COMPETING RISK THEORY AND RADIATION RISK ASSESSMENT

Peter G. Groer

Institute for Energy Analysis, Oak Ridge Associated Universities, Oak Ridge, TN, U.S.A.

The paper presents a summary of the research in competing risk theory during the last decade and applies some new statistical procedures to estimate cumulative distribution functions (c.d.f.), force of mortality, and latent period for radiation-induced malignancies. It is demonstrated that correction for competing risks influences the shape of dose-response curves, estimates of the latent period, and of the risk from ionizing radiations. We show the equivalence of the following concepts: force of mortality, hazard rate, and age or time specific incidence. This equivalence makes it possible to use procedures from reliability analysis and demography for radiation risk assessment. Two methods used by reliability analysts — hazard plotting and total time on test plots — are discussed in some detail and are applied to characterize the hazard rate in radiation carcinogenesis. C.d.f.'s with increasing, decreasing, or constant hazard rate have different shapes and are shown to yield different dose-response curves for continuous irradiation. We point out that the absolute risk is a sound estimator only if the force of mortality is constant for the exposed and the control group. Dose-response relationships that use the absolute risk as a measure for the effect turn out to be special cases of dose-response relationships that measure the effect with cumulative incidence. We explain how life tables — a popular demographic tool — should be used to calculate the risk to a population from a risk estimate obtained from another exposed population.

INTRODUCTION

The basic idea of competing risk theory was first outlined by Daniel Bernoulli in his "Memoir" published in 1760 (1). In this publication he attempted to answer the question: Is mandatory vaccination against smallpox beneficial, and what are the quantitative effects of vaccinations on the survival experience of a population (1)? Each individual was considered as exposed to two risks: death from smallpox and death from other causes. The analogous "modern" question is: Is exposure to a certain dose of ionizing radiation detrimental, and what are the quantitative effects of a radiation exposure on the survival experience of a population? Each indidivual is again subject to two competing risks: death from radiation-induced cancer and death from other causes not related to the radiation exposure. During the last few decades competing risk theory developed rapidly because of the need to answer very similar questions in reliability analysis. There a device can fail due to different failure modes, and it is desired, for example, to estimate the probability that the device will fail due to one particular failure mode not later than a certain time t. The life of a person or a device is therefore a non-negative random variable T [$P(T < 0) = 0$]. In the

field of radiation risk assessment, we are interested in the estimation and comparison of $F_T(t,D)$, the cumulative distribution function of T for a control population radiation dose (D = 0) and an exposed population (D > 0). T is the life length from exposure to death or diagnosis of a radiation-induced malignancy. In the following section we will introduce some concepts related to F_T and discuss their estimation and connection with dose-response curves.

CUMULATIVE HAZARD, DISTRIBUTION FUNCTIONS, AND DOSE-RESPONSE CURVES

If $F_T(t,D)$ or, for short, F is the c.d.f. for the life or in our context synonymously the tumor appearance time (latent period) after exposure then

$\bar{F} = 1 - F$ = survival function
$f = dF/dt = F'$ = probability density function
$h = f/\bar{F}$ = hazard function or age (time) specific tumor rate
$H = \int_0^t dt' h(t')$ = cumulative hazard

The arguments t,D have been suppressed for brevity. One easily sees that

$$F = 1 - \exp(-H) \qquad (1)$$

Intuitively $h(t,D)\Delta t$ can be interpreted as the conditional probability that an individual will die from a tumor in the interval $(t,t+\Delta t)$ having survived to age t. For this reason h is sometimes also called the force of mortality. Every c.d.f. of tumor appearance times has a corresponding force of mortality h(t). If $F = 1-\exp(-\lambda t)$, the force of mortality is λ = constant. This is a unique characterization of the exponential c.d.f. These probabilistic concepts and the different relationships among them are well known and very simple. The difficult aspect is the estimation of F, $\bar{F}$, or H from observed quantities. To understand why this is so, consider the following situation: Groups of N_i individuals are exposed to doses D_i $(i = 0,1,2...; D_0 = 0)$. The exposure is instantaneous and takes place at t = 0. As t increases, we observe for each dose group D_i a sequence of N_i indicators like

0,0,1,0,1,1,0,1,1,0,1,1,1,0,0,0,1,0,0

A "1" means in our context that the individual died from cancer possibly induced by radiation. A "0" means that the individual died from another cause, was lost from the study, or is still alive. Each 0 or 1 has associated with it the time when the event occurred. All the times where a 0 occurred can be considered as observations of a random time variable L. "L" stands for loss to indicate that the 0 — events represent lost information for the estimation of $F_T(t)$. The problem of estimating F if losses (0 — events) occur was solved by Kaplan and Meier (2) under the assumption that T and L are statistically independent. An estimator for H is also available in the literature (3,4).

A dose-response curve at a fixed time t_0 for instantaneously exposed individuals (e.g., atomic bomb survivors) can be defined as a

plot of $F_T(t_o,D_i)$ versus D_i on linear graph paper (5). This replaces the plotting of the ratio, number of tumors, n_i/number of individuals exposed, N_i. The magnitude of n_i/N_i is clearly influenced by the number of 0 — events (e.g., accidents) and does not measure solely the effect of the radiation exposure. The same dose D_i can therefore produce different effects — measured by n_i/N_i — depending on how many other deaths occur. Since $F_T(t_o,D_i)$ differs from this ratio, the shape of $F_T(t_o,D_i)$ versus D_i will differ in most cases from n_i/N_i versus D_i [see (5) for more details]. Most of the time the ratio n_i/N_i is used to measure the effect of D_i in exposed animals. In human epidemiological studies the fraction, n_i/total number of person-years, is used instead, and sometimes the difference $\Delta\lambda$ or ratio ρ of these fractions for an exposed and an unexposed group are plotted versus D_i [see e.g. (6)]. The fraction $\alpha = \Delta\lambda/D_i$ is the absolute risk, and the ratio ρ is the relative risk (6). Both are incorrect measures of the radiation risk because of hidden and unwarranted assumptions. To see the mistake, consider Equation 1. For $H \ll 1$, one obtains

$$F \approx H \tag{1'}$$

For the exponential distribution — cf. the earlier remark — $H = \lambda t$, where λ, the force of mortality, is constant. If F is exponential, λ can be estimated by n_i/total number of person-years (7), but the assumption of exponentiality (i.e., λ = constant) is incorrect for both the unexposed and the exposed group for time periods longer than two to three years [see e.g. (8)]. For spontaneous and radiation-induced cancer $h = h(t)$. This fact can be demonstrated by graphical techniques-hazard plotting (3,4) and total time on test (TTT) plots (9). If Equation 1' holds and the force of mortality is time dependent, then only $\Delta H = H(t_o,D_i) - H(t_o,D_o)$ and $H(t_o,D_i)/H(t_o,D_o)$ are meaningful measures of the radiation effect at t_o. The net radiation risk $R_N(t_o,D_i)$ at time t_o due to an instantaneous dose D_i should be defined as the difference of the cumulative incidences:

$$R_N(t_o,D_i) = F_T(t_o,D_i) - F_T(t_o,D_o) \tag{2}$$

This definition assumes that cancer is the only risk acting. If Equation 1' holds, $h_T(t,D_i) = \lambda_i$ = constant and $h_T(t,D_o) = \lambda_o$ = constant, then Equation 2 becomes

$$\begin{aligned} R_N(t_o,D_i) &\approx H_T(t_o,D_i) - H_T(t_o,D_o) \\ &= (\lambda_i-\lambda_o)t_o = \Delta\lambda t_o \end{aligned} \tag{3}$$

If in addition $\Delta\lambda = \alpha D_i$, then

$$R_N(t_o,D_i) \approx \alpha D_i t_o \tag{4}$$

The derivation of Equation 4 shows that the absolute risk concept and linear dose-response curves based on this concept are valid only under very special circumstances.

For continuous radiation exposure, the dose $D(t)$ is an increasing function of time. If $F_T(t)$ has been estimated, $G_D(d)$, the c.d.f. for

the random variable D, can be obtained by a simple transformation (10). For $D = \delta T$ — the simplest case with constant dose rate δ — one obtains $G_D(d) = Pr\{\text{tumor for } D \leq d\} = F_T(d/\delta)$. If $F_T \approx H_T$, then G_D increases like H_T. A plot of G_D versus d is a possible definition of the dose-response curve for continuous irradiation. The shape of G_D depends on the behavior of $H_T(t)$ and will be different for increasing (decreasing) hazard rate $h_T(t)$. A serious problem with this definition stems from the fact that one does not know up to what time after first exposure dose effectively induces cancer. The dose delivered after this time is "wasted." A deeper understanding of radiation carcinogenesis is necessary to solve the "wasted" radiation problem.

The general relationship $\bar{F} = \exp(-H)$ can be used to calculate the potential crude radiation risk from D_i at t_o to a so far unexposed population, if ΔH has been estimated from data on an exposed population. The survival function S(t) for the actual life of the population can be found in a life table. The crude radiation risk can then be defined as

$$R_C(t_o, D_i) = S(t_o)\ [1-\exp(-\Delta H)] \qquad (5)$$

The crude radiation risk in Equation 5 is the additional risk from radiation exposure in the presence of all other competing risks.

ACKNOWLEDGMENT

This paper is based on work performed under Contract Number DE-AC05-76OR00033 between the U.S. Department of Energy, Office of Health and Environmental Research, and Oak Ridge Associated Universities.

REFERENCES

1. Bernoulli, D. (1760): Memoires de Mathématique et de Physique de l'Académie Royale des Sciences, 1-45.
2. Kaplan, E.L., and Meier, P. (1958): J. Am. Stat. Assoc. 53, 457.
3. Nelson, W. (1972): Technometrics 14, 945.
4. Aalen, O. (1976): Scand. J. Stat. 3, 15.
5. Groer, P.G. (1978): Proc. Natl. Acad. Sci. USA 75, 4087.
6. National Academy of Sciences USA (1972): Report of the Adv. Comm. Bioi. Effects Ionizing Rad. (BEIR). National Academy of Sciences USA, Washington, D.C.
7. Epstein, B. (1960): Technometrics 2, 403.
8. Doll, R. (1971): J. R. Stat. Soc. A, 134, 133.
9. Barlow, R.E., and Campo, R. (1975): In: Reliability and Fault Tree Analysis, 451. SIAM, Philadelphia, PA.
10. Renyi, A. (1970): Probability Theory. North-Holland Publ. Co., Amsterdam-London.