Lung Cancer: Risk from Smoking and Asbestos

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Epidemiology

The study of how a disease is distributed within a population and the factors that influence the distribution
Terminology: Incidence

Number of new cases that occur in a time period in a population at risk for developing the disease:

\[ I = \frac{\text{Number of new cases (per time)}}{\text{Population at risk}} \]


- 80/100,000 (males)
- 55/100,000 (females)
Epidemiology Process

☑ Determine if an association exists between an exposure or a characteristic and disease development

- Example: ↑Blood pressure & cardiac disease

☑ If association exists, infer and assess potential causal relationship

(attributes of causal relationships will not be discussed in this Webinar)
Epidemiology Study Types

Prospective studies: looking forward
- Evaluate outcomes during the study period

- Good for common diseases
- Measures disease incidence
- Drawback – time/money
Epidemiology Study Types

- Retrospective studies: looking back
  - Evaluate contribution of past exposures to current outcome

- Good for rare diseases
- Relatively inexpensive and fast assessment
- Subject to recall bias

<table>
<thead>
<tr>
<th>Exposure Status</th>
<th>Disease Status</th>
<th>Analysis &amp; Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated</td>
<td>Known</td>
<td>2014</td>
</tr>
</tbody>
</table>

hmmm, what was I doing 30 years ago?
# Study Strength

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Descriptive Studies</strong></td>
<td></td>
</tr>
<tr>
<td>Case</td>
<td>what clinicians see</td>
</tr>
<tr>
<td>Ecological</td>
<td>geographical comparisons</td>
</tr>
<tr>
<td>Cross sectional</td>
<td>survey, a snapshot in time</td>
</tr>
<tr>
<td><strong>Analytical Studies</strong></td>
<td></td>
</tr>
<tr>
<td>Case-control</td>
<td>compare people with and without a disease</td>
</tr>
<tr>
<td>Cohort</td>
<td>follow people over time to see who gets the disease</td>
</tr>
<tr>
<td>Randomized controlled trial (RCT)</td>
<td>the human experiment</td>
</tr>
</tbody>
</table>
Epidemiology Study Types

Cohort

- Exposed
  - Develops disease
  - Does not develop disease

- Not Exposed
  - Develops disease
  - Does not develop disease

Case/Control

- Exposed
  - Disease
  - Not exposed

- Not exposed
  - No Disease
  - Exposed
  - Not exposed
Terminology: Relative Risk

- Ratio of incidence in exposed population to the incidence in non-exposed population
  - calculated from cohort studies

\[
RR = \frac{\text{Incidence}_{\text{Exposed}}}{\text{Incidence}_{\text{Non-exposed}}}
\]
No Change in Risk

Exposed Group

Controls

\[
\text{Risk}_{\text{Exposure}} = \frac{2}{2} = 1
\]
Exposure Increases Risk

Exposed Group

Controls

Risk_{Exposure} = \frac{6}{2} = 3
Understanding “Risk”

These risk concepts apply to groups of people as opposed to any individual.

On average, 2 of 13 exposed get disease vs.

Risk of disease for an individual.
Lung Cancer

- Lung cancer: uncontrolled growth of abnormal cells in one or both lungs.

- Any specific individual either has cancer (100% disease risk) or does not have cancer (0% disease risk).
Lung Cancer Rates

- Approximately 399,431 Americans are living with lung cancer. (NIH 2010)
  - The majority of living lung cancer patients were diagnosed within the last five years.

2014 Estimates: (ACS)
- 224,210 new cases
  - 116,000 men;
  - 108,210 women
- 159,260 deaths
  - 86,930 men;
  - 72,330 women
Causes of Lung Cancer

- aluminum production
- arsenic and inorganic arsenic compounds
- asbestos (all forms)
- beryllium and beryllium compounds
- bis(chloromethyl)ether
- cadmium and cadmium compounds
- chloromethyl methyl ether (technical grade)
- chromium (VI) compounds
- coal gasification
- coal tar pitch
- coal, indoor emissions from household combustion
- coke production
- hematite mining (underground)
- iron and steel founding
- MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture) chemotherapy agent
- nickel compounds
- painting
- plutonium
- radiation (X and gamma)
- radon-222 and its decay products
- rubber production industry
- silica dust, crystalline
- soot
- sulfur mustard
- tobacco smoking
Smoking & Lung Cancer
Smoking & Lung Cancer

- Smoking is responsible for 94% of all lung cancer deaths in the USA (Jha 2013)

- Risk of lung cancer is 3- to 30-fold higher for smokers than non-smokers (USDHS 2004, Thun 2013)
Risk of lung cancer from smoking depends on

- intensity (amount smoked per day)
- duration
- age started
“Pack Years”

- Risk increases with increasing duration and intensity of smoking. (USDHS 2004, Thun 2013)
- Intensity and duration of smoking history are commonly combined and referred to as “pack-year”
  
  - Example:
    
    1 pack per day (ppd)  
    X 20 years duration  
    20 pk-yr
Quitting

- When smoking is stopped, lung cancer risk decreases.

- Former smokers are still at increased risk of death from lung cancer compared with non-smokers (USDHS 2004, Thun 2013)
Cigarette smoking is the primary cause of lung cancer
Asbestos & Lung Cancer
Asbestos & Lung Cancer

- Asbestos exposure may cause:
  - Mesothelioma
  - Asbestosis/Fibrosis
  - Lung Cancer

- Lung Cancer has been associated with asbestos exposure in heavily exposed groups of workers.
“Fiber Years”

- Asbestos concentrations:
  - fibers per milliliter (or cubic cm) of air (f/mL or f/cc)
  - f/cc

- Cumulative asbestos exposure:
  - fiber years = f/mL x years
  - f-yr
Asbestos Risk Variables

- Risk of disease (lung cancer) from asbestos depends on
  - intensity (fiber concentration)
  - duration
  - fiber type
Asbestos Exposure and Neoplasia

Irving J. Selikoff, MD, Jacob Churg, MD, and E. Cuyler Hammond, DSc, New York

Building trades insulation workers have relatively light, intermittent, exposure to asbestos. Of 632 insulation workers, who had been employed for 10 or more years, 34.2% had pleural plaques. Of 581 insulation and maintenance workers, who had been employed for 10 or more years, 30.9% had pleural plaques. Of 226 insulation and boiler workers, who had been employed for 10 or more years, 24.7% had pleural plaques.
Asbestos Exposures Decreased Dramatically
Plummeting Occupational Exposure Limits

ACGIH TLVs

OSHA PELs
Plummeting Exposures Matched Import Rates

- Highest asbestos exposures: pre-1970s

- Industrial concentrations decreased through reduced domestic use and strict regulatory limits
Asbestosis

- Diffuse interstitial lung fibrosis
- Caused by inhalation of asbestos fibers of respirable size
- Associated with exposures of >10 f-yr

Friedman 2006
Controversy:

- Is increased risk caused by heavy asbestos exposure?
- Is increased risk caused by asbestosis?
Asbestos, Lung Cancer, and Asbestosis

Controversy:

- Can lung cancer be attributed to asbestos exposure without asbestosis (lung fibrosis) or heavy asbestos exposure?
Risk of Lung Cancer in Asbestos Cohorts

Weight of evidence indicates

- Risk of lung cancer from asbestos exposure doubles for groups exposed to 25 – 100 f-yr

-or-

- Risk of lung cancer from asbestos exposure increases 0.01-0.04 per f-yr
Smoking + Asbestos
Smoking is a strong carcinogen

Risk = 1 + 0.282(pack year)

Examples

<table>
<thead>
<tr>
<th>Cumulative Smoking History</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 pk/day for 1 year</td>
<td>1 pk-yr</td>
</tr>
<tr>
<td>1 pk/day for 4 years</td>
<td>4 pk-yr</td>
</tr>
<tr>
<td>1 pk/day for 30 years</td>
<td>30 pk-yr</td>
</tr>
</tbody>
</table>
Lung Cancer Risk

Asbestos is a weaker carcinogen than smoking

Risk = 1 + 0.04(fiber year)

- Examples

<table>
<thead>
<tr>
<th>Cumulative Asbestos History</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 f-yr</td>
<td>1.04</td>
</tr>
<tr>
<td>4 f-yr</td>
<td>1.16</td>
</tr>
<tr>
<td>30 f-yr</td>
<td>2.20</td>
</tr>
</tbody>
</table>

What about smokers who worked with asbestos?
How can factors interact in causing disease?

- Additive
  - Total risk is the sum of individual risks

- Multiplicative (synergistic)
  - Total risk is individual risks multiplied together

Hypothetical data

<table>
<thead>
<tr>
<th>Risk (1)</th>
<th>Risk (2)</th>
<th>Interaction</th>
<th>Total Risk (1 and 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>7</td>
<td>Additive</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>Multiplicative</td>
<td>21</td>
</tr>
</tbody>
</table>
Lung Cancer Risk – Asbestos and Smoking

- **Early studies**
  - suggested risk of lung cancer in smoking asbestos workers was consistent with multiplying individual risks (*i.e.*, *suggested multiplicative*)

- **More recent studies**
  - show “multiplicative” relationships exist only for groups with heavy smoking histories and high asbestos exposure.
Early Studies

- Dose issues
  - Asbestos
    - Highly exposed groups
  - Smoking
    - Status varied by study but none include cumulative or “pack/yr” data
    - Potential for misclassification of former smoker as never smoker
      » *Important because smoking is the primary risk factor for lung cancer*
**Lung Cancer Risk—Early Studies**

- **Selikoff and Hammond, 1975**
  - Exposure began prior to 1922 through 1962

- **Hammond et al., 1979**
  - US & Canada union members, 1966

- **Meurman et al., 1994**
  - "Heavy" exposure worked in mines or in mill (1953-67)

- **Selikoff et al., 1980**
  - Twenty-yrs post exposure (1941-54)

- **Berry et al. 1985**
  - "Severe" exposure, Employment started 1933-55 (M), 1936-42 (F)
# Lung Cancer Risk – Early Studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Occupation</th>
<th>Occupational timeframe</th>
<th>Asbestos dose* (f-yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selikoff &amp; Hammond, 1975</td>
<td>Insulators</td>
<td>Began before 1922; Ended by 1962</td>
<td>135</td>
</tr>
<tr>
<td>Hammond et al., 1979</td>
<td>Insulators</td>
<td>Began before 1966; Ended by 1976</td>
<td>135</td>
</tr>
<tr>
<td>Meurman et al., 1994</td>
<td>Mine &amp; mill workers</td>
<td>1953-1967</td>
<td>270</td>
</tr>
<tr>
<td>Selikoff et al., 1980</td>
<td>Unibestos manufacturing</td>
<td>1941-1954</td>
<td>600</td>
</tr>
<tr>
<td>Berry et al. 1985</td>
<td>Factory workers</td>
<td>Began factory work between 1933-55 (men) 1936-42 (women)</td>
<td>195</td>
</tr>
<tr>
<td>Construction workers</td>
<td></td>
<td>Worked with asbestos 15 yrs 1986 – 2001</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Asbestos and Smoking Interaction

Then

Now
Cohorts consistent with those in the early studies no longer exist due to declining asbestos use and exposure regulations
Only one study evaluated combined risk using both cumulative smoking and asbestos exposures

- Case-control study from 8 Canadian provinces
- 1681 lung cancer cases (1994-1997)
  2053 controls
Smoking Parameters

- **Heavy Smoking History:**
  - 40 pk-yr
  - e.g. 1 pack per day for 40 years

- **Light Smoking History:**
  - <10 pk-yr
  - e.g. 0.5 packs per day for 20 years
Asbestos Parameters

- **High Exposure**
  - 25 f-yr
  - *e.g.*, 1950s career pipe lagger

- **Low Exposure**
  - 3 f-yr
  - *e.g.*, mid-1980s career construction worker

Villeneuve 2012
Interpreting Results

Risk associated with exposure reported as an “Odds Ratio”

\[
\frac{\text{Odds (disease with exposure)}}{\text{Odds (disease without exposure)}}
\]

Odds refresher:

\[
\text{Odds} = \frac{P \text{ (event occurs)}}{P \text{ (event does not occur)}} = \frac{60\%}{40\%} = 1.5
\]
Interpreting Results

- Reporting Results
  - Odds Ratio
  - Confidence Interval

- To Illustrate:
  - Value (low CI limit, high CI limit)
  - 1.8 (0.8, 1.6)
95% Confidence Interval

- The upper and lower bounds for the true value for the population
  - Larger confidence interval range for small groups or for groups with misclassified individuals
  - Statistically determined

Example
- OR = 6 (4, 8)
Interpretation of Results

- When 95% CI’s **do not** overlap:
  - groups **can** be classified as different
Interpretation of Results

- When 95% CI’s do overlap:
  - groups cannot be classified as different
Asbestos Exposure and Cigarette Smoking

<10 pack years

Villeneuve 2012
Asbestos Exposure and Cigarette Smoking

10 – <40 pack years

Villeneuve 2012

Odds Ratio

No Asbestos  Low Asbestos  High Asbestos
Asbestos Exposure and Heavy Cigarette Smoking

≥ 40 pack years

Villeneuve 2012
Asbestos Exposure and Cigarette Smoking

Asbestos exposure

Smoking history

- <10 pk yrs
- 10-<40 pk yrs
- >40 pk yrs

Odds Ratio

Villeneuve 2012
Asbestos Exposure and Cigarette Smoking

Villeneuve 2012

Odds Ratio

Asbestos exposure

Smoking history

<10 pk yrs

10-<40 pk yrs

>40 pk yrs
Risk attributable to asbestos in smokers is not substantial unless there is a high cumulative exposure to both asbestos and smoking.
Conclusions

- Cigarette smoking is the primary cause of lung cancer
- Multiplicative interaction between smoking and asbestos exposure (reported in early studies) was observed in heavy smokers with high asbestos exposure
- Cohorts consistent with those in the early studies no longer exist due to declining asbestos use and exposure regulations
- Risk attributable to asbestos in smokers is not substantial unless there is a high cumulative exposure to both asbestos and smoking
References


**No Safe Level / Linear No Threshold Model**

- Ignores the fundamental toxicological principle of dose – response

- Expert opinions based on this the No Safe Level have been rejected and excluded
  
  - “the linear non-threshold model cannot be falsified nor can it be validated. To the extent that it has been subjected to peer review and publication, it has been rejected by the overwhelming majority of the scientific community. It has no known or potential rate of error. It is merely a hypothesis.”

  - There is no scientific evidence that the linear no safe threshold analysis is an acceptable scientific technique used by experts in determining causation in an individual instance.

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Risk is not Causation


- "proof of risk and proof of causation entail somewhat different questions because risk assessment frequently calls for a cost benefit analysis…

Consequently risk assessors may pay heed to any evidence that points to a need for causation, rather than assess the likelihood that a causal relationship in a specific case is more likely than not.”

Berger M. Reference Manual on Scientific Evidence 33
(Federal Judicial Center 2d ed. 2000)
Regulatory Assessment

Substantial Difference in approach re Public Health Guidelines and determining whether a particular chemical caused or contributed to a particular disease or illness in a given person.

- The resulting regulatory levels generally overestimate potential Toxicity Levels for nearly all individuals.
- [the] Risk Utility analysis involves a much lower standard than that demanded by a court of law.

Eaton D, 12 L.J. & Pol’y 5

Rider v. Sandoz Pharm. Corp. 295 F.3d 1194 (11th Cir 2002)

- Unreliable Proof of Medical Causation
Every Breath You Take: The Any Exposure Theory

- Ignores
  - Potency of Fibers
  - Dose
  - Duration of Exposures

- Tautology
  - This theory is fundamentally inconsistent with substantial factor causation since the former obviates the latter by converting proof of the very smallest exposure into causation.
  - Renders Substantial Factor Test Meaningless

Martin v. Cincinnati Gas & Elec. Co.,
561 F3d 439 (6th Cir 2009)

Betz v. Pneumo Abex
615 Pa 504, 44 A.3d 37 (2012)

Anderson WL et al,
Causation

Toxicologists have reached a generally-accepted consensus on the methodology and criteria that must be taken into account in reaching any conclusions as to whether exposure to a chemical has caused an adverse effect to an individual. The following criteria must be met in order to establish that an adverse effect in an individual has been caused by exposure to a specific chemical.

1. The chemical(s) in question must first be present.

2. Toxicological and/or epidemiological studies must show that the chemical(s) in question are able to cause the claimed adverse effect.

3. Exposure of an individual(s) to the chemical(s) must be in sufficient quantities and length of time, and in a manner that can result in absorption into the body to cause the claimed adverse effect.

4. Exposure to the chemical(s) must precede the claimed adverse effect with an appropriate time frame specific to the individual chemical in which the development of the effect occurs.

5. If the above criteria are met then alternative known causes of the claimed adverse effect must be considered and weighed against the probability that the chemical(s) in question caused or contributed to the illness, disease, injury or adverse effect.
In a situation in which a preexisting condition is identical or very similar to the claimed injury, establishment of causation from a subsequent chemical exposure is virtually precluded. For example, if an individual has a history of preexisting asthma that is aggravated by physical, psychological, or chemical stimuli, then a claim that asthma has been caused by exposure to chemicals in the indoor environment or elsewhere is untenable.

Diagnostic opinions based on exclusion should be avoided, that is, “I don’t know how ‘A’ could have caused ‘B’ but I have no other explanation for ‘B’.” This type of unsupported statement may be “safe” for the practitioner and will avoid the professional embarrassment of simply stating “I don’t know,” but it surely does disservice to the objectivity of scientifically based medicine.

(Citations omitted.)
GENERAL CAUSATION

“is concerned with whether an agent increases the incidence of disease in a group and not whether the agent caused an individual’s disease.”

Has the toxic substance in question been demonstrated to cause the type of disease or illness in question.

McClain v. Metabolife Int’l Inc.
401 F.3d 1233 (11 Cir. 2005)

Rodricks, JV (2011),
Toxic Tort Case – Proof

A Plaintiff must demonstrate the levels of exposure that are hazardous to human beings generally as well as the Plaintiff’s actual level of exposure to the Defendant’s toxic substance.

Allen v. Penn. Eng’g Corp.
102 F.3d 194 (5th Cir. 1996)

McClain v. Metabolife Int’l Inc., supra, 401 F.3d 1233 (11 Cir. 2005)

Hendricksen, supra, 605 F. Supp. 2d 1142
Specific Causation

- Assumed general causation has been proven.
- Whether Plaintiff’s disease or illness was caused by the exposure to the chemical at issue.

Proof – Specific Causation

1. Was there an Exposure
2. Was the Plaintiff exposed to a sufficient amount of the substance to elicit the health effect in question
3. Was the dose and duration of exposure a sufficient quantity to cause the specific illness.


McClain, supra, 401 F.3d 1233

Hendricksen, supra, 605 F. Supp. 2d 1142
Importance of Dose – Asbestos-Related Diseases

- Asbestosis
- Lung Cancer
- Mesothelioma
Career – Drywall Contractor

- The Question framed was whether low doses of Chrysotile are known to cause Mesothelioma.

- The court Rejected Plaintiff Expert Opinions because none of the articles relied upon by Plaintiff’s experts actually identified what dose of Chrysotile asbestos would be required to cause Mesothelioma . . .

- See also: In Re Lockheed Litigation cases


- The court found the studies Plaintiff’s expert did do not support his opinions.

Borg-Warner v. Flores 232 S.W. 3d 765 (Tex 2007)
What dose of Chrysotile has been shown to cause lung cancer/Mesothelioma/Asbestosis

Absent proof of dose can Plaintiff prove that exposure attributed to Plaintiff – cause or contributing cause of disease

- How can existing epidemiology studies inform this argument.
- Is there sufficient case law and adequate science to permit the argument Plaintiff must show the exposure to Defendant’s asbestos in and of itself would have caused the disease.
Hypothetical:

Exposures to Chemical

- $\geq 100$ PPM –
  Shown to be capable of causing cancer
- Exposure to Chemical X at
  $\leq 5$ PPM shown to cause no adverse health effect
- At the lower dose chemical X is not capable of causing disease.
- Highlights importance of Epidemiology and Toxicology
Gatekeeper Role

- All Gatekeeper Cases on State and Federal Level inform discussion regarding Scientific Methodology to be employed in assessing reliability of the foundation of Expert Testimony –

- Purpose is to exclude speculative and, thus, irrelevant expert opinion
CONCLUSION

- General Causation – Epidemiology
- Specific Causation – Toxicology

Dose/Response

Fundamental considerations necessary to prove cause and effect.

Science – it’s the law.
Substantial Factor

- Exposure... was a substantial factor causing illness by showing through expert testimony that there was a reasonable medical probability that the exposure was a substantial factor contributing to his/her risk of developing cancer
Rutherford —

Says two things

1. Legal cause

   a) Plaintiff must establish some threshold exposure to the Defendant’s asbestos, and

   b) Must further establish to a reasonable degree of medical probability that a particular exposure or series of exposures was a legal cause of injury; that is, a substantial factor in bringing about the injury.

2. Risk

   Defendant’s asbestos was a substantial factor contributing to… [the] RISK of developing cancer

   - Risk is not Causation
   - Problem: every exposure theoretically increases risk of disease in some infinitesimal and unquantified increment.
   - This is a defacto every fiber counts theory / any exposure theory