Causation in the Presence of Weak Associations

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Despite their observational nature, epidemiologic studies have been used to make inductive inferences about the causes of human diseases. In this context, I mainly consider the term “cause” in its cognitive (explanatory) meaning, that is, by detecting causal factors and identifying mechanisms of diseases.

The development of a theoretical framework for the establishment of causation in the absence of experimental evidence represents an important conceptual development in the interpretation and explanation of biological phenomena. The framework is based on a combination of convergent lines of evidence, none of which is sufficient per se to establish a cause-effect relationship. The criteria proposed by Hill (1965), which he derived from the list prepared in the US Surgeon General’s report Smoking and Health (1964), to interpret the epidemiologic results on lung cancer risk from tobacco smoking, have been used as a paradigm for causation in observational epidemiology. Despite the fact that Hill emphasized the importance of other factors in the causal inferential process, these criteria continue to be used in the interpretation of epidemiologic studies (see Table 1 for a summary).

The strength of the association is one of the original criteria that have been maintained in all of the subsequent formulations. The observation of a strong statistical association between a suspected risk (or a protective) factor and a condition or disease, typically determined by a measure of the incidence (or prevalence) of the condition among the exposed relative to that among the unexposed (often loosely defined as “relative risk”), adds credibility to its causal nature (Rothman et al., 2008a). The modern interpretation of this criterion, which has an instinctive appeal, is that chance, bias, and unmeasured confounding are less likely to explain (or at least to completely explain) a relative risk that is further away from the null. Although any measure of risk would follow a continuous distribution and there are no predefined values that separate “strong” from “moderate” or “weak” associations, relative risks below 3 are considered moderate or weak (Wynder, 1987).

Most of the carcinogens identified in the early decades of cancer epidemiologic research were characterized by strong associations with at least one type of cancer (Table 2). However, it has become clear in recent decades that known carcinogenic exposures explain only a proportion of human cancers (Boffetta et al., 2009), and it is unlikely that many strong carcinogens exist that have not yet been discovered. However, biological agents might represent an exception as demonstrated by the human papilloma virus, whose strong carcinogenic role on the uterine cervix and other genital organs was demonstrated in epidemiologic studies in the early 1990s (International Agency for Research on Cancer, 1995). It is therefore plausible to expect a relatively weak effect (if any) of suspected carcinogenic agents.

The study of weak associations magnifies the three major methodological problems faced by observational research: chance, bias, and confounding.

Epidemiological research typically relies on the evaluation of the role of chance (random error) in generating the observed results (Rothman et al., 2008b), which is typically performed by applying the appropriate tests to assess whether the probability of obtaining the observed results, under the null hypothesis, exceeds a given value. The probability depends, in addition to the level of significance chosen, on the magnitude of the observed effect and the total number of observations, and their repartition between the different groups (e.g., cases and controls, exposed and unexposed). For a given level of statistical significance, the number of subjects to be included in the study is inversely correlated with the magnitude of the effect to be detected.

Bias (systematic error) is a violation of the internal validity of a study because of factors related to study design, data acquisition, data analysis, and results reporting (Rothman et al., 2008c). In epidemiology, typical examples of bias are the lack of comparability of study groups (e.g., cases and controls selected from two different populations), lack of comparability of exposure or outcome
Table 1  Guidelines for causality in epidemiologic studies, according to Hill (1965)

**Strength of Association.** The stronger the relationship between the independent variable and the dependent variable, the less likely it is that the relationship is because of an extraneous variable.

**Temporality.** It is logically necessary for a cause to precede an effect in time.

**Consistency.** Multiple observations, of an association, with different people under different circumstances and with different measurement instruments increase the credibility of a finding.

**Theoretical Plausibility.** It is easier to accept an association as causal when there is a rational and theoretical basis for such a conclusion.

**Coherence.** A cause-and-effect interpretation for an association is clearest when it does not conflict with what is known about the variables under study and when there are no plausible competing theories or rival hypotheses. In other words, the association must be coherent with other knowledge.

**Specificity in the Causes.** In the ideal situation, the effect has only one cause. In other words, showing that an outcome is best predicted by one primary factor adds credibility to a causal claim.

**Dose-Response Relationship.** There should be a direct relationship between the risk factor (i.e., the independent variable) and people’s status on the disease variable (i.e., the dependent variable).

**Experimental Evidence.** Any related research that is based on experiments will make a causal inference more plausible.

**Analogy.** Sometimes a commonly accepted phenomenon in one area can be applied to another area.

Confounding is a specific type of bias that originates from an undetected causal relationship between the determinant, the outcome of interest, and a third (unmeasured) factor that is causally related to the outcome and associated with the determinant (Rothman et al., 2008b). For example, an association between drinking alcohol and the incidence of lung cancer can be explained by the fact that (in many populations) drinkers tend to smoke more frequently and at higher doses (a cause of lung cancer) than nondrinkers. The magnitude of the confounding effect depends on the strength of the association between the confounder and the determinant (e.g., How much more do drinkers smoke compared to nondrinkers?) and on the strength of the association between the confounder and the outcome (e.g., What is the risk of lung cancer among smokers compared to nonsmokers?). As in the general case of bias discussed above, confounding would more easily generate a weak (spurious) association than a strong one.

Epidemiology, therefore, faces the challenge of identifying the weak causal associations that require large study populations and taking special care to exclude bias and confounding, and it is not surprising that the evidence on which these associations are based is often challenged. The case of lung cancer risk from exposure to second-hand smoke among nonsmokers is a good example of the difficulty in establishing the causal nature of a weak association. Early epidemiologic studies date from the early 1980s that showed an increased risk of lung cancer among nonsmoking women married to smokers as compared with nonsmoking women married to nonsmokers. Since then, a large body of evidence has accumulated that, by and large, consistently shows a weak overall association between various measures of exposure to second-hand smoke and lung cancer risk with limited evidence of a dose relationship (see Boffetta, 2002 for a cumulative meta-analysis that shows how the

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Table 2  Carcinogenic agents identified in an early report of the World Health Organization (1964)

| Agent                                | Target Organs                     |
|--------------------------------------|-----------------------------------|
| Sunlight                             | Skin                              |
| Betel, nass, tobacco chewing         | Oropharynx                        |
| Alcohol                              | Oral cavity, larynx, esophagus    |
| Tobacco                              | Lung                              |
| Circumcision                         | Penis, cervix in the partner      |
| Nulliparity                          | Breast                            |
| Atmospheric pollution                | Lung                              |
| Ionizing radiation                   | Skin, bone, lung, lymphohematopoietic |
| PAH-containing mixtures              | Skin, lung                        |
| Aromatic amines                      | Bladder                           |
| Chromium, nickel                     | Lung, nasal sinuses               |
| Inorganic arsenic                    | Skin, lung                        |
| Asbestos                             | Lung                              |
| Isopropyl oil                        | Nasal sinuses                     |
| Thorotrast                           | Not specified                     |

Abbreviation: PAH, polycyclic aromatic hydrocarbons.

*Occupational agents.

†Medications.
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