Determining work-related causation in individual patients

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MARCOEM

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I have no conflict of interest in presenting this material.
Educational Objectives

At the conclusion of this session, you will be better able to:

1. Explain basic concepts of work-related causation
2. Recognize some common types of biases, non-causal associations, and epidemiologic/statistical misconceptions
3. Judge work-related causation in individual patients
Determining causation of illness in individual patients is important

 ICU patient with acute kidney injury while being treated for a life threatening multi-drug-resistant infection with a potentially nephrotoxic antibiotic.  
* The patient has had recent imaging with a potentially nephrotoxic contrast agent  
* Second line antibiotic is known to be much less effective.

Continue, change or stop the antibiotic? 

Forced to determine the cause of the kidney injury: antibiotic, contrast medium, both, something else?

Forced decision making under uncertainty, requiring determination of causation in individual patients
Determining WR causation of disease in individual patients is important

- Improve overall health of patient
  - Optimize treatment of some diseases
  - Prevent delays in correct medical diagnosis

- Prevention
  - Continue working safely, or safe return to work
  - Co-workers may be at risk from same exposures
  - Failure of prevention can create need for compensation

- Compensation for losses after WRI has already occurred
  - Workers’ Compensation
  - Tort Lawsuits
  - Prevention, if possible, is preferable to Compensation
Work-Related Injury or Illness

“You must consider an injury or illness to be work-related if an event or exposure in the work environment either caused or contributed to the resulting condition or significantly aggravated a pre-existing injury or illness.”

Source: OSHA Standard 1904.5
Causal Inference in Statistics
Pearl et al (2015)
What is a cause?

Statistical definition (Pearl)

“A variable X is a cause of a variable Y if Y in any way relies on X for its value.”

- Useful in artificial intelligence theory
- Tested thoroughly by computer simulations
- Applicable to individuals and groups
- Quite abstract and not very practical for medical decision making.
What is a cause?

Medical definition (AMA):

“There is causation only when one factor necessarily alters the probability of a second.”

- Simple and short but mathematically ambiguous
- Applicable to population studies but not individuals
- Smoking would be called a cause of lung cancer in a smoker who has not developed lung cancer
- Not very practical for occupational medicine decision making
What is a cause?

Medical definition (Ranavana):

“Causation refers to an association in which one condition precedes an outcome and must be present for the outcome to occur.”

- Short, simple but leads to logical inconsistencies and not useful for medical decision making
- In a population smoking would not be considered a cause of lung cancer because cases occur in nonsmokers
- In an individual who smokes, smoking would not be considered a cause of lung cancer in a smoker because the cancer could have occurred due to some cause other than smoking in that person (eg, radon or asbestos)
What is a cause?

Epidemiologic definition (Rothman):

“an event, condition or characteristic that preceded the disease onset and that, had the event, condition or characteristic been different in a specified way, the disease either would not have occurred or would have occurred at a later time.”

- Applicable to the cause of a specific disease occurrence in a single individual and in populations
- Explicitly considers time of occurrence
- Mathematically more precise and is more useful for medical decision making than the other definitions
Population and Individual level determination of causation of Work-Related Diseases

Population level (general or type causation): Can the work exposure cause the disease in question?
- Can working with asbestos cause lung cancer?

Individual level (specific or token causation): Did the exposure cause the disease in this patient?
- Did working with asbestos cause Mr. X’s lung cancer?
Some examples of diseases that can be WR

- Mesothelioma
- Sensorineural hearing loss
- Lung cancer
- Asthma
- COPD
- Pulmonary fibrosis
- Carpal Tunnel Syndrome
- Hypertension
Determining Work-Related (WR) Causation in Individual Patients

- Importance of accurate determination of WR causation in individual patients
- Types of causation scenarios common in individual occupational medicine patients
- Current approaches to causation analysis
- Recent scientific developments relevant to determination of WR causation in individuals
- Suggestions to help improve our ability to determine WR causation in individual patients
Accuracy of determination of WR causation is important

- Diagnostic accuracy is fundamental to high quality medical and surgical practice
- Diagnostic errors are most common, costly and dangerous category of medical mistakes
- In OM we have an additional diagnostic dimension: determination of WR causation
- Errors in determining WR causation can harm patients, families, employers and other parties
Accuracy of determination of WR causation

<table>
<thead>
<tr>
<th>“Truth” Determination</th>
<th>WR Causation</th>
<th>Not WR Causation</th>
</tr>
</thead>
<tbody>
<tr>
<td>WR by Clinical Eval</td>
<td>TP</td>
<td>FP</td>
</tr>
<tr>
<td>Not WR by Clinical Eval</td>
<td>FN</td>
<td>TN</td>
</tr>
</tbody>
</table>
Harm from FP determination of WR causation in a patient

- Elimination of job exposures that are in fact not related to the patient’s illness will not improve the illness
- Absences, change or loss of job or profession, demotion, lost productivity harm worker, family, employer
- Filing of Workers’ Comp case that may be established inappropriately or may be delayed for years and denied
- Third party medical insurance carriers sometimes deny future coverage for that condition during controversy
- Delay or loss of access to medical care for that condition
- Delay or failure to make the correct medical diagnosis can delay medical treatment of the correct illness
Harm from FN determination of WR causation in a patient

- Non-financial and financial costs
- Delay or complete failure to identify and correctly treat the WR disease or injury
- Disease worsening with continued causal exposure
- Can jeopardize safe return to work after med leave
- Frequent or long absences from work due to incompletely treated disease of unclear etiology
- Job loss and periods of unemployment, generally accompanied by consequent psychosocial effects
Harm from FN determination of WR causation in a patient

- Lack of WC benefits can cause severe financial problems
  - Poverty
  - Family relationship difficulties
  - Loss of home

- Cost shifting of costs from WC / employer to
  - Worker/patient and family
  - Private med insurance carrier, Medicaid, Medicare
  - Unemployment and disability insurance
  - Loss of incentive to abate the hazards can lead to higher risk of WR injuries and illnesses for others
Improving accuracy of determination of WR causation

- Probabilities of FP and FN determinations may be unnecessarily high and can often be reduced
  - Incomplete clinical and exposure evaluations
  - Misinterpretation of available research results
- Could reduce probabilities of both FN and FP simultaneously by improving the quality of components of the determination of WR causation
- How to do this?
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WR causation scenarios common in individual Occ Med patients

- Single event “obvious” cause with no other plausible competing or contributing causes
- WR cause being evaluated plus one plausible contributing or competing cause
- WR cause being evaluated plus one plausible competing (not contributing) cause
- Repeated WR exposure episodes associated in time with repeated illness episodes
Single event “obvious” cause, no other plausible competing or contributing causes

- Box falls on warehouse worker, she falls on outstretched arm and fractures clavicle
- New onset asthma same day as high level exposure to strong respiratory irritant (RADS)
- Mesothelioma in sheet metal worker 40 years after job with 10 years asbestos exposure
- Acute hepatitis C infection in HCW 3 months after needlestick, unknown source pt HCV
WR exposure plus one plausible contributing or competing cause

- Lung cancer in smoking asbestos worker
- COPD in cadmium fume exposed worker who smokes cigarettes
- CTS in diabetic worker who does forceful repetitive grasping motions on assembly line
- HTN in chronically lead exposed bridge repainting worker with FH of HTN
WR exposure plus one plausible competing (not contributing) cause

- Recurrent abdominal pain caused either by gastritis or by lead poisoning, not both
- New back pain caused either by workplace injury or motor vehicle crash injury
Repeated WR exposure episodes associated in time with repeated illness episodes

New onset asthma in auto body shop worker with asthma attacks on most days or nights after using spray paint containing hexamethylene diisocyanate (HDI) but rarely has asthma symptoms on days off

Progressive sensorineural hearing loss in musician who plays frequently in local clubs, with tinnitus and worse hearing loss the night and next day after most gigs
Different approaches needed for different occupational diseases

- Immediate cause/effect: may be “obvious” but clinical judgment is still often needed
  - Slip & fall
  - Instantaneous lifting injury that happened at work
- Short latency with WR reversible symptom pattern and physiology. Also may require clinical judgment if high quality diagnostic testing is not available or achievable.
  - WRA
  - Acute EAA/HP
  - Mechanical LBP
- Toxicologic syndrome with validated biomarkers. Also requires clinical judgment, epidemiology
  - Pb, Hg
  - A few acute solvent-related CNS illnesses..
Different approaches needed for different occupational diseases

- Specific recognizable patterns on imaging, combined with history, clinical judgment, and sometimes histologic confirmation
  - Asbestosis
  - Silicosis
  - Diacetyl-induced obliterative bronchiolitis
  - Chronic EAA/HP

- Immunologic, also requires clinical judgment
  - EAA (HP) with positive IgG precipitins
  - SIOA with positive ICT or WCT or SPT
  - Allergic contact dermatitis with positive patch test

- Tendinitides and back pain with ergonomic/biomechanical exposure, also require clinical judgment, epidemiologic knowledge
  - Lateral epicondylitis
  - Trigger finger
  - Chronic rotator cuff injuries
  - Low back pain
Different approaches needed for different occupational diseases

- Multicausal chronic disease requiring epidemiologic, exposure assessment, clinical judgment
  - Occupational cancers (IARC/NTP)
  - Occ COPD/Vapors Gases Dusts Fumes
  - Occ CTS
  - WRA in unemployed workers

- Presumption of causation legislatively mandated for specific diagnoses among members of groups with similar exposures based on epidemiologic, exposure, other criteria
  - Firefighters
  - WTC responders
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NIOSH 6 step approach to decision making (1979)

Consideration of:

1) Evidence of disease
2) Epidemiologic data
3) Evidence of individual exposure
4) Validity of testimony
5) Other relevant factors and finally,
6) Evaluation of these 5 steps and conclusion

Two phases of Causation Analysis

- **Provisional (Initial) on first visit**
  - Used to initiate treatment, file for Workers’ Comp
  - Often based on incomplete information that is immediately available

- **Definitive (Confirmatory) after gathering all available information**
  - Utilizes all information gathered eg, individual exposures, medical work-up, review of epi literature

Central role of Probability of Causation in deciding if WR Causation is more likely than not
Definition of the “disease” may be complex or still evolving

Source: UpToDate September 2019 Meilan King Han et al. COPD definition, clinical manifestations, diagnosis and staging
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Scientific developments in 1965-1980s relevant to determining WR causation in individuals

- 1965 Hill contributions to causal inference in landmark paper
- 1965 Mackie: Insufficient but Necessary components of an Unnecessary but Sufficient cause (INUS)
- Rothman develops INUS into Sufficient Component Cause model, improves understanding of multiple competing and contributing causes of disease
- Improvements in observational epidemiology including deeper understanding of confounding, selection bias and measurement error
- Robins/Greenland identified important mathematical flaws in use of epidemiologic data to estimate Probability of Causation
- Improvements in exposure assessment methods
Scientific developments in 1990s-present relevant to determining WR causation in individuals

- Recognition of strengths and limitations of randomized controlled trials for causal inference
- Improved understanding of study design, p-values, confidence intervals, hypothesis testing, parameter estimation and interpretation of epidemiologic results
- Expert panels integrate research results from epidemiology, toxicology, exposure assessment and more accurately identify carcinogens and other toxicants (IARC, NTP)
- Development of Directed Acyclic Graphs (DAGs) to aid in epi study design, analysis and interpretation
Did asbestos cause Lung CA in a smoking asbestos worker?

- 76 year old man, Mr. A.S., current 40 PY smoker with intractable nonproductive cough for 3 months, 10 lb unintentional weight loss, recent hemoptysis
- 13 year history of asbestos insulation work, ending 1973
- Chest CT, PET scan and bronchoscopic biopsy: metastatic lung cancer
In the simplest possible model, 4 ways Mr. A.S. could get LC:

- SC1, SC2, SC3, SC4 are 4 distinct Sufficient Causes of lung cancer LC. Any one of these could occur in Mr. A.S.
- Each SC is a set of Component Causes that, if and when it is completed, would be sufficient to cause LC in Mr. A.S.
- Each Sufficient Cause includes all the Component Causes necessary to complete that particular SC mechanism.
- Some are known (e.g., Smoking SMK) others unmeasured U.
Rothman (1976) “Pie Model” of Sufficient Component Causes

SC1

U1

LC can occur in nonsmokers with no asbestos exposure by genetic and environmental mechanisms we can call SC1.

Mr. A.S. could get LC by this mechanism SC1 with no contribution from his smoking SMK or asbestos ASB exposures.

U1 is shorthand for an Unmeasured set of genetic, epigenetic and environmental Component Causes that are sufficient to cause LC in Mr. A.S. without involving either ASB or SMK.
Rothman (1976) “Pie Model” of Sufficient Component Causes

SC2

- SC2 is a different sufficient cause that requires Component Cause ASB and Component Causes U2
- U2 is different from U1, does not include ASB or SMK
- Both U2 and ASB are necessary to complete SC2 and cause LC
- LC will not occur with ASB without U2
By itself the CC Smoking is insufficient to cause LC without other CCs U3 that are unmeasured and may be unknown.

The CC U3 might include unmeasured factors such as:

- RAS oncogene or other genetic factors
- Downregulation of tumor suppressor microRNA let-7 that targets RAS oncogene, or other epigenetic factors
- Adequate latency period for clinical manifestation of the LC
Rothman (1976) “Pie Model” of Sufficient Component Causes

- SC4 requires both ASB and SMK as necessary Component Causes, plus unmeasured Component Causes U4
- Likewise, U4 includes the factors necessary to cause LC when combined with both ASB and SMK
- SC4 might involve ASB damaging pulmonary macrophages, which then are effective eliminating carcinogens from SMK
Rothman (1976) “Pie Model” of Sufficient Component Causes

- SC1
  - U1

- SC2
  - U2
  - ASB

- SC3
  - U3
  - SMK

- SC4
  - U4
  - ASB
  - SMK

So his LC could have been caused by SC4 requiring both ASB and SMK, by SC3 requiring SMK but not ASB, by SC2 requiring ASB but not SMK or by SC1 which requires neither SMK or ASB.

A particular SC can be completely prevented by preventing any one or more of its Component Causes.

SC3 and SC4 would both be prevented by preventing SMK.

SC2 and SC4 would both be prevented by preventing ASB.
Rothman (1976) “Pie Model” of Sufficient Component Causes

- Sufficient causes SC1, SC2, SC3 and SC4 are competing (mutually exclusive) causes.
- Only one happens in Mr. A.S., we don’t know which one.
- Component causes U2 and ASB are insufficient, necessary components of the unnecessary sufficient cause SC2.
- Likewise, U4, ASB and SMK are INUS Component Causes of SC4.
- INUS Component Causes are contributing causes in Mr. A.S.
# Asbestos, Smoking, and Lung Cancer, Insulators vs Blue Collar Cohort (Markowitz 2013)

## Table 2. Age-Adjusted Lung Cancer Mortality Rate Ratios, by Smoking, Asbestos, and Asbestosis Status, Insulators versus Cancer Prevention Study II Blue Collar Cohort, 1981–2008

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of People</th>
<th>No. of Lung Cancer Deaths</th>
<th>No. of Person-Years</th>
<th>No. Lung Cancer Deaths/Person-Years × 10^4</th>
<th>Rate Ratio</th>
<th>Poisson Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPSE II (n = 54,243) vs all insulators (n = 2,377)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS II, nonsmokers</td>
<td>18,843</td>
<td>151</td>
<td>377,396</td>
<td>4.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Insulators, nonsmokers</td>
<td>468</td>
<td>18</td>
<td>8,706</td>
<td>20.68</td>
<td>5.17</td>
<td>5.20</td>
</tr>
<tr>
<td>CPS II, smokers</td>
<td>35,400</td>
<td>2,540</td>
<td>652,533</td>
<td>38.93</td>
<td>9.73</td>
<td>10.31</td>
</tr>
<tr>
<td>Insulators, smokers</td>
<td>1,909</td>
<td>321</td>
<td>29,950</td>
<td>107.18</td>
<td>26.79</td>
<td>28.36</td>
</tr>
<tr>
<td><strong>CPSSII (n = 54,243) vs. insulators without asbestosis (n = 918)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPS II, nonsmokers</td>
<td>18,843</td>
<td>151</td>
<td>377,396</td>
<td>4.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Insulators without asbestosis, nonsmokers</td>
<td>253</td>
<td>7</td>
<td>5,205</td>
<td>13.45</td>
<td>3.36</td>
<td>3.55</td>
</tr>
<tr>
<td>CPS II smokers</td>
<td>35,400</td>
<td>2,540</td>
<td>652,533</td>
<td>38.93</td>
<td>9.73</td>
<td>10.31</td>
</tr>
<tr>
<td>Insulators without asbestosis, smokers</td>
<td>665</td>
<td>62</td>
<td>12,057</td>
<td>51.42</td>
<td>12.85</td>
<td>14.44</td>
</tr>
<tr>
<td><strong>CPSS II (n = 54,243) vs. insulators with asbestosis (n = 1,459)</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>CPS II, nonsmokers</td>
<td>18,843</td>
<td>151</td>
<td>377,396</td>
<td>4.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Insulators with asbestosis, nonsmokers</td>
<td>215</td>
<td>11</td>
<td>3,501</td>
<td>31.42</td>
<td>7.85</td>
<td>7.40</td>
</tr>
<tr>
<td>CPS II, smokers</td>
<td>35,400</td>
<td>2,540</td>
<td>652,533</td>
<td>38.93</td>
<td>9.73</td>
<td>10.29</td>
</tr>
<tr>
<td>Insulators with asbestosis, smokers</td>
<td>1,244</td>
<td>259</td>
<td>17,893</td>
<td>144.75</td>
<td>36.18</td>
<td>36.79</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: CI = confidence interval; CPS II = Cancer Prevention Study II.*
## Lung Cancers by ASB and SMK exposure status (Markowitz, 2013)

<table>
<thead>
<tr>
<th></th>
<th>NoA NoS</th>
<th>A NoS</th>
<th>NoA S</th>
<th>ASB SMK</th>
</tr>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>18,843</td>
<td>468</td>
<td>35,400</td>
<td>1,909</td>
</tr>
<tr>
<td><strong>LC cases</strong></td>
<td>151</td>
<td>18</td>
<td>2,540</td>
<td>321</td>
</tr>
<tr>
<td><strong>Person Yr</strong></td>
<td>377,396</td>
<td>8,706</td>
<td>652,533</td>
<td>29,950</td>
</tr>
<tr>
<td><strong>LC/10^4 PY</strong></td>
<td>4</td>
<td>21</td>
<td>39</td>
<td>107</td>
</tr>
<tr>
<td><strong>Excess</strong></td>
<td>0</td>
<td>17</td>
<td>35</td>
<td>51</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td>1</td>
<td>5.2</td>
<td>9.8</td>
<td>27</td>
</tr>
</tbody>
</table>
Lung Cancers by ASB and SMK exposure status (Markowitz, 2013)

- For a group of 10,000 NoA NoS workers followed for one year, 4 LC occur.
- For a group of 10,000 A NoS workers followed for one year, 21 LC occur, including 4 that would have gotten LC without ASB and 17 excess cases that got it due to ASB.
- For a group of 10,000 NoA S workers followed for one year, 39 LC occur, 4 would have gotten it without SMK and 35 excess due to SMK.
Lung Cancers by ASB and SMK exposure status (Markowitz, 2013)

- For a group of 10,000 A S workers followed for one year, 107 LC occur
  - 4 would have gotten it without ASB or SMK
  - 17 got it due to ASB only, these could have been prevented by preventing ASB
  - 35 due to SMK only, these could have been prevented by preventing SMK
  - 107-4-17-35 = 51 excess cases due to joint effect of ASB and SMK not including the 17 ASB alone or the 35 SMK alone

- These 51 LC could have been prevented by preventing either ASB or SMK in that group

- 17+51=68 of the 107 LC cases could have been prevented by preventing ASB
- 35+51=86 of the 107 LC cases could have been prevented by preventing SMK
Recognition of common misinterpretation of p-value

“the p-value is the conditional probability of the null hypothesis being correct”

“the p-value measures how likely it is that the null hypothesis is correct.”

“Biostatistics can never establish exact cause and effect but gives the probability (eg, p ≤ 0.05) that A contributed to B.”

“Most medical studies refer to results as statistically significant when there is a less than 5% chance that a given result could have resulted from random variation (results indicated as p < 0.05)...”
Definition of p-value for test of the null hypothesis

A p-value is the probability that, assuming the null hypothesis is true, the underlying statistical model is correct, and the study is free of bias and confounding, the test statistic would have deviated from its null value by as much or more than the observed deviation due to random variation.
P-Value is not the probability the null hypothesis is correct

A single simple counterexample proves this.
Say we flip a “fair” coin 4 times, get 4 heads.
“Fair” means probability of heads is ½ so we know the probability the null hypothesis is true is 100%.
We know coins are fair from mechanistic information and centuries of experience.
The probability of all 4 flips being heads, assuming the null hypothesis, is \( \left(\frac{1}{2}\right)^4 = 1/16 = 6\% \).
So \( p(\text{one-sided}) = \text{probability of 4 heads} = 6\% \).
\( p(\text{2-sided}) = \text{prob of 4 heads or 4 tails} = 12\% \).
So \( p \) is clearly not a measure of the probability that the null hypothesis is true, which is 100%.
Statistics Textbook Author’s Erratum statement in blog, 2017


Andrew Gelman, PhD, Higgins Professor of Statistics, Columbia University
Recent recommendations to place less emphasis on p-values and statistical significance

“Control of Confounding and Reporting of Results in Causal Inference Studies: Guidance for Authors from (48) Editors of Respiratory, Sleep and Critical Care Journals”. Lederer, et al. Annals ATS 2019: Quote from Table 1

Key Principle #2: Interpretation of results should not rely on the magnitude of P values

- P values should rarely be presented in isolation
- Present effect estimates and measures of variability with or without P values
- Variability around effect estimates should inform conclusions
- A conclusion of “no association” should require exclusion of meaningful effect sizes
- Avoid the word “significant” in favor of more specific language.
More likely than not Criterion

Bradford Hill’s fundamental question,

“Is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”

Bradford-Hill, 1965, p. 299
“More Likely Than Not” Criterion and Probability of Causation

Probability of Causation (PC) is defined as the probability that occupation causally contributed to development of the patient’s disease (Greenland & Robins, Jurimetrics, 2000).

“More likely than not” implies that PC>50%.

AMA Guides recommend using Relative Risk (RR) to estimate the incidence Rate Fraction (RF), then using RF as an estimate of PC. (p. 117)

\[ RF = \frac{(RR-1)}{RR} \]

This formula implies algebraically that when RR>2 then RF>50% and when RR<2 then RF<50%.
“More Likely Than Not” Criterion and Probability of Causation

- Greenland and Robins have shown that, under most real life conditions, RF is a lower limit of PC, not equal to PC.
- So RR>2 implies PC >50%, but RR<2 DOES NOT imply that PC<50%, unless strong assumptions are true.
- If the causal effect includes acceleration of the disease development, even if RR is much less than 2, PC can be greater than 50%, even up to 100%. (Cox, 1984; Robins, 1989; Greenland, 2000)
- In addition, all calculations of PC assume a biologic model and different biological models can give very different PCs with the same epidemiologic data.
Assumptions needed for PC to equal RF


1. Risk measure is judged to be causal, **statistically unbiased and there is no confounding** (General Causation is accepted).

2. Patient in question is similar to study subjects, with regard to all measured and unmeasured risk factors for the disease.

3. **Exposure does not accelerate development of disease** that would have occurred later in patient’s lifetime if unexposed.

4. Agent operates Independent Of Baseline risk of disease (IOB), ie, **adds the same absolute risk** to each subject’s risk regardless of baseline (unexposed) risk that varies with other risk factors.

5. Agent of interest does not cause any fatal diseases other than the disease of interest.

6. Exposure is never preventive in any individual.
“More Likely Than Not” Criterion and Probability of Causation

Neither the assumption of no acceleration nor that of Independence of Baseline Risk and exposure effect can be tested epidemiologically.

Both these assumptions are unlikely to be true, and both require support from biological models or mechanistic information.
NIOSH Probability of Causation Calculator for Nuclear Workers

- Calculates PC of various cancers for workers exposed to external low-LET ionizing radiation
- All workers wore personal ionizing radiation dosimeters every work day
- Uses EF = (RR-1)/RR with RR calculated from cumulative dose of ionizing radiation
- NCRP committee recommended to change terminology “Probability of Causation” to “Assigned Share” to avoid implying erroneously that EF equals PC
- Acknowledged the downward bias in PC as estimated by EF
- Instead, for “more likely than not” decisions, replaced EF>50% with upper 99% CI bound of EF> 50%
- This countervailing upward bias in EF believed to consistently be greater than the downward bias and favor the claimant
Updated Hill’s Criteria for evaluating epi evidence of causal association

a. Temporality
b. Strength of association
c. Dose–response
d. Consistency
e. Coherence
f. Specificity
g. Plausibility
h. Reversibility
i. Prevention/Elimination
j. Experiment
k. Predictive Performance
Sir Austin Bradford Hill warned against developing “Causal Criteria”

From Bradford Hill, 1965, p. 299,

“Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe - and this has been suggested - is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect.”
Pearl (2009): Need for expert judgment in causal inference

“Behind every causal claim there must lie some causal assumption that is not discernable from the joint distribution and, hence, not testable in observational studies. Such assumptions are usually provided by humans, resting on expert judgment.”

Pearl, Causality p. 40, 2009
Inference to the Best Explanation, at both population and individual levels

- Lipton, 2004, p. 58, “The best of the available potential explanations is an actual explanation”

- “Better” explanations explain
  - more types of phenomena
  - with greater precision
  - provide more information about underlying mechanisms
  - unify apparently disparate phenomena, or
  - simplify our overall picture of the world.

(Lipton, Encyclopedia.com, 2005)

- When used as viewpoints rather than checklist type criteria, Hill’s viewpoints have been interpreted to be similar to IBE (Ward, 2009)
Directed Acyclic Graphs (DAGs)

Recently developed tool to help epidemiologic design of causal association studies, choice of variables for statistical control (or not), interpretation of epi studies and causal inference
Confounding (backdoor path)  
Common cause of E and D

Source: Lederer et al, 2019
Mediation: indirect causal path or Intermediate variable on causal path

Source: Lederer et al, 2019
Collider: Common Effect of E and D Control can cause Collider Bias

Source: Lederer et al, 2019
M-Bias

Source: Lederer et al, 2019
Illustrative DAG for study of whether Personal Smoking causes Adult Asthma

Research Doldrums: NIOSH funds few new R01s

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Source: https://www.cdc.gov/niosh/oep/fundingsummary.html
Determining Work-Related (WR) Causation in Individual Patients

- Importance of accurate determination of WR causation in individual patients
- WR causation scenarios common in individual occupational medicine patients
- Current approaches to causation analysis
- Recent scientific developments relevant to determination of WR causation in individuals

Suggestions to help improve our ability to determine WR causation in individual patients
Suggestions to improve determination of WR causation in individual patients

- Strive to reduce FP and FN determinations of WR causation
- Different approaches for different WR diseases
- Improve clinicians’ understanding of modern tools to aid determinations of WR causation in individuals
- Better methods for exposure assessment that do not rely on employer controlling access to workplace for industrial hygienist or ergonomist (eg, job exposure matrices, validated exposure biomarkers for more toxicants)
- Recognize the ongoing need for clinical judgment in determination of WR causation
- Fund more OM research that supports causal inferences
- Improvement of prevention of WR illnesses and injuries offers a way to avoid the difficulties, costs and errors inherent in determining WR causation in individuals
MOC Question 3: Multiple Potential Causes

If the lung cancer RR among nonsmokers is 3 for asbestos insulation workers compared with non-asbestos exposed workers, and the lung cancer RR among non-asbestos exposed workers is 10 for smokers compared with nonsmokers, which of the following is the best answer?

a) Most cases of lung cancer among asbestos workers who smoke could be prevented by preventing smoking.

b) Most cases of lung cancer among asbestos workers who smoke could be prevented by preventing asbestos exposure.

c) a and b are both true.

d) a and b are both false.