Beyond Dose Response: Describing Long-Term Health Effects of Radiation Exposure

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Abstract

Radiation exposure is one of the most widely perceived and extensively studied environmental risk factors. Considerable effort is devoted to the development of radiation protection guidelines and regulations at the national and international level. In this presentation I discuss age- and time- patterns of the radiation-associated excess cancer risks indicating the limits of the traditional constant excess relative risks models and describing some alternative.

Introduction

Cohort studies of Japanese atomic bomb survivors are being conducted by the Radiation Effects Research Foundation (RERF) to characterize the long-term health effects of radiation. The RERF Life Span Study (LSS) includes more than 86,000 Japanese atomic bomb victims with individual dose estimates who were living in the cities in late 1950. There is virtually complete mortality follow-up since 1950 and cancer morbidity data are available from 1958. The results of recent analyses of these data are presented in (1-3). Data sets that can be used to reproduce the analyses in these reports are available from (www.rerf.or.jp).

The primary emphasis in the survivor studies was focused on the detection of exposure effects for solid cancer and leukemia and the computation of simple estimates of the risks associated with radiation exposure. However as the amount of relevant information has increased and it becomes clearer that radiation-related changes in disease rates persist throughout lifetime, increasing attention is being paid to issues other than basic questions about dose response. These issues include details about the shape of the dose response, as well as gender effects, age-at-exposure effects, and age-time-patterns of excess risk. There is increasing interest in descriptions of the excess risk in terms of both (excess) relative risks and excess rates.

The LSS solid cancer incidence data

Table 1 summarizes the LSS solid cancer incidence data for the period from 1958 through 1995. Although only seven dose categories are shown in this table, the analyses are carried out using a much more detailed person-year table with more than 24,000 records. The expected number of cases are based on a semi-parametric model in which rates for the unexposed are described using stratification on gender, city, age at exposure and birth cohort (more than 450 strata) with the radiation-associated excess relative risk modeled as a gender, age and age at exposure dependent linear function of dose.

Table 1: Atomic bomb survivor solid cancer incidence Hiroshima and Nagasaki 1958 - 1995

Dose (Sievert)	People	Person-years	Observed Cases	Expected Cases	Radiation-Associated Cases	Attributable fraction
< 0.005	34,582	1,003,500	4,845	4,842	3	0%
- 0.1	29,352	849,511	4,143	4,095	48	1%
- 0.2	5,316	151,970	871	789	82	9%
- 0.5	5,897	166,684	1,034	862	172	17%
- 1	3,057	86,252	614	427	187	30%
- 2	1,503	42,423	388	200	188	48%
2+	436	11,805	114	48	66	58%
Total	*80,143*	*2,312,145*	*12,009*	*11,263*	*746*	6%

The rightmost columns in this table clearly indicate a dose response although only about 6% of the 12,000 cancer cases are associated with the radiation exposure. Since radiation-associated cancers are (currently) indistinguishable from those in which radiation had no effect, careful statistical analyses are crucial to our understanding of the nature of radiation effects on cancer. Extensions and alternatives to the standard survival analysis methods and models are crucial to the understanding radiation risks on disease risks in the atomic bomb survivors.

Relative risk models: Multiplicative proportional hazards and excess relative risks

In the 30 years since publication of Cox's seminal paper on lifetable regression models (4) the log-linear (multiplicative) proportional hazards model and partial likelihood methods have come to dominate analyses of failure time data. The multiplicative proportional hazards (MPH) model can be written as

$$\lambda_0(a)\, e^{\beta z(a)} \qquad (1)$$

where $\lambda_0(a)$ is a baseline or background hazard that depends on age, *a,* and the parametric function $e^{\beta z(a)}$ describes the dependence of the hazard function on covariates *z(a).* In our work with the LSS data we have found it useful to consider generalized excess relative risk (ERR) models like

$$\lambda_0(a, z_0, \beta_0)\left(1+ \rho(d, \beta_d)\,\varepsilon(z_1(a), \beta_1)\right) \qquad (2)$$

where z_o are covariates (possibly time-dependent) that modify the baseline rates, $\rho(d, \beta_d)$ describes the shape of the dose response, and $\varepsilon(z_1(a), \beta_1)$ describes how the ERR varies with time or other factors. We typically use linear or simple non-linear (e.g. quadratic) functions of dose in $\rho(d, \beta_d)$ while effect modifiers and age-time effects on the ERR are modeled as log-linear functions of the factors of interest.

With suitable software, such as Epicure (5), models with this type of relative risk function can easily be fit using either partial likelihood methods for individual data or Poisson regression (6) for rates. With Poisson regression methods it is also easy to model the baseline rates explicitly.

The generalized ERR model presented here has several features that make it more attractive than the multiplicative proportional hazards model for modeling dose response data. Among these reasons are: a) simple models for the description of linear or concave downward dose response functions and b) description of effect modification in terms of relative changes in the excess risk rather than as changes relative to background rates. A careful analysis of the solid cancer incidence data described above based on the MPH model leads to the following descriptive model:

$$RR = \exp(0.67\,d - 0.13\,d^2 - 0.02(agex - 30)\,d + 0.004(agex - 30)\,d^2)$$

With some thought (and a plot or two) it is possible to see that the relative risk tends to decrease with age at exposure but further interpretation is difficult. An analysis based on the ERR model leads to the following descriptive model

$$RR = 1 + 0.60\,d\exp(-0.04(agex - 30))$$

which, despite having fewer parameters, describes the data somewhat better than the MPH model. Furthermore, interpretation is (fairly) simple: The excess risk is linear in dose but the risk per unit dose decreases with increasing age at exposure. For a person exposed at age 30 the ERR per Sievert (Sv) is 0.6. The ERR decreases (increases) by about 4% per year increase (decrease) in the age at exposure. A more thorough ERR analyses reveals a significant dependence on both gender and age at diagnosis. Considerably more effort in both analysis and interpretation is needed to reach these conclusions based on an MPH analysis.

Excess rate models

An unfortunate consequence of the dominance of Cox regression in the analysis of survival data is that insufficient attention is paid to excess rates. Analyses of excess rates can lead to important insights into the nature of the risk and interpretation of excess rates can be more straightforward than interpretation of relative risks. Furthermore, when rates are analyzed directly using Poisson regression methods it is no more difficult to work with excess rate (rate difference) models than with relative risk models. A useful, but simple excess absolute rate (EAR) model has the form:

$$\lambda_0(a, z_0, \beta_0) + \rho(d, \beta_d)\varepsilon(z_1(a), \beta_1) \qquad (3)$$

As in the ERR models described earlier, we typically use linear or quadratic models for the dose-response shape function and log-linear models for effect modification and age0-time patterns. One reason for the appeal of multiplicative models, such as (1) or (2), is that explicit modeling of the baseline hazard is unnecessary since stratified models are easily handled in by with either partial likelihood or Poisson regression methods. There has recently been some progress in the development of partial-likelihood-like methods for additive models (7). But more importantly, when rates are modeled using Poisson regression, baseline rates ($\lambda_0(a, z_0, \beta_0)$) can be described quite well using parametric, generally log-linear, models.

An EAR model for the LSS data that describes the data as well as the ERR model described earlier allows for gender specific increases in the EAR with age at diagnosis and a common age at exposure effect. The fitted models (in excess cases per 10,000 person years per Sv) are:

$$EAR = \begin{cases} 31\,d\,(\frac{age}{60})^{3.3}\,e^{-0.02(agex-30)} & \text{Male} \\ 39\,d\,(\frac{age}{60})^{2.0}\,e^{-0.02(agex-30)} & \text{Female} \end{cases}$$

Thus the excess rates for men increase in proportion to age at diagnosis cubed for men and age at diagnosis squared for women. For both sexes the excess rates appear to decrease with increasing age at exposure at a rate of about 20% per decade. This model illustrates one of the most important recent findings of the survivor studies —excess rates for solid cancers are increasing throughout life following exposure at any age.

References

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Resume

Au-delà de l'effet-dose: Description des effets à long terme, sur la santé de l'exposition aux radiations ionisantes.

L'exposition aux radiations est sans doute le facteur de risque lié à l'environnement le plus étudié mais aussi le plus sensible. D'importants moyens ont été consentis pour développer directives et règlements sur la radioprotection, au niveau national et international. Au cours de cette présentation, je discuterai du risque en excès de cancer lié aux radiations parmi les survivants de la bombe atomique, en fonction de l'âge et du temps, en indiquant les limites des modèles traditionnels de risque relatif. Je décrirai ensuite quelques modèles alternatifs utiles, impliquant risque relatif et risque attribuable.