MATHEMATICAL MODELS OF CANCER AND THEIR USE IN RISK ASSESSMENT

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1. Introduction

The assessment of cancer risk associated with environmental exposures necessarily entails the use of mathematical models. A mathematical model or quantitative theory of carcinogenesis is a set of assumptions about the mechanisms by which cancer is induced, together with deduction of the consequences of these assumptions for cancer risk. Because of our limited understanding of the processes by which cancers occur, the assumptions themselves cannot be directly verified. Although some of them can greatly influence predictions for risk, they are frequently forgotten when the model is used. The following examples illustrate how the alteration of one or more pivotal assumptions can have a large impact on assessed risk.

2. Risk vs. Dose

Two sets of assumptions must be made in order to extrapolate cancer risk from animal studies at high dose rates to human population risks at low dose rates. One set concerns the form of the function relating animal risk at high dose rates to animal risk at low dose rates. The magnitude of low dose risk is extremely dependent upon the assumed shape of this dose-response curve (3). The first example in this section shows that the form of this function at low dose rates can be more sensitive to implicit value judgments in the extrapolation procedure than to the experimental data.

Another set of assumptions concerns the relationship between animal and human risk. The second example demonstrates that quantitative models tailored to describe carcinogenesis in one species can be inappropriate tools for predicting risk in another species when implicit assumptions about the distribution, metabolism and elimination of carcinogens in the two species do not hold.

Animal risk at high or low dose rates

Mathematical models of carcinogenesis have been invoked to gain insight

into whether or not a linear, nonthreshold relationship prevails between dose and excess response at low constant dose rates of a test agent. For example, Crump et al. (3,5) invoke the multistage theories of carcinogenesis, discussed in the next section, to posit that the probability $P(d)$ of response at dose rate d is given by

$$P(d) = 1 - \exp \{-(a_0 + a_1 d + a_2 d^2 + \dots)\}, \quad a_i \geq 0.$$

When $P(d)$ is small, the excess risk $P(d) - P(0)$ is approximately

$$P(d) - P(0) = a_1 d + a_2 d^2 + \dots, \quad (1)$$

and the question of nonthreshold low-dose linearity is determined by whether or not the coefficient a_1 is zero. There are plausible assumptions, such as detoxification mechanisms or the necessity for multiple molecular interactions, that lead to $a_1 = 0$. There are equally plausible assumptions that lead to positive values for a_1 . In the absence of knowledge to discriminate between these alternatives, it seems reasonable to use an extrapolation procedure that makes efficient use of the experimental data. However, the use of upper confidence limits in place of expected values for the coefficients a_i in (1) incorporates a value judgment in the extrapolation procedure that frequently outweighs the information inherent in the data. The use of an upper confidence limit for a_1 in (1) is equivalent to admitting the possibility that a_1 is positive, and at low dose rates this upper confidence limit dominates the remaining terms in (1). Thus the use of upper confidence limits guarantees nonthreshold linearity of low dose rates. Consequently this procedure is so insensitive to response at experimental dosages that it fails to distinguish between low levels of potent carcinogens and noncarcinogenic substances. Crump et al. (5) have illustrated this fact by using the procedure on two data sets simulated from

a "true" dose-response function $P(d) \equiv 0.1$ for a noncarcinogenic agent. One simulation involved 150 responses at each of ten dose rates. In both cases the 90% upper confidence limit on a_1 was positive, so that the two upper confidence curves relating extra response to dose rate were virtually linear at low dose rates. Such false positive risk estimates suggest that the value judgment inherent in the use of upper confidence limits should be separated from the quantitative model. Instead, it should be considered explicitly at a later stage of the decision process. The following recommendation, made by the Scientific Committee of the Food Safety Council (14), reflects this need: "Although the value judgment involved in the use of conservative risk assessments may seem appropriate in the light of the many scientific unknowns involved, once formalized as a specific mathematical procedure it escapes the control of the decision-maker and can lead to undesirable and unsound results by distorting the balance between risk and benefit. We therefore recommend the separation of the mathematical and societal aspects of the problems, with the extrapolation procedure chosen to provide 'best estimates' of risk as well as their upper or lower limits".

Interspecies extrapolation

A second example of how changes in a model assumption can have a large impact on risk assessment can be obtained from the work of White (12) on murine pulmonary adenomas following single injections of urethane. The relationship between mean tumor numbers and injected dose was found to have a strong quadratic component, as shown in Figure 1A.

To account for this observation, Neyman and Scott (8) devised a quantitative theory involving two urethane related events in cellular transformation. Use of such a model to extrapolate to another species assumes that urethane induces pulmonary adenomas by a common mechanism in the two species. A less obvious

assumption is that the relationship between external dosage and cellular concentrations is linear for both species. In a later experiment using urethane labeled with radionuclides (12), White estimated the internal dose to a mouse over the twenty-four hour period subsequent to injection of a single dose of urethane. Her estimates of internal exposure, measured in milligram hours per gram of body weight, are plotted against injected dose in Fig. 1B. It is evident that these estimates of internal exposure are quadratic rather than linear functions of dose. Average number of tumors per mouse is plotted against estimated internal dose in Fig. 1C. A comparison of Figures 1A and 1C shows that while tumor numbers depend quadratically upon injected dose, they vary in proportion to estimated internal exposure. A two-hit model is thus an inappropriate description of the cancer mechanism. If the second species differs from the mouse in the elimination of urethane, then use of such a model to dictate the shape of the dose response curve in that species would underestimate risk at low doses. This difficulty suggests that future experiments and models should emphasize incorporation of physiological, pharmacological and biochemical information. The model of Cornfield (2) represents a step in this direction.

3. Risk vs. Age

Certain subgroups of the human population may be particularly vulnerable to carcinogenic exposures by virtue of their age, sex, genetic inheritance or exposure to other carcinogens. Quantitative theories have been used to estimate and predict such variation in susceptibility. The two examples presented in this section show how changes in model assumptions can affect predictions for excess risk versus age at start of carcinogenic exposure and versus age at cancer occurrence.

Age at start of exposure

The question of how the effects of a fixed exposure pattern vary with age

at start of exposure has been addressed by Whittemore (13) within the framework of a multistage theory in which one or more sequential, heritable cellular changes are necessary for malignant transformation. The transition rates at which the cells progress toward malignancy may vary with age, reflecting variations both in endogenous factors, such as hormone levels, metabolic rates, cellular division, etc., and in exogenous carcinogenic exposure. Let us assume, however, that the endogenous components of these rates are independent of age. Thus, given constant exposure, the transition rates are independent of the host's age. The resulting theory predicts that when the carcinogen increases the rate at which target cells experience the first damaging event, then extra risk is independent of age at exposure onset. If on the other hand the agent affects transition to later stages, then extra risk increases with age at start of exposure. This is because those who are older at start of exposure have experienced more spontaneous and background damage, and thus have, on average, more partially transformed cells at risk of further damage by the carcinogen. How do these predictions compare with epidemiological observations?

The predictions are in agreement with the recent findings of Ichimaru et al. (6) on excess leukemias among survivors of the atomic bombs in Hiroshima and Nagasaki. These investigators find that the total excess numbers both of acute and chronic leukemias are independent of age at time of bomb. This is consistent with a theory in which ionizing radiation initiates leukemia, with the endogenous contributions to the transition rates independent of age.

The above predictions are also in agreement with the data of Court-Brown and Doll on excess acute and chronic leukemias among those X-irradiated as treatment for ankylosing spondylitis (4). As seen in Fig. 2, these data show an increase in excess incidence with age at exposure. Increased incidence with age at onset of additional exposure is also demonstrated by the data of Court-Brown

and Doll (4) on nasal sinus cancer among men employed in the nickel refining industry in South Wales, shown in Fig. 3. Both of these results support the above theory with radiation affecting a later stage in the induction of the cancers.

However, there are data for breast cancer risk vs. age at irradiation which are incompatible with the predictions of the above theory in which the endogenous rates are independent of age. Both the findings of Boice et al. (1) for breast cancer among women exposed to repeated chest X-rays for tuberculosis and of McGregor et al. (7) for breast cancer among female survivors of the atomic bomb show a marked increase in excess risk among women who were under the age of 30 at time of exposure, as compared with those who were older at exposure onset. These findings indicate that the endogenous rates may increase during periods of increased mammary stem cell proliferation during puberty. They suggest that age at exposure is an important component of breast cancer risk. This has preventive implications for the use of radiation for therapy, diagnosis and screening. In addition, there is now evidence (9) that long-term oral contraceptive (OC) use may increase the risk of breast cancer. If OC's act as initiating agents, then young users may be especially vulnerable. However, if OC's promote the neoplastic development of initiated cells, then older users, with more such cells, would experience increased risk.

Age at cancer occurrence

As a final example, suppose we observe a population of individuals of various ages that is exposed to a suspected carcinogen, the intensity of which may vary over the observation period. Suppose that the age-specific cancer incidence rates in the absence of exposure (the "background" rates) increase with age but do not vary appreciably over the period. Which age groups are most likely to exhibit a

significantly increased cancer risk? This question was considered by Pochin (10) who studied total cancer mortality rates in populations exposed to high levels of natural radiation. If for each age group we know the background rates, the extra rates due to increased exposure, and the person years at risk in the period, we can predict the numbers of background and extra cancers observed in the period for each age category. If the background rates are high, it will be difficult to detect the effects of increased exposure. Suppose that the number of extra cancers needed to yield a significant excess is twice the standard error of the number of background cases. This means that an excess will be detected among those of age x only if

$$E_x > 2\sqrt{B_x},$$

where E_x and B_x denote the numbers of excess and background cancers. Thus we might ask, which age groups x maximize the ratio E_x^2/B_x of squared number of excess cancers to number of background cancers?

To illustrate how completely the answer depends upon our assumptions about the interaction of the agent with background mechanisms, consider the following two extreme cases: (i) the extra rates are proportional to the background rates; (ii) the extra rates are independent of age. If the age distributions of the two populations remain stable over the observation period, the ratio of squared excess cancers to background cancers will be largest for the older age groups in case (i) but largest among the younger groups in case (ii) (13).

Each of the above two forms for the extra rates are consequences of certain assumptions about the cancer mechanism. Form (i) would apply if the population is exposed to constant levels of an agent which increases one or more of the

cellular transition rates in a multistage progression to malignancy. Form (i) is also predicted with variable exposure if the agent affects only the last stage of a multistage process, say by enhancing the clonal growth of cells in the penultimate stage, or by increasing the rate at which they become malignant. Form (ii) on the other hand, is predicted if the agent induces cancer in one stage independently of the background mechanism, at a rate which does not vary with age at exposure.

The quite different consequences of (i) and (ii) show that limitation of study to subgroups of the population on the basis of age should be based upon additional evidence about the way the carcinogen acts. For example, the bronchial carcinomas found among workers exposed to chloromethyl methyl ether (CMME) were small cell in type and appeared as little as ten years after exposure. The carcinomas linked to cigarette smoking in the general population, however, are more often squamous cell in type and tend to occur late in life. This is evidence that CMME acts independently of and in fewer stages than cigarette smoking and other background exposures. Such evidence, either from experimental or epidemiologic data, would suggest restriction of study to the young.

Pochin's analysis (10) assumes that the extra rates for the exposed population are of form (ii). He concludes that confining study to malignancies fatal by age thirty-five would substantially reduce the time necessary to detect excess cancer mortality. However, the independence assumption associated with form (ii) seems highly untenable for this situation. It means that the additional radiation induces all cancers in one stage independently of the background radiation, the latter doing so in more than one stage. Since he assumes constant exposure for both populations, form (i) seems much more appropriate. As shown above, this implies that the study should be restricted to the elderly.

4. Conclusion

The preceding examples illustrate the sensitivity of risk predictions to certain assumptions in the underlying mathematical model. To avoid the misleading and erroneous predictions that can result from the use of models incorporating assumptions whose validity is questionable, the following steps should be taken.

First, state the assumptions used in a proposed model in terms that are clear to all who will use the model to assess risk. Second, assess the sensitivity of predictions to changes in model assumptions. When possible, uncertainty estimates should include a component due to the effects of altering assumptions. Third, scrutinize pivotal assumptions in light of the best available human and animal data. This is particularly important for those carcinogens with extensive human exposure. Fourth, stress inconsistencies between model assumptions and experimental or epidemiological observations. Investigators often regard the good fit of a putative model as evidence in its support, to the exclusion of competing theories. But a wide variety of models will generally fit the data equally well. The model fitting procedure will yield the most information when the data discriminates between theories because of their inconsistency with one or more assumptions. In this sense, mathematical theories are most successful when they fail. Finally, exclude value judgments from the quantitative procedures used to assess risk; instead include them explicitly in that part of the decision process concerned with cost-benefit analysis.

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Figure Legends

Fig. 1. A) Average number of pulmonary adenomas per mouse as a function of injected dose of ethyl carbonate measured in milligrams per weight of mouse.

B) Internal exposure versus injected dose in mice treated with ethyl carbonate (carbonyl- ^{14}C). Internal exposure, measured in milligram-hours per gram weight of mouse (mg-hrs/g), was estimated by computing the areas under the curves giving amount of expired and eliminated ^{14}C atom as a function of time after urethane injection, for times up to 24 hours. The calculations assume that at any instant the amount of unrecovered ^{14}C atom is still in the animal.

C) Mean tumor numbers versus estimated internal exposure. The straight lines in A) and C) connect extreme points. Reprinted with permission from White (12).

Fig. 2. Extra incidence of leukemia induced by ionizing radiations at different ages: patients irradiated for ankylosing spondylitis in Britain. Reprinted with permission from Doll (4).

Fig. 3. Incidence rate of occupational nasal sinus cancer in nickel refiners first employed at different ages. Reprinted with permission from Doll (4).

Figure 1A

Figure 1B

Figure 1C

Figure 2

Figure 3