Paper

THE IMPORTANCE OF SPECIFYING THE UNDERLYING BIOLOGIC MODEL IN ESTIMATING THE PROBABILITY OF CAUSATION

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Abstract—**There are a number of contexts in which interested parties wish to estimate the probability that an individual's injury was caused by radiation or a toxic chemical. It has been shown, however, that such calculations cannot be made based on epidemiologic data alone, without assumption of a biologic model for the disease process and without a specific definition of causation. To illustrate the relevant theorems, we present a number of examples in which different biologic models produce different values for the probability of causation for individuals from the same population-based epidemiologic data and dose-response curves. As a result of these ambiguities, it is important that anyone attempting to calculate probability of causation for individuals explicitly state the biologic model that has been assumed, as well as state the definition of causation being used. The analyst should test the robustness of the calculations by repeating them for a broad range of underlying biologic models.**
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BACKGROUND

A RIDER in the 1983 Orphan Drug Act (Public Law 97-414) directed the Secretary of Health and Human Services to provide a method for evaluating the merits of claims that a personal injury had been caused by fallout to nuclear tests and other nuclear events. This directive spawned the creation of a set of "radioepidemiological tables" by an *ad hoc* working group of the National Institutes of Health (DHHS 1985), which used epidemiologic data and a simple formula for probability of causation (hereafter, PC),

$$PC = R/(B + R),$$

where R is the "radiogenic risk" of disease, estimated as the observed increase in the rate among those exposed to radiation, and B is the "background risk" of disease, estimated as the rate among the unexposed. Most epidemiologic studies provide separate estimates of these rates, and thus it is tempting to use the preceding formula for practical reasons. A more precise and neutral term for the formula is "rate fraction" (Greenland and Robins 1988; Rothman and Greenland 1998). The formula is often written as $PC = (RR - 1)/RR$, where $RR = (B + R)/B$ is the rate ratio comparing exposed and unexposed populations. It is equivalent to the "attributable fraction" formula given by many epidemiology textbooks.

Criticisms of the method appeared from the beginning and have followed its use in other contexts ever since. For instance, in 1987, the Scientific Council of the American Medical Association succinctly stated the two basic criticisms of the original formulation:

- "The basic premise of probability of causation is that individual risk can be determined from epidemiological data for a representative population; however, the premise holds only if the individual is truly representative of the reference population."
- "The formula is not applicable when there are multiple causative agents unless their cumulative effect is well understood" (AMA 1987).

Other authors discussed the limitations of both the simple PC model (Cox 1984, 1987; Seiler and Scott 1987; Lagakos and Mosteller 1986; Jose 1988; Robins and Greenland 1989a) and related formulas (Greenland and Robins 1988; Robins and Greenland 1989b).

Probability of causation is not the only measure used to assign individual causation in medical and legal contexts. Harber and Shusterman (1996) list 18 different heuristics, including "probability-based models, application of group-based data (epidemiology) to individuals, Bayesian analysis, a priori assumptions about which conclusions are better, and others." Robins and Greenland (1991) showed that estimates of expected years of life lost could be made more robust to model mispecification than estimates of probability of causation.

Nevertheless, because of the utility of having a straightforward formula for determining compensation in difficult situations, the use of probability of causation has

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continued, almost always relying on the "attributable fraction" or "attributable risk" formulas (Wakeford et al. 1998; Bhatia and Murthy 1992; Breitenstein 1988; Mettler and Upton 1995; Zeighami and Morris 1986). Its use has been considered reasonable by the NCRP, despite recognition of its limitations (NCRP 1992).

The simple PC formula is often used by the defense in legal cases related to radiation injuries (Mettler and Upton 1995). The formula has also been used in compensation of uranium miners, other nuclear workers, and atomic veterans. Recent activity has been initiated by the President's Advisory Committee on Human Radiation Experiments, which recommended in 1995 that the radioepidemiological tables be updated (ACHRE 1995). President Clinton has submitted legislation to Congress that includes this recommendation (HRIWG 1997). The idea has been expressed that the use of genetic markers may improve the method (Fry 1996).

Although the PC formula is extensively used in connection with radiation injuries, it has also been used in many other contexts. For example, the Quebec Workers' Compensation Board has used it to compensate workers exposed to benzo[a]pyrene (Armstrong et al. 1988) and coal tar pitch volatiles (Armstrong and Theriault 1996).

REMOVING AMBIGUITIES IN THE CONCEPT OF CAUSATION

Although it may seem like a simple concept, there are many possible definitions of causation, and even more models for calculating probability of causation. The intricacies and problems of various definitions of causation have been discussed in many places (Rothman and Greenland 1998; Greenland 1998). We revisit these issues only to argue that analysts should explicitly indicate the approach to causality they are adopting, with appropriate reference to the literature. Mathematical definitions should be used, even if expressed verbally, since they allow greater precision and help identify hidden problems.

One issue in the definition of causation involves the timing of disease. Suppose a toxic agent accelerates the time of onset of a disease without changing the lifetime probability of getting the disease subsequent to exposure. Is not the agent then causally linked to the disease both biologically and ethically? Is it possible to separate issues concerning the time course of a disease from the issue of probability of causation?

We think not, but will show that the underlying biologic model affects the estimated probability of causation regardless of whether or not time of disease onset is a consideration.

Perhaps no mathematical representation of causation can capture all the nuances of the word, nor will any one representation be appropriate for all contexts. In our view, however, anyone making use of the term "probability of causation" should refer to a precise definition of causation.

Calculating probability of causation from causal models

Even with a definition of causation specified, the probability of causation for an injured person can be calculated with precision only if one has a mathematical model of disease biology and a model of the way radiation and other risk factors affect the course of disease development.

Although the mathematical demonstration of these points appeared some time ago in the biostatistical literature (Robins and Greenland 1989a), they have been largely ignored. In practice, a mathematical definition is usually written down that may be valid for an individual, but then a naïve estimate of the probability is produced by substituting epidemiologic quantities for individual parameters in the definition. Robins and Greenland (1989a) showed that such naïve substitutions generally yield invalid answers, except under very restrictive biologic assumptions that cannot be tested using epidemiologic data. As a consequence, probability of causation for an individual cannot be estimated from epidemiologic data alone. When population data are all that are available for the substitution formulas, the term "probability of causation" is inappropriate; less misleading terms are "excess fraction" (Greenland and Robins 1988) and "assigned share" (Lagakos and Mosteller 1986; Cox 1987).

The standard derivation of the simple PC formula implicitly assumes that the excess radiogenic risk is independent of background, i.e., that the amount added to the risk by radiogenic exposure does not depend on the level of risk that would exist in the absence of exposure. We call a biologic model that satisfies this assumption an "Independent of Background" (IOB) model (Robins and Greenland 1989a, b).

As we illustrate in examples below, there are always biologic models other than IOB models that are just as consistent with epidemiologic data, no matter what the data show. These models can give values for individual probabilities of causation that differ significantly from those derived under an IOB model. As a result, in the legal context, different experts in disease could come into court or before a compensation arbitrator with different implicit biologic models for the disease in question. They might reach different conclusions about the probability that an individual's disease was caused by a toxic substance, even if there was no disagreement about the relevant epidemiology.

Some of the confusion over the probability of causation would be alleviated by explicitly recognizing that one cannot calculate the quantity without assuming a biologic model of the disease process. The probability of causation is thus a function of the underlying biologic model. For instance, to say "there is a 37% chance that this individual's lung cancer was caused by a certain radiation dose" is misleading, unless one adds a qualification such as "according to an IOB model."

Users of the concept of probability of causation should understand that they have no choice but to assume

a biologic model. They should be able to articulate the model in their articles and reports. By always "subscripting" the PC estimate with its associated model, the validity of both the underlying model and the epidemiologic data will be seen as important issues. Such a convention would make it clear that epidemiologic observations cannot pin down a unique value for the probability of causation. For example, it is not true in all biologic models that the dose at which rates are doubled is the dose at which the probability of causation is one-half.

In both research reports and testimony, it is important to acknowledge that a PC estimate requires biologic modeling. As more is learned about the biology of a particular disease, the underlying model used in estimation of the probability of causation for that disease should be updated. Analysts who develop PC estimates should consult with medical and biological experts to learn the latest thinking in the relevant field. Analysts should test the sensitivity of their PC calculations to use of alternate models, as has been done by Chmelevsky et al. (1994). It is also important to consider variation in expert judgments on the rate estimates that enter into a PC calculation (Evans et al. 1994).

In identifying the assumed biologic model, it is not even enough to say that one is assuming a linear, no-threshold model or a multiplicative model, because that does not tell enough about how the radiation interacts with other factors. Does radiation act as a promoter following cancer initiation? Can radiation-induced damage be promoted by other chemicals, diet, or smoking? Many different underlying models can lead to linear behavior over the range of doses observed in epidemiologic studies. Even a threshold model for individuals can lead to a linear dose-response for populations, if the threshold value is uniformly distributed over the population as a result of varying individual susceptibilities (Greenland 1995).

In some cases, analysts may focus on just one biologic model. Even then, it is unlikely that all risk factors will be included in the model, so the analyst needs to articulate what is being assumed about potential interactions with risk factors outside of the model.

EXAMPLES OF UNDERLYING BIOLOGIC MODELS THAT GIVE DIFFERENT PROBABILITIES OF CAUSATION USING THE SAME EPIDEMIOLOGIC DATA

In the examples below, we first state a definition for causation and then calculate the probability of developing disease for an individual with and without exposure under alternate biologic models. The models in each example have been chosen to produce the same epidemiologic data for populations. Having the models to work with, we can calculate individual probabilities of causation for the different biologic models and compare the results.

Example I

In our first example we consider a definition of causation taken from the biostatistics literature (Robins and Greenland 1989a): The exposure shortens the time at which a particular disease appears. Without the exposure, the disease would either never have occurred or would have occurred later.

Having provided the definition of causation to be used, we consider two different simplified biologic models for invasive melanoma in a cohort of 100,000 women of age 50 y at start of follow-up, each of whom has a single blue nevus. The cohort is followed for 10 y during a period of elevated exposure to ionizing radiation. Model I makes three assumptions that naturally lead to the simple PC formula given earlier: 1) for each year there are 10 women in the cohort who will develop invasive melanoma in that year regardless of the radiation level, for a total of 100 "background" cases; 2) another 10 women in the cohort carry a genetic mutation rendering them incapable of permanently repairing the damage to nevus cells produced by the elevated radiation, and as a consequence all 10 of these women also develop invasive melanoma uniformly over the 10 y; and 3) the remaining women are not affected by the radiation.

Under this model, in each year of follow-up, the cohort has an incidence of 10 cases per year without the elevated radiation, but with the radiation the cohort would have an incidence of $(100 + 10)/10 = 11$ cases per year. Thus the rate ratio (RR) for the radiation effect is $11/10 = 1.1$. Only 10 cases have elevated radiation as a contributing cause of their invasive melanoma, and so the proportion of cases affected by the elevated radiation is $10/(100 + 10) = 0.091$, in agreement with the simple PC formula of $(RR-1)/RR = (1.1 - 1)/1.1 = 0.091$.

Now consider Model II, which assumes instead that 1) a woman in this cohort develops invasive melanoma when and only when she accumulates at least 10^8 neoplastic cells in the nevus (this number representing a theoretical maximum that the immune system can confine *in situ*); 2) every woman steadily accumulates neoplastic nevus cells at the rate of 10^4 per year during follow-up; 3) in every woman, the elevated radiation raises this accumulation rate by 10%; and and 4) at the start of follow-up, the number of neoplastic cells per nevus (woman) is uniformly distributed from zero in increments of 1,000 up to $10^8 - 1{,}000$.

Under this model, 10 women per year would pass the 10^8-cell threshold if radiation was not elevated, whereas 11 women would pass the threshold if radiation was elevated. Thus, as with Model I, there would be an incidence of 10 cases per year without the elevated radiation and 11 cases per year with the elevated radiation, for a rate ratio of $11/10 = 1.1$. Now, however, every single case that occurred would have elevated radiation as a contributing cause of the transition to invasive melanoma, so that the proportion of cases affected by exposure (and hence the probability of causation for any given case) is 100%. In every case, the radiation produced a more rapid accumulation of malignant cells,

which in turn led to an earlier crossing of the invasive threshold of 10^8 malignant cells. In other words, the excess radiation exposure played a significant role in the development of every one of the 110 cases. In particular, 100 of the 110 cases would have lost about a year of melanoma-free life because of the elevated radiation.

Epidemiologic data alone cannot tell us which model is correct, because each model yields exactly the same exposure-specific incidence rate of invasive melanoma at each age; that is, each model yields exactly the same exposure-specific age-incidence curves.

Example II: Thyroid cancer induced by chronic radiation

In this second example, we focus on thyroid cancer. The conditions of exposure and approach to causation have been chosen to minimize issues involving time of onset of disease. As we shall show, the choice of biologic model still affects the probability of causation assigned to a cancer.

We begin by specifying the definition of causation that will be used in the example.

Causation definition II. A toxic agent is a contributing cause of a cancer if it produces some of the biologic damage leading to the cancer. The probability that a toxic agent caused a particular cancer is determined from the share of biologic damage that it initiates. In this definition, the burden in estimating probabilities of causation is shifted to estimating the share of biologic damage that is the cause of the cancer. Nevertheless, as with all logically sound causation definitions, the actual PC value will depend on the biologic mechanisms leading to cancer.

Having provided a definition of causation, we now turn to our specific example of radiation-induced thyroid cancer. We make the following three assumptions:

1. Exposure to radiation is constant and continuous for the exposed population, with the dose rate per year denoted by D;
2. Natural background radiation is small compared to the elevated radiation and hence can be ignored; and
3. Persons living in the exposed region have an incidence rate of thyroid cancer that is 25% higher than they would have in the absence of exposure; that is the true causal rate ratio, RR, is 1.25.

We again consider two different biologic models for the disease in question. Thyroid models I and II have five biologic assumptions in common:

1. Damage to DNA is the initiator of thyroid cancer. The rate of damage events per unit time is proportional to the number of undamaged targets;
2. The half-life for repair is fast compared to a human lifetime, fast enough so that the fraction of damaged thyroid cells rapidly reaches an equilibrium. Thus, the effect of exposure is to produce a higher level of damaged DNA;
3. The probability of getting thyroid cancer at any time is proportional to the number of cells with the necessary DNA damage;
4. There are one or more "background" causes of biologic damage that can also lead to thyroid cancer;
5. All persons respond identically to the radiation exposure; and
6. All persons respond identically to the background causes of thyroid cancer.

Thyroid model I makes the following assumptions, which distinguish it from model II:

Ia. Radiation causes a genetic mutation that is distinct from the initiating damage produced by background causes;
Ib. A cell may suffer either or both types of damage, and the presence of either form of damage does not alter the cellular susceptibility to, or repair of, the other form of damage; and
Ic. The rate of promotion to neoplasia among doubly-damaged cells is just the sum of the rates among radiation damaged and background-damaged cells.

Under these assumptions, radiation acts independently of background causes of thyroid cancer. Model I thus becomes an "IOB" model. In this situation, the assumptions of the traditional PC model hold and the probability of causation is 20% = (1.25 − 1.00)/1.25, since the rate ratio for chronic exposure is 1.25.

In contrast, thyroid model II assumes that both radiation and background causes of thyroid cancer affect the same strands of DNA in the same way. This model is explicitly interactive and not "independent of background." As shown in the Appendix, model II leads to a rate of disease proportional to $(C + \beta D)/(C + \beta D + \lambda)$, where C is the rate at which the background causes produce damage per year, D is the radiation dose per year, β is the dose coefficient, and λ is the repair rate. Under this model, the rate of disease is *not* a sum of terms involving background agents and radiation separately.

To simplify the numerical analysis, let us assume that the radiation exposure level is just high enough so that, under model II, it produces damage to cells at the same rate produced by background agents (acting as a group). (In the formula above, this amounts to choosing D so that βD equals C.) It follows, then, that both the background agents and radiation cause an equal amount of biologic damage and, hence, have a 50% probability of causation under model II. Given a particular thyroid cancer cell, there is an equal probability that either radiation or a background agent produced the damage that led to the cell becoming cancerous. It is certainly conceivable, given the facts as presented, that a legal or compensation proceeding would assign to the radiation exposure an equal responsibility for causing thyroid cancer.

However, we note that the rate of cancer in model II, and hence any epidemiologic data derived from it, is a function of the repair rate. As the value of λ is varied, the epidemiologic data varies widely, while the share of biologic damage and the probability of causation remains at 50%. In particular, setting $\lambda = 2C/3$ and $D = C/\beta$ in

model II produces the 1.25 rate ratio assumed in this example without changing the 50% PC value. A value of 50% is considerably higher than the value of 20% under model I using the standard PC formula evaluated with epidemiologic data.

The contradiction between the two models arises because different assumptions are made about how radiation interacts with background causes of thyroid cancer. Under model I, the total rate of cancer is the sum of the rate from background causes alone and the rate from radiation alone. Robins and Greenland (1989a,b) call this property "additivity of effects." In contrast, under model II, radiation and background compete to produce cancer, leading to sub-additive effects on the rate of cell transformation. The extent of this subadditivity depends on the repair rate, λ. Many other biologic models would also lead to the same final pattern of disease rates but with other values for PC.

As shown in the Appendix, the dose response function has identical mathematical form in both models, although the coefficients have different meanings. The unknown coefficients in each model can be chosen to generate the exact same formula for the ratio of cancer incidence rates, which can be written as $RR = (1 + aD)/(1 + bD)$, where a and b are constants. The models for thyroid cancer used in this example were not chosen by considering real dose-response data, since we are not aware of such data on human thyroid cancer. Data on short-term exposures are compatible with linearity (Ron et al. 1995), although these data are also compatible with many other possibilities. In any case, for small values of the dose term (bD) in the RR denominator, the dose response can be approximated by a model that is linear in both dose rate and cumulative dose.

CONCLUSION

Different biologic models can lead to different probabilities of causation even when they lead to the same epidemiologic data and population dose-response curve. Some of the confusion over the probability of causation can be alleviated by explicitly recognizing that no estimate of its value can be made without assuming a biologic model for the disease process. If a satisfactory biologic model is not available, analysts should avoid use of the term "probability of causation" to describe their estimates, and use instead more descriptive terms such as "rate fraction" or "assigned share."

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APPENDIX: EQUILIBRIUM DAMAGE MODELS

Both models I and II are based on simple equilibrium considerations. At equilibrium, the rate of damage must equal the rate of repair. Let

1. N_0 equal the total number of thyroid cells;
2. N equal the number of damaged cells at equilibrium;
3. $\lambda^* N$ equal the number of cells repaired per unit time; and
4. $C^*(N_0 - N)$ equal the number of cells damaged per unit time, where C is a constant.

At equilibrium, $\lambda^* N$ must equal $C^*(N_0 - N)$. It follows that the fractional amount of damage, N/N_0, equals $C/(C + \lambda)$.

In model I the rate of thyroid cancer in the exposed region is given by a background term plus a term proportional to $C_R/(C_R + \lambda)$, where C_R is the damage-rate constant for radiation: $R_I = K_I[A + C_R/(C_R + \lambda_I)]$, where K_I is a proportionality constant.

In model II, we have the background agents included in the term C, so we replace C_R with $C_B + C_R$, where C_B is the damage rate constant for background agents. The rate of thyroid cancer is then equal to $R_{II} = K_{II}[(C_B + C_R)/(C_B + C_R + \lambda_{II})]$, where K_{II} is the proportionality constant for model II.

By judicious choice of the various parameters, it is possible to rearrange both rate formulas to give a rate ratio equal to $(1 + aC_R)/(1 + bC_R)$. This may be done by setting λ_I equal to $C_B + \lambda_{II}$ and setting A equal to $[(K_{II}/K_I)(C_B + C_R) - C_R]/(C_B + C_R + \lambda_{II})$. It is then straightforward to compute the ratio of rates with and without exposure, which necessarily must be the same for both models. The constant a turns out to equal β/C_B and the constant b turns out to equal $\beta/(C_B + \lambda_{II})$.

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