Epidemiology approach to association and causation

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Outline

1. The concept of causation
2. Historical development of theories of causation
3. General model of causation
4. From association to causation
Definition of *cause*

- “Something that brings about an effect or a result” (Webster’s new collegiate dictionary)
Problem:
How do we know when something makes a difference?

• Association is not equal to causation

• Consider the following statement:
  – *If the rooster crows at the break of dawn, then the rooster caused the sun to rise.*
Causation in Medical Textbooks

• In medical textbooks, cause is usually discussed under such headings as:
  – “etiology”
  – “pathogenesis”
  – “mechanisms” or
  – “risk factors”
The Importance of Cause

• Cause is important to practicing physicians primarily in guiding their approach to three clinical tasks:
  – prevention,
  – diagnosis, and
  – treatment
Historical Development of Theories of Causation

1. **Divine retribution**: Imbalance in body humors caused by air, water, land, stars; spontaneous generation

2. **Miasma**: Disease transmitted by miasmas or clouds clinging to earth’s surface
Historical Development of Theories of Causation

3. Germ Theory of Disease and Henle-Koch Postulates:

Most important postulate is that the microorganism must always be found with the disease. This postulate embodies the idea of specificity of a cause. That is, a one to one relationship between an exposure and a disease.
Historical Development of Theories of Causation

4. Web of Causation

A paradigm for the causes of chronic diseases. Most important shift from Henle-Koch Postulates is the idea of multiple causes. Postulates were also revised for establishing causation in chronic diseases.
Historical Development of Theories of Causation

5. Recent Controversies

Causation cannot be established. Causal criteria should be abandoned. Has anyone seen the spider that produced the web?
General Model of Causation (Causal Pies)
By KJ Rothman

Sufficient cause:
• A set of conditions without any one of which the disease would not have occurred. (This is one whole pie).
Component cause:

• Any one of the set of conditions which are necessary for the completion of a sufficient cause (This is a piece of the pie).
General Model of Causation
(Causal Pies)
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Necessary cause:

• A component cause that is a member of every sufficient cause.
This illustration shows a disease that has 3 sufficient causal complexes, each having 5 component causes. A is a necessary cause since it appears as a member of each sufficient cause. B, C, and F are not necessary causes since they fail to appear in all 3 sufficient causes.
Attributes of the causal pie

1. Completion of a sufficient cause is synonymous with occurrence (although not necessarily diagnosis) of disease.

2. Component causes can act far apart in time.
Attributes of the causal pie (cont’d)

3. A component cause can involve the presence of a causative exposure or the lack of a preventive exposure.

4. Blocking the action of any component cause prevents the completion of the sufficient cause and therefore prevents the disease by that pathway.
From Association to Causation: Deriving Inferences from Epidemiologic Studies

Figure 14-1. A, Do we observe an association between exposure and disease? B, Is the observed association between exposure and disease causal?
Figure 14-2. A frequent sequence of studies in human populations.
Figure 14-3. Another example of association or causation. (DILBERT © 2011 Scott Adams. Used by permission of UNIVERSAL UCLICK. All rights reserved.)
Figure 14-4. Types of associations.
Figure 14-5. Interpreting an observed association between increased coffee drinking and increased risk of pancreatic cancer.
Figure 14-6. Interpreting an observed association between increased cholesterol level and increased risk of coronary heart disease (CHD).
Smoking and low birth weight

• For many years it has been known that cigarette smoking by pregnant women is associated with low birth weight in their infants.
Cigarette smoking by pregnant women is associated with low birth weight in their infants. The effect is not just the result of the birth of a few low-birth-weight babies in this group of women. Rather, the entire weight distribution curve is shifted to the left in the babies born to smokers.
The babies of smokers are smaller than those of nonsmokers at each gestational age.
A dose-response relationship is also seen. The more a woman smokes, the greater her risk of having a low-birth-weight baby.
Smoking and low birth weight

• A comparison of smokers and nonsmokers shows that the two differ markedly along many environmental, behavioral and biologic variables.

• In view of these many differences between smokers and nonsmokers, Yerushalmy believed that it was not the smoking that caused the low birth weight, but rather that the low weight was attributable to other characteristics of the smokers.
On the basis of these data, Yerushalmy came to the conclusion that it was not the smoking but rather some characteristic of the smoker that caused the low birth weight.
Smoking and low birth weight

• Today, however, it is virtually universally accepted that smoking is a cause of low birth weight.

• The causal nature of this relation has also been demonstrated in randomized trials that have reduced the frequency of low birth weight by initiating programs for smoking cessation in pregnant women.
Figure 14-11. Direct versus indirect causes of disease.
Figure 14-12. Types of causal relationships: I. Factor A is both necessary and sufficient.
Figure 14-13. Types of causal relationships: II. Each factor is necessary, but not sufficient.
Figure 14-14. Types of causal relationships: III. Each factor is sufficient, but not necessary.
Figure 14-15. Types of causal relationships: IV. Each factor is neither sufficient nor necessary.
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<th>TABLE 14-1. <strong>Guidelines for Judging Whether an Observed Association Is Causal</strong></th>
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The pattern of a rise in particle concentration followed by a rise in mortality and a subsequent decline in particle concentration followed by a decline in mortality strongly supported the increase in mortality being due to the increase in air pollution.
Figure 14-17 shows an example of the dose-response relationship for cigarette smoking and lung cancer. If a dose-response relationship is present, it is strong evidence for a causal relationship.
Figure 14-18. Effects of terminating exposure: lung cancer death rates, standardized for age and amount smoked, among men continuing to smoke cigarettes and men who gave up smoking for different periods. The corresponding rate for nonsmokers was 0.07 per 1,000. (Adapted from Doll R, Hill AB: Mortality in relation to smoking: Ten years’ observations of British doctors. BMJ 1:1399–1410, 1964.)

If a factor is a cause of a disease, we would expect the risk of the disease to decline when exposure to the factor is reduced or eliminated.
Eosinophilia-myalgia syndrome (EMS) reached epidemic proportions in 1989. Characterized by severe muscle pain and a high blood eosinophil count, the syndrome was found to be associated with manufactured preparations of L-tryptophan. In November 1989, a nationwide recall by the Food and Drug Administration of over-the-counter preparations of L-tryptophan was followed by dramatic reductions in numbers of cases of EMS reported each month.
If a relationship is causal, we would expect the findings to be consistent with other data. For example, Figure 14-20 shows data regarding lung cancer rates in men and women and cigarette smoking in men and women.
DERIVING CAUSAL INFERENCES:

Peptic Ulcers and Gastric Cancer in Relation to Infection with *Helicobacter pylori*
1. Temporal relationship

• *Helicobacter pylori* is clearly linked to chronic gastritis. About 11% of chronic gastritis patients will go on to have duodenal ulcers over a 10-year period.

• In one study of 454 patients who underwent endoscopy 10 years earlier, 34 of 321 patients who had been positive for *Helicobacter pylori* (11%) had duodenal ulcer compared with 1 of 133 *Helicobacter pylori*–negative patients (0.8%).
2. Strength of the association

- *Helicobacter pylori* is found in at least 90% of patients with duodenal ulcer. In at least one population reported to lack duodenal ulcers, a northern Australian aboriginal tribe that is isolated from other people, it has never been found.
3. Dose-response relationship

• Density of *Helicobacter pylori* per square millimeter of gastric mucosa is higher in patients with duodenal ulcer than in patients without duodenal ulcer. Also see item 2 above.
4. Replication of the findings

• Many of the observations regarding *Helicobacter pylori* have been replicated repeatedly.
5. Biologic plausibility

• Although originally it was difficult to envision a bacterium that infects the stomach antrum causing ulcers in the duodenum, it is now recognized that *Helicobacter pylori* has binding sites on antral cells and can follow these cells into the duodenum.

• *Helicobacter pylori* also induces mediators of inflammation.

• *Helicobacter pylori*–infected mucosa is weakened and is susceptible to the damaging effects of acid.
6. Consideration of alternate explanations

• Data suggest that smoking can increase the risk of duodenal ulcer in *Helicobacter pylori*–infected patients but is not a risk factor in patients in whom *Helicobacter pylori* has been eradicated.
7. Cessation of exposure

- Eradication of *Helicobacter pylori* heals duodenal ulcers at the same rate as histamine receptor antagonists.
- Long-term ulcer recurrence rates were zero after *Helicobacter pylori* was eradicated using triple-antimicrobial therapy, compared with a 60% to 80% relapse rate often found in patients with duodenal ulcers treated with histamine receptor antagonists.
8. Consistency with other knowledge

• Prevalence of *Helicobacter pylori* infection is the same in men as in women. The incidence of duodenal ulcer, which in earlier years was believed to be higher in men than in women, has been equal in recent years.

• The prevalence of ulcer disease is believed to have peaked in the latter part of the 19th century, and the prevalence of *Helicobacter pylori* may have been much higher at that time because of poor living conditions. This reasoning is also based on observations today that the prevalence of *Helicobacter pylori* is much higher in developing countries.
9. Specificity of the association

• Prevalence of *Helicobacter pylori* in patients with duodenal ulcers is 90% to 100%. However, it is found in some patients with gastric ulcer and even in asymptomatic individuals.
Questions?