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Joint Analysis of Site-specific Cancer Risks for the Atomic Bomb Survivors

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業績報告書シリーズ

原爆被爆者の部位別癌リスクに関する同時解析§

Joint Analysis of Site-specific Cancer Risks for the Atomic Bomb Survivors

Donald A. Pierce[a] Dale L. Preston[b]

要 約

原爆被爆者の部位別癌リスクを同時解析するための統計学的方法について述べる。このリスク・データに関する以前の解析は，白血病の場合を除いて，癌の病型に関係なく解析されたり，癌の病型または分類群ごとに分けて行われたりした。癌の病型を無視した解析は明らかに十分なものではない。病型または分類群ごとの解析に比べて同時解析の長所は主として次のとおりである。（1）種々の癌の病型に共通したパラメータをモデルに当てはめることができるので，関心の的となっている影響をより正確に推定できる。（2）病型別リスクの比較に有意性検定を使用できる。（3）性，被爆時年齢や被爆後経過時間などのリスク修飾因子についてより明確に理解できる。同時解析は単純明快な解析方法であり，通常の交差分割表によるデータ解析に癌の病型を示す因子をもう一つ組み込むことが主体となる。BEIR V 委員会によって検討が行われた消化器腫瘍，呼吸器腫瘍およびその他の充実性腫瘍の三つの癌の分類について解析する場合にこの方法を使用したので例示する。この解析に基づいて，BEIR V で用いられたモデルについて若干の批評を行う。我々が提案する方法は，相対リスクモデルにも絶対リスクモデルにも適用できるので，絶対過剰リスクにいくつかの具体的なモデルが使用できることについても若干の意見を述べる。同時解析の利点のいくつかは本報に示す結果から明らかであるが，もっと適当な癌の種類を選び，かつ診断がより正確な癌発生率データについてこの方法を使用することが重要である。

§本報告にはこの要約以外に訳文はない。承認 1991 年 11 月 19 日。印刷 1993 年 1 月。

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Technical Report Series

Joint Analysis of Site-specific Cancer Risks for the Atomic Bomb Survivors§

Donald A. Pierce, Ph.D.[a]; Dale L. Preston, Ph.D.[b]

Summary

Statistical methods are presented for joint analysis of site-specific cancer risks for the atomic-bomb survivors. Previous analyses of these data, aside from those on leukemia, have been made either without regard to cancer type, or separately for types or classes of cancers. Clearly, analyses without regard to cancer type are less than satisfactory. The primary advantages of joint, rather than separate, analyses are that (1) models can be fitted with parameters common to cancer types, which can allow more-precise estimation of effects of interest, (2) significance tests can be used to compare type-specific risks, and (3) a clearer understanding may be obtained of risk-modification factors such as sex, age at exposure, and time since exposure. Joint analysis is straightforward, entailing primarily the incorporation of another factor for cancer type in the usual cross-tabulation of the data for analysis. The use of these methods is illustrated in an analysis of three categories of cancer studied by the fifth Advisory Committee on the Biological Effects of Ionizing Radiation (BEIR V): digestive, respiratory, and other solid tumors. Based on this analysis, some criticism is made of the BEIR V–preferred models. Since the proposed methods are applicable to models for either relative or absolute risks, some comments on the use of explicit models for the absolute excess risk are also given. Although some of the gains from joint analysis are apparent from the results here, it will be important to use these methods with a more suitable choice of cancer classes and for cancer incidence data in which the diagnoses are more accurate.

Introduction

Previous analyses of the Radiation Effects Research Foundation (RERF) data on excess cancers other than leukemia among the atomic bomb (A-bomb) survivors have been done either for all cancers together or separately by cancer types or classes of types. In this report we discuss methods for joint analyses of data on several specific types or classes of types. Although results are given for three classes of cancers considered by the fifth Advisory Committee on the Biological

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Effects of Ionizing Radiation (BEIR V),[1] the primary aim is to indicate in a more general sense the advantages of such joint analyses. These advantages include not only improved comparison of general levels of excess risk by type but also opportunities for better understanding of variations in risk with sex, age at exposure, time since exposure, and age at risk.

Much of what is known about time and age patterns of excess risk in the RERF data has been learned from analyses of all cancers, except leukemia, as a group. We will refer to these as *pooled analyses*. In particular, this approach has indicated that, for a given age at exposure and sex, excess cancer risks tend to increase with time (or attained age) in a way similar to the increase in natural background risk with attained age. Also, it is suggested in this broad analysis that the ratio of sex-specific excess relative risks is reciprocal to the ratio of sex-specific background risks, so that the absolute excess risks for males and females are generally similar. Reports of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR),[2] BEIR III,[3] and RERF,[4–7] although using some analyses by cancer type, have relied mainly on pooled analyses to estimate overall risks. The BEIR V report[1] made extensive use of separate, type-specific analyses.

Analysis of all cancers except leukemia as a group is unsatisfactory in many respects. However, inferences regarding specific cancer types, or even classes such as respiratory cancers, are generally limited by the smaller number of cases. It is especially difficult to draw reliable conclusions about patterns of risk with time and age. Even differences by cancer type in general levels of excess risk, without regard to sex and modifying factors, are not well estimated. It is clear that the best approach, so far, has been to combine informally what can be learned from pooled analyses of all cancers with the apparent distinctions that arise in site-specific analyses. The right balance in this compromise, however, is difficult to achieve.

In this report we demonstrate a method for joint analysis of data on various types or classes of cancer. There are four primary advantages of such analysis, relative to either pooled analyses or separate analyses by cancer type.

1. The ability to formulate and test unified models, which may improve understanding of the effects on excess risk of sex, age at exposure, and time since exposure
2. The ability to fit models in which some parameters are common across cancer types and others are type-specific, which allows formal tests of hypotheses about similarities of various types
3. The availability of significance tests for comparison of type-specific risks, which makes it easier to appreciate the weakness of apparent contrasts between risk estimates obtained from separate analyses
4. The ability to use doses appropriate for each type of interest, which is not possible in pooled analyses

Joint analyses in which no parameters in the excess-relative-risk model depend on cancer type are equivalent to pooled analyses, except that it possible to use type-specific organ doses. At the other extreme, joint analyses in which all parameters in the model are type-specific give rise to the parameter estimates

that would be obtained from separate analyses. However, unlike separate analyses, joint analyses provide for formal comparison of type-specific parameter estimates.

Our approach is contrasted with that used in the BEIR V report,[1] which included separate analyses of leukemia; respiratory, digestive, and female breast tumors; and other solid tumors. Since female breast cancer appears to have special distinguishing features and the leukemia risks are quite different from those for other cancers, we have limited our analyses to the categories for respiratory, digestive, and other solid tumors. The categories of respiratory and digestive cancers were selected by the BEIR V committee because of the limited data on subtypes and the increased likelihood of errors in the cause of death as stated on the death certificate if finer categories had been used.

We intend to apply these methods to the tumor registry cancer incidence data, in which diagnoses are more accurate, and to use other classes or types of cancer. It may also be interesting to consider classes defined on the basis of the similarity of tissues, rather than on physical proximity.

Materials and Methods

The data used here are those of the Life Span Study (LSS) Report 11[4,5] in the format provided to the BEIR V committee. This data set, which is available on computer diskette from RERF,* summarizes cancer mortality during the period 1950–85 for 75,991 members of the RERF LSS cohort for whom dose estimates were available in 1988. Roughly half of the survivors in the cohort had significant exposures, whereas the remainder is a comparison group of survivors who were in the cities at the time of the bombings but received little or no radiation exposure. The data set contains the number of cancer deaths and person-years at risk cross-classified by city, sex, 10 kerma exposure categories, 5-year intervals of age at exposure, and 5-year intervals of follow-up. This cross-classification contains 3399 cells with nonzero time at risk. Other covariables, such as cell means for gamma-ray and neutron exposures and mean age of those at risk, are also provided.

Summaries for the digestive and respiratory cancer categories are given with precise definitions on the diskette. The other-solid-tumor category is here taken as the remaining nonleukemic cancers, excluding cancers of the breast, ovary, and prostate. Although one might wish to exclude other sex-specific cancers, the three excluded types are the only sex-specific cancers described on the diskette. Since our primary focus is on methodology and since we would like this analysis to be reproducible by others, we have limited attention to analyses that can be made using publicly available LSS data. Except for the exclusion of ovary and prostate from the other-solid-tumor ("Other") category, our groupings are identical to those used by BEIR V.

*To obtain copies of this data set on DOS-formatted floppy disk, contact the RERF Publication and Documentation Center, Administration and Support Section, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732 Japan. Facsimile: 81-82-263-7279. There is a charge of US $50 per disk. Please specify the type of disk required—3.5 or 5.25 in.

Sex-specific and age-at-exposure-specific transmission factors listed on the diskette were used to compute organ doses from the average whole-body gamma-ray and neutron kerma estimates for each cell in the person-year table. As in the BEIR V analyses, a dose equivalent in sievert obtained by summing the gamma-ray organ dose and 20 times the neutron organ dose was used to allow for the larger relative biological effectiveness (RBE) of neutrons. Since the neutron doses received by A-bomb survivors were small, our results are not sensitive to the choice of 20 for RBE. For separate or joint analysis of the three categories of cancers it is preferable to use doses for organs representative of each category. As in BEIR V, these are taken as "stomach" for digestive cancers, "lung" for respiratory cancers, and "intestine" for other cancers.

In the analyses for this paper, we have not adjusted for dose-estimation errors[8] because such adjustments would have little impact on the inferences of interest here and because we want to compare our results to those of BEIR V. The primary effect of such adjustments would be to increase excess risk estimates by 5%–10%. Dose estimates used in all analyses were computed using the original version of Dosimetry System 1986 (DS86).[9]

In these analyses, as in BEIR V, data were restricted to exclude (1) follow-up before 1955, to allow for a 10-year minimal latent period; (2) those with organ doses above 4 Sv, due to nonlinearity in dose response above that level; and (3) follow-up beyond 75 years of age, due to presumed inadequacy of death-certificate information beyond that age. With these exclusions there remain 2153 cells with nonzero time at risk. Although restriction (2) is important when focusing on the values of linear risk estimates, it is less important when investigating effects of sex and time. Some indication of the effect of dropping this restriction is given.

Appropriate statistical methods for joint analysis of risks for several types (or classes) of cancer are remarkably straightforward in principle. The theory for this is based on the idea of cause-specific hazard functions, as discussed in Kalbfleisch and Prentice[10] (Chapter 7), where it is shown that the likelihood function for such models can be written as the product of type-specific terms and that each term is identical to the likelihood obtained if that type were the only cause of death; that is, deaths from other causes are treated as censored. This means that, when the aim is simultaneous estimation of the risks for several types of cancer, problematic assumptions regarding independent competing risks are not required. This also means that, except for possible connections due to parameters in common to different cause-specific hazards, the risk for each type of cancer can be estimated as though it were the only type under consideration. We will provide details of the implementation of this after setting the stage in terms of the standard approach to analysis of these data.

The standard analyses of RERF cancer data are made using a grouped-data version of conventional survival analysis methods, namely semiparametric relative risk regression (Cox regression).[10,11] For analysis of a single type of cancer, this leads to treatment of the number of cancer deaths in each cell of the cross-tabulation described above as independent Poisson random variables. Strictly speaking, the Poisson probability model is not in principle correct; with certain approximations, however, the parameter estimates, their standard errors, and goodness-of-fit tests corresponding to this model are the same as those for an appropriate survival analysis formulation.[12–14] The primary approxima-

tion leading to the Poisson model involves treating the cancer risks as constant within follow-up intervals. Although this approximation alone leads to a likelihood identical to that of a Poisson model, the conventional usage of these methods also involves treating the rates as constant within cells defined by a cross-classification of follow-up time over other factors, such as age-at-exposure groups and dose.

More precisely, analysis is made as though the number of cancer deaths D_c in the cells $c = 1, \ldots, C$ of the cross-classified data are independent Poisson random variables with means $R_c\lambda_c$, where R_c is the person-years at risk and λ_c is the cancer rate for the cell. The term λ_c, which involves parameters to be estimated, represents the model to be fit.

For joint analysis of several types of cancer, this approach for grouped data generalizes as follows. For each cell of the table there are cancer deaths D_{ck}, for types $k = 1, \ldots, K$. The aim is to model the rates, λ_{ck}. The theory for inference about cause-specific hazard functions implies that this may be done as though all the observations D_{ck} were independent Poisson random variables with means $R_c\lambda_{ck}$. The treatment of observations on types as independent for each cell is not based on an assumption but follows from this theory. The models for the rates λ_{ck} will typically have some parameters common to types and others that are type-specific. Having all parameters type-specific would be equivalent to separate analyses; having all parameters common would be equivalent to pooled analyses.

In organizing the data for a joint analysis, cancer type is treated as a special kind of factor that differs from the other factors used to define the cross-classification in that person-years are accumulated for all persons at risk for each cancer type of interest. In practical terms this means that separate person tables are made for each type and that these tables are then appended to one another to create the data set used in the analyses. Since separate tables are made for each type, one can allow the dose variable (or other factors) to depend on type. Thus, it is simple to use organ doses appropriate for each type of interest. For the analyses in this paper, dose categories were determined by whole-body exposure kerma, which does not depend on type, and then, as noted earlier, type-specific organ dose estimates were computed using the mean gamma and neutron kerma values for each cell of the cross-tabulation.

Once the expanded tabulation has been made, joint analyses can be done using the same methods and software used at RERF.[15] The only change is that the cancer risk models depend upon type. Risks are modeled in terms of the available covariates: cancer type (k), city (c), sex (s), calendar time and time since exposure (t), age at exposure (e), age at risk ($a = e + t$), and dose (d_k). The variable t pertains to secular trends in cancer risks when used in the background rate and to time since exposure when used in the excess risk. Since $a = e + t$, it is not possible to distinguish fully between effects of all three of these variables; the variable a is mainly used in background rates, and (e,t) in the excess risk. The excess risk for cancers other than leukemia is remarkably linear in dose in the range 0–4 Sv,[16] and we will only consider models of this form since the concern here is not with extrapolation to low doses.

Models for the cancer rate, background plus excess, for a given type or class of cancer are usually taken as specializations of generic models of the following form

$$\mu_{csat} + d_k \varepsilon_{set} \tag{1}$$

or

$$\mu_{csat}[1 + d_k \rho_{set}] \quad . \tag{2}$$

The term μ_{csat} is the age-specific background risk. The terms ε_{set} and ρ_{set} are, respectively, the excess absolute risk and excess relative risk, per unit dose, for given sex, age at exposure, and time since exposure. The dose variable (d_k) is subscripted to indicate explicitly that different doses can be used for different cancer types. City differences in both relative and absolute excess risks are small (not statistically significant) and were not included in the models used in this report.

In fitting models in which the excess relative risk is constant in time, the variation in background rates with city, sex, age at risk, and time (μ_{csat}) is ordinarily accounted for by stratification. Although models with time-varying relative risks can also be fitted in this way, we chose to focus on analyses in which the background risk was modeled parametrically. Although it is straightforward to use stratified models, we feel that clearer interpretations of time trends in the relative risk are possible when parameter estimates for age trends in the background rates are available. In addition, the use of parametric background models facilitates comparisons with excess absolute risk models, for which our current software requires the use of fully specified models. In the models used here, the logarithm of the cancer rate was modeled as linear in log age with sex, city, and birth-cohort effects. The rate of increase in the rates with age was allowed to depend on sex. Although there is some evidence for nonlinearity in the relationships between log rate and log age, the restriction to linearity had little effect on inferences about the excess relative risk. Model comparisons were based on chi-square approximations to likelihood ratio tests, which provide more-reliable inferences than do tests based on point estimates and standard errors.

Results

Effects of sex and age at exposure in time-constant relative risk models

We first consider models in which the excess relative risk per unit dose is constant in time, given sex, and age at exposure. These models are cancer-type-specific models, of the form of Equation (2), in which ρ_{set} does not depend on t. Using these models we investigate the variation of baseline relative risks (defined below), sex effects, and age-at-exposure effects with type. After introducing the basic model and some additional notation we describe a special parameterization designed to assess a specific hypothesis about the nature of the effects of sex on the excess relative risk in these data. We then present the results of a series of analyses that test for the presence of the sex and age-at-exposure effects and for variability of these effects by type.

The specific model used here is of a form commonly used in both type-specific and pooled analyses of the RERF cancer mortality data. This model can be written

$$\mu_{kcsat}[1 + \beta_k \gamma_{s:k} \delta_{e:k} d_k] \quad , \tag{3}$$

where β_k is a baseline excess relative risk for type k, $\lambda_{s:k}$ is a modifier for sex within each type, and $\delta_{e:k}$ represents an age-at-exposure effect for each type. In this context, the *baseline* refers to type-specific risks for arbitrarily defined reference values of sex and age at exposure. Note that the baseline risk refers to radiation effects and should not be confused with *background* rates, which are rates in an unexposed population. In our models, the baseline risk is the unweighted geometric mean of the sex-specific risks for a person exposed at age 30 yr.

We were particularly interested in the sex effect since it is appears from previous analyses of the LSS data that the substantial sex effect in the excess relative risk may serve largely to offset sex effects in the background rates. That is, there may be little or no sex effect in the absolute excess risks. This is an important hypothesis, and joint analysis provides a better way to investigate it than either pooled or separate analyses. Investigation of this in pooled analyses cannot take advantage of the differences in background-rate sex effects among cancer types. This limitation is avoided in separate analyses, but the estimation of the type-specific sex effects is imprecise, and traditional methods offer no formal method for assessing the significance of variation in the type-specific estimates.

In terms of Equation (2), the hypothesis of interest regarding sex effects is, in essence, that for each β_k, the products $\mu_{kcsat}\gamma_{s:k}$ do not depend upon s, since these represent the contribution of sex effects to the absolute excess risk. Some approximation must be made in formulating a general model useful for investigating this, since the background rates μ_{kcsat} do not factor adequately into a form $\mu_{ks}\mu_{cat}$, primarily because the rates at which background rates increase with age depend considerably on sex.

The approximation made here is as follows. For each cancer type we compute a summary ratio, rr_k(m:f), of the male background rate to the female background rate as

$$rr_k\,(\text{m:f}) = \frac{D_{0km}/R_{0m}}{D_{0kf}/R_{0f}} \tag{4}$$

where D_{0km} and R_{0m} are, respectively, the numbers of deaths from cancer k and total person-years for males with DS86 total kerma less than 0.1 Gy and D_{0kf} and R_{0f} are the corresponding values for females. Then special values of the parameters $\gamma_{s:k}$, referred to as $\gamma^0_{s:k}$, are defined so that for each type the product of $\gamma^0_{s:k}$ and rr_k(m:f) does not depend on sex.

Finally, the relative risk in Equation (2) is re-expressed as

$$\mu_{kcsat}[1 + \beta_k (\gamma^0_{s:k})^{\theta} \delta_{e:k} d_k] \quad , \tag{5}$$

where θ is a parameter to be estimated from the data. When θ equals one this model corresponds to the hypothesis that the sex effect in the relative risk offsets

the sex ratio in background rates, as these were defined above. Values of θ other than one indicate a systematic departure from this hypothesis, and θ equal to zero corresponds to no sex effect in the excess relative risks. Also note that if rr_k(m:f) is identically equal to one, the sex effect parameter, θ, does not have a unique value.

When the above model was fit to the data, the estimate of θ was 1.04 ± 0.60. The likelihood ratio test of the hypothesis that θ equals one against the alternative that it is some other value resulted in a *P*-value of .95. Type-specific estimates of θ are also of interest. These are

Digestive: 1.09 ± 0.84
Respiratory: 0.96 ± 0.84
Other: 1.60 ± 7.30

The large standard error for the Other cancer category arises because the sex ratio in background rates is nearly one, in which case, as noted above, the issue under discussion has little meaning. This analysis adds some support to the interpretation that absolute excess risks do not depend on sex; however, this hypothesis deserves further investigation.

In the remainder of this subsection we focus our attention on the comparison of baseline risks by cancer type and age-at-exposure effects on the excess relative risk. Following a standard statistical approach, we began with a simple relative-risk (RR) model, $[1 + \beta d_k]$, and assess the importance of effects in a model of the form of Equation (3) by successively adding these effects to the model and monitoring the improvement in fit. This is done by first adding an age-at-exposure effect, followed by the sex effect, and then allowing these effects to depend

Table 1. Analysis of deviance for cancer type and effects of sex and age at exposure

Source of variation	df [a]	Chi-square	*P*-value
Age at exposure	1	13.80	.0002
Hypothesized sex effect (θ = 1)[b]	1	3.35	.07
All type effects	7	4.13	.76
Decomposed as			
Type (baseline)	2	0.48	.79
Type by age at exposure	2	3.58	.17
Type by sex[c]	3	0.07	.99

[a] df = degrees of freedom.

[b]This is a test of θ = 0 versus θ = 1, which is negligibly different from that of testing θ = 0 versus the maximum likelihood estimate θ = 1.04.

[c]This alternative allows sex effects to vary freely by cancer type, as a departure from the hypothesized sex effect.

on type. The aim is to find the simplest model that fits the data. The results are summarized in Table 1. The chi-square statistics in the table are likelihood ratio tests for the significance of the effect indicated in the *Source of variation* column.

This analysis shows that within the class of models in which the excess relative risk per unit dose is constant in time, for given type, sex, and age at exposure, there are no statistically significant effects associated with cancer type for the three categories considered. It is again emphasized that these categories were not chosen by the BEIR V committee because there is some reason to expect differences but rather to avoid using more-detailed, but less-precise type-specific estimates and to reduce effects of misclassification on death certificates. Interpretation of results for the Other cancer category is particularly difficult.

The restriction to those with dose less than 4 Sv has little effect on these results. The largest change is that the *P*-value for the type by age-at-exposure effect, that is, different slopes by type for log $\delta_{e:k}$ versus e, increases to .26. Although this effect is not statistically significant in either analysis, it is the only type-related effect for which there is even marginal evidence. It seems likely, on closer examination, that this effect has to do with something rather special about respiratory cancers. Only for this category is there any apparent difference between sexes for the age-at-exposure effect: women having an effect that is not dissimilar to that for other categories and men having a somewhat different effect. Such a distinction might be related to effects of cigarette smoking and will be explored elsewhere.

Effects of time on relative risk

We now turn to analyses of trends, with time since exposure, in the excess relative risk, focusing on evidence for a trend independent of cancer type and for differences by type in such trends. Joint analysis is more appropriate than a pooled analysis for this issue since differences in age-specific background risks may interfere with inferences about a common time trend in the relative risks in a pooled analysis. Also, only in this joint approach can one use models for excess risk in which some parameters depend on cancer type and others are common across types.

The model of interest here takes the form

$$\mu_{kcsat}[1 + \beta_k \gamma_{s:k} \delta_{e:k} \xi_{t:k} d_k] \quad , \tag{6}$$

where log ($\xi_{t:k}$) is linear in log (t), with slope possibly depending on k. This is the most commonly used form of model for time trends in the excess relative risk. The sex effect is taken as discussed above, fixing $\gamma_{s:k} = \gamma^0_{s:k}$; age-at-exposure effects, $\delta_{e:k}$, are modeled as described following Equation (3). Even though differences in the β_k are not significant, these parameters must be free to vary in models in which the slope of log ($\xi_{t:k}$) is allowed to depend on k. As noted earlier, parametric background-rate models were used for these analyses. In these models, the logarithm of the background rates were linear in log (a) with sex-specific slopes and intercepts. The background model also included a city effect not dependent on sex.

Table 2. Analysis of deviance for time trends in the excess relative risks using a parametric background model

Source of variation	df [a]	Chi-square	*P*-value
Common time trend	1	1.04	.31
Differences in time trend by type	2	0.53	.77

[a]df = degrees of freedom.

Table 2 presents an analysis of deviance for the time trends. There is no indication of statistical significance either for a trend in time common to types or for differences by type in such trends. These calculations are made using a model in which the age-at-exposure effects, $\delta_{e:k}$, do not depend on k, but the results are similar even if this interaction is included.

Despite the lack of statistical significance, the estimated time trends have an interesting feature that can be seen by comparing the slope estimates for the background and excess risks. The estimates of the slope of the log background rates in log age, averaged over sex, are 5.1 for digestive, 6.3 for respiratory, and 4.1 for Other. These differences are statistically highly significant. The estimates of slopes in log excess relative risk with log time are 0.37 ± 0.66 for digestive, -1.03 ± 0.97 for respiratory, and -0.26 ± 0.94 for Other. The point estimates of the time trend in the excess relative risk are roughly inversely related to the rate of increase in the background rates with age. This pattern of type-specific trends suggests, rather weakly, that the temporal pattern of the absolute excess risk may be more similar over types than that for the relative risks, and we return to this issue later in this section. When a model with a common time trend in the excess relative risk is fit to the data, the slope estimate is -0.53 ± 0.50.

The results of analyses in which a stratified-background-rate model was used are similar to those shown in Table 2. The primary change is that inclusion of a type by age-at-exposure effect reduces the *P*-value for a common trend with time to $P = .14$. The point estimates for the time trends are similar to those given above. Again, the restriction to those with dose less than 4 Sv has little effect on these results.

Comparison to BEIR V models

The BEIR V committee recommended, aside from issues involving low doses, use of models for these three categories of cancer that have relative risks of the form

$$[1 + \beta_k \gamma_{s:k} \delta_{e:k} \xi_{a:k} d_k] \quad . \tag{7}$$

Their approach involved exploring, separately for each type, forms for $\delta_{e:k}$ and $\zeta_{a:k}$ and electing a "best-fitting" form, including possible omission of either of these or of $\gamma_{s:k}$. The nature of the resulting models can be described roughly as follows:

Digestive

a) sex effect

b) age-at-exposure effect "step-function-like," dropping markedly at ages between 25–35 yr and constant outside this range

c) relative risk constant in time

Respiratory

a) sex effect

b) no age-at-exposure effect

c) decreasing relative risk with time since exposure

Other

a) no sex effect

b) age-at-exposure effect with logarithm decreasing linearly above age 10 yr

c) relative risk constant in time

Exploratory analyses reveal that these models do indeed describe the data reasonably well within the class of models described by Equation (7). A single parameter carrying the above age-at-exposure effect for digestive cancers does improve the fit relative to a log linear trend. There is a larger negative trend with time since exposure for respiratory cancers than for the other types. The BEIR committee realized that it was not statistically significant but chose to include that term largely because of further evidence for such an effect in the data on a cohort of patients irradiated to treat ankylosing spondylitis.[17] The estimated sex effect for the Other category is negligible. For this class the change in slope at 10 yr for the age-at-exposure effect was probably selected due to the large, but imprecise, estimate of relative risk for the very young that would arise without this feature. The BEIR V definition of the other-solid-tumor category is slightly different from that used here since we have excluded cancer of the ovary and prostate, but this has little effect.

Although the BEIR V models may be quite detailed, we have doubts about their usefulness in representing conclusions about the nature of radiogenic cancer risks. In particular, it seems likely that sampling variations have been overemphasized in the selection of specific models. Simpler descriptions may reflect the actual risks at least as accurately and may be more useful in many respects, such as in comparisons with the results of other studies or with the results of subsequent analyses of these data.

It is of interest to compare the BEIR V model to simpler descriptions, based on the model suggested by Table 1, with the relative risk taking the form

$$[1 + \beta\gamma^0_{s:k}\delta_e d_k] \quad , \tag{8}$$

where β is a common baseline excess relative risk independent of type, the sex effect is fixed at values offsetting sex ratios in background rates, and log δ_e is linear with slope independent of type. This model effectively has two parameters,

since the sex effect is not estimated from the apparent excess but from the large number of background cases. We do not claim that the Equation (8) model is the "true model." Rather, in the standard manner of statistical significance testing, we aim to assess the evidence against it provided by the BEIR V analysis.

The likelihood ratio chi-square statistic measuring the improvement of fit to the BEIR V model relative to the fit of the model described by the Equation (8) model is 10.2. The number of degrees of freedom to associate with this is not precisely defined. It is at least six, since there are eight explicit parameters in the BEIR V model and two in the Equation (8) model. But, the BEIR V model was arrived at by exploratory analysis, in which many parameters were considered, and the final model was chosen to include the most significant ones. The "step-function-like" effect for age at exposure in digestive cancers would, in particular, require a rich a priori parametric specification to arise formally. If that effect is modeled in the more conventional way, with log $\delta_{e:k}$ linear in e, the deviance for the BEIR V model increases by 5.3, and the chi-square statistic comparing the BEIR V model to the Equation (8) model reduces to 4.9. We believe it is fair to say that, if indeed the Equation (8) model were correct, the chance that the approach of the BEIR V committee would have led to a model fitting better than the Equation (8) model, to the extent of a chi-square of 10.2, would exceed 50%.

Models for the excess absolute risk

There are several reasons to consider explicit models for the excess absolute risk, as a function of time since exposure. The excess absolute risk has been seen to differ less by sex than dose the excess relative risk. Although the constant relative-risk model provides a useful summary of the data, there is little, if any, reason to believe that it is the "true model." There is some evidence, although not strong, that the excess relative risk may decrease with time, especially in the younger survivors.[4,18] Models for the excess relative risk lose much of their appeal and interpretability when the relative risk is taken to vary with time, in which case descriptions of the time dependence of the excess absolute risk may be at least as useful.

It is useful to formulate excess absolute risk models of the form:

$$\mu_{kcsat} + \beta_k \gamma_{s:k} \delta_{e:k} \varepsilon_{t:k} d_k \quad . \tag{9}$$

The conventional approach involves the use of a parametric specification of the background rates. In these analyses we have used a background model of the same form as presented for the Equation (6) model.

We consider models for the absolute excess risk of the form of the Equation (9) model with log ($\varepsilon_{t:k}$) linear in log (t), where the slope may depend on k. As in Equation (3) we take log ($\delta_{t:k}$) to be linear in e. Further, since the analyses summarized in Table 2 provide no evidence against the hypothesis that the baseline excess *relative* risks are independent of type, we express the models so as to give this hypothesis prominence. This is done using an approach analogous to the treatment of sex effects in the relative-risk models. That is, the "hypothesized" type effect will correspond to constraining the ratios of the β_k in Equation (9) to agree with the ratios of background risks for the three cancer

categories. These ratios, as computed from that portion of the LSS subcohort with DS86 dose estimates less than 0.1 Sv, are 1.98 for Digestive:Other and 0.50 for Respiratory:Other.

Table 3 presents an analysis of deviance table, describing evidence for successively added effects in the Equation (9) model. The *P*-value of .01 for "Hypothesized type effect" pertains to a test of no dose effect against the alternative of an effect of the hypothesized form; that is, that the excess for each type is proportional to the background risk for that type. The *P*-value of .92 for "Type (departure from hypothesis)" indicates that there is no evidence at all against the hypothesized form for this. There is a strong age-at-exposure effect in the absolute excess risk, opposite in sense to that found in the relative excess risk. That is, at any given time since exposure those who were older at exposure have greater absolute excess risks. There is a strongly increasing time-since-exposure effect and, as indicated earlier, no significant sex effect. Aside from the dose effect, which includes type effects of the hypothesized form, there is no statistically significant evidence of type effects in the absolute excess risk. Type-specific parameter estimates, for effects of age at exposure and time since exposure, show considerable variation, but they are not well enough estimated for these differences to be statistically significant.

This analysis indicates there is no significant lack of fit to a model for the absolute excess risk of form

$$\beta \rho_k^0 \delta_e \varepsilon_t d_k \quad , \tag{10}$$

where the ρ_k^0 are fixed numbers corresponding to ratios of background rates, log (δ_e) is linear in e, and log (ε_t) is linear in log (t), where neither slope depends on

Table 3. Analysis of deviance table for excess absolute risk models

Source of variation	df[a]	Chi-square	*P*-value
Dose effect (of hypothesized form)[b]	1	6.57	.01
Age at exposure (log linear)	1	16.24	.0001
Time since exposure (log linear)	1	11.68	.0006
Sex	1	0.003	.98
All other type effects	7	6.65	.57
Decomposed as			
Type (departure from hypothesis)	2	0.16	.92
Type by age at exposure	2	2.94	.23
Type by sex	2	0.42	.81
Type by time since exposure	2	3.13	.2

[a]df = degrees of freedom.

[b]Under the hypothesized dose-response model, the excess absolute risk for each type is proportional to the average background risk for that type.

type. Comparison of this model to the Equation (6) model for the relative excess risk is discussed below.

Discussion and Conclusions

We preface this section with some perspective on the evolution of statistical methods for the A-bomb survivor data. The methods developed and used during the 1970s were Mantel–Haenszel-like procedures designed for testing for the presence of a significant dose response.[19] Since there was clearly a significant effect for leukemia and for all cancers except leukemia together, the primary use of these methods was in analyses of data for specific cancer types. These methods are not readily extended from hypothesis testing to parameter estimation. The estimation methods used, eg, by the BEIR III committee,[3] involved regression analyses of the data after "collapsing" over the follow-up time. These regressions, which were usually carried out separately for various sex and age-at-exposure groups, were done using the number of cases and person-years at risk for the entire follow-up without regard to age at risk and time since exposure. This approach has two primary inadequacies: (1) it does not lend itself well to studying effects of time since exposure, which has become an issue of primary interest, and (2) it does not properly control for age at risk, which dominates all other factors (including radiation effects) in affecting cancer rates.

By the late 1970s it became clear that survival analysis methods developed by Cox,[11] being ideally suited for dealing with the two points raised above, should form the basis for analyses of these data. Implementation of these methods for such a large data set was, however, not feasible without further development. In the early 1980s, based on an important observation by Holford[12] on connections between survival analysis for grouped data and Poisson regression models, the authors developed methods and computer programs for the analysis these data.[20–24]

Others[12,14,25–28] were also developing similar methods for cohort studies more generally. The new methods and software came into full use for the RERF cancer data in LSS Report 10,[6] and since then they have been the primary statistical basis for all RERF reports and many other reports on radiation effects on cancer.

The ability to carry out more-incisive analyses, particularly in regard to effects of age at exposure and time since exposure, may have led to increased emphasis on pooled analyses of all cancers except leukemia. The weaknesses of such pooling were to an extent understood. However, even more clear was the dilemma that, with some exceptions such as breast cancer, the data on specific cancer types are too limited to present a clear picture from these more-detailed analyses. The possibilities for overfitting the data, that is, drawing distinctions for which there is no statistical support, is one of the most serious problems facing those who analyze the RERF cancer data.

We feel that the type of statistical methods presented here are naturally suited to dealing with these difficulties. They do not remove them but provide tools that, if thoughtfully used, may allow progress on these difficult issues. This application has been mainly for illustrative purposes. The remainder of the discussion is oriented toward more-general use of these methods.

One reason that these methods have not been used before is that they are computationally intensive. The cross-tabulation used by the BEIR V committee, after the three restrictions described earlier, contained 2153 cells. For our analyses this was simply "replicated" for each of the three cancer categories, giving 6459 cells. This would have been difficult to deal with 10 yr ago, but now the fitting of models such as those used in this report takes at most a few minutes on a fast personal computer.

With some modifications, it would be computationally feasible to carry out joint analyses for up to about 10 types of cancer. The tabulation used here has 10 dose categories, but for fitting models linear in dose about half as many would suffice. Other reorganizations of the cross-tabulation might also be useful. The more-serious difficulty is not the size of the cross-tabulation involved but the potential complexity of models and the number of parameters to be considered.

The specific software used (the AMFIT program from the EPICURE risk modeling package) is important in this, since it allows for large numbers of stratum parameters and flexible model formulation. This computer program is especially well suited for models such as the Equation (6) model, in which the excess risk involves products of terms. Analysis with parametric background models rather than stratification, as used for Table 2, requires more computation. For joint analysis of larger numbers of types, it would probably be best to fit background models for each type in separate analyses, using the conventional simple model of recent RERF reports for the excess relative risk. Then, since the parameter estimates for the background models change little under different models for the excess risk, these could be taken as fixed for the joint analysis.

If this were done the proliferation of parameters would be mainly of concern only for the dose-response part of the model, and here the computational difficulties are less critical than the statistical and scientific issues. Strategies are needed for the systematic investigation of the issues of interest, in a way likely to succeed. For example, further examination of the "hypothesized" sex effect discussed above would be useful. It seems unlikely that an analysis of the form given in Table 1, for some collection of 10 categories, eg, will show any statistically significant type effects. As the number of types increases, the statistical power of tests becomes more diffuse and the number of cases per type will be smaller as well.

Failure to find statistically significant type-specific differences does not mean that they do not exist. However, a recognition on biological grounds that there are likely to be real differences should not lead to uncritical acceptance of poorly estimated apparent differences. There is a substantial scientific and statistical challenge in dealing with these issues. The methods suggested here seem especially well suited to this endeavor, but progress will depend on using them carefully and creatively.

Much of the gain in type-specific modeling will be better understanding of basic forms of models for the excess risk. For example, the observation made previously in pooled analyses that the sex effect in the excess relative risk is small becomes more meaningful when it is seen, as was shown earlier, that this is true for each of the three cancer categories considered. Comparisons of simple models for relative and absolute excess risks are much-more incisive when these models are type-specific.

It is remarkable that neither the simple two-parameter model for the relative excess risk,

$$[1 + \beta\gamma^0_{s:k}\delta_e d_k] \quad , \tag{11}$$

nor the simple three-parameter model for the absolute excess risk discussed before,

$$\beta\rho^0_k\delta_e\varepsilon_t d \quad , \tag{12}$$

is significantly improved by further distinctions among the cancer types considered here. Although suitably general relative and absolute risk models provide similar fits to the LSS data to date, models of the form of the Equation (11) model are more in line with current interpretations of the LSS data. Pooled analyses are often interpreted in terms of relative risks, and such models were the basis of the separate analyses in BEIR V.

The model represented by Equation (11) appears to be slightly simpler than that represented by Equation (12), since the latter requires the term ε_t to describe the increase in absolute excess risk with time since exposure. Although the Equation (11) model is certainly useful in providing a succinct description of the data, we see no statistical or biological reason to think that it is any more true than the Equation (12) model. The latter is also quite simple and provides a description of the data that may be equally important. Moreover, the apparent complexity of the Equation (12) model is mitigated by the fact that a primary issue from the viewpoint of the Equation (11) model is possible evidence of additional dependence on time since exposure. Models for the excess relative risk with such time dependence are no simpler, and, indeed, can be harder to interpret, than those for the absolute excess risk.

The examples in this report were intended mainly to illustrate the methods for type-specific analyses and to make some points regarding the BEIR V models. They do not go far towards what might be learned in cancer-type-specific analyses, largely due to inadequacies in the classification of cancers used. Much more might be learned through application of these methods to data on cancer incidence in which diagnoses are more accurate and in which categories can be used that have a more-rational biological basis. Work of this nature will be carried out in the near future.

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