Risky Concepts: Methods in Cancer Research

The Essential Tension Between Absolute and Relative Causality

In a recent issue of *Scientific American*, columnist Steve Mirsky wrote that "epidemiologists drive us crazy" because they seemingly produce contradictory reports on the potential effects of some exposures.[1] Mirsky reported the results of studies indicating that beer drinking could either reduce cardiovascular risk[2] or increase the risk of sexually transmitted diseases[3] and that tofu, a healthy source of proteins, was a possible cause of late dementia.[4] This led him to conclude mysteriously that epidemiologists were "the unsung heroes of medicine" and that "a TV show about epidemiologists would be as exciting as vanilla ice cream."

These acerbic remarks can be contrasted with a real-life conversation between 2 parents, one of whom wondered whether all the artificial ingredients in vanilla ice cream (e.g., flavors, colors) endangered children's health. If that were so, said the other parent, epidemiologists would have already alerted us.

Excess confidence? Maybe, but this conversation suggests that the population is not so much impressed by the controversies in epidemiology as by the overall record of the discipline. Epidemiologists can be viewed as risk sentinels who explore the possible health consequences of many changes in mass behaviors, environmental exposures, or societal changes that have occurred since World War II. Take the example of oral contraceptives. In Western societies in the 1950s, they were not used at all; in the 1990s, about 80% of women had used them for at least 6 months.[5] Although oral contraceptives were thought to pose a potentially serious threat to women's health, overall, epidemiologic studies have been reassuring.[6] Similarly, there is a wealth of epidemiologic results on the health effects of hormone replacement therapy, coffee, alcohol, tea, sedentary lifestyle, dietary fat, obesity, and so forth. Some factors have been associated with major health damage (e.g., exposure to tobacco smoke or the broadening of social inequalities), but many others do not appear to be deleterious.

Even though there are reasons to rejoice, some situations are a matter of concern because of their harmful consequences for the community. We need to draw lessons from these negative experiences in order not to reproduce them in the future. This point is illustrated by an adverse consequence of the research on oral contraceptives that occurred in the mid-1990s.

A Historical Case in Point

Two case–control studies with similar designs, published in December 1995[7] and January 1996,[8] suggested that risk for cardiovascular disease varied according to the progestogen component of the oral contraceptive women used. Oral contraceptives containing gestodene or desogestrel (so-called third-generation progestogen pills) were compared with those containing norgestrel (second-generation pills). The third-generation oral contraceptives were found to reduce the risk of myocardial infarction but to increase the risk of venous thrombosis.[9] The findings were highly publicized in Europe. Public health authorities reacted swiftly in the wake of their delay over informing the public of problems with the blood supply.[10] During the weeks following the publication of the report, it was later claimed, large numbers of women stopped taking their oral contraceptives and, through June of 1996, there were 30 000 excess conceptions and 10 000 excess abortions, mostly in women in the United Kingdom younger than 25 years.[11] To make the story even more shattering, unwanted pregnancies and abortions are associated with a much larger risk of venous thrombosis than the potentially preventable risks related to oral contraceptive use.

There is a legitimate basis for concern here, even if we do not consider the ongoing controversy over whether the so-called third-generation oral contraceptives are truly associated with more venous thromboembolism and less myocardial infarction than second-generation products. Potentially useful information from well-conducted epidemiologic studies generated widespread anxiety and inappropriate reactions in the public. The clinician's dilemma appeared to be between increasing the risk of myocardial infarction when prescribing third-generation oral contraceptives or increasing the risk of deep venous thrombosis when prescribing the earlier forms. In this medical decision making, a key piece of information missing from the reports was the size of the subgroup of the population in which there could be an excess risk of myocardial infarction associated with oral contraceptive use. This subgroup essentially comprised women older than 35 years who were simultaneous oral contraceptive users and smokers.[6] In Geneva, oral contraceptive use among smokers older than 35 years accounts for 13% of woman-years of oral contraceptive users.[5]

While 13% is not trivial, it clearly limits the magnitude of the problem to a specific subgroup of the population. Thus, for the overwhelming majority of oral contraceptive users, it was possible, if a woman or her physician wished, to switch back to a second-generation oral contraceptive pill without incurring new risks. A more differentiated approach had to be used for women who smoked, especially those older than 35. By using the relevant relative risk and prevalence of exposure in the population, it was possible to circumscribe the magnitude of the problem in the population and probably avoid much of the crisis.

Relative vs Absolute Causality

The foregoing example suggests that reporting association without indicating the attributable disease burden is a source of misinterpretation and controversy. Indeed, epidemiologists rely on 2 types of causal inference. One type is related to the interpretation of relative risk, a very intuitive concept; for example, the risk in the exposed is 2-fold or 3-fold greater (or smaller) relative to the risk in the unexposed. We can think of it as *relative caus-*

ality. Relative risks are a very handy tool for screening for risk factors, even when the disease is extremely rare. Relative risks do not require population data on prevalence or incidence and therefore can also be estimated from a case–control study. As public health researchers know full well, however, a relative risk gives no indication of the absolute number of individuals affected as a result of the exposure. A relative risk of 10 can be obtained from a ratio of 10:1, 100:10, or 10 000:1000.

In contrast, the various forms of *attributable* risk (synonymously defined as risk difference, excess risk, and absolute risk) have a straightforward public health interpretation.[12,13] That is, the attributable risks corresponding to the previously mentioned relative risks of 10 are 9, 90, and 9000 cases per million, respectively, over a given period. However, measures of attributable risk require direct or indirect population-based information such as the prevalence of the studied exposure or the number of incident cases. Let's label this type of interpretation as *absolute causality*: the exposure that causes an absolute excess of a number of cases over a given period.

The Essential Tension

The epidemiologic "self" encounters tension when pulled between absolute and relative causality. The challenge is to find the right balance for this "essential tension." Kuhn coined this expression to indicate a force that pushes science forward and that originates from the need for scientists to be simultaneously traditionalists and iconoclasts.[14] In epidemiology, the essential tension between absolute and relative causality also pushes us to constantly discover new risk factors, invent new preventive strategies, and keep the right balance between them. On the one hand, the search for causal relationships can improve scientific knowledge and medical practice (relative causality). On the other hand, the population perspective (absolute causality) compels epidemiologists toward a constant preoccupation with the relevance of research findings for the public's health. This issue of the Journal contains 2 contributions that aim to stimulate our thinking regarding ways of dealing with relative and absolute causality.

Two Contributions to Causal Thinking

The innovative report by Begg[15] seeks to answer the question "When do we know that most causes of a given disease have been identified?" His point is that the use of population attributable risk does not allow us to determine whether or not there are more risk factors to be discovered than those already known or postulated for a given cancer. Instead, the excess risk of a second primary cancer in an individual reflects the total excess risk (beyond random occurrence) due to risk factors. If one or many risk factors are involved, the incidence of the second primary cancer divided by the incidence of the first primary cancer in the population will be greater than unity. This excess risk can then be decomposed into known and unknown components from prevalence and relative risks reported in epidemiologic studies, typically case–control analyses.

The method has limitations, which Begg carefully lays out (e.g., the recurrence risk should not be affected by the occurrence of the first event because of treatment, organ removal, etc.). However, his contribution has an important practical implication: a more thorough identification of causes helps us to better define the range of public health or clinical interventions capable of successfully preventing disease, whether oriented toward the population or subgroups at high risk.

The example in Begg's article suggests that there may be still-undiscovered genetic causes of melanoma. Colditz, in his commentary,[16] reacts to what he views as Begg's criticism of the population-based strategy for reducing sun exposure. However, population attributable risks (PARs) are not necessarily associated with modifiable behavioral and environmental causes. They are only functions of the prevalence and effect magnitude of the studied cause. A prevalent gene with a moderate effect can have a large PAR. Thus, it is to be hoped that the debate on Begg's article will not be focused on this specific example. Rather, it should explore whether and under which conditions, if valid, the suggestion of using second primary cancers for assessing the total excess risk can complement the PAR approach to identify environmental or genetic causes of disease.

While Begg questions the bases for supporting only broad population-based prevention for all cancers, Rockhill[17] discusses the dangers associated with the individualization of risk, that is, applying to individuals risk derived from a population. As argued by Rose,[18] risk factors can predict the incidence of disease in a population but do not allow us to predict whether a given individual will have the disease. Nevertheless, deriving individual risk from population data is a tempting development of epidemiologic inquiry. Rockhill discusses the example of breast cancer prevention, and there are many other areas in which estimates of individual risk are currently used.[19,20] Clinicians, for example, have long been guided by tables indicating their patients' risk of coronary heart disease on the basis of blood pressure, total cholesterol, smoking, age, and sex.[19]

The individualization of risk is likely to remain a common practice. However, as Rockhill stresses, it should not become the foundation of a philosophy of prevention that seeks to act primarily on the individual, as opposed to implementing strategies at the population level. □

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