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Radiation and Smoking Effects on Lung Cancer Incidence among Atomic Bomb Survivors

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While radiation increases the risk of lung cancer among members of the Life Span Study (LSS) cohort of atomic bomb survivors, there are still important questions about the nature of its interaction with smoking, the predominant cause of lung cancer. Among 105,404 LSS subjects, 1,803 primary lung cancer incident cases were identified for the period 1958–1999. Individual smoking history information and the latest radiation dose estimates were used to investigate the joint effects of radiation and smoking on lung cancer rates using Poisson grouped survival regression methods. Relative to never-smokers, lung cancer risks increased with the amount and duration of smoking and decreased with time since quitting smoking at any level of radiation exposure. Models assuming generalized interactions of smoking and radiation fit markedly better than simple additive or multiplicative interaction models. The joint effect appeared to be super-multiplicative for light/moderate smokers, with a rapid increase in excess risk with smoking intensity up to about 10 cigarettes per day, but additive or sub-additive for heavy smokers smoking a pack or more per day, with little indication of any radiation-associated excess risk. The gender-averaged excess relative risk per Gy of lung cancer (at age 70 after radiation exposure at 30) was estimated as 0.59 (95% confidence interval: 0.31–1.00) for nonsmokers with a female:male ratio of 3.1. About one-third of the lung cancer cases in this cohort were estimated to be attributable to smoking while about 7% were associated with radiation. The joint effect of smoking and radiation on lung cancer in the LSS is dependent on smoking intensity and is best described by the generalized interaction model rather than a simple additive or multiplicative model. © 2010 by Radiation Research Society

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INTRODUCTION

Lung cancer is the most common cancer worldwide (*1*). While lung cancer rates are largely determined by smoking patterns, medical, occupational and environmental radiation exposures have also been shown to increase risks of lung cancer (*2*). There is considerable interest from both biological and practical perspectives in the joint effect of radiation and smoking on lung cancer. The Life Span Study (LSS) is a long-term continuing follow-up of a cohort of atomic bomb survivors in Hiroshima and Nagasaki, Japan, comprising a large number of men and women exposed at all ages to a range of radiation doses from 0–4 Gy, mostly γ rays, from the bombs. With detailed information on smoking available for most cohort members, the LSS offers one of the best opportunities for investigating the joint effects of radiation and smoking on lung cancer risks.

Lung cancer is the second most common cancer in the LSS, with world-population age-standardized rates of 76.8 per 100,000 persons for men and 25.1 for women. LSS lung cancer rates are also strongly associated with radiation, with an estimated excess relative risk (ERR) per Gy of 0.81 and excess absolute risk (EAR) of 7.5 per 10,000 person-year Gy (*3*). Those estimates do not take into account a possible modifying effect of smoking on the radiation risk. While earlier analyses (*4, 5*) of the LSS data were unable to describe sufficiently the nature of the interaction between radiation and smoking for lung cancer risk, due mostly to limited numbers of cases, the latest analysis by Pierce *et al.* (*6*) suggested that the interaction was sub-multiplicative and consistent with additivity.

The present study was based on lung cancer incidence data from a special pathology review that provided diagnostic confirmation on cases diagnosed between 1958 and 1999. A reassessment of smoking history data assembled from multiple sources provided enough detailed information to consider models in which the

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effect of cumulative amount smoked could be modified by smoking duration and intensity and to consider both the additive and multiplicative interaction models used in many analyses of the joint effects of carcinogenic agents and some useful generalizations of these models. In this study, we present the results from the effort to evaluate all types of lung cancer as a group. We will report separately on results regarding different histological types.

MATERIALS AND METHODS

Study Population and Case Ascertainment

The LSS cohort includes 120,321 residents of Hiroshima and Nagasaki who were born prior to the atomic bombings in August 1945 and were still alive on October 1, 1950. Additional details about the cohort can be found in ref. (*7*). For the present analyses, we excluded cohort members who could not be traced, had died or were known to have had cancer prior to January 1, 1958 (8,396 subjects) or those with radiation dose estimates not available (6,521 subjects), resulting in a total of 105,404 eligible subjects. A special pathology review provided diagnostic confirmation for lung cancer cases. The primary sources used to identify potential cases for pathology review were the Hiroshima and Nagasaki tumor and tissue registries. Additional sources included the RERF autopsy program and death certificate data routinely obtained for LSS follow-up. The review considered cases diagnosed through the end of 1999, resulting in followed-up ages ranging from about 12 to more than 100 and ages at diagnosis from 27 to 104.

An initial screening identified 5,711 LSS cohort members who were coded as having tumors of the lung or related regions. Three study pathologists independently reviewed those cases and developed a consensus diagnosis for each potential case. The reviews were based on all available information, including tumor tissue slides, pathology and clinical records, and death certificates. Lung tumors were diagnosed using the latest WHO diagnostic criteria (*8*). The review identified 2,446 lung tumors, including 2,368 cancers.

Cases were ineligible for the analyses if they were not the first primary tumors (242 cases) or were not classified as malignant tumors (52 cases). Cases were excluded if the individual was not resident in Hiroshima or Nagasaki prefecture at the time of diagnosis (171 cases diagnosed primarily from death certificate information), was diagnosed or lost to follow-up prior to 1958 (47 cases), or did not have a radiation dose estimate computed (131 cases). The primary analyses described herein considered 1,803 primary lung cancer cases diagnosed among 105,404 cohort members, including 40,980 subjects (677 cases) with no information on smoking status prior to the diagnosis date.

Radiation Dose and Smoking Information

Weighted DS02 (*9*) lung dose estimates computed as sum of the γ-ray dose and 10 times the neutron dose were used for these analyses. As in ref. (*3*), cohort members who were not in either Hiroshima or Nagasaki at the times of the bombings were included in the analysis to improve the characterization of the variation in the baseline (zero dose) lung cancer rates by age, gender and birth cohort. However, radiation effects were quantified in relation to rates for survivors who were in the cities at the time of the bombings but received negligible radiation from the bombs, due to their large distances from the hypocenter.

Most of the data on smoking habits of LSS cohort members comes from a series of mail surveys conducted between 1965 and 1991. The 1965 survey was limited to men who were between ages 40 and 69, and the 1969 survey included only females. The 1978 and 1991 surveys included all surviving cohort members who were in the cities at the time of the bombings. Information on smoking habits included amount smoked, duration of smoking, and, for past-smokers, when he/she stopped. Additional information on smoking was available from a series of questionnaires administered to members of a fixed subset of the full LSS cohort known as the Adult Health Study (AHS), who participated in biennial clinical examinations (*10*). We used summary information on smoking history that made use of the AHS data for the previous analyses by Pierce *et al.* (*6*).

Smoking history was summarized by an indicator of smoking status (never-smoker, past-smoker or current-smoker) at the time of the latest information, age started smoking, age stopped smoking, the average number of cigarettes smoked per day, and the year in which data on smoking were first obtained. Age started smoking was defined as the minimum starting age reported from all surveys to which a person responded; a person was taken to be a past-smoker only if they indicated that they had quit smoking at the time of their most recent survey response, and the number of cigarettes per day was defined as the average of the numbers of cigarettes per day over all surveys in which a person reported having smoked. In some cases, smokers did not answer questions about the amount smoked or age at start of smoking. Values were imputed for those subjects as the gender- and birth cohort-specific mean values among smokers with complete information.

Smoking information was available for 62% of the eligible cohort members. The smoking summary data were based on one or more of the four mail surveys for 92% of the subjects with smoking data. The amount smoked was imputed for 4% of those who indicated that they had ever smoked while the age at the start of smoking was imputed for 9.5% of this group. Additional information on smoking status in the cohort is given in the Results section with further details concerning the creation of the smoking summary variables in the Supplementary Information.

Data Organization for Analyses

The risk analyses were based on incidence rates computed from a table of person-years and lung cancer cases stratified by general factors, radiation exposure-related factors, and smoking-related factors. The general stratification factors included city (Hiroshima and Nagasaki), gender, attained age (5-year categories from age 15 to 85 with categories for subjects less than 15 or 85 or more), and period (nine 5-year categories from 1961 through 1999 plus a category for 1958–1960). The radiation exposure-related stratification factors were age at exposure (14 5-year categories to age 70 and a category for subjects aged 70 or more), exposure status (within 3 km of the hypocenter, 3–10 km from the hypocenter, or not in city), and radiation dose (14 categories with cutpoints at 0.005, 0.05, 0.1, 0.15, 0.2, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5 and 3 Gy).

The time-dependent smoking-related stratification factors used in analyses were smoking status (unknown, never-, current- and past-smoker), average number of cigarettes per day (seven categories with cutpoints at 0, 7.5, 12.5, 17.5, 22.5 and 27.5 and a category for unknown smoking status), years smoked (six categories with cutpoints at 0, 5, 10, 20 and 30 for ever-smokers and categories for never-smokers and unknown smoking status), and years since quitting smoking (four categories with cutpoints at 5, 10 and 15 for past-smokers and categories for unknown smoking status and current-/never-smokers). Note that a smoker was considered as a current-smoker from the date at which he/she first provided information on smoking habits to either the date of the end of follow-up or the date of reported cessation of smoking, whichever came first. All cohort members were classified as unknown smoking status prior to the date at which they first provided information on smoking habits to avoid biasing risk estimates by overcounting person years in known smoking-status categories.

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Since cancer case ascertainment is incomplete for subjects who have left the tumor registry catchment areas, it is necessary to allow for the effects of migration on risk estimates. As in all recent analyses of the LSS cancer incidence data, the analyses were limited to cases diagnosed among residents of the tumor registry catchment areas. Because individual residence history data were not available for all cohort members, city-, gender-, age- and time-dependent residence probabilities estimated from AHS clinical contact data were used to compute migration-adjusted person years (*11*).

Statistical Analysis

1. Smoking and radiation joint effects

These analyses focused on the joint effects of radiation and smoking in terms of risks relative to attained age (a), gender (g) and birth cohort (b)-specific baseline rates for nonsmokers with no radiation exposure. That model can be written as $\lambda_0(a,g,b)RR(C,D)$, where RR is a relative risk function that depends on smoking-related variables (C) and radiation dose-related variables (D). The smoking-related variables included years smoked (y), cigarettes smoked per day (c), and years since last known quitting (q) for past smokers and other factors such as gender and birth cohort. The radiation-related variables included dose (d) and effect modifiers such as age at exposure (e), gender and attained age.

The simplest joint effects model is the *additive excess relative risk* (ERR) model:

$$RR(C,D) = 1 + \phi(C) + \rho(D), \quad \text{[Additive]}$$

where ϕ and ρ are functions that describe the ERRs for smoking- and radiation-related variables, respectively. Under this model, smoking and radiation have independent effects on the baseline rate for nonsmokers. The most commonly used alternative to the additive ERR model is the *multiplicative ERR* model:

$$\begin{aligned} RR(C,D) &= [1 + \phi(C)][1 + \rho(D)] \\ &= 1 + \phi(C) + \rho(D) + \phi(C)\ \rho(D). \quad \text{[Multiplicative]} \end{aligned}$$

With this model, a given radiation exposure (or a given smoking history) increases the risk by the same proportion for any smoking history (or radiation exposure).

These two models are special cases of more generalized joint effect models, which we call the *generalized additive* and *multiplicative ERR* interaction models:

$$RR(C,D) = 1 + \phi(C) + \rho(D)\ \omega(C), \quad \text{[Generalized additive]}$$

$$RR(C,D) = [1 + \phi(C)][1 + \rho(D)\ \omega(C)], \quad \text{[Generalized multiplicative]}$$

where ω is a function of smoking variables with $\omega(C) = 1$ for lifelong nonsmokers. In these models, the effect of smoking on the radiation dose response is neither independent of dose (as in the simple additive model) nor constrained to be proportional to the main effect of smoking, $\phi(C)$ (as in the simple multiplicative model). A form of the generalized additive interaction model was considered by Pierce *et al.* (*6*).

2. Baseline rate (zero-dose, nonsmokers) model

The baseline rate model allows for gender-specific rates. The log rate was assumed to be proportional to a quadratic function of log attained age with a birth-cohort effect that is proportional to the year of birth. The baseline rate model also included a multiplicative city effect.

3. Smoking effect model

Analyses of smoking effects on lung cancer risk often describe the effects in terms of the cumulative amount of smoking which, in the simplest cases, is defined as the product of intensity and duration of smoking. In this study, we expressed the cumulative amount by *pack-years* (p), defined as the product of packs smoked per day (one pack = 20 cigarettes) and years smoked (defined as the maximum of 0 and "attained age – age started smoking"). Then we described the smoking ERR as the product of a function of pack-years and an effect modification term that was allowed to depend on smoking intensity (c), duration (y), time since quitting (q) with allowance for birth cohort (b) and gender (g). Note that time since quitting is defined as the maximum of 0 and attained age – age at quitting smoking.

After preliminary analyses, we decided to use a model for the smoking ERR $\phi(C)$ of the form

$$\begin{aligned} \phi_{smk}(C) &= \phi_{0g} p \exp\left\{\phi_{1g} b + \lambda_1 \log(y) + \lambda_2 \log(y)^2 + \nu \log(q+1)\right\} \\ &= \phi_{0g} \exp\{\phi_{1g} b\}\, c y^{1+\lambda_1+\lambda_2 \log(y)} (q+1)^{\nu} \end{aligned}$$

for follow-up periods during which smoking history information was available or $\phi_{unksmk}(g,b) = \xi_{g,b}$ for periods during which smoking status was unknown. In this model, smoking duration (y) and birth year (b) were centered so that ϕ_{0g} is interpreted as the gender-specific risk for a current smoker who was born in 1915 and smoked a pack of cigarettes per day for 50 years. The smoking ERR included a gender-dependent birth-cohort effect ($\exp\{\phi_{1g}b\}$), a time-since-quitting effect ($(q+1)^{\nu}$), and a smoking-duration effect ($y^{\lambda_1+\lambda_2\log(y)}$). We considered more general models for the smoking-intensity effects, such as those considered in ref. (*12*), but did not find any evidence that the power of the intensity effects differed from one in the data. We also found no indication of gender dependence in the duration or intensity effects. For follow-up during which smoking status is unknown, the "smoking" effect was allowed to depend on gender and birth-cohort strata.

4. Radiation effect models

As in most recent work on risk modeling in the LSS (*3, 13*), radiation main effects, $\rho(D)$, were modeled as a product of a gender-specific dose–response shape function, $\eta(d,g)$, and an effect-modification function $\varepsilon(a,e) = a^{\beta}\exp(\gamma e)$. In fitting the models, attained age and age at exposure were scaled so that the gender-specific dose effect $\eta(d,g)$ corresponds to the risk for a 70-year-old survivor who was exposed at 30 years of age. The excess risk is often summarized by a gender-averaged value, which is defined in this paper as the unweighted mean of the dose–effect parameters for men and women. The shape of a dose response, $\eta(d,g)$, considered in the modeling included linear ($\delta_g d$); linear-quadratic ($\delta_g(d + \delta d^2)$), linear-spline ($\delta_g[d + \theta(d - d_0)I(d > d_0)]$), and linear-threshold ($\delta_g\ (d - d_0)I(d > d_0)$) models.

Poisson regression maximum likelihood methods were used for parameter estimation, hypothesis testing and the computation of confidence intervals (CI) for specific parameters. Model fitting was carried out using Epicure (*14*) and the generalized non-linear model package (gnm) in R (*15*). We also used the Akaike Information Criteria (AIC) (*16*) for comparison of non-nested models involving different numbers of parameters. The program codes used to draw graphs in the Results section are available upon request from the authors.

RESULTS

Data on smoking were available for about 60% of men and 64% of women. Roughly 85% of the men and 18% of the women who provided information on smoking habits indicated that they had ever smoked. The proportion of ever-smokers among men was similar

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over birth-cohort and radiation dose categories. Women who were over 20 at the time of the bombings were somewhat more likely to have smoked than younger women, and the proportion of ever-smokers increased slightly with decreasing distance from the hypocenters (and hence with increasing dose). Men reported smoking about twice as many cigarettes per day (mean 19.6) as women (mean 10.6) and tended to start smoking younger (mean starting ages of 21 and 31.6, respectively). About one-third of ever-smokers reported having stopped smoking prior to the last survey to which they responded. By the end of follow-up, those who reported having stopped had smoked for roughly 20 years less than those who did not. Additional information on smoking status and the availability of data on smoking is given in the Supplementary Information (Table S1).

Table 1 summarizes the distribution of the first primary lung cancers, study population and crude incidence rates by smoking status at the end of follow-up, age at exposure and radiation dose by gender. Incidence rates were higher for current smokers than for never- or past-smokers. Crude rates for a given smoking category were about twice as high for men as for women and increased with increasing age at exposure (or decreasing calendar year of birth) as well as with radiation dose.

Nonsmoker Baseline Rates and Smoking Effects

Smoking effects were modeled using ERR models and expressed relative to gender-specific baseline rates for nonsmokers with allowance for radiation effects. As discussed later, neither the baseline rate nor the smoking-effect parameter estimates were particularly sensitive to the form of the radiation-by-smoking interaction, and therefore the main results in this section were based on the generalized multiplicative interaction model unless otherwise noted.

The nonsmoker baseline rates for men and women increased markedly with attained age. There was a statistically significant gender difference in the attained-age trend ($P = 0.05$). The increase was well described using a simple Armitage-Doll-like model in which the rates were proportional to attained age to the power 5.6 (95% CI: 5.2, 6.1) with age-specific rates for women being 61% of those for men (95% CI: 48%, 80%). Age-specific rates exhibited a statistically significant ($P < 0.001$) increase of 17% (95% CI: 10%, 25%) per decade in year of birth. The final baseline rate model allowed a more rapid increase in the risk at younger ages, which resulted in a statistically significant improvement in the fit ($P < 0.001$).

Table 2A presents smoking-effect parameters estimated using the generalized multiplicative and simple additive radiation-smoking interaction models, together with modifying effects of birth year and smoking duration. Assumptions about the nature of the interaction had little effect on the smoking risk estimates. With the generalized multiplicative model, the gender-averaged ERR associated with smoking 20 cigarettes per day for 50 years (i.e., 50 pack-years) for an unexposed individual born in 1915 was estimated to be 4.7 (95% CI: 3.6, 5.9). This was only slightly lower than that of 5.3 based on the additive model. The ERR associated with smoking was statistically significantly higher for women than for men ($P = 0.02$), with the gender difference being greater with the additive model estimates. Age-specific ERRs for a given smoking history exhibited a statistically significant increase ($P < 0.001$) with decreasing birth year without an indication of a gender difference ($P = 0.4$, data not shown).

In our modeling of the smoking ERR, the pack-year effect was allowed to vary depending on smoking duration and/or intensity. The addition of linear and quadratic effects of smoking intensity (packs per day) did not significantly improve the basic pack-year effect model ($P = 0.2$). However, the addition of both linear and quadratic log-linear terms in log smoking duration significantly improved the basic model ($P = 0.001$). While the pack-year effect was highly statistically significant, the negative coefficients for the duration effects imply that the increase in rates is not linear in years smoked and that this departure from linearity becomes more marked at longer durations. Under this duration-modified pack-year model, smoking had little impact on lung cancer rates for the first 20 years of smoking, after which the effect of smoking increases dramatically (Fig. 1A). This model implies a reduced potency at higher smoking intensities (Fig. 1B) like the pattern suggested in refs. (*12, 17*), where the departures from a linear pack-years effect were attributed to modifying effects of intensity and not duration.

There was a statistically significant time-dependent reduction ($P < 0.006$) in the ERR for those who reported that they had stopped smoking. The estimated decline for past smokers (relative to that for nonsmokers of the same age) was approximately proportional to one over the square root of time since quitting. While the smoking ERR declines after smoking cessation (Fig. 2A), lung cancer rates for past-smokers never return to the level for nonsmokers (Fig. 2B). Although women have larger ERRs than men for those smoking patterns, the absolute rate estimates for male and female smokers are similar (Fig. 2B).

Radiation Effects and Radiation-by-Smoking Interactions

Table 2B presents parameter estimates for radiation effects and their risk-modifying factors, together with 95% CIs and information about the fit, from the ERR interaction models described earlier. The table also includes results from a model in which the radiation-effect parameters were estimated without allowance for

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TABLE 1
Distribution of Cases, Study Population and Crude Incidence Rates[a] in Final Smoking Status Categories by Age at Radiation Exposure, and Radiation Dose by Gender

		Smoking status				
		Never	Past	Current	Unknown	Total
Total	Cases	304	142	680	677	1,803
	People	35,555	9,022	19,847	40,980	105,404
	Rate	4.88	9.85	22.90	3.89	6.43
			Age at exposure, years			
0–9	Cases	17	7	21	31	76
	People	8,160	1,930	4,974	7,617	22,681
	Rate	1.25	2.83	3.26	0.7	1.1
10–19	Cases	49	29	85	87	250
	People	8,654	2,363	4,675	7,365	23,057
	Rate	2.99	8.33	11.94	1.93	3.48
20–39	Cases	150	60	346	178	734
	People	12,700	2,991	6,181	8,200	30,072
	Rate	6.00	9.63	29.55	3.6	7.98
40+	Cases	88	46	228	381	743
	People	6,041	1,738	4,016	17,798	29,593
	Rate	11.89	20.56	51.65	11.6	15.87
			Men by dose, Gy			
NIC	Cases	7	15	143	107	272
	Rate	7.28	15.66	25.78	5.62	10.27
<0.005	Cases	14	49	172	116	351
	Rate	7.74	12.82	25.85	5.32	10.29
−0.1	Cases	14	33	122	81	250
	Rate	8.67	9.70	21.65	4.83	9.12
−0.5	Cases	0	11	62	35	108
	Rate	0.00	8.01	22.95	5.32	9.50
−1	Cases	1	3	26	12	42
	Rate	4.96	7.43	32.11	6.75	13.15
1+	Cases	0	5	26	18	49
	Rate	0.00	15.88	32.66	11.86	17.52
Total	Cases	36	116	551	369	1,072
	People	3,623	6,578	15,185	17,503	42,889
	Rate	6.58	11.29	24.88	5.46	10.17
			Women by dose, Gy			
NIC	Cases	53	1	23	74	151
	Rate	3.86	2.19	11.99	2.80	3.55
<0.005	Cases	73	10	30	104	217
	Rate	4.21	7.49	15.02	2.85	3.80
−0.1	Cases	64	6	24	80	174
	Rate	4.07	4.21	12.41	2.99	3.79
−0.5	Cases	41	5	33	33	112
	Rate	6.01	7.56	30.71	2.93	5.65
−1	Cases	20	1	5	7	33
	Rate	10.27	5.87	13.97	2.17	5.79
1+	Cases	17	3	14	10	44
	Rate	13.16	31.58	51.44	4.57	11.43
Total	Cases	268	26	129	308	731
	People	31,932	2,444	4,661	23,477	62,514
	Rate	4.71	6.28	17.07	2.90	4.18

[a] Cases per 10,000 person years.

smoking effects (radiation-only) as in most LSS reports (*3, 7*).

Both the deviance and AIC values suggest that the generalized-interaction models fit better than the simple interaction models and that the generalized multiplicative model described the data somewhat better than the generalized additive model. Models in which the generalized interaction was modeled in terms of pack-years or years smoked were also considered, but they did not describe the data any better than the smoking-intensity models given in Table 2B.

Since most men smoke and most women do not, without allowance for smoking the estimated ERR/Gy for men was similar to that for a simple multiplicative

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TABLE 2
Parameter Estimates for Smoking Effects (Panel A) and Radiation Effects (Panel B) and Modifying Effects with 95% (likelihood-based) Confidence Intervals

A. Smoking effect

Effect	Simple additive	Generalized multiplicative
	ERR per 50 pack-years (born in 1915)	
Gender-average	5.32 (4.10, 6.70)	4.69 (3.65, 5.94)
Male	3.48 (2.40, 5.00)	3.60 (2.60, 5.10)
Female	7.16 (5.20, 9.70)	5.77 (4.10, 7.90)
Female:Male ratio	2.15 (1.30, 3.40)	1.61 (1.00, 2.50)
	Birth-cohort effect (percentage change per decade decrease in birth year)	
Percentage per decade decrease in birth year	0.38 (18%, 61%)	0.33 (15%, 54%)
	Smoking-duration effect (log-linear)	
Log (duration/50)	−0.30 (−1.26, 0.60)	−0.24 (−1.20, 0.69)
Log (duration/50) squared	−2.58 (−5.30, −0.63)	−2.51 (−5.20, −0.56)
	Years since quitting effect	
Power of years since quitting plus 1	−0.50 (−0.90, −0.29)	−0.47 (−0.77, −0.27)

B. Radiation effect

Effect	Radiation only	Simple additive	Simple multiplicative	Generalized additive	Generalized multiplicative
	ERR per Gy (age 70, age at exposure 30, never-smoker)				
Gender-averaged	0.83 (0.55, 1.20)	0.98 (0.59, 1.50)	0.68 (0.43, 1.00)	0.65 (0.31, 1.10)	0.59 (0.31, 1.00)
Male	0.34 (0.15, 0.60)	0.69 (0.26, 1.30)	0.31 (0.13, 0.56)	0.30 (0.01, 0.56)	0.29 (0.10, 0.62)
Female	1.31 (0.83, 1.90)	1.27 (0.73, 2.00)	1.06 (0.64, 1.60)	1.00 (0.77, 2.30)	0.90 (0.47, 1.50)
Female:Male ratio	3.82 (2.00, 9.00)	1.85 (0.84, 5.10)	3.44 (1.70, 9.00)	3.38 (1.40, 11.0)	3.13 (1.60, 7.00)
	Attained-age effect (power)				
Attained age	−2.00 (−4.0, −0.03)	−2.70 (−4.7, −0.6)	−2.50 (−4.5, −0.4)	−3.05 (−5.2, −0.9)	−2.78 (−4.9, −0.7)
	Age-at-exposure effect (percentage change per decade increase)				
Age at exposure	21% (−6%, 55%)	31% (−2%, 77%)	26% (−5%, 69%)	50% (9%, 111%)	30% (−3%, 77%)
	Smoking-intensity effect				
Packs per day	—	—	—	10.20 (4.6, 17.0)	9.20 (3.8, 15.0)
Packs per day squared	—	—	—	−15.30 (−30.0, 5.4)	−16.6 (−30.0, −6.6)
	Model and fit summary information				
Deviance	9815.5	9428.7	9425.1	9415.7	9410.3
Parameters	14	26	26	28	28
AIC	9843.5	9480.7	9477.1	9471.7	9466.3

model while that for women similar to that for a simple additive model. In all of the models except the simple additive model, the ERR/Gy was significantly larger for women than for men. The radiation-associated ERRs declined with increasing attained age while rising with increasing age at exposure (Fig. 3).

There was no indication of statistically significant curvature in the radiation dose response ($P > 0.5$) over the full dose range or when the data were restricted to the 0–2-Gy range ($P = 0.3$). Furthermore, the gender-averaged dose–response slope for the restricted range (0.67 per Gy) was similar to that for the full range (0.59). There were no indications of gender dependence in effect modification by attained age ($P > 0.5$) or age at exposure ($P > 0.5$), nor was there evidence of nonlinearity (on a log scale) for those effects ($P = 0.3$ for attained age and $P = 0.5$ for age at exposure).

Figure 4 illustrates how the ERR changes with smoking intensity and dose under three interaction models. The points in this figure are category-specific estimates from a generalized multiplicative model in which smoking-intensity categories replaced the linear-quadratic function of log intensity in the radiation model. The left panel describes the joint effect of radiation and smoking relative to the rates for non-smokers with no radiation exposure. The right panel describes the radiation effect in terms of the ERR/Gy relative to the risk for an unexposed individual with the same smoking history. The generalized interaction model suggests that at lower smoking intensities (≤10 cigarettes per day) the radiation effect tends to be greater than predicted by either the simple additive or multiplicative models but that there is little or no apparent radiation effect for heavy smokers (≥20

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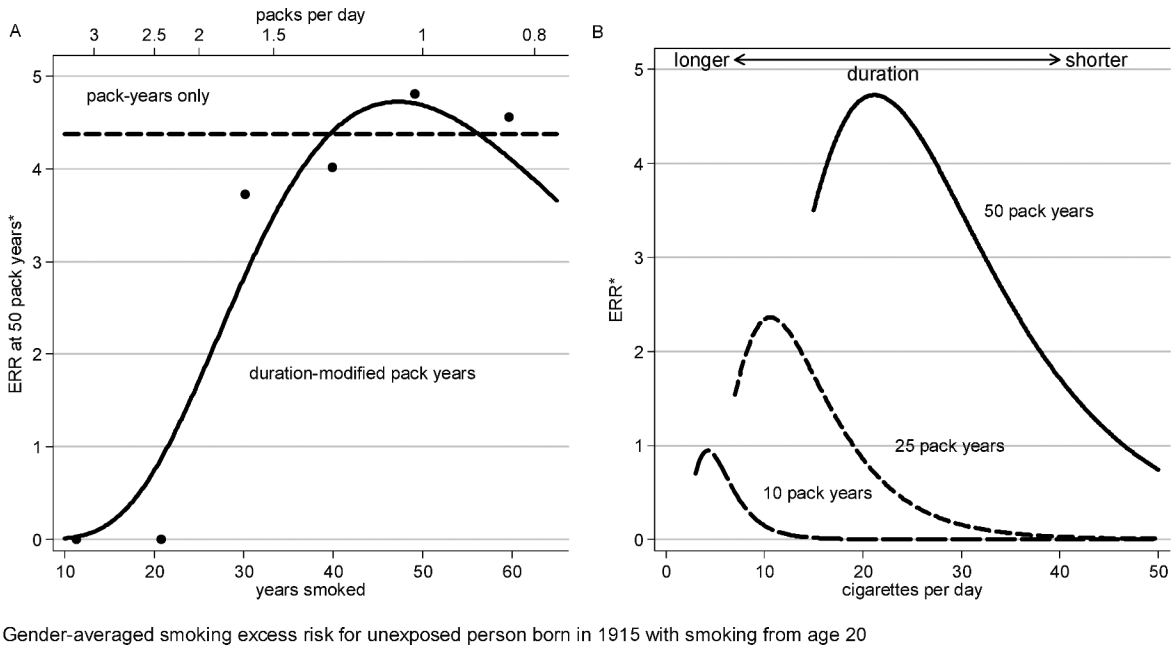

FIG. 1. Smoking-related excess relative risk (ERR) as a function of duration and intensity. Panel A: ERR for a 50-pack-year smoker as a function of smoking duration. The upper axis indicates the smoking intensity (packs per day) required to reach 50 pack-years for the duration indicated on the lower axis. The fitted risk for a model that is linear in pack-years with a log-quadratic duration effect is indicated with the solid line. The fitted ERR for the pack-years-only model is indicated by the dashed line. The points are estimates of the risk in smoking-duration categories. Panel B: Variation in the lung cancer ERR with smoking intensity (cigarettes per day) for fixed numbers of pack years.

cigarettes per day). There was no indication that the risk pattern in the generalized interaction models depended on gender ($P > 0.5$).

The upper portion of Table 3 summarizes the distribution of observed and fitted cases over dose categories for the generalized multiplicative model. The fitted cases are broken down into background cases (i.e., those that would have occurred in unexposed nonsmokers), excess cases associated with radiation exposure, smoking or radiation-smoking interaction, and among those with no smoking history data over predictions for unexposed nonsmokers in the same dose group. Almost

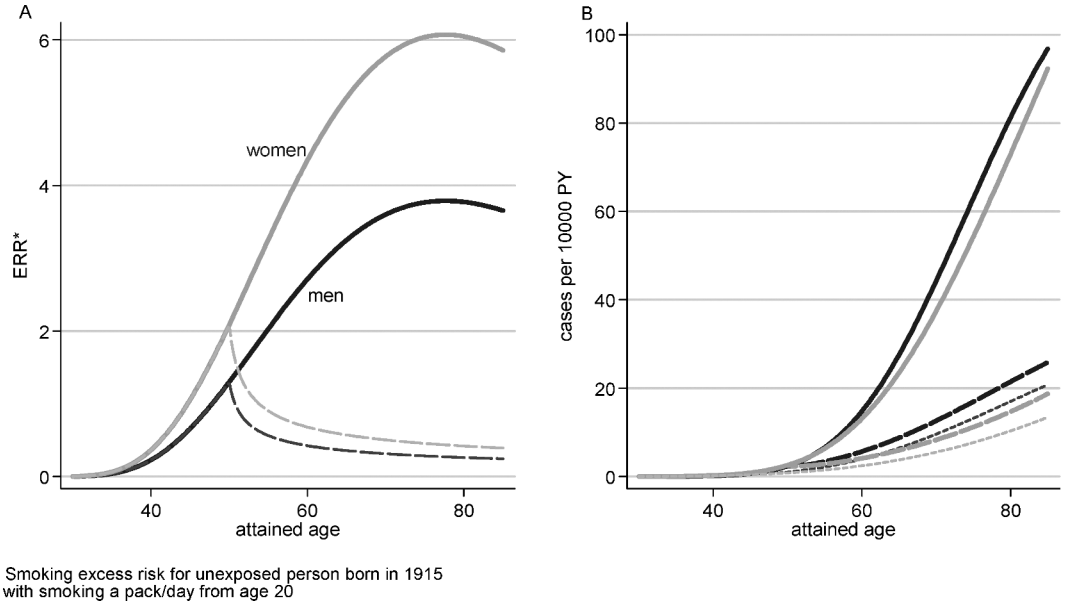

FIG. 2. Gender-specific smoking effects on the excess relative risk (panel A) and absolute rate (panel B) as a function of age. The darker curves are for men and the lighter ones for women. The solid curves illustrate the modeled lung cancer risks for a person who smokes 20 cigarettes (one pack) per day from age 20. The long-dashed lines indicate the risk for an individual who stopped smoking at age 50. The short-dashed lines in panel B indicate the risk for nonsmokers. The curves correspond to risk for an unexposed person born in 1915.

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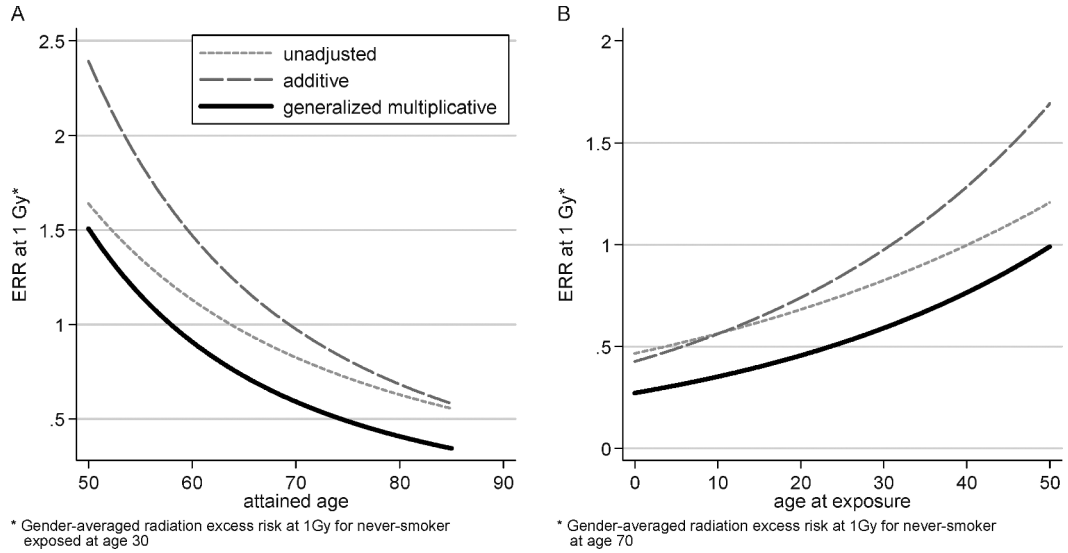

FIG. 3. Effects of attained age (panel A) and age at exposure (panel B) on the excess relative risk (ERR) per Gy. The plots compare the gender-averaged risk estimates for three joint effect models. The generalized multiplicative model for nonsmokers is indicated by the dark solid line while the additive model is indicated by the long-dashed line. For both of these models the ERR is relative to the risk for nonsmokers. The short-dashed line is for a model with no adjustment for smoking. In this model the ERR is relative to the risk for an unexposed cohort member without regard to smoking status.

half (555 of 1126 cases) of the cases among subjects with smoking history data and 40% (270 of 677) of those without smoking data were estimated to be associated with smoking (details not shown). Only about 6% of all the cases appeared to be associated with radiation exposure in the cohort, but this proportion increased to more than 40% among those with lung doses of 1 Gy or more. In the interaction models, only 2–3% of the cases and one-third of the radiation-associated cases were attributed to the joint effect of radiation and smoking. Regardless of the type of interaction, the total estimated numbers of radiation-associated cases were generally similar (102–106), but the model with no smoking adjustment provided the largest estimate of radiation-related excess cases (126). Supplementary Tables 2 and 3 include summaries of the estimated numbers of cases attributable to radiation and smoking stratified by smoking intensity and pack-years.

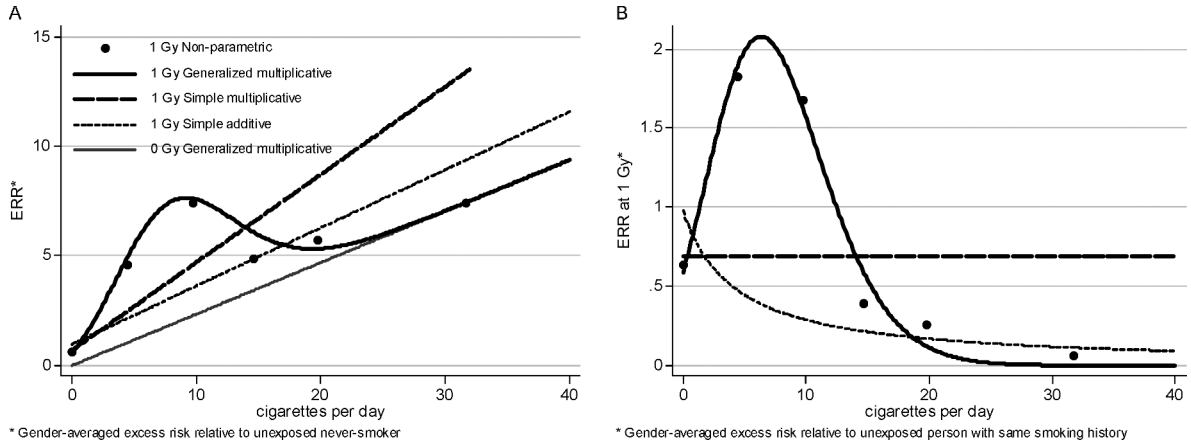

FIG. 4. Variation of the excess relative risk (ERR) with smoking intensity. The gender-averaged risk estimates at age 70 after radiation exposure at age 30. Smoking was assumed to start at age 20 so that smoking duration was fixed at 50 years in this figure. Panel A describes the joint effect of radiation and smoking relative to the baseline rate for a nonexposed nonsmoker. The thin long-dashed line is the fitted ERR for a person with no radiation exposure. The solid line is the fitted ERR after exposure to 1 Gy under the generalized multiplicative model, the thick dashed line is the fitted risk under a simple multiplicative model, and the short-dashed line is the fitted ERR under a simple additive joint effect model. The points are based on a generalized multiplicative model in which smoking intensity categories replaced the linear-quadratic function of log intensity used in the generalized multiplicative model. Panel B presents radiation-associated excess risks for an exposure of 1 Gy relative to the risk of an unexposed person with the same smoking history.

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TABLE 3
Observed and Fitted Cases by Dose Category for the Generalized Multiplicative Model with Totals for Alternative Models

Dose (Gy)	Cases	Baseline (no smoking)	Excess cases: Radiation only	Radiation and smoking	Smoking only	Unknown smoking	Total	Total radiation excess[a]	Total smoking excess
Generalized multiplicative model									
0 (NIC)	423	215.3	0.0	0.0	138.6	69.1	207.7	0.0	138.6
<0.005	568	309.0	0.2	0.1	154.6	90.3	245.2	0.3	154.7
−0.1	424	234.5	5.5	2.3	123.7	62.1	193.7	7.8	126.1
−0.2	101	51.7	5.7	3.0	31.0	14.0	53.7	8.7	34.0
−0.5	119	52.1	13.1	7.3	33.7	14.5	68.6	20.4	41.0
−1	75	29.7	15.9	9.2	19.5	9.6	54.3	25.1	28.8
−2	69	15.8	15.3	10.2	12.5	6.7	44.5	25.2	22.5
2+	24	5.2	9.7	5.4	3.9	3.3	22.3	15.1	9.3
Total	1803	913.2	65.4	37.2	517.7	269.6	889.8	102.6	554.9
Alternative model (totals only)									
Radiation only		1677.3	125.7	—	—	—	—	125.7	—
Additive		901.7	104.7	0.0	530.5	266.1	901.3	104.7	530.5
Multiplicative		932.9	75.0	28.1	508.9	258.2	870.1	103.1	536.9
Generalized additive		901.5	75.9	30.5	520.5	274.7	901.5	106.4	550.9

[a] For the multiplicative and generalized multiplicative models there are some cases that arise due to the interaction between unknown smoking status and radiation effects, these cases (a total of about 13 for both models) are not separated from the other cases associated with unknown smoking status, but are included in the total radiation excess.

DISCUSSION

Questions about the joint effect of radiation and smoking are generally framed in terms of a choice between simple additive and multiplicative models. The analysis by Pierce *et al.* (*6*), which found a pattern for the joint effect that was qualitatively similar to ours, rejected a simple multiplicative model but not a simple additive model. With additional follow-up data from more cohort members and more parsimonious description of the departures from simple models, we were able to reject both the simple additive and multiplicative models. Under our fitted generalized multiplicative model, the joint effect appears to be super-multiplicative for light to moderate smokers (smoking less than a pack of cigarettes per day) but additive or even sub-additive for heavy smokers (smoking a pack or more per day).

How smoking modifies the radiation-related risk of lung cancer has both biological and practical implications. The practical interest arises in medical, occupational and environmental exposure scenarios: namely, implications in risk/benefit analyses of lung cancer CT screening programs targeted at smokers (*18*), concern for the risk from the increasing use of CT scans and other radiological procedures (*19, 20*), interpretation of the dose response found for lung cancer in a large population of nuclear industry workers with low-dose radiation exposure (*21*), and estimation of the proportion of lung cancers attributed to residential radon exposures (*22*). Since γ rays account for most of the dose received by atomic bomb survivors, the LSS data may be directly relevant in the first three cases. To the extent that the biological nature of the radiation-smoking interaction is similar for γ rays and radon α particles, information from the LSS may also be important in the fourth case.

Studies of Hodgkin lymphoma patients treated with radiotherapy (*23, 24*) suggested a multiplicative interaction between radiation and smoking effects on lung cancer risks. The doses received by cancer patients were orders of magnitude greater than those received by atomic bomb survivors and the ERR/Gy (0.15) was considerably lower than the LSS risk estimates. The National Research Council reviewed data from studies of underground miners for the joint effect of smoking and radon exposure (*22, 25*) and concluded that the interaction could be most consistently described as less than multiplicative, although evidence from individual studies varied considerably. The multiplicative effect of smoking and residential radon exposure was suggested in a Swedish study (*26*) and a pooled analysis of European residential radon exposure studies (*27, 28*). None of those studies investigated the kind of departures from simple interaction models that we found in the LSS data.

Adjustment for smoking can affect the modifying effects of gender and age factors on the radiation-related lung cancer risk. Our estimate of the ERR/Gy of 0.59 was smaller than that of 0.89 from the previous analysis by Pierce *et al.* (*6*) and that of 0.81 from the recent analysis of LSS lung cancer incidence with no adjustment for smoking (*3*). The present estimate of the female:male ratio of ERR/Gy of 3.1 was smaller than that of 4.8 from the unadjusted analysis (*3*) but larger than smoking-adjusted estimate of 1.6 in ref. (*6*). For many types of solid cancers, the ERR/Gy decreases with increasing age at exposure (*3, 7*), but the unadjusted

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ERR/Gy for lung cancer has been found to increase with increasing age at exposure. Although it was suggested in ref. (*3*) that this pattern might be a consequence of the failure to adjust for the effect of smoking, the current analyses indicate that this may not be the case. It may be that there is a certain pool of people who are genetically susceptible to lung cancer and that high levels of smoking have saturated that pool so that there is little room for an additional radiation effect. Another possible explanation is that radiation exposure prior to the start of smoking may be less harmful than radiation exposure after smoking initiation. In the LSS, age at exposure is highly correlated with whether radiation exposure occurred before or after initiation of smoking, making it difficult to address this question. However, in an analysis in which the radiation effect was allowed to depend on whether one reported smoking before exposure, we found that radiation risks were not significantly higher for those who smoked before exposure and that the age-at-exposure effect became even more pronounced.

We estimated that smoking related relative risks were 4.6 for males and 6.8 for females who smoked a pack a day for 50 years. If the smoking duration and intensity were averaged over the general population, those values would be close to the risk estimates of 4.5 and 4.2 for male and female smokers, respectively, from another Japanese cohort study (*29*). These values are much smaller than those reported from Western populations (*30, 31*). This may in part reflect the higher lung cancer rates among nonsmokers in Japan and other Asian countries than in the West. A recent study (*32*) suggested that lung cancer rates might be higher among Japanese nonsmokers and relative risks lower among Japanese smokers compared with their U.S. white counterparts. Our estimates of lung cancer rates for nonsmokers were similar to those found for Japanese and Korean populations in an international comparison of lung cancer risks among nonsmokers (*33*).

The major limitation of this study arises from the use of incomplete, historical smoking data derived from mail surveys. While all of the eligible cases in the cohort were used to estimate radiation effects, the power to describe the radiation-smoking interaction was reduced because smoking status was unknown for about 60% of the total follow-up time and smoking status at the time of diagnosis was unknown for about 40% of the cases. Use of singly imputed values for the age at which smoking started or intensity of smoking can lead to some underestimation of the uncertainty in risk estimates. Estimates of the effect of smoking cessation can be underestimated due to smoking recidivism, because the most recent smoking data used were obtained in the early 1990s. However, it is also likely that many people who reported smoking at the time of their last survey response have since quit smoking, which would tend to result in underestimation of the effect of smoking in later years. While the present analysis considered all lung cancer types together, smoking and radiation may have different effects on different subtypes of lung cancer; this will be reported in a forthcoming paper.

Despite these limitations, we believe that this study provides the most comprehensive characterization of the joint effects of low-dose radiation and smoking on lung cancer in any radiation-exposed population. The results suggest that simple additive or multiplicative models may not adequately describe the complex interaction between smoking intensity and radiation and that a similar comprehensive analytical approach may be needed in risk estimation for smokers with medical or occupational radiation exposures. We think that further efforts should be made to develop methods for using generalized interaction models in radiation risk assessment. This study is also one of the most detailed quantitative analyses of smoking effects on lung cancer rates in a Japanese population, and whether the present findings are duplicated in other Japanese cohorts would be of interest because they have an important public health implication for one of the major cancer problems in Japan.

SUPPLEMENTARY INFORMATION

Additional information on the smoking history data (including Tables S1 and S2). DOI: 10.1667/RR2083.1.S1

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