RADIATION RESEARCH **159**, 511–520 (2003)
0033-7587/03 $5.00

Joint Effects of Radiation and Smoking on Lung Cancer Risk among Atomic Bomb Survivors

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Pierce, D. A., Sharp, G. B. and Mabuchi, K. Joint Effects of Radiation and Smoking on Lung Cancer Risk among Atomic Bomb Survivors. *Radiat. Res.* 159, 511–520 (2003).

Results are given on the joint effect of radiation exposure and cigarette smoking on lung cancer risks among A-bomb survivors, based on 592 cases through 1994. Information on smoking was derived from mail surveys and clinical interviews of 45,113 persons in the Radiation Effects Research Foundation cohort. Radiation and smoking effects on lung cancer are found to be significantly sub-multiplicative and quite consistent with additivity. The smoking relative risk, previously very low in studies of this cohort, is now similar to that found in Western populations. This increase is likely to be related to the scarcity of cigarettes during and after the war. The smoking relative risk depends little on sex. After adjusting for smoking, the radiation-related risks relative to background rates for nonsmokers are similar to those for other solid cancers: a sex-averaged ERR/Sv of about 0.9 with a female:male sex ratio of about 1.6. Adjusting for smoking removes a spuriously large female:male ratio in radiation relative risk due to confounding between sex and smoking level. The adjustment also removes an artifactual age-at-exposure effect in the radiation relative risk, opposite in direction to other cancers, which is due to birth cohort variation in lung cancer rates.

INTRODUCTION

We investigated the joint effects of cigarette smoking and radiation on lung cancer rates among A-bomb survivors followed up by the Radiation Effects Research Foundation (RERF).[2] The information on smoking is derived from mail surveys aimed at the entire cohort and from interviews of the subcohort involved in the RERF clinical follow-up. Data on lung cancer incidence through 1994 were used, starting follow-up at the time of the first information on smoking. In the subcohort for whom adequate information on smoking is available, there are about 600 lung cancer cases, of which we estimate about 50 to be related to radiation and about 320 to be related to smoking. Since there is essentially no correlation between radiation and smoking levels, those estimates can be made simply and do not depend on considerations of this paper.

Table 1, although hypothetical and oversimplified, is realistic enough to provide some perspective on the aims and limitations of our investigation. The radiation levels indicated there are in the context of RERF A-bomb survivors. Interest in this area focuses on notions of multiplicative and additive effects, both being idealizations. For joint exposures in Table 1, the upper relative risk (RR) in each cell corresponds to an additive effect and the lower value to a multiplicative effect. Note that the differences between these are rather modest except for those at the highest levels of both exposures. There are only a few hundred persons in our study with both high radiation exposures and heavy smoking exposures, making it challenging to distinguish between the two types of joint effect. Previous RERF studies found much smaller apparent smoking risks than presumed in Table 1, leading to an inability to distinguish between multiplicative and additive effects. In this report the apparent smoking risks are much higher than before, leading to more success in that endeavor.

Reasons to be interested in such distinctions, and the nature of the joint effects more generally, include:

1. The possibility of misleading inferences about radiation risks among A-bomb survivors when ignoring smoking effects.
2. More generally, to aid in generalizing from this study to settings with different smoking patterns, and from other radiation studies where there is either a limited scope of smoking variation or no smoking information.
3. Possible insights regarding mechanisms of both radiation and smoking in carcinogenesis.

Previous investigations of the joint effect of smoking and radiation in the RERF cohort include those by Prentice *et al.* (*1*) and Kopecky *et al.* (*2*). Prentice *et al.* found the joint

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[2] Abbreviations used: AHS, Adult Health Study; BEIR, Biological Effects of Ionizing Radiation; ERR, excess relative risk; LSS, Life Span Study; RR, relative risk = 1+ERR; RERF, Radiation Effects Research Foundation.

TABLE 1
Hypothetical Relative Risks Corresponding to Additive and Multiplicative Joint Effects

	Radiation		
Smoking	None	Moderate	High
None	1	1.25	1.5
Moderate	10	10.25	10.5
		12.5	15.0
Heavy	20	20.25	20.5
		25	30

TABLE 2
Numbers of Persons Providing Information on Smoking during Various Age Ranges

First information	Last information					
Ages	<40	40–50	50–60	60–70	70–80	>80
<40	1460	3059	3320	1026		
40–50		2612	3862	3088	810	
50–60			5232	3698	2189	503
60–70				4843	2276	1335
70–80					2976	1134
>80						1690

effects to be significantly sub-multiplicative for solid cancers in general, but for lung cancer they could not distinguish statistically, based on 281 cases, between additive and multiplicative effects. Kopecky *et al.* found no statistically significant departure from an additive model, based on 351 lung cancer cases, but did not evaluate the fit to a multiplicative model. However, analysis of closely related A-bomb survivor data by the National Academy of Sciences BEIR IV Committee (*3*, Appendix VII) indicated compatibility with either multiplicative or additive models. As indicated above, our results differ from all these studies because the apparent smoking risk in this cohort has greatly increased since those studies, for reasons that will be considered.

The National Academy of Sciences BEIR IV Committee (*3*) and BEIR VI Committee (*4*) studied the joint effects of smoking and radon exposure on lung cancer risk for selected cohorts of underground miners. For a Chinese cohort with 936 cases they found sub-additive effects, and for a Colorado cohort with 377 cases they found significant departure from additivity and slightly but not significantly sub-multiplicative effects. For the remaining cohorts, with smaller numbers of cases, there was no ability to distinguish between additive and multiplicative models. The results of a Swedish study of residential radon exposure by Pershagen *et al.* (*5*), which was based on 1360 lung cancer cases, were interpreted as showing smoking and radon effects significantly greater than additive and closer to multiplicative, but we will comment on this interpretation in the final section. We note that the dose mechanism for radon progeny in the lungs is very different (*4*, Appendix B) from that for external exposures of A-bomb survivors, and it would not be implausible that the smoking effect on radiation risks is different for the two settings.

MATERIALS AND METHODS

Study Population and Follow-up

The basis for the study is the merging of data on lung cancer incidence in the RERF A-bomb survivor cohort, routinely gathered on all cancer types for more general purposes (*6*), with information on smoking obtained in several mail surveys and clinical interviews between 1964 and 1992. This merging resulted in the follow-up of 45,113 persons from 1958 through 1994, the time when the tumor registries first became adequate through the latest time with adequate registry information when this study began. During that follow-up, 592 first primary lung cancer cases were reported.

The framework for the investigation is the RERF Life Span Study (LSS) comprising about 100,000 A-bomb survivors followed up through death certificate and tumor registry information. Information on smoking was obtained from mail surveys of the LSS members carried out in 1965 (males age 40–70 only), 1970 (females only), 1980 and 1992. The mail survey response rates averaged about 70%. Information on smoking was additionally obtained within the Adult Health Study (AHS), a subset of LSS members followed up by biennial clinical examinations, initially in 1958 numbering about 20,000. Relevant interview programs in the AHS were conducted with all participants in 1963–1964, 1964–1968, 1968–1970 and 1980–1993.

RERF cancer incidence studies are limited to about 80,000 of the 100,000 LSS members mentioned above, first to about 87,000 for whom radiation dose estimates can be made, and further to those who were alive and cancer-free in 1958 when the tumor registry information in the two cities became sufficiently complete. In that cohort of 80,000 there were 1154 first primary lung cancer cases during 1958–1994. Of that same cohort, about 54,300 responded to at least one mail or clinical survey, among whom there were 722 lung cancer cases from the time of first survey through 1994. Of these, about 2,400 had either totally missing or inconsistent information on smoking, leaving about 51,900 with valid information, presenting 680 lung cancer cases. About 6,800 of these persons reported stopping smoking in their latest response, and for reasons discussed below we have eliminated these from the analysis. This leaves for the analysis here a total of 45,113 persons presenting 592 lung cancer cases. Table 2 indicates the age ranges during which information on smoking was obtained for these individuals. For example, there were 2189 individuals who first reported smoking information during age range 50–60 and last reported during age range 70–80.

Ideally, in evaluating age-specific lung cancer rates, one should attempt to use each person's entire smoking history to that age: age starting, variations in smoking rate with age, and age stopping for those who do. However, it would be very difficult to incorporate all this information into smoking risk analysis even if the detailed information were exactly available. Moreover, as in most epidemiological studies, what is available in our study is in many respects very far from this ideal. We make one simplification by considering only those we can presume to be continuing or never smokers, omitting those who reported stopping. This is largely to simplify analytical issues, but it is also because we found that a large proportion of those who reported having stopped and responded to later surveys reported smoking again (about 70% for men, 20% for women). What bias there is regarding the matter of cessation of smoking, regarding risks for continuing smokers, will not come from omitting those who reported stopping but will come from including those who may have stopped after the survey information was collected. Although this results in some underestimation of smoking risks and should be kept in mind, the difficulty is unavoidable. We also do not attempt to use reported information on the age at which smoking started. Again, a primary reason

is the analytical difficulty of using such information even if it were perfectly available. But there is a special and important issue in this regard for which we do attempt to make some allowance in a way that may be better than using the reported age at which smoking started. Cigarettes were very scarce in Japan during and shortly after the war. This introduces birth cohort variation in the discrepancy between reported smoking levels and the extent of smoking at early ages. Our allowance for this consists of estimating the birth cohort dependence of the smoking relative risk.

In regard to these many uncertainties and analytical difficulties, we emphasize that it is not the aim here to carefully quantify the complex matter of smoking risks for lung cancer, but only to obtain a general idea of how smoking level affects radiation risk. For these reasons we simply categorize persons into smoking rate groups of 0, 1–15, 16–25 and >25 cigarettes per day, based on the mean of the smoking rates reported by each person on the one or more surveys to which they responded, not only grouping on average reported smoking rate but also ignoring inadequate information on age starting and omitting those who reported stopping.

The information on cancer incidence was obtained from the Hiroshima and Nagasaki tumor registries (*6*). Judging from the small proportion of cancer cases identified from death certificates only, case ascertainment through 1994 was adequate at the time work on this paper began. Information is not available on migration of individual LSS members from the registry catchment areas, so as in all RERF reports on cancer incidence, a statistical adjustment of the cohort person-years is made to allow for this. This adjustment is based on historical information on individuals in the AHS, with person-year adjustment factors being specific to sex, birth cohort, and calendar time (*7*).

For analysis, the data are summarized into a detailed cross-tabulation of cases and person-years. The marginal factors of the cross-tabulation are city, sex and categories of attained age, calendar time, birth cohort, radiation dose, and cigarettes per day. Age, time and birth cohort categories are 5 years. Smoking categories are 0, 1–15, 16–25, 26–35, and >35 cigarettes per day, although the last two categories are combined for analyses. These categories were chosen to best deal with some limitations of the various questionnaires. Radiation dose has 12 categories, with cut points 0.005, 0.02, 0.05, 0.1, 0.2, 0.5, 0.75, 1.0, 1.5, 2 and 3 Sv.

The dose used is that to the lung as provided by the RERF DS86 dosimetry system, with a weighting factor of 10 for neutrons relative to γ rays. Although survivors with dose estimates >4 Sv are not omitted here, as in some reports, doses in that range are truncated to 4 Sv as in current LSS reports.

It sometimes provides helpful perspective on the results reported here to compare them to results for other solid cancers in the general LSS study, ignoring smoking, since information on smoking is not available for the full cohort. This is done informally without documentation, using LSS cancer incidence data through 1995 that will be the basis for a forthcoming RERF general report. However, such results are similar to those reported in ref. (*8*).

Statistical Methods

The simplest mode of analysis, but of limited value for the needs, consists of estimating the radiation relative risk in the usual manner but with stratification on smoking level in addition to the usual factors of age, birth cohort and gender. The resulting radiation risk estimate for each smoking level is relative to those at the same smoking level with no radiation exposure. The stratification on age in 5-year intervals can be thought of as essentially equivalent to Cox regression (*9*) of ages at cancer incidence, where the age dependence in baseline cancer rates is taken as an arbitrary function of age. We used birth cohort stratification in 10-year intervals, rather than the 5-year intervals of the data tabulation. Analysis is greatly simplified by taking the radiation ERR as linear in radiation dose, which is generally very adequate for RERF cancer data. For almost any cancer type in the RERF studies, the ERR/Sv depends on gender and either (attained) age or age at exposure. In this instance there is a substantial effect of age but not of age at exposure, and to avoid more restrictive assumptions we approximate the age effects as unrestricted constants within five categories of age with cut points {40, 50, 60, 70}. As an approximation it is assumed that the gender and age effects in the radiation ERR are the same for smoking levels. In the following we write *a* for age, *b* for birth cohort, *g* for gender, and *s* for smoking level.

The analysis just described corresponds to a model for lung cancer rates of form

$$rate(a,b,g,s,d) = \nu_{a,b,g,s}\{1 + (\beta_s d)\delta_g\varphi_a\}, \tag{1}$$

where the $\nu_{a,b,g,s}$ are stratum parameters representing background rates (specific to smoking level), d is radiation dose (Sv), β is the smoking-specific radiation ERR/Sv, δ_g represents the gender effect in the radiation ERR, and φ_a represents the age variation in the radiation ERR as described above. This model makes no strong assumptions regarding joint effects of radiation and smoking because the parameter β_s is allowed to vary with smoking level. A model representing multiplicative effects is obtained by taking $\beta_s \equiv \beta$, not depending on smoking level. This provides a significance test for departure from multiplicative effects, but analysis along these lines does not lend itself well to investigation of additivity or to investigation of smoking risks or the most useful representation of radiation effects adjusted for smoking.

For these further purposes we need an explicit model for the smoking relative risks and proceed as follows. Ignoring radiation for the moment, we consider a model of the form

$$rate(a,b,g,s) = \nu_{a,b,g}\{1 + \theta_{g,s}\xi_a\eta_{g,b}\}, \tag{2}$$

where stratum parameters $\nu_{a,b,g}$ represent lung cancer rates for nonsmokers and the relative risk depends on smoking level, gender, birth cohort and age. The parameters $\theta_{g,s}$ representing the smoking ERR vary freely for each sex with the categorical smoking levels {0, 1–15, 15–25, >25}. The modifying effects of age and birth cohort are taken to apply equally to all smoking levels. The parameters ξ_a are defined in terms of categories of age analogously to those defined above for the radiation ERR. The parameters $\eta_{g,b}$ are defined in terms of birth cohort categories that correspond to ages at the time of bombings {<20, 20–40, >40}.

This model is extended in two ways to incorporate radiation effects. One is simply a modification of model (1) using the explicit model for smoking RR, namely

$$rate(a,\ b,\ g,\ s,\ d) = \nu_{a,b,g}\{1 + \theta_{g,s}\xi_a\eta_{g,b}\}\{1 + (\beta_s d)\delta_g\varphi_a\}. \tag{3}$$

The final factor has the same interpretation as in Eq. (1), and in particular if we take $\beta \equiv \beta$ this is a multiplicative model.

More importantly, the explicit model for smoking RR provides for another model of form

$$rate(a,\ b,\ g,\ s,\ d) = \nu_{a,b,g}\{1 + \theta_{a,b,g}\xi_a\eta_{g,b} + (\alpha_s d)\delta_g\varphi_a\}, \tag{4}$$

where α_s is a smoking-specific excess relative risk, relative to the background rates for nonsmokers, modified as before by parameters for effect of gender and age. If we take $\alpha_s \equiv \alpha$, this corresponds to an additive model. Models (3) and (4) are both free of the multiplicative-additive assumptions, and although they are very similar, they are not identical. For inferences about smoking effects, and radiation effects adjusted for smoking, some use is made of the simplification of Eq. (4) where $\theta_{g,s}$ is factored as the product of gender and smoking effects, and the parameters $\eta_{g,b}$ are taken as gender-specific third-degree polynomials in birth year.

All models are fitted using the rate analysis program AMFIT in the Epicure suite of programs (*10*), using the cross-tabulated data described at the end of the previous subsection. Significance tests are done by χ^2 approximations to likelihood ratio tests. Special statistical methods are used to reduce bias due to imprecision of dose estimates (*11*).

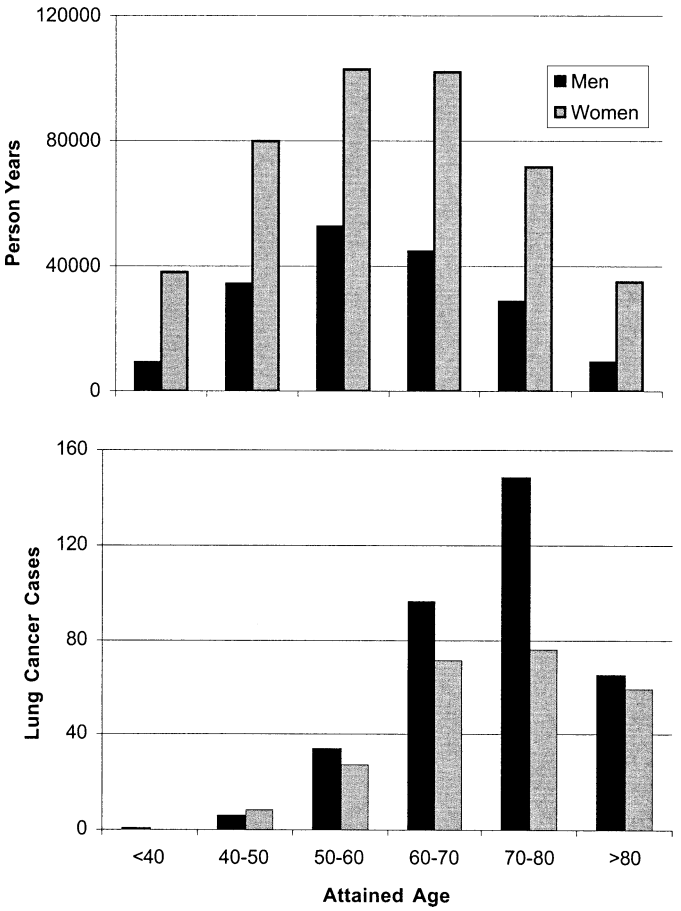

FIG. 1. Follow-up time and numbers of lung cancer cases in categories of age.

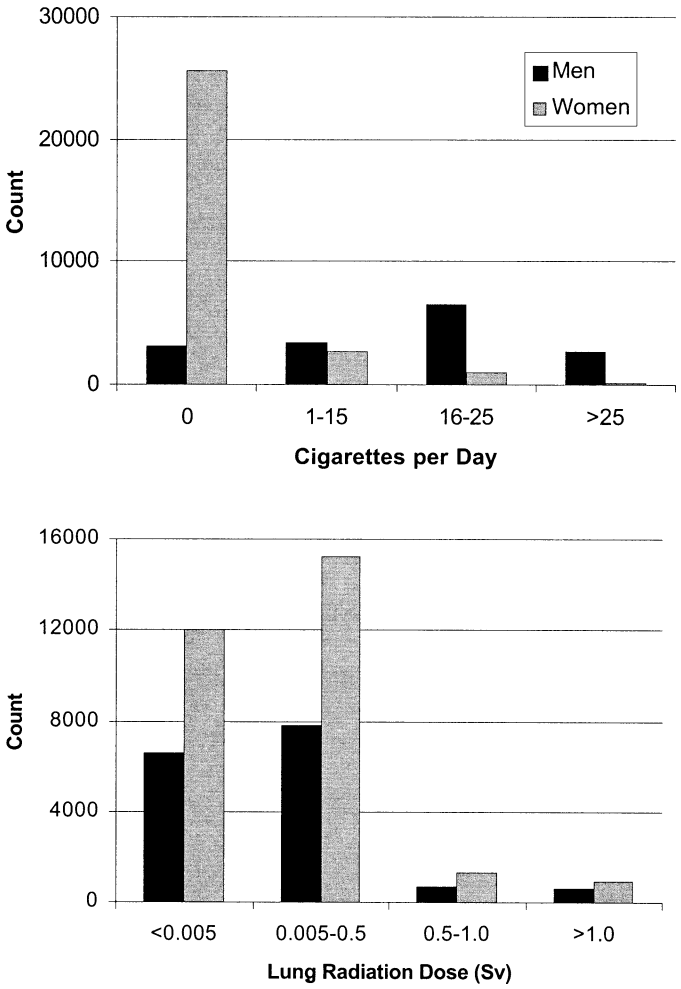

FIG. 2. Distribution of persons by smoking level and radiation dose.

PRELIMINARY RESULTS

Results in this section mainly serve to document the extent of information available for the main analysis reported in the following section, which can initially be grasped without the results below. The information available differs from other RERF studies since information on smoking is available for only part of the cohort and even for these, subject follow-up begins at the time of the smoking survey. Descriptions here pertain to the data analyzed for main results, omitting those with missing information on smoking and those who reported having stopped smoking.

Figure 1 indicates by sex and attained age the number of person-years of follow-up and the number of lung cancer cases. In the full LSS there are about 50% more females than males, whereas in this study there are about twice as many females because of matters involving the nature of and response to the mail surveys and because women live longer than men. Although there is relatively less follow-up at younger ages than in other RERF studies, there are few lung cancer cases at those ages. However, it will be seen that this is when the radiation relative risk is largest, so there is something lost by the later-than-usual entry to follow-up. Figure 2 shows the number of persons in categories of smoking rate and of radiation dose. As indicated below, there is little association between these two factors. The proportions reporting that they are smokers, 80% for men and 13% for women, are very similar to these in the all-Japan statistics for the period 1965–1975 corresponding to most of our survey information (*12*).

Figure 3 gives the distribution of ages at radiation exposure for the persons with adequate information on smoking used in the main analyses. This distribution has relatively more persons who were younger at exposure than for the full RERF cohort, due to the requirement of being alive and cancer-free at the time of the smoking surveys. In both the full LSS and this study, there is a dearth of males who were age 20–40 at exposure, due to military service away from the two cities.

Table 3 gives the number of lung cancer cases by smoking level and radiation dose, along with crude lung cancer rates given by the ratio of cases to follow-up time. The cancer rates are of course estimated very imprecisely in such a cross-tabulation, particularly at the higher dose levels. Although this tabulation provides useful perspective, risk analysis cannot be based on it because age and birth cohort are critical variables.

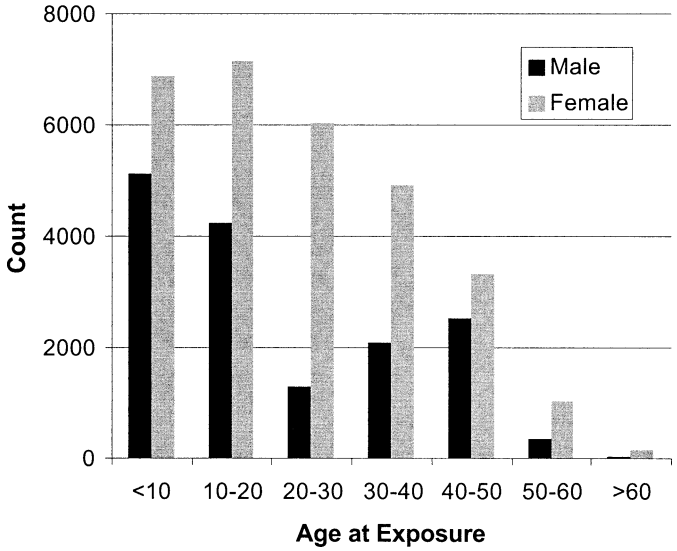

FIG. 3. Distribution of persons by age at radiation exposure.

Although the analysis here makes no assumption about an association between smoking rates and radiation exposure, there is general interest in that matter. Table 4 summarizes the proportion of persons who smoke, by radiation dose categories. It is only for Hiroshima women that there is any appreciable trend-like relationship between smoking rate and radiation dose. The number of cigarettes per day, for smokers, is essentially constant over radiation dose categories.

MAIN RESULTS AND INTERPRETATIONS

Joint Effects of Smoking and Radiation

We first present a limited form of analysis that is useful mainly due to its simplicity. The meaning of ''multiplicative'' effects of smoking and radiation is that the ERR/Sv, relative to smoking-level-specific background rates, is the same for all smoking levels. Values of the ERR/Sv defined in this way, either with or without the constraint that they be equal over smoking levels, can be estimated simply by stratifying on smoking level groups, specifically, using the model of Eq. (1). Results of such analysis (estimates of parameters β) are given in Fig. 4, where it is seen that the ERR/Sv is much smaller for heavy smokers, as would be the case if the effects were more additive than multiplicative. There is statistically significant evidence against the hypothesis that the ERR/Sv is constant with smoking level ($P < 0.01$), with this P value being about the same whether the test is for a trend or simply for heterogeneity. The ERR/Sv in this and subsequent analyses decreases strongly with age (represented by parameters φ_a in Eq. 1), having no statistically significant variation with sex or age at exposure. The points plotted correspond to age 60–70 years, averaged over sex; the variation with age is discussed later. The limitations of this analysis are that it provides no direct assessment of compatibility with the hypothesis of additive effects, no assessment of smoking effects, and less useful information than can be obtained regarding the effect of radiation adjusted for smoking.

The ERR/Sv estimates in Fig. 4 are relative to background rates for the respective smoking level groups, but it is at least equally important to consider estimates relative to background rates for nonsmokers as in Eq. (4) (and in Table 1). Such alternative values of ERR/Sv would be independent of smoking level if effects were additive and

TABLE 3
Lung Cancer Cases and the Crude Rate[a] per 10,000 PY

Sex	Cigarettes/day	Dose (Sv) <0.005	0.005–0.50	0.50–1	>1
Male	0	9 (6)	12 (6)	1 (5)	0 (0)
	1–15	36 (20)	35 (18)	14 (50)	8 (34)
	16–25	85 (28)	82 (22)	4 (10)	12 (31)
	>25	23 (25)	26 (19)	2 (18)	2 (22)
Female	0	55 (4)	79 (4)	15 (8)	13 (10)
	1–15	21 (16)	27 (14)	4 (16)	10 (53)
	16–25	6 (16)	9 (13)	1 (16)	1 (20)
	>25	0 (0)	0 (0)	0 (0)	0 (0)

[a] In parentheses.

TABLE 4
Percentage Smokers by Radiation Dose

Dose (Sv)	Hiroshima Men (%)	Hiroshima Women (%)	Nagasaki Men (%)	Nagasaki Women (%)
0	86	15	84	15
0–0.5	85	17	83	18
0.5–1	85	22	83	13
>1	90	22	87	15

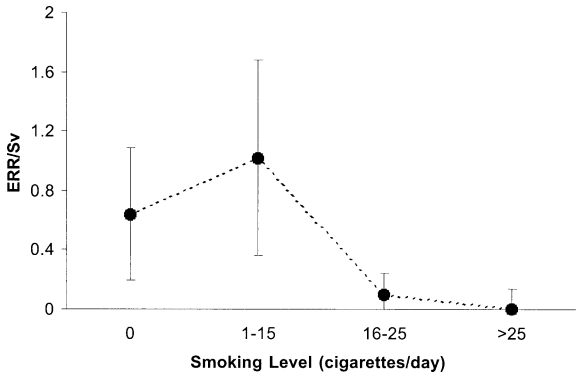

FIG. 4. Estimated ERR/Sv relative to background rates for the respective smoking levels, represented for ages 60–70. Error bars are ± one standard error. If effects were multiplicative these relative risks would be equal, and if effects were additive the heavier smokers would, as indicated, have much smaller relative risks than nonsmokers. There is statistically significant evidence that the ERR/Sv decreases with increasing smoking level. There is no statistically significant variation in the ERR/Sv with sex or age at exposure, although it decreases substantially with attained age.

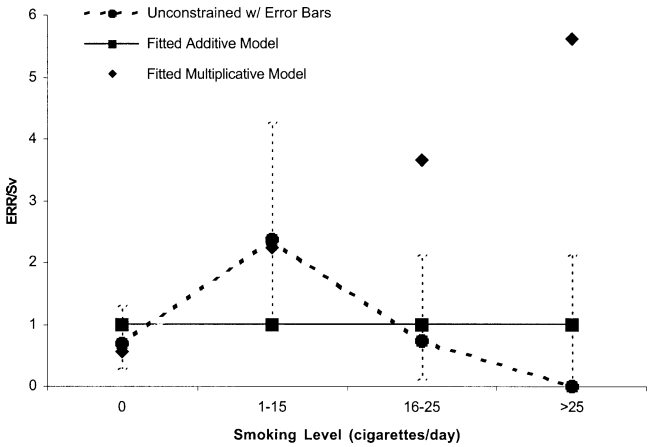

FIG. 5. Estimated radiation ERR/Sv at various smoking levels, fitted under additive and multiplicative models, and without such constraints. All risks are relative to nonsmokers with no radiation exposure. Error bars are ± one standard error for points of the unconstrained fit. Although all the data are used, risks are presented in terms of those for age at exposure 20–40, attained age 60–70, and averaged over a modest sex difference. There is statistically significant evidence against the multiplicative, but not the additive, model.

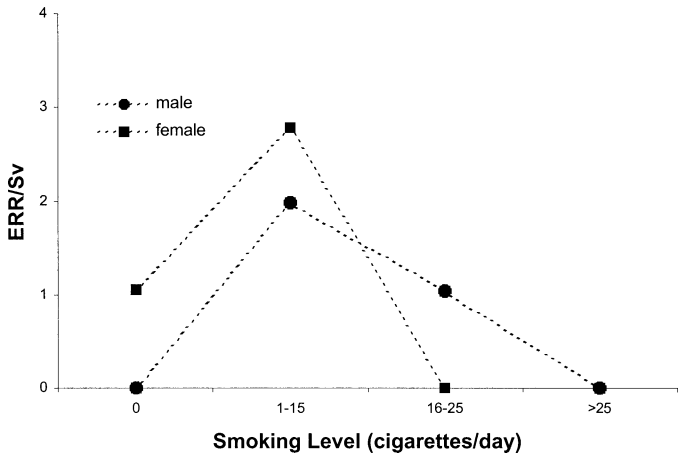

FIG. 6. The unconstrained ERR/Sv as in Fig. 5, estimated specifically to each sex. The sex variations seen here are not statistically significant.

would increase proportionally to the smoking RR if effects were multiplicative.

Figure 5 presents the main results of this paper in terms of ERR/Sv estimates relative to background rates for nonsmokers, averaged over sex. Points connected by dashed lines describe the data, being estimated without constraints regarding the nature of the joint effect, and the error bars are ± one standard error of the those points. The horizontal line is the fit to the data when assuming that the joint effects are additive, and the increasing shaded line is the fit when assuming that the effects are multiplicative. There is statistically significant evidence against the multiplicative model ($P = 0.03$) but not against the additive model ($P = 0.19$).

Technically, the descriptive points and the fitted additive model represent estimates of the parameters α_s in Eq. (4), first without and then with the constraint $\alpha_s \equiv \alpha$. The multiplicative fit as shown on this scale is obtained by fitting model (3) with $\beta_s \equiv \beta$, then multiplying the radiation and smoking ERRs in that model to obtain the ERR/Sv relative to nonsmoker background rates.

The ERR/Sv depends strongly on age, as discussed in detail later, and the points plotted again correspond to age 60–70. Although the ERR/Sv does not depend significantly on age at exposure, there is a large variation with birth cohort in smoking risks, also discussed later, and the multiplicative fit in Fig. 5 pertains to those age 20–40 at the time of the bombs. We note that the statistically significant evidence against the multiplicative joint effect of smoking and radiation is maintained whether or not the analysis allows for these birth cohort variations.

The additive model is at least a reasonable working approximation for many purposes, and further analyses reported below are based on that model. The weak (not statistically significant) indication seen in Fig. 5 that effects may tend to be multiplicative for light smokers should be given more consideration than the apparent sub-additive radiation risk for heavy smokers, since the heavy-smoker risk is so great as to dominate any approximately additive radiation risk for this group. Under the additive model (4) with $\alpha_s \equiv \alpha$, the ERR/Sv relative to background rates for nonsmokers is estimated as 1.01 ± 0.75 for all smoking levels, as indicated in Fig. 5. This is the estimate averaging over sex, but there is virtually no sex difference in that particular analysis. The large standard error is typical of results when analyzing the joint effects of radiation and smoking, since the smoking effects tend to dominate the radiation effects. For perspective, the ERR/Sv at age 60 seen in the full LSS for all solid cancers together when ignoring smoking, averaging over sex and for age at exposure 30, is about 0.65.

Particularly since there is a strong association between smoking level and gender, it is useful to see in Fig. 6 that the patterns by sex are similar to those in Fig. 5. This suggests that the effects seen in Fig. 5 are not the result of a type of confounding where a sex difference appears to be one related to smoking level because the men are heavier smokers. However, we note that such subset analyses provide little confirmatory evidence for the effects seen in Fig. 5 that are purely suggested by the analysis outcome, in particular that the joint effects appear multiplicative for light smokers.

Smoking Effects Adjusted for Radiation Exposure

Before turning to further details of the effect of radiation adjusted for smoking, our primary interest, we consider the smoking effect, because this brings us to make a minor modification in the model of Eq. (4). Although much is known about smoking and lung cancer risks in general, there are reasons to be particularly concerned about the risks for this cohort. Much of the reason for previous failures in discriminating between additive and multiplicative models for smoking and radiation effects in this cohort is

TABLE 5
Lung Cancer RR for Smoking
Age-at-Exposure 30 and Attained Age 60–70

Cigarettes per day[a]	RR
1–15	4.9 ± 2.1
16–25	8 ± 3.8
>25	13.3 ± 6.3

[a] As reported in 1964–1992.

because the apparent smoking risks have heretofore been very small in relation to what is expected based on results from Western countries. For example, Kopecky *et al.* (*2*) estimated a sharply age-increasing RR that was nevertheless only 2.7 at age 65 for those smoking >20 cigarettes per day. Similarly, Prentice *et al.* (*1*) estimated an RR of about 4 for those smoking >30 cigarettes per day for >20 years. As discussed in the following, we can now begin to see the reason for such unusual results, and we find that the apparent smoking risks are becoming larger, so that discrimination between multiplicative and additive models is possible.

There are statistically significant birth cohort variations in the smoking RR, represented by the categorical parameters $\eta_{g,h}$ in Eq. (4). Estimates of these parameters are too imprecise for the following needs, so this effect was smoothed in terms of gender-specific third-degree polynomials in birth year (or age in 1945). Further, there is no statistically significant loss in replacing the smoking ERRs $\theta_{g,s}$ in that model by the product of gender and smoking effects. For the remainder of results here, we use that modified form of Eq. (4) and the approximation of an additive model so that $\alpha_s \equiv \alpha$.

Under that model, Table 5 presents the estimated lung cancer RR by smoking level for those age 30 in 1945, with negligible (<10%) difference by sex, and for attained age 60–70. The standard errors are large, and there are the additional uncertainties discussed above. Although estimation of smoking risks is not the primary point of the paper, it is important that the indications are more than three times the levels found in previous investigations of this cohort.

The estimated RRs are moderately smaller than in Table 5 for both ages <60 and >70. Quite imprecisely estimated factors to adjust the ERR = RR − 1 estimates there for other birth cohorts are as follows:

	Age 10 in 1945	Age 50 in 1945
Males	2.0	1.2
Females	0.01	1.0

We emphasize that the apparent birth cohort variations in smoking RR are in terms of smoking levels reported in the period 1964–1992, and they probably reflect differences by birth cohort in smoking level at young ages among those reporting the same level during 1964–1992 rather than any real birth cohort variation in the effect of smoking. We consider below reasons for the birth cohort factor for men. Reasons for the very small factor for women who where children in 1945 are less clear, but the risk information on smoking for women is much weaker than for men.

It seems likely that the greater RR for men who were children in 1945 than for those who were young adults is because cigarettes were extremely scarce in Japan during and shortly after the war, and the smoking rates used in our analysis fail to indicate the consequent variation with birth cohort of important aspects of individual smoking history. The smoking surveys did gather information on the age at which smoking started, and these data support the conjecture just made. Some statistics on reported age of starting are:

Age in 1945	<20	20–30	30–40	40–50	>50
Mean	22	26	25	25	28
Quartiles 1, 3	19, 22	20, 30	20, 29	20, 26	20, 34

We chose not to use the reported age of starting in the analysis mainly for two reasons: (1) This would not reflect people being lighter smokers, even having started, when cigarettes were scarce, and (2) the difficulties in using the starting age in statistical modeling even when reliably known. In regard to (2), we are generally not satisfied with using cumulative smoking (pack-years) as a single summary measure when analyzing age-specific risks. In view of the several difficulties, we are more comfortable with the approach of ignoring some information regarding age at starting and instead incorporating the birth cohort variation in smoking risks. Note that we are analyzing *age-specific* lung cancer rates, not some average rate over the follow-up period, and if it were not for these complications (if all started smoking at similar ages and rates) the relevant durations of smoking would not vary with birth cohort.

Radiation Effects Adjusted for Smoking

It was reported above that when adjusting for smoking, the ERR/Sv under the approximation of additive effects is about 1.0 for both sexes, and that it decreases strongly with increasing age. Figure 5 indicates the nature of any possible lack of additivity, but this is not statistically significant. Since the smoking risks dominate the risks due to radiation in this cohort, more thorough and precise investigation of radiation effects adjusted for smoking is somewhat sensitive to the choice of the statistical model for the smoking risks. We report some further results based on the model described in the previous section for obtaining the smoking risks, and following Eq. (4) in the Statistical Methods section. Recall that this model when fitted has virtually no sex dependence in smoking RRs except for those who were children in 1945.

Under this model the radiation ERR/Sv relative to nonsmoker background rates, at ages 60–70 and averaged over sex, is 0.89 ± 0.64 and the female:male sex ratio is 1.6. Both of these numbers are similar to those for all solid cancers together in the LSS. That the ERR/Sv sex ratio was

about 1.0 in the analysis for Fig. 5 using Eq. (4) without modification and is 1.5 using the slightly modified version of Eq. (4) indicates the sensitivity of such inferences to the model for smoking used. Estimated factors for the age dependence in the ERR/Sv are:

Age	<40	40–50	50–60	60–70	>70
Factor	6.6	4.0	1	1.2	0.7

This decrease with age is stronger than for solid cancers in general in the LSS, but it is not statistically significantly greater (the fitted log-log slope in age is -3.6 ± 1.8, whereas the slopes for solid cancers in the LSS ranges from about -1.6 ± 0.4 to -2.2 ± 0.3, depending on whether or not the model includes an age-at-exposure effect). In analyses ignoring smoking, the age trend is somewhat more modest but is still strong.

One of the most important issues to be explored is whether the usual analyses of lung cancer radiation risk without regard to smoking may be misleading. There are two respects in which they are, regarding the apparent sex ratio and age-at-exposure variation in the ERR/Sv. As detailed below, when ignoring smoking, the female:male sex ratio in the ERR/Sv is unusually large, and this is greatly reduced by adjusting for smoking. This is because however the ERR/Sv is defined, heavy smokers have very small values and men are far more likely than women to be heavy smokers. Adjusting for smoking level of course reduces this type of confounding. Further, when ignoring smoking, there is a substantial age-at-exposure effect even when allowing the ERR to vary with age, but it is in the opposite direction to that found for other solid cancers. This is due to a type of confounding with birth cohort variations in the lung cancer risk, discussed below and in the final section of this paper; this confounding is removed by adjusting for smoking.

More specifically, analysis of the present data without regard to smoking, using the models of Eq. (4) without the smoking term, yields a female:male sex ratio in the ERR/Sv of 5.8, with the value for females being 1.2 ± 0.6 and for males being 0.2 ± 0.2. Similar results are found for lung cancer in the entire LSS: a sex ratio of 4 with estimates being 1.6 ± 0.3 for females and 0.4 ± 0.2 for males. For all solid cancers together, in the current LSS cancer incidence data this sex ratio is about 1.8, and is about 1.7 if lung cancer is omitted. On the other hand, after adjusting for smoking, the female:male sex ratio for ERR/Sv estimated from the data of this paper is reduced to the range of 1–1.6, depending on the model used for smoking effects. Since the smoking RR is largely independent of sex, the sex ratio applying to radiation risks relative to nonsmokers also applies to those relative to smokers as considered at the outset of this section and in Eq. (3).

In a cohort study such as this it is generally difficult to distinguish between variations in ERR/Sv with age and with age at exposure. For all solid cancers together in the LSS, there is some decrease in the ERR with increasing age at exposure, but the decrease with increasing attained age is more important. But for lung cancer in the LSS there is a substantial age-at-exposure effect in the opposite direction from other cancers: an increasing ERR with increasing age at exposure. In the analysis reported here, adjusting for smoking, there is no statistically significant age-at-exposure effect when allowing the ERR to decrease with attained age. The spurious and strange age-at-exposure effect for lung cancer when ignoring smoking is due to the birth cohort trend (for males) in the smoking effect. Since the joint effects are additive, and those young at exposure have much higher background rates when ignoring smoking than those who were older at exposure, the apparent ERR/Sv when ignoring smoking increases with age at exposure.

Background Lung Cancer Rates Adjusted for Smoking

Males have substantially higher lung cancer rates than females in this cohort, and with the resources at hand we can assess to what extent this is due to their being heavier smokers. A detailed analysis of this would be rather complicated and beyond the scope of this paper, but useful indications are obtained with fairly simple analyses. As for most cancers, the ratio of female to male lung cancer rates depends on age. If we restrict the age range to 50–80, it is reasonably adequate to consider the logarithms of lung cancer rates for each sex to be linear in log age. Using sex-specific log-log-linear age trends and restricting the analysis to age 50–80, we can estimate the sex ratio in background lung cancer rates at various ages, either adjusted for smoking by stratifying on this, or ignoring smoking. To avoid uncertainties of modeling the joint effects of smoking and radiation, we have done this when restricting the analysis to those at <0.2 Sv, where the radiation risk is small. The estimated ratio of female:male background lung cancer rates at various ages is then

	Age			
	50	60	70	80
No adjustment for smoking	0.45	0.31	0.22	0.16
Adjustment for smoking	1.9	1.1	0.70	0.47

Thus, for this cohort and for ages in the range 50–80, the apparent female:male ratio in background rates is increased by factors of about 3–4 by accounting for the males being heavier smokers. The ratio for young ages, adjusted for smoking, is larger than for most cancers in the LSS.

SUMMARY AND CONCLUSIONS

It has become clear that for A-bomb survivors the joint effects on lung cancer of smoking and radiation are largely additive and almost certainly are not multiplicative. The reason this conclusion was not reached in previous studies of this cohort is that the apparent smoking risks were heretofore remarkably small, so the distinction between the two

models was modest. It is fairly clear why the apparent smoking risks have become greater with continued follow-up. Particularly for men, there is substantial birth cohort variation in the smoking RR, with those who were young in 1945 having the larger values. This is probably because cigarettes were scarce during and shortly after the war, so those who were young at that time tend to have a longer duration of heavy smoking. Although for the main conclusion here it is useful to model this birth cohort effect, this is not essential since as the cohort ages the apparent smoking RR without this adjustment is increasing.

In fact, there have been substantial but less firm indications without even using information on smoking, based on the full LSS cohort where that information is not available, that the smoking and radiation effects are more additive than multiplicative. In part, this is because without information on smoking we can estimate the (additive) radiation-related absolute cancer rate increases as well as the relative risks; for example, see ref. (*13*). As discussed, the female:male sex ratio in the ERR/Sv without adjusting for smoking is much larger than for most solid cancers. Since far more males than females are smokers, this suggests a type of confounding where smokers have smaller ERR/Sv than nonsmokers (relative to sex-specific background rates), which would be the case if the joint effects were more nearly additive than multiplicative. Indeed, this large sex ratio has not been seen in the radiation-related absolute rate increase estimated without information on smoking. Furthermore, whereas for many solid cancers those young at radiation exposure have greater ERR/Sv than those older at exposure, for lung cancer this effect is reversed when not adjusting for smoking. Even without information on smoking, the likely explanation for this has been that those who were young at exposure have greater smoking risk than those who were older, for reasons indicated above, and that the smoking–radiation effects are more additive than multiplicative. That is, roughly the same absolute excess rate related to radiation is divided by larger background rates for those young at exposure than for those older at exposure. Although it was to some extent possible to understand these atypical patterns without explicit information on smoking, it is now possible to see more clearly that (smoking-adjusted) lung cancer radiation risks have sex and age–time patterns similar to those seen for solid cancers that are not strongly related to smoking.

Our view of the best approach for computing lifetime risk estimates for the A-bomb exposures and other acute single exposures is as follows. Lifetime risk computations involve estimating age-specific absolute lung cancer rate increases and then summing these over age with weights corresponding to the chance of survival to each age. The absolute rate increases may best be estimated by multiplying lung cancer rates for nonsmokers and the ERR/Sv relative to nonsmokers. Averaged over sex, this ERR/Sv at any smoking level is estimated as about 0.9 for age 60–70, and the factors required to modify this for other ages can be estimated. The sex ratio in the ERR/Sv is rather uncertain, but for most solid cancers this sex ratio tends to offset a reciprocal sex ratio in background rates, so that the absolute rate increases are similar for the sexes. Since estimating sex- and age-specific background rates for nonsmokers is also difficult, our approach might thus be to ignore sex in both the ERR/Sv and background rates. Note that in the additive model, the only effect of smoking level on the estimated lifetime risk would be due to smokers dying earlier. That is, when summing absolute age-specific lung cancer rate increases with weights corresponding to the chance of survival to that age, the weights should depend on assumed smoking level.

The apparently additive effects of smoking and radiation for A-bomb survivors cannot be generalized to the setting of radon exposure in homes with confidence. Primarily, this is because the radiation dose to the lung from inhaling radon progeny involves very different issues, including inhaled particulate matter such as in cigarette smoke, than that from the external exposures of A-bomb survivors *(3, 4,* Appendix B). The most relevant study involving smoking and radon in homes is by Pershagen (*5*), where the conclusion is that effects appear more multiplicative than additive. However, although those authors state that the multiplicative effect is particularly evident at the highest radon levels, one might alternatively say that the departure from additivity is seen only at the highest radon levels, where the inference is highly uncertain. If their highest radon category is omitted, then there seems to be almost no evidence against additive effects. Their analysis was not done using radon dose categories, but it seems likely that even so, their conclusions were driven by those few cases at very high radon levels.

Finally, there are issues in mechanisms of radiation-related and smoking-related carcinogenesis that should be considered. Radiation probably contributes to carcinogenesis largely by causing mutations. If the effect of smoking was also primarily to cause mutations, then one would expect the joint effects to be more or less additive. On the other hand, it is not difficult to think of types of smoking-effect mechanisms that would lead to multiplicative joint effects. This would happen if smoking somehow set the stage for increased mutation rates due to other factors, such as radiation exposure, or if it facilitated the progress toward malignancy of cells with mutations caused by other factors. It seems not unlikely that the effects of smoking are more complicated than those of radiation, e.g. involving both of the types of mechanisms just described. This might explain what is weakly suggested by the data here, that light smoking tends to act multiplicatively with radiation whereas heavy smoking acts additively. More importantly, it might explain why studies of radon exposure have largely indicated effects intermediate between additive and multiplicative.

ACKNOWLEDGMENTS

This work is made possible by the dedicated efforts of RERF staff dealing with LSS tumor registry and mail survey information. Its publication is based on research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private nonprofit foundation funded equally by the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy through the National Academy of Sciences. The work was also supported in part by the National Cancer Institute (NCI) contract number NCI-4893-8-001.

Received: September 9, 2002; accepted: December 6, 2002

REFERENCES

1. R. L. Prentice, Y. Yoshimoto and M. W. Mason, Relationship of cigarette smoking and radiation exposure to cancer mortality in Hiroshima and Nagasaki. *J. Natl. Cancer Inst.* **70**, 611–621 (1983).
2. K. J. Kopecky, E. Nakashima, T. Yamamoto and H. Kato, *Lung Cancer, Radiation, and Smoking among A-bomb Survivors, Hiroshima and Nagasaki*. TR 13-86, Radiation Effects Research Foundation, Hiroshima, 1986.
3. National Research Council, Committee on the Biological Effects of Ionizing Radiation, *Health Risks of Radon and other Internally Deposited Alpha Emitters (BEIR IV)*. National Academy Press, Washington, DC, 1988.
4. National Research Council, Committee on the Biological Effects of Ionizing Radiation, Health *Effects of Exposure to Radon (BEIR VI)*. National Academy Press, Washington, DC, 1999.
5. G. Pershagen, M. D. Åkerblom, O. X. Axelson, B. Clavensjö, L. Damber, G. Desai, A. Enflo, F. Lagarde, H. Mellander and G. A. Swedjemark, Residential radon exposure and lung cancer in Sweden. *N. Engl. J. Med.* **330**, 159–164 (1994).
6. K. Mabuchi, S. Soda, E. Ron, M. Tokunaga, S. Ochikubo, S. Sugimoto, T. Ikeda, M. Terasaki, D. L. Preston and D. E. Thompson, Cancer incidence in atomic bomb survivors. Part I: Use of tumor registries in Hiroshima and Nagasaki for incidence studies. *Radiat. Res.* **137** (Suppl.), S1–S16 (1994).
7. R. Sposto and D. L. Preston, *Correction for Catchment Area Nonresidency in Tumor-registry-based Cohort Studies.* CR 1-92, Radiation Effects Research Foundation, Hiroshima,1992.
8. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochikubo, S. Sugimota, T. Ikeda, M. Terasaki and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat. Res.* **137** (Suppl.), S17–S67 (1994).
9. D. W. Hosmer and S. Lemeshow, *Applied Survival Analysis.* Wiley, New York, 1999.
10. D. L. Preston, J. H. Lubin and D. A. Pierce, *Epicure User's Guide.* Hirosoft International Corp., Seattle, 1993.
11. D. A. Pierce, D. O. Stram and M. Vaeth, Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat. Res.* **123**, 275–284 (1990).
12. T. Kakizoe, Ed., *Cancer Statistics in Japan.* Foundation for Promotion of Cancer Research, National Cancer Center, Tokyo, 1999.
13. D. A. Pierce, Y. Shimizu, D. L. Preston, M. Vaeth and K. Mabuchi, Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat. Res.* **146**, 1–27 (1996).