
2) MM risk remains high

Conclusion: Asbestos exposure initiates MM

Asbestos exposure promotes bronchogenic lung cancer development initiated by other agents (e.g. smoking)

Paradoxical conclusions?
No- Bronchial Ca requires smoking

Public Health Intervention

Miner, factory worker, shipyard studies led to many studies in other asbestos manufacturing industries

⇓

Similar evidence of MM

⇓

U.S. EPA lists as Group A Chemical, i.e., "known human carcinogen"

⇓

Regulation- 1970's- prevent new products

1990's- abatement from thousands of public buildings, homes, & schools because of "friability exposure"

⇓

"New exposed groups?"

1) Removal workers
2) Inhabitants

After 1970's MM incidence has decreased dramatically
1990's case thought to reflect earlier exposure

In 1993 in U.S., MM was 5% of lung cancers not associated with cigarette smoking (≈ 100 cases)

Today total incidence ≈ 2000 cases per yr (≈ 0.7 per 100,000)

However, "background would be 0.1 per 100,000"

Asbestos-related disease is still prevalent in countries where it is mined w/o regulatory restrictions (e.g. South Africa)

However, in U.S. decline is <u>not</u> approaching <u>0.1 per 100,000</u>

Why?

1) Continued effective environmental exposure level?
    - -product breakdown (brake pads)
    - -continue manufacturing
    - -abatement exposure
    - -?

Asbestos Toxicology

Some understanding of toxic mechanisms, but basis for mesothelioma formation is unknown.

Rate of Exposure

Asbestos is inert in natural rock form.
Must create fine flakes or dust that can be inhaled.

$\Rightarrow$ risk in mining, milling, abatement, and with friability
$\Rightarrow$ safety device = respirator

However, dust & fibers go home on clothes of workers
$\Rightarrow$ self-exposure
family exposure
(10x increased risk of MM in women who live with asbestos workers)

Hazard depends on fiber size!

Length
2 μm $\rightarrow$ asbestosis
5 μm $\rightarrow$ mesothelioma, asbestosis
10 μm $\rightarrow$ bronchogenic lung cancers associated with cigarette smoking, asbestosis

Diameter
> 3 μm $\rightarrow$ no mesothelioma
< 0.5 μm $\rightarrow$ mesothelioma

Size explanations

Short- phagocytosed by alveolar *MØ*'s
carried out of lungs by mucous and cilia motion
⇒ only asbestosis

Long- may not reach lower airways
⇒**promotes** bronchogenic (in upper bronchioles) cancers initiated by other carcinogens?

Medium- phagocytosis by alveolar *MØ*'s incomplete
⇒lysis
cytokine release ⇒ cell proliferation
⇒fibrosis due to collagen production
MØ recruitment ⇒ reactive oxygen species (ROS) generation ⇒ DNA damage

How are cell proliferation and DNA damage accomplished outside the lung (pleura and peritoneum)?

1) Penetration of lung parenchyma into pleural space
   0.5 μm is sharp enough to pierce
2) Enter lymphatic system to spread to peritoneum
3) Why mesothelial cells?

Toxicology

The toxic effects of asbestos are not due to its chemical make-up, but its structural features- fibers

Chrysotile accounts for 90% of the world's asbestos production

5-10% amphiboles- rod forms associated w/ MM even when chrysotile is present

There is an association between MM & chrysotile when chrysotile is present at 400 times the lung burden of amosite

Reasons?

Chrysotile breaks down in humans much faster than amphiboles forms that persist for long periods

Animal Studies

Chrysotile much more potent inducer of MM than amphiboles fibers!

In rodents, amphiboles and chrysotile break down at similar rates

Other fibers (e.g. fiberglass) are carcinogens in rats, but not in humans

Fiber types may differ in ability to catalyze (surface properties) reactions between $Fe^2 + O_2$ to generate HOOH +
HO· ⇒ lipid peroxidation ⇒ fibrosis response
⇒ DNA damage ⇒ mutation ⇒ cancer?

Cell studies

Non-genotoxic or epigenetic chemical
"I.e., doesn't cause point mutations"

However: 1) clastogenic ⇒ chromosome aberration
due to mitotic spindle interaction?
2) carcinogenic: increased cell proliferation
⇒cell transformation in vitro

How?
Why mesothelial cell specific? Target access?
Not cell type-specific in in vitro studies though!

Synergistic Effects
1) Smoking
2) Arsenic in smelters <another non-genotoxic>

Have Cause-Effect criteria been met?
Sufficient?
Necessary?

Other Theories?

MM has long latency after exposure 20-40 years

Is it really the *cause*?

Also, 1) Only 10% of exposed develop MM
and
2) 20% of MM is not associated with a known exposure

The SV40 Theory

1955-1963 Introduction of polio vaccines & adeno vaccines
Some later found to be contaminated with SV40

1961- 80-90% of all US children vaccinated w/ potentially contaminated vaccines

98 million children **& adults *may*** have been exposed

Hamster studies- SV40 causes pleural mesotheliomas

Human tumor analysis-

European Consortium Study

83% of human MMs have SV40 DNA & T-antigen protein activity

But, Finnish tumor set- 0%!

Final Problems

1) Small Numbers
2) Exposure uncertainty

Talking to the Public about Asbestos

Abatement $\Rightarrow$ risk for exposure

So, why do we remove it?

Public perceptions-
1) can't see it
2) delayed effects
3) forced upon them, involuntary
4) feelings of dread
5) fatal outcome
6) unfair risk distribution (kids in school)