JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Causal Association

Sukon Kanchanaraksa, PhD
Johns Hopkins University

From Association to Causation

- The following conditions have been met:
  - The study has an adequate sample size
  - The study is free of bias
  - Adjustment for possible confounders has been done
- There is an association between exposure of interest and the disease outcome
- Is the association causal?

Henle-Koch's Postulates (1884 and 1890)

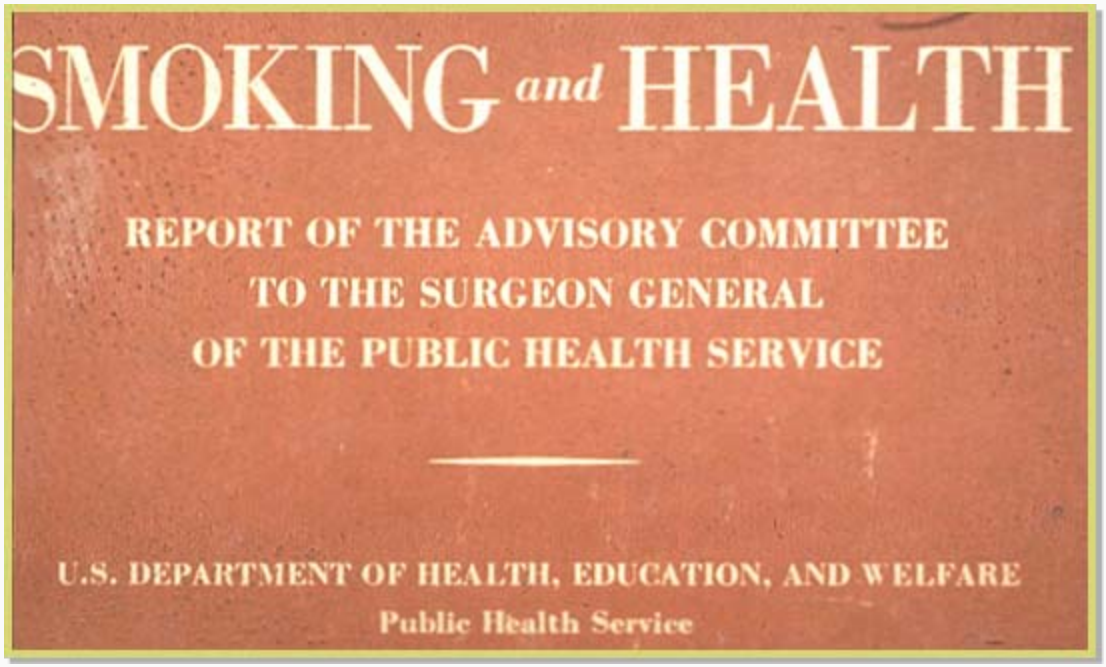
To establish a causal relationship between a parasite and a disease, all four must be fulfilled:

1. The organism must be found in all animals suffering from the disease—but not in healthy animals
2. The organism must be isolated from a diseased animal and grown in pure culture
3. The cultured organism should cause disease when introduced into a healthy animals
4. The organism must be re-isolated from the experimentally infected animal

— Wikipedia

Picture is from http://en.wikipedia.org/wiki/Robert_Koch

1964 Surgeon General's Report



What Is a Cause?

"The characterization of the assessment called for a specific term. The chief terms considered were factor, determinant, and cause. The Committee agreed that while a factor could be a source of variation, not all sources of variation are causes. It is recognized that often the coexistence of several factors is required for the occurrence of a disease, and that one of the factors may play a determinant role, i.e., without it the other factors (as genetic susceptibility) are impotent. Hormones in breast cancer can play such a determinant role. The word **cause** is the one in general usage in connection with matters considered in this study, and it **is capable of conveying the notion of a significant, effectual relationship between an agent and an associated disorder or disease in the host."**

— 1964 Surgeon General Report

Criteria for Causal Association

"Statistical methods cannot establish proof of a causal relationship in an association. **The causal significance of an association is a matter of judgment** which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between the attribute or agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis for judgment."

— 1964 Surgeon General Report

Criteria for Causal Association

Surgeon General's Report (1964)

1. Consistency
2. Strength
   — Dose-response
3. Specificity
4. Temporality
5. Coherence

Hill's Criteria (1965)

1. Strength
2. Consistency
3. Specificity
4. Temporality
5. Biological gradient
6. Plausibility
7. Coherence
8. Experiment
9. Analogy

Source: Hill AB. The Environment and Disease: Association or Causation? Proceedings of the Royal Society of Medicine 1965; 58:295-300.

Criteria for Causal Association (Gordis)

1. Temporal relationship
2. Strength of the association
3. Biologic plausibility
4. Dose–response relationship
5. Replication of the findings
6. Effect of removing the exposure
7. Extent to which alternate explanations have been considered
8. Specificity of the association
9. Consistency with other knowledge

1. Temporal Relationship

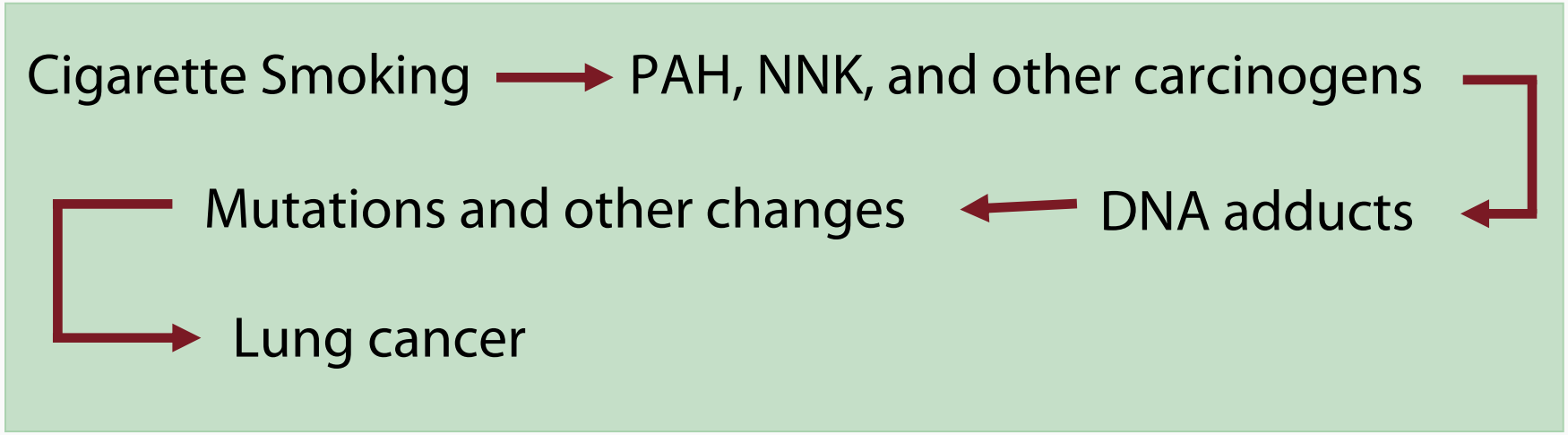
- Most important criterion that must always be met
- Exposure precedes disease development with adequate elapsed time
  - **Latency period:** time from initial exposure to an agent to the onset of disease
    - **Incubation period:** exposure to infectious agents
- Study designs with temporal relationship
  - Cohort, case-control, and RCT

2. Strength of the Association

- Measures of the association
  - Relative risk
  - Odds ratio
- Stronger association is more likely to be causal, but a weak association can also be causal
- Examples
  - RR for lung cancer and cigarette smoking from various studies are around 10
  - RR for breast cancer and cigarette smoking from various studies are between 1–1.5
    - This suggests that the association between smoking and lung cancer is more likely to be causal than smoking and breast cancer

3. Biological Plausibility

- Example:



- PAH polycyclic aromatic hydrocarbons
- NNK 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone

The Health Consequences of Smoking. 2004 Surgeon General Report. Figure 2.1
Hecht 1999, p. 1195.

4. Dose-Response Relationship

- If risk increases with increasing exposure, it supports the notion of a causal association
  - However, the absence of dose-response does not preclude causal association
- There is almost always a dose **below** which no response occurs or can be measured
- There is also a dose **above** which any further increases in the dose will not result in any increased effect
- For some substances, some dose levels may be beneficial
  - "The right dose differentiates a poison from a remedy" (Paracelsus)

5. Replication of the Findings

- It is supportive of causal association if the same finding can be replicated in different populations and/or by using various study designs

Example: Cohort Studies of Esophageal Cancer and Cigarette Smoking

Doll et al. 1994	Never smoked regularly‡	1.0
	Current smokers	
British physicians 1951–1991,	1–14 cigarettes/day‡	4.25
40-year follow-up (34,440	15–24 cigarettes/day‡	8.25
men; 172 deaths)	≥25 cigarettes/day‡	11.25
McLaughlin et al. 1995a	Never smoked‡	1.0
	Current smokers	
U.S. veterans, 1954–1980,	1–9 cigarettes/day‡	1.4
26-year follow-up (177,903	10–20 cigarettes/day‡	3.3
men aged 31–84 years;	21–39 cigarettes/day‡	6.7
318 deaths)	≥40 cigarettes/day‡	6.1
Burns et al. 1997	Never smoked (30)	1.0
	Current smokers	
Cancer Prevention Study I,	1–19 cigarettes/day‡	2.4
1959–1972, 12-year follow-up	20 cigarettes/day‡	3.9
(456,491 men; 190 deaths)	≥21 cigarettes/day‡	5.4

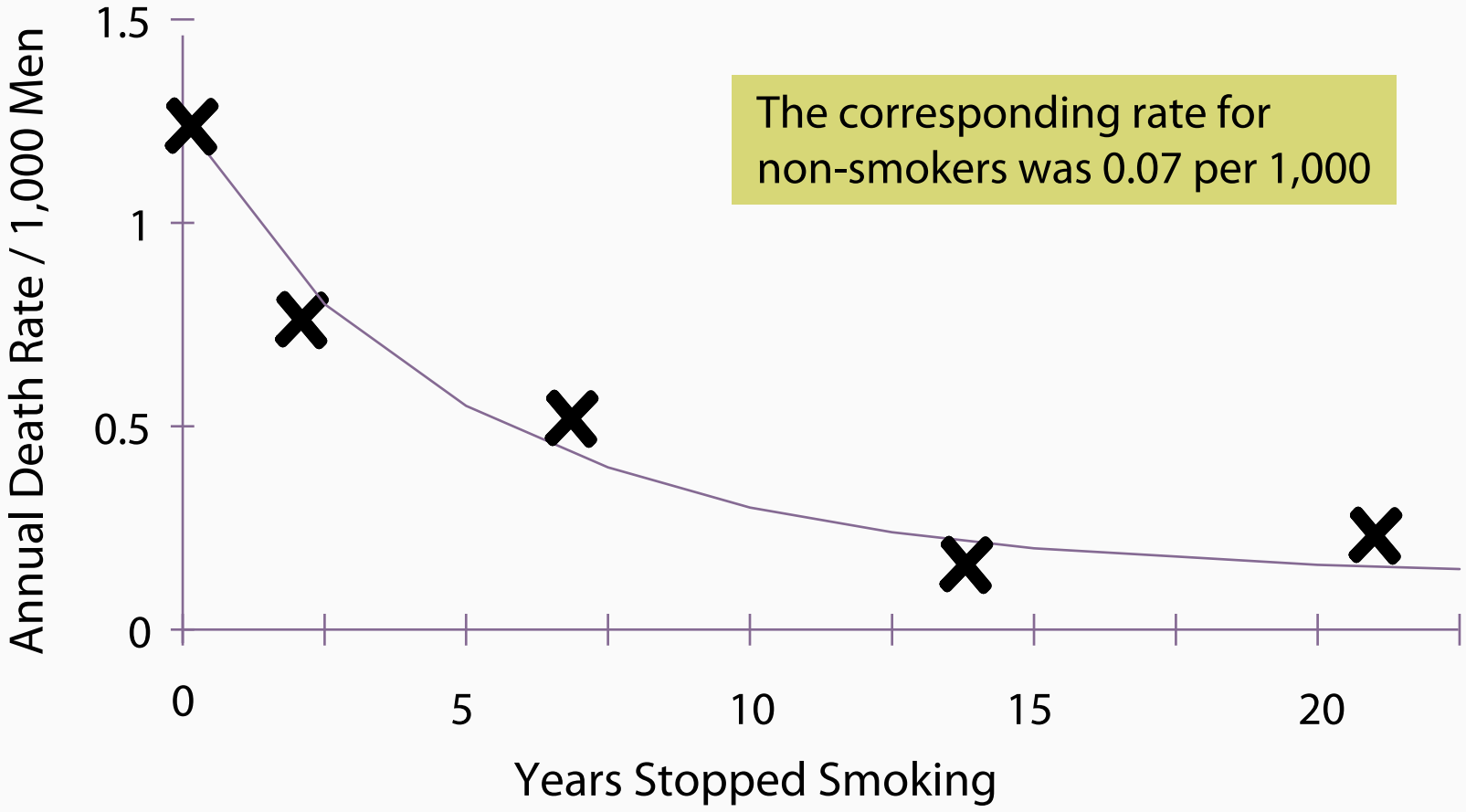
Surgeon General Report 2004; The Health Consequences of Smoking.

6. Effect of Removal of Exposure on the Outcome

- Similar to the dose-response relationship, the presence of this criterion supports the notion of causal association
  - However, the absence does not preclude it
- Example: after quitting smoking, the amount of specific-DNA adducts decreases in blood

Effect of Removing Exposure

Lung Cancer Death Rates, Standardized for Age and Amount Smoked, among Men Continuing to Smoke Cigarettes and Men Who have Given up Smoking



Benefits of Quitting Smoking

- Stroke risk is reduced to that of a person who never smoked after 5–15 years of not smoking
- Cancers of the mouth, throat, and esophagus risks are halved five years after quitting
- Cancer of the larynx risk is reduced after quitting
- Coronary heart disease risk is cut by half one year after quitting and is nearly the same as someone who never smoked 15 years after quitting
- Chronic obstructive pulmonary disease risk of death is reduced after quitting
- Lung cancer risk drops by as much as half 10 years after quitting

Benefits of Quitting Smoking

- Ulcer risk drops after quitting
- Bladder cancer risk is halved a few years after quitting
- Peripheral artery disease risk goes down after quitting
- Cervical cancer risk is reduced a few years after quitting
- Risk of having a low birth-weight baby drops to normal if quitting before pregnancy or during the first trimester

Source: http://www.cdc.gov/tobacco/sgr/sgr_2004/posters/benefits.htm

7. Extent to Which Alternate Explanations Have Been Considered in the Study

- Adjustment for confounding

8. Specificity of the Association

- Specificity of the association suggests that one exposure is specific to one disease
- This criterion is not applicable to all exposure-disease associations because a disease may be caused by several exposures, and an exposure may cause several diseases
  - An exposure is likely to have a deleterious effect on a specific mechanism (at a cellular or molecular level) that may then lead to one or more diseases
  - An exposure, such as smoke from cigarette smoking, is comprised of many smaller chemical components

9. Consistency with Other Knowledge

- In vitro studies
- Animal studies
- Other studies such as ecological studies, cross-sectional studies
- Other types of data such as sales data, time trend

Modification of the Guidelines (1990)

- Quality of data sources (by descending order of quality)
  - Randomized clinical trials
  - Cohort studies
  - Case-control studies
  - Time-series studies
  - Case-series studies

Modification of the Guidelines (1990)

- Evidence of a causal relationship
  - Major category
    - Temporal
    - Biological plausibility
    - Consistency and replications
    - Alternative explanations
  - Minor category
    - Dose-response
    - Strength of association
    - Cessation effects

Guidelines of Causality: Lung Cancer and Smoking

	Active Smoking	Passive Smoking
Temporality	+	+
Plausibility	+	+
Consistency	+	±
Alternate explanation	+	±
Dose-response	+	±
Strength	+	–
Cessation	+	–

Use of Guidelines

- Causal association is mostly a judgmental process based on available information
- Epidemiologic process is continual
  - New evidence may be discovered that supports or refutes the current understanding of the relationship between exposure and disease