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Lung, Laryngeal and Other Respiratory Cancer Incidence among Japanese Atomic Bomb Survivors: An Updated Analysis from 1958 through 2009

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The Life Span Study (LSS) of Japanese atomic bomb survivors is comprised of a large, population-based cohort offering one of the best opportunities to study the relationship between exposure to radiation and incidence of respiratory cancers. Risks of lung, laryngeal and other cancers of the respiratory system were evaluated among 105,444 LSS subjects followed from 1958 to 2009. During this period, we identified 2,446 lung, 180 laryngeal and 115 other respiratory (trachea, mediastinum and other ill-defined sites) first primary incident cancer cases. Ten additional years of follow-up, improved radiation dose estimates, revised smoking data, and updated migration information were used to investigate the joint effects of radiation and smoking using Poisson regression methods. For nonsmokers, the sex-averaged excess relative risk per Gy (ERR/Gy) for lung cancer (at age 70 after radiation exposure at age 30) was estimated as 0.81 (95% CI: 0.51, 1.18) with a female-to-male ratio of 2.83. There was no evidence of curvature in the radiation dose-response relationship overall or by sex. Lung cancer risks increased with pack-years of smoking and decreased with time since quitting smoking at any level of radiation exposure. Similar to the previously reported study, which followed cohort members through 1999, the ERR/Gy for lung cancer was significantly higher for low-to-moderate smokers than for heavy smokers, with little evidence of any radiation-associated excess risk in heavy smokers. Of 2,446 lung cancer cases, 113 (5%) could be attributed to radiation exposure. Of the 1,165 lung cancer cases occurring among smokers, 886 (76%) could be attributed to smoking. While there was little evidence of a radiation effect for laryngeal cancer, a nonsignificantly elevated risk of other respiratory cancers was observed. However, significant smoking effects were observed for both laryngeal (ERR per 50 pack-years = 23.57; 95% CI: 8.44, 71.05) and other respiratory cancers (ERR per 50 pack-years = 1.21; 95% CI: 0.10, 3.25). **© 2017 by Radiation Research Society**

INTRODUCTION

Risks of respiratory cancers related to radiation exposure from occupational, accidental and medical sources continues to be of public health significance and regulatory concern. Quantification of the joint effects of radiation and smoking provides important information for radiation risk assessment models and risk/benefit analyses of lung cancer screening programs. The Life Span Study (LSS) is a prospective population-based cohort of Japanese atomic bomb survivors exposed to radiation doses ranging from 0 to 4 Gy, with follow-up of cancer incidence since 1958. Because detailed smoking information is available for most cohort members and smoking is a well-established cause of lung and other respiratory cancers, the LSS offers a valuable opportunity to investigate the long-term joint effects of radiation and smoking on respiratory cancer risks.

Incidence of lung cancer, which is the second most common cancer in the LSS, has been most recently examined using follow-up through the year 1999 (*1, 2*). Furukawa and colleagues reported a sex-averaged excess relative risk per Gy (ERR/Gy) of lung cancer (at age 70 after radiation exposure at age 30) to be 0.59 (95% CI: 0.31–1.00) for nonsmokers with a female-to-male ratio of 3.1 (*1*). They also reported a super-multiplicative interaction for cohort members who smoked approximately 10 cigarettes per day, but little radiation-related risk in heavy smokers. Following the report of most recently updated cancer incidence data in the LSS (*5*), the analyses in the

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current study make use of ten additional years of follow-up (through 2009), revised smoking data, improved radiation dose estimates and updated migration information for cohort participants. Here, we evaluate the relationship between radiation exposure and lung cancer risk, paying special attention to the nature of the joint effect of radiation and smoking. We also evaluate the radiation- and smoking-related risks for laryngeal and other respiratory cancers, which include malignant first primary cancers of the trachea, mediastinum and other ill-defined sites as a group (*3*).

MATERIALS AND METHODS

Study Population and Follow-up

The LSS cohort includes 120,321 subjects born prior to the atomic bombings in August 1945 and still alive on October 1, 1950. Subjects of this study comprise 93,741 atomic bomb survivors of Hiroshima and Nagasaki and 26,580 persons who were not in either city at the time of the bomb. We excluded LSS cohort members who had died or had cancer prior to January 1, 1958 (n = 8,317 subjects), could not be traced (n = 86), as well as those for whom DS02R1 radiation dose estimates were unavailable (6,473 subjects). After these exclusions were made, there were 105,444 eligible subjects including 80,205 survivors and 25,239 subjects who were not in either city at the time of the bombs. Follow-up began on January 1, 1958 and continued until the earlier of first primary cancer diagnosis, death or December 31, 2009. Additional details about the cohort have been given elsewhere (*4, 5*).

Case Ascertainment

Cases were ascertained through the Hiroshima and Nagasaki tumor registries, which were started in 1958. Additional information was available through the Radiation Research Effects Foundation autopsy program and death certificates routinely obtained for LSS follow-up. Eligible cases were subjects with primary malignant incident cancers of the lung (ICD10 C34), larynx (ICD10 C32), and other respiratory cancers as a group comprised of cancers of the trachea, anterior/posterior mediastinum and other ill-defined sites of the respiratory system (ICD10 C33, C381–C383, C388, C390, C398, C399) diagnosed within the catchment areas from 1958 to 2009 among the 105,444 subjects in the final analysis cohort. After we excluded cases diagnosed only by autopsy (83 lung cancer cases), 2,446 lung, 180 laryngeal and 115 other respiratory cancer cases remained for analysis.

Since cancer case ascertainment is incomplete for subjects who have left the Hiroshima and Nagasaki tumor registry catchment areas, we accounted for the effects of migration on risk estimates. Because individual residence history data were not available for all cohort members, city-, sex-, age- and time-dependent residence probabilities estimated from the Adult Health Study (AHS) clinical contact data were used to compute migration-adjusted person years (*5*).

Radiation Dosimetry

Weighted lung dose estimates computed as sum of the DS02R1 gamma-ray dose estimate and 10 times the DS02R1 neutron dose estimate were used for these analyses (*4, 5*). As in previous analyses, cohort members who were not in either city (NIC) of Hiroshima or Nagasaki at the times of the bombings were included in the analysis to improve the characterization of the variation in the unexposed (zero dose) baseline cancer rates by age, sex and birth cohort. However, radiation effects were quantified among 80,205 survivors who were within 10 km of the hypocenters at the time of the bombings.

Smoking Information

Data on smoking habits of LSS cohort members were derived from four mailed and three clinic-based questionnaires administered between 1963 and 1991. The 1963 survey was administered to the AHS participants. The 1965 survey was administered to men between the ages of 40 and 69. The 1969 survey included only females. The 1978 and 1991 surveys were mailed to all surviving cohort members who were in the cities at the time of the bombings. Among eligible cohort members, smoking information was available for 64,465 subjects (61%).

Smoking history was summarized by a time-dependent indicator of smoking status (unknown, never-smoker, past-smoker or current-smoker). All cohort members were classified as having unknown smoking status prior to the date at which they first provided information on smoking habits to prevent biasing risk estimates by over-counting person years in known smoking categories. A person was considered a past-smoker if they indicated that they had quit smoking at the time of their most recent survey response, which unfortunately was not later than 1991. A smoker was considered a current smoker from the date at which he/she first provided information on smoking until either the end of follow-up (December 31, 2009 or first cancer diagnosis) or the date of reported quitting, whichever came first.

More detailed information on smoking included ''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 of smoking reported from all surveys to which a person responded. ''Cigarettes per day'' was defined as the average number of cigarettes per day over all surveys in which a person reported having smoked. For those with known smoking status, smoking duration was defined as the difference between attained age and age started smoking, while time since quitting was defined as the difference between attained age and age at quitting. Cumulative smoking amount was expressed in pack-years, defined as the product of packs smoked per day (20 cigarettes per pack) and years smoked. In some cases, smokers did not answer more detailed questions about the amount smoked or age at start of smoking. These values were imputed as the sex- and birth cohort-specific means among smokers with complete information.

Statistical Analysis

Parameter estimation, hypothesis testing and the computation of confidence intervals are based on Poisson regression maximum likelihood methods. To enable these analyses, we created a table of person-years and cancer cases based on the following stratification factors: city, sex, attained age, calendar time, age at exposure, radiation dose and time-dependent smoking-related factors: smoking status (unknown, never, past and current), average number of cigarettes per day, years smoked and years since quitting. For laryngeal cancer, we also considered time-dependent measures of alcohol use: drinking status (unknown, never, past and current) and average number of drinks per day. We used the same stratification cut points as previously reported to facilitate comparison of findings (*1, 6*).

The analytic approach was also similar to that used by Furukawa and colleagues in that we focus on understanding the joint effects of radiation and smoking on respiratory cancer risks (*1*). For lung cancer, the logarithm of the baseline rate is expressed as a sex-specific linear-quadratic spline function of log of attained age, sex-specific birth cohort, city (Hiroshima or Nagasaki) and not in city separately for Hiroshima and Nagasaki. For laryngeal and other respiratory cancer risks, the logarithm of the baseline rate is expressed as a simpler function of sex, log of attained age, birth cohort and city (Hiroshima or Nagasaki, NIC of Hiroshima, NIC of Nagasaki). We use ERR models where the total risk or hazard is given by:

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$$Risk = B \times RR(smk, rad) = B \times [1 + ERR(smk, rad)],$$

for which B is the baseline rate, RR is the relative risk, and ERR is the excess risk relative to the baseline.

To characterize the joint effect of radiation and smoking, we considered both additive and multiplicative ERR models [Eqs. (1–4)]. In a simple additive model, the joint effect of radiation and smoking is equal to the sum of the ERR for smoking and the ERR/Gy [Eq. (1)], while in a simple multiplicative model the joint effect is equal to the sum of the ERRs plus the product of the ERR/Gy and smoking ERR values [Eq. (3)]. We also evaluated generalized forms of these models in which 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, as in the simple multiplicative model [Eqs. (2) and (4)]. All four models are summarized below:

Additive model (AM):

$$Risk = B \times RR(smk, rad) = B(1 + ERR_{smk} + ERR_{rad}). \quad (1)$$

Generalized additive model (GAM):

$$Risk = B \times RR(smk, rad) = B[1 + ERR_{smk} + f(smk)ERR_{rad}]. \quad (2)$$

Multiplicative model (MM):

$$\begin{aligned} Risk &= B \times RR(smk, rad) = B(1 + ERR_{smk})(1 + ERR_{rad}) \\ &= B(1 + ERR_{rad} + ERR_{smk} + ERR_{rad}ERR_{smk}). \end{aligned} \quad (3)$$

Generalized multiplicative model (GMM):

$$Risk = B \times RR(smk, rad) = B(1 + ERR_{smk})[1 + f(smk)ERR_{rad}]. \quad (4)$$

For lung cancer, the ERR/Gy, ERR_{rad}, was best described by the product of a sex-averaged function of dose (d) and an effect modification term that depends on attained age (a) and age at exposure (e):

$$ERR_{rad} = \beta_g d \times \left(\frac{a}{70}\right)^{\eta} \times e^{\gamma\left(\frac{e-30}{10}\right)}.$$

Attained age and age at exposure were scaled so that the sex-average dose effect corresponds to the risk for a 70-year-old survivor who was exposed at 30 years of age. Sex-specific ERRs/Gy were also computed. Radiation-related excess absolute risk per Gy (EAR/Gy) was calculated based on parameters estimated from the best fitting model and plotted by attained age. We also examined whether the shape of the dose response was better described by linear-quadratic or sex-specific linear-quadratic models, but it was not.

The smoking ERR (ERR_{smk}), was best described as the product of a function of pack-years and an effect modification term that depends on cigarettes smoked per day (c), smoking duration in years (y), years since quitting (q) with allowance for birth year (b), sex (g) and unknown smoking status. For follow-up during which smoking status is unknown, the smoking effect depends on sex and birth-cohort strata. Among those with information on smoking:

$$\begin{aligned} ERR_{smk} &= \left(\phi_{0g} \times \frac{p}{50}\right) \times \exp\left[\phi_{1g}\left(\frac{b - 1915}{10}\right) + \lambda_1 \ln\left(\frac{y}{50}\right)\right. \\ &\quad \left. + \lambda_2 \ln(c) + \nu \ln(q + 1)\right] \\ &= \left(\phi_{0g} \times \frac{p}{50}\right) \times e^{\phi_{1g}\left(\frac{b-1915}{10}\right)} \times \left(\frac{y}{50}\right)^{\lambda_1} \times (c)^{\lambda_2} \times (q + 1)^{\nu}. \end{aligned}$$

Smoking duration and birth cohort were centered so that ϕ_{0g} is interpreted as the sex-specific ERR for a current smoker who was born in 1915 and smoked one pack per day for 50 years. The excess smoking risk associated with 50 pack-years of smoking was summarized by a sex-averaged value, ϕ_{0g}, which we define as the unweighted mean of the 50 pack-years effect parameters for men and women, but sex-specific ERRs are also presented (Table 3). Since $\frac{p}{50} = c \times \left(\frac{y}{50}\right)$, the previous equation reduces to:

$$ERR_{smk} = e^{\phi_{1g}\left(\frac{b-1915}{10}\right)} \times \left(\frac{y}{50}\right)^{1+\lambda_1} \times c^{1+\lambda_2} \times (q + 1)^{\nu}.$$

The generalized additive [Eq. (2)] and generalized multiplicative [Eq. (4)] models also multiplied the ERR_{rad} by the following linear-quadratic function of cigarettes per day,

$$f(smk) = \exp[\omega_1(c) + \omega_2(c)^2]. \quad (5)$$

For lifelong nonsmokers, $f(smk) = 1$.

The joint RR for laryngeal cancer and other respiratory cancers as a group was described by a simple multiplicative model of the following form for those with known smoking status:

$$\begin{aligned} R(smk, rad) &= (1 + ERR_{smk})(1 + ERR_{rad}) \\ &= \left[1 + e^{\lambda_1 I_{evr,smk}}\left(\frac{y}{50}\right) \times c\right](1 + \beta d). \end{aligned}$$

Likelihood ratio tests were used to select between nested models. To compare non-nested models, we used the Akaike Information Criteria (AIC). Two-sided P values are referred to as significant if they are less than $\alpha = 0.05$. Sensitivity analyses restricting follow-up through 1999 (as in the previous report) were performed to determine whether any differences in lung cancer results could be attributed to additional follow-up, or whether they were due to relatively minor changes in smoking or dose data. We also performed a sensitivity analysis to examine the radiation effect and smoking radiation effect modification under scenarios of quitting smoking between 1991 and 2009, when smoking information was not available in our cohort. We also examined EAR models for the joint effect of radiation and smoking on cancer rates of the form:

$$Risk = B_{ns} + EAR_{smk} + EAR_{rad},$$

where B_{ns} is the baseline rate among never-smokers, and EAR_{smk} and EAR_{rad} are the excess absolute risk associated with smoking and radiation, respectively. Model fitting was performed using the AMFIT module of the software package Epicure (Risk Sciences International Inc., Ottawa, Canada) (*7*).

Ethical Considerations

This study was approved by the Human Investigation Committee of the Radiation Effects Research Foundation via approval of RP 1-75 (Research plan for RERF study of Life-span of A-bomb survivors, Hiroshima and Nagasaki) and RP 18-61 (Tumor registry study in Hiroshima and Nagasaki). The Hiroshima and Nagasaki Prefectures and the city of Hiroshima approved the linkages between LSS cohort members and data from the Cancer Registries.

RESULTS

Smoking

Data on smoking are available for 60% of men and 62% of women. Among those who provided information on smoking, 86% of the men and 18% of the women indicated that they had ever smoked. The proportion of ever-smokers among men is similar over birth-cohort and radiation dose categories. Among women, the proportion of ever-smokers decreases slightly with increasing distance from the hypocenters and increases with increasing dose. Women under 20 at the time of the bombings are less likely to have ever smoked than women who were older. Male smokers

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TABLE 1
Cases and Crude Respiratory Cancer Rates (per 10,000 Person-Years) among Japanese Atomic Bomb Survivors from 1958 to 2009

	Lung cancer				Laryngeal cancer				Other respiratory cancers			
	Males		Females		Males		Females		Males		Females	
	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
City												
Hiroshima	997	12.34	708	5.11	101	1.25	21	0.15	34	0.42	39	0.28
Nagasaki	448	13.39	293	5.31	53	1.58	5	0.09	18	0.54	24	0.43
Age at exposure												
0–19	594	8.16	280	3.11	67	0.92	5	0.06	16	0.22	11	0.12
20–39	166	15.76	245	5.88	15	1.42	4	0.10	7	0.66	17	0.41
40–49	271	20.34	237	7.11	30	2.25	5	0.15	15	1.13	14	0.42
50+	414	23.54	239	8.35	42	2.39	12	0.42	14	0.80	21	0.73
Attained age												
0–39	3	0.10	3	0.08	0	0.00	0	0.00	2	0.07	1	0.03
40–49	22	1.17	16	0.54	4	0.21	0	0.00	4	0.21	8	0.27
50–59	147	6.40	96	2.49	31	1.35	4	0.10	9	0.39	13	0.34
60–69	466	19.57	252	6.10	51	2.14	7	0.17	25	1.05	15	0.36
70–79	542	37.69	343	10.95	53	3.69	11	0.35	6	0.42	19	0.61
80+	265	52.43	291	16.77	15	2.97	4	0.23	6	1.19	7	0.40
Radiation dose (Gy)												
NIC	373	12.96	227	4.79	28	0.97	5	0.11	8	0.28	12	0.25
0–0.005	476	12.80	297	4.65	56	1.51	7	0.11	16	0.43	23	0.36
0.005–0.1	338	11.24	242	4.79	44	1.46	11	0.22	15	0.50	12	0.24
0.1–0.2	68	11.53	65	6.17	6	1.02	2	0.19	6	1.02	5	0.47
0.2–0.5	78	12.82	76	6.75	8	1.32	1	0.09	1	0.16	5	0.44
0.5–1	53	15.68	43	6.92	8	2.37	0	0.00	3	0.89	3	0.48
1–2	40	19.39	39	13.57	1	0.48	0	0.00	3	1.45	2	0.70
2+	19	24.73	12	11.57	3	3.90	0	0.00	0	0.00	1	0.96
Smoking status												
Never	40	6.08	392	5.65	2	0.30	4	0.06	3	0.46	16	0.23
Past	141	15.91	39	11.98	18	2.03	2	0.61	6	0.68	2	0.61
Current	802	28.19	183	18.85	76	2.67	8	0.82	25	0.88	5	0.52
Unknown	462	6.57	387	3.48	58	0.82	12	0.11	18	0.26	40	0.36
Total	1,445	12.65	1,001	5.17	154	1.35	26	0.13	52	0.46	63	0.33

Note. NIC = Not in either city of Hiroshima or Nagasaki at the time of bombing.

smoke approximately twice as many cigarettes per day (mean 19.1) as female smokers (mean 10.1) and tended to start smoking earlier (mean starting ages of 21.5 and 32.2, respectively). Approximately 30% of ever-smokers reported having stopped smoking prior to the last survey to which they responded.

Lung Cancer

Sex-specific distributions of the first primary lung cancer cases by city, age at exposure, attained age, radiation dose and smoking status at the end of follow-up are shown in Table 1. Crude incidence rates of lung cancer are higher for current smokers than for never- or past-smokers. Lung cancer rates increase with higher age at exposure, attained age and radiation dose. The distribution of lung cancers by sex, smoking status and radiation dose is shown in Table 2. Incidence rates for lung cancer are higher for current smokers than for never- or past-smokers within each radiation dose category.

Lung cancer ERR estimates and 95% CIs for selected parameters are shown in Table 3. Parameters come from the four interaction models described above and a model with only radiation effects. The GMM performs better than the other interaction models for lung cancer based on the AIC.

Baseline rates. There is little variation in fitted baseline rates between the models considered for lung cancer. The baseline rate of lung cancer was larger for men than for women, with the male:female ratio at age 70 estimated to be 1.26. Baseline lung cancer rate is proportional to attained age/70 to a power of 5.67 (95% CI: 5.22, 6.12) in men and attained age/70 to a power of 5.26 (95% CI: 4.80, 5.72) in women (P for sex difference = 0.184). Baseline rate estimates are higher in Nagasaki than in Hiroshima for lung cancer ($P < 0.001$).

Smoking effects. Table 3 shows lung cancer smoking-effect parameters estimated using the GMM 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 GMM, the sex-averaged ERR associated with smoking 20 cigarettes per day for 50 years (i.e., 50 pack-years) for an unexposed individual born in 1915 is estimated to be 5.77 (95% CI:

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TABLE 2
Cases and Crude Respiratory Cancer Rates (per 10,000 Person-Years) by Radiation Dose, Sex and Smoking Status at End of Follow-up among Japanese Atomic Bomb Survivors from 1958 to 2009

	Radiation dose (Gy)															
	NIC		0–0.005		0.005–0.1		0.1–0.2		0.2–0.5		0.5–1		1+		Total	
Smoking status	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
Men																
Lung cancer																
Never	7	7.20	16	6.92	14	7.20	1	2.30	1	2.17	1	3.86	0	0.00	40	6.08
Past	15	15.31	58	17.67	44	14.97	5	9.32	13	23.13	3	9.56	3	12.14	141	15.91
Current	178	30.88	270	28.95	191	24.83	43	25.43	48	25.82	33	31.16	39	36.72	802	28.19
Unknown	173	8.21	132	5.93	89	5.09	19	5.87	16	5.00	16	9.15	17	12.81	462	6.57
Total	373	12.96	476	12.80	338	11.24	68	11.53	78	12.82	53	15.68	59	20.84	1445	12.65
Laryngeal cancer																
Never	0	0.00	1	0.43	0	0.00	1	2.30	0	0.00	0	0.00	0	0.00	2	0.30
Past	1	1.02	6	1.83	7	2.38	0	0.00	1	1.78	3	9.56	0	0.00	18	2.03
Current	12	2.08	28	3.00	25	3.25	3	1.77	3	1.61	3	2.83	2	1.88	76	2.67
Unknown	15	0.71	21	0.94	12	0.69	2	0.62	4	1.25	2	1.14	2	1.51	58	0.82
Total	28	0.97	56	1.51	44	1.46	6	1.02	8	1.32	8	2.37	4	1.41	154	1.35
Other respiratory cancers																
Never	0	0.00	3	1.30	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	3	0.46
Past	0	0.00	1	0.30	3	1.02	0	0.00	0	0.00	0	0.00	2	8.09	6	0.68
Current	3	0.52	9	0.97	4	0.52	4	2.37	1	0.54	3	2.83	1	0.94	25	0.88
Unknown	5	0.24	3	0.13	8	0.46	2	0.62	0	0.00	0	0.00	0	0.00	18	2.56
Total	8	0.28	16	0.43	15	0.50	6	1.02	1	0.16	3	0.89	3	1.06	52	0.46
Women																
Lung cancer																
Never	76	5.06	111	4.90	99	5.37	32	7.77	23	5.05	29	10.35	22	11.87	392	5.65
Past	1	2.29	16	15.05	13	12.65	1	3.67	5	20.60	1	8.30	2	21.48	39	11.98
Current	36	17.79	48	17.27	41	15.65	11	15.88	26	31.71	8	17.36	13	41.83	183	18.85
Unknown	114	3.81	122	3.27	89	3.13	21	3.85	22	3.89	5	1.77	14	8.46	387	3.48
Total	227	4.79	297	4.65	242	4.79	65	6.17	76	6.75	43	6.92	51	13.04	1001	5.17
Laryngeal cancer																
Never	0	0.00	1	0.04	3	0.16	0	0.00	0	0.00	0	0.00	0	0.00	4	0.06
Past	0	0.00	0	0.00	1	0.97	0	0.00	1	4.12	0	0.00	0	0.00	2	0.61
Current	1	0.49	3	1.08	3	1.15	1	1.44	0	0.00	0	0.00	0	0.00	8	0.82
Unknown	4	0.13	3	0.08	4	0.14	1	0.18	0	0.00	0	0.00	0	0.00	12	0.11
Total	5	0.11	7	0.11	11	0.22	2	0.19	1	0.09	0	0.00	0	0.00	26	0.13
Other respiratory cancers																
Never	1	0.07	6	0.26	3	0.16	3	0.73	1	0.22	1	0.36	1	0.54	16	0.23
Past	0	0.00	2	1.88	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	2	0.61
Current	1	0.49	2	0.72	1	0.38	0	0.00	0	0.00	0	0.00	1	3.22	5	0.52
Unknown	10	0.33	13	0.35	8	0.28	2	0.37	4	0.71	2	0.71	1	0.60	40	0.36
Total	12	0.25	23	0.36	12	0.24	5	0.47	5	0.44	3	0.48	3	0.77	63	0.33

Note. NIC = Not in either city of Hiroshima or Nagasaki at the time of bombing.

4.68, 7.11). The ERR associated with smoking is not statistically different for men and women followed through 2009 (Table 3), while females tended to have a higher risk than men associated with cumulative smoking for follow-up through 1999 when using the same model and doses (Suppelmentary Table S1; http://dx.doi.org/10.1667/RR14583.1.S1). Age-specific ERRs for a given smoking history exhibited a statistically significant increase ($P = 0.026$) with decreasing birth year.

In our modeling of the smoking ERR, we allowed the pack-year effect to vary with log smoking duration and log packs per day, which significantly improved the model fit ($P < 0.001$, degrees of freedom = 2). Under this modified pack-year model, lung cancer rates are proportional to: 1. Smoking duration (years smoked/50) to the power of $1 + 1.09 = 2.09$; and 2. Packs per day to the power of $1 - 0.33 = 0.67$ (Table 3). This suggests an increased potency at the higher smoking durations (Fig. 1A) and a reduced potency at higher number of cigarettes per day (Fig. 1B) among participants with the same cumulative smoking. Risk of lung cancer stopped increasing upon smoking cessation, compared to those who continue smoking, and even decreased over time (Table 3). However, lung cancer risk never returns to the level of a never-smoker (Fig. 2).

Radiation and radiation-by-smoking interactions. Table 3 shows effect estimates for radiation exposure and risk-modifying factors, together with 95% confidence intervals and information about the fit for the radiation dose-response ERR interaction models described in the methods. The GMM described the data somewhat better than the simple

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TABLE 3
Lung Cancer Parameter Estimates and 95% Likelihood-Based Confidence Intervals for Smoking and Radiation Effects among Japanese Atomic Bomb Survivors from 1958 to 2009

	Radiation only	Simple additive	Simple multiplicative	Generalized multiplicative
Smoking parameters				
ERR/50 pack-years (born in 1915)				
Sex-average, $e^{\varphi 0g}$		6.02 (4.91, 7.41)	5.50 (4.50, 6.75)	5.77 (4.68, 7.11)
Female, $e^{\varphi 0f}$		6.34 (4.84, 8.19)	5.49 (4.22, 7.03)	5.83 (4.42, 7.55)
Male, $e^{\varphi 0m}$		5.70 (4.10, 8.07)	5.51 (4.00, 7.72)	5.71 (4.14, 8.00)
Female:male ratio, $e^{\varphi 0f}/e^{\varphi 0m}$		1.11 (0.71, 1.72)	1.00 (0.64, 1.52)	1.02 (0.66, 1.56)
Birth cohort (percentage change per decade decrease in birth year), $100(1 - e^{\varphi 1g})$		9% (1%, 16%)	9% (1%, 16%)	9% (1%, 16%)
Log(duration/50), λ_1		1.13 (0.55, 1.76)	1.11 (0.54, 1.74)	1.09 (0.52, 1.71)
Log(pack/day), λ_2		–0.39 (–0.55, –0.22)	–0.41 (–0.56, –0.24)	–0.33 (–0.50, –0.16)
Log(years since quit+1), ν		–0.18 (–0.32, –0.05)	–0.18 (–0.32, –0.05)	–0.18 (–0.32, –0.05)
Radiation parameters				
ERR/Gy (age 70, age at exposure 30, never-smoker)				
Sex-average, β_g	0.83 (0.58, 1.09)	1.16 (0.72, 1.71)	0.73 (0.50, 0.99)	0.81 (0.51, 1.18)
Female, β_f	1.32 (0.90, 1.82)	1.55 (1.00, 2.23)	1.17 (0.77, 1.64)	1.20 (0.74, 1.75)
Male, β_m	0.34 (0.14, 0.58)	0.76 (0.18, 1.65)	0.29 (0.11, 0.52)	0.42 (0.16, 0.84)
Female:male ratio, β_f/β_m	3.91 (2.03, 9.79)	2.04 (0.86, 8.53)	3.99 (1.99, 11.14)	2.83 (1.38, 7.23)
Log(attained age/70), η	–2.11 (–3.85, –0.32)	–2.60 (–4.46, –0.73)	–2.59 (–4.38, –0.78)	–2.50 (–4.30, –0.71)
Age at exposure (% change per decade increase), $100(1 - e^{\gamma})$	16% (–7%, 46%)	17% (–9%, 50%)	15% (–10%, 47%)	7% (–16%, 35%)
Linear-quadratic function of cigarettes per day, f(smk)				
Cigarettes/day, ω_1	-	-	-	0.15 (–0.05, 0.46)
(Cigarettes/day)^2, ω_2	-	-	-	–0.01 (–0.04, 0.002)
Akaike information criterion	14,231.3	13,637.3	13,636.1	13,630.7

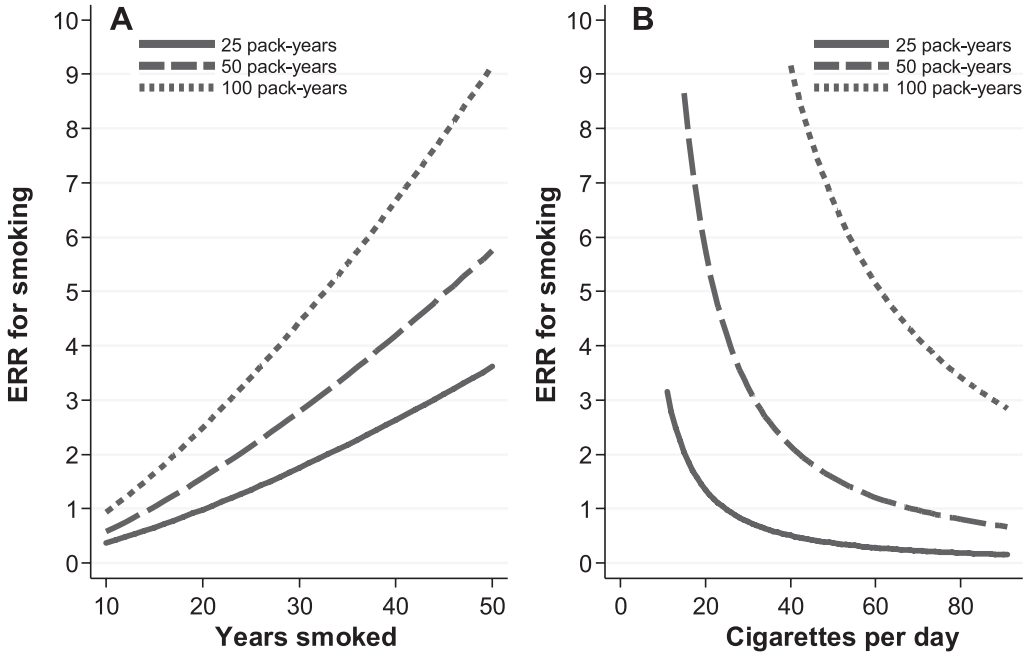


FIG. 1. Smoking-related excess relative risk (ERR) of lung cancer related to years smoked and cigarettes per day among Japanese atomic bomb survivors from 1958 to 2009. The smoking ERR here applies to an unexposed person born in 1915 and smoking since age 20 relative to a never-smoker of the same age and sex.

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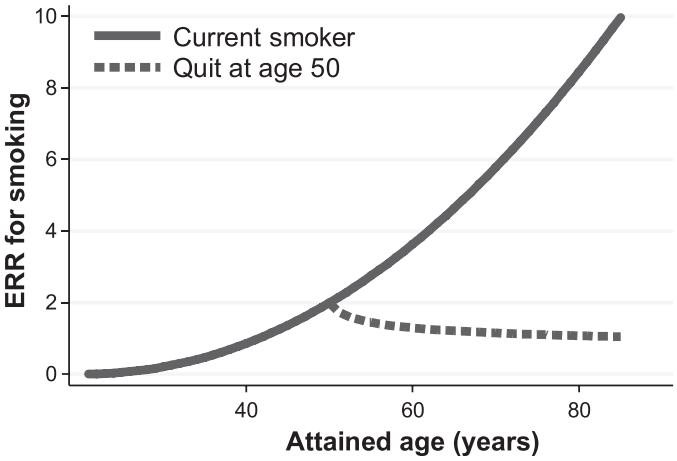


FIG. 2. Smoking-related excess relative risk (ERR) of lung cancer related to attained age among Japanese atomic bomb survivors from 1958–2009. The smoking-related ERR here applies to the sex-averaged smoking ERR for an unexposed person born in 1915 who smoked one pack per day since age 20.

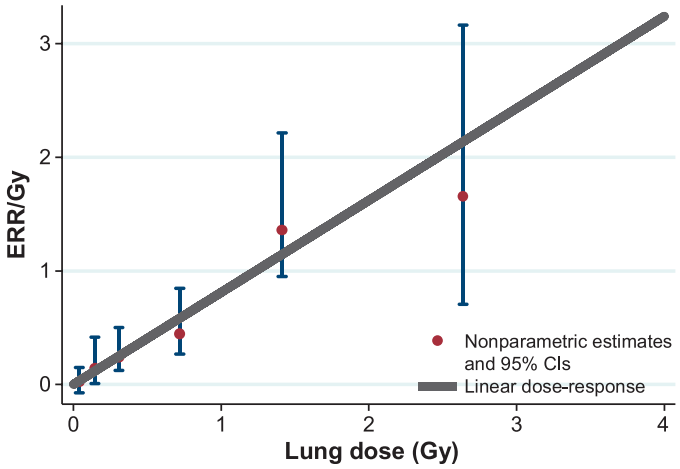


FIG. 3. Radiation-related excess relative risk (ERR/Gy) of lung cancer among never-smoking Japanese atomic bomb survivors from 1958–2009. The radiation-related ERR here applies to sex-averaged ERR/Gy using the GMM for a 70-year-old never-smoker with exposure at age 30.

additive or multiplicative models. The ERR/Gy was significantly larger for women than for men. The dose response is shown for never-smokers in Fig. 3. Inclusion of a quadratic term for dose provides little evidence of curvature in the radiation dose-response relationship overall ($P > 0.5$) or by sex ($P > 0.5$). Furthermore, the sex-averaged dose-response relationship for a restricted range of 0–1.0 Gy (ERR/Gy = 0.65; 95% CI: 0.19, 1.21) is similar to that for the full range of 0–3.5 Gy (ERR/Gy = 0.81; 95% CI: 0.51, 1.18).

The ERR/Gy increases with increasing age at exposure (Table 3), but declines with increasing attained age (Fig. 4A). Despite a decline in the ERR/Gy with attained age, the EAR/Gy increases with age (Fig. 4B). There are no indications of sex dependence in effect modification by attained age or age at exposure. Nor is there evidence of nonlinearity (on a log scale) for those effects.

A linear-quadratic function of cigarettes per day [the term $f(smk)$ in Eq. (9)] allowing smoking to modify the radiation effect, significantly improves model fit over the simple additive or multiplicative models (Table 3). Models in which the generalized interaction was modeled in terms of pack-years or years smoked were also considered, however, they do not describe the data better than the models given in Table 3. Figure 5 summarizes the model-specific estimated ERR/Gy as a function of cigarettes per day relative to the baseline rate for an unexposed never-smoker (Fig. 5A) and the ERR/Gy relative to a person with the same smoking history (Fig. 5B). These were computed as the sex-averaged risks at age 70 for a person born in 1915 who was exposed at age 30 and smoked a fixed number of cigarettes per day since age 20. For the GMM, as cigarettes per day increases, the ERR/Gy tends to increase up to approximately 10 cigarettes per day and then decreases, approaching no radiation-associated excess risk at 20 or more cigarettes per day. The Fig. 5B inset portrays the degree of uncertainty for the ERR/Gy curve using the best fitting model. For <1 Gy exposures, the total estimated numbers of radiation-associated cases were generally less than the number of smoking-associated cases in this population (Table 4). Lung cancer ERRs by categories of cigarettes smoked per day are shown in Supplementary Table S2 (http://dx.doi.org/10.1667/RR14583.1.S1).

To disentangle the effects of follow up versus updated radiation dose data, a sensitivity analysis restricting follow-up through 1999 and using the current model is shown in Supplementary Table S1 (http://dx.doi.org/10.1667/RR14583.1.S1). Inclusion of an indicator representing before and after year 2000 provided no evidence of a difference in the ERR's Gy during these two time periods ($P > 0.05$). In a sensitivity analysis, which assumed that 50% of last known current smokers quit over the remainder of follow-up, the ERR/Gy increased to 0.88 (95% CI: 0.56, 1.27) and the smoking-radiation effect modification parameters were slightly lower [cigarettes/day: 0.12 (95% CI: –0.06, 0.42); and cigarettes/day^2: –0.01 (95% CI: –0.04, NE)].

Laryngeal and Other Respiratory Cancers

Laryngeal and other respiratory cancer rates are higher for men than for women and tend to increase with higher age at exposure and attained age (Table 1). Crude incidence rates of laryngeal and other respiratory cancers are lower for never-smokers than for current- or past-smokers (Tables 1 and 2). Fitted baseline rates of laryngeal and other respiratory cancers are larger for men than for women with the male:female ratio at age 70 estimated as 2.07 for laryngeal and 1.60 for other respiratory cancers. The sex-averaged increases are proportional to attained age to a power of 3.66 (95% CI: 2.91, 4.44) for laryngeal cancer and 1.29 (95% CI: 0.31, 2.30) for other respiratory cancers.

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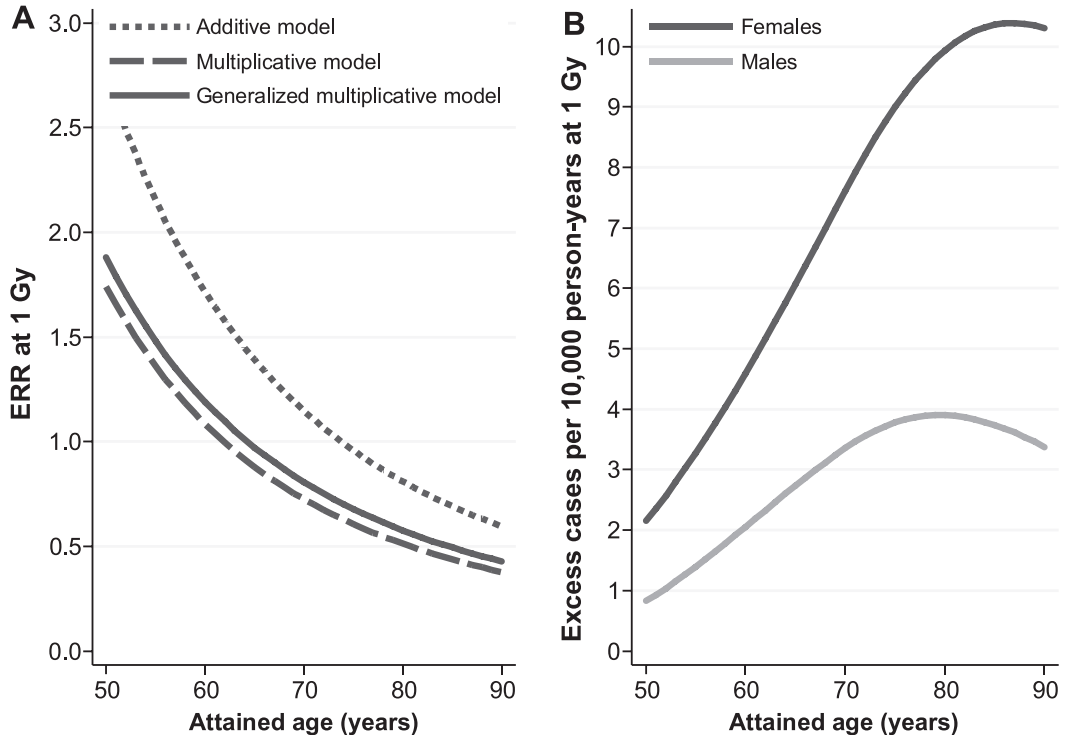


FIG. 4. Radiation-related excess relative risk (ERR/Gy) and excess attributable risk (EAR) of lung cancer at 1 Gy by attained age among Japanese atomic bomb survivors from 1958–2009. Panel A: Sex-averaged ERR for a never-smoker exposed at age 30. Panel B: Sex-specific EAR for a never-smoker exposed at age 30 (GMM).

Fitted baseline rate estimates are higher in Nagasaki than in Hiroshima for other respiratory cancers ($P = 0.025$), but not for cancer of the larynx ($P = 0.15$). For laryngeal and other respiratory cancers, the simple multiplicative interaction models have the smallest AIC values (Table 5). There was no evidence of statistically significant radiation effects for either laryngeal or other cancers of the respiratory system (Table 5). Among never-smokers, the laryngeal ERR/Gy was estimated as 0.05 (95% CI: –0.25, 0.65) and for other respiratory cancers the ERR/Gy was estimated as 0.82 (95% CI: –0.02, 2.23). The ERR associated with 50 pack-years of smoking for an unexposed individual born in 1915 was significantly elevated for both laryngeal (ERR/50 pack-years = 23.52; 95% CI: 8.44, 71.05) and other respiratory cancers (ERR/50 pack-years = 1.21; 95% CI: 0.10, 3.25). There was no significant effect for time since quitting for either laryngeal or other respiratory sites.

DISCUSSION

This study provides a detailed characterization of the joint effects of low-dose radiation and smoking on lung cancer risk in the long-term prospective Life Span Study of Japanese atomic bomb survivors. With an additional 10 years of follow-up, our results suggest that the GMM [Eq. (4)] continues to best describe the complex interaction between radiation and cigarettes smoked per day on lung cancer risk.

In contrast to the recent findings of curvature in the radiation dose response for all solid cancers as a group (including lung), the dose response for lung cancer is linear, with no evidence of nonlinearity for males and females combined or separately, and the dose response is similar for the restricted lower dose and full-dose ranges. A significant linear dose response was observed over the full range of doses. While this model may provide reasonable point estimates for the risk of low doses of radiation, due to the inherent limitations of epidemiological data, the statistical uncertainty of linear-model-based estimates of the dose response at low doses is understated. This problem is particularly pronounced for site-specific analyses. We note that the dose response for all solid cancers was significant down to the range of 0–100 mGy using a linear dose response (*5*). The lowest dose range for a significant dose response for lung cancer is considerably greater than that seen for all solid cancers. However, this is largely due to smaller case counts and lower statistical power. Plans are underway to provide further discussion of the cancer risks at low doses in a future article.

Unlike all solid cancers, the ERR/Gy for lung cancer increases with increasing age at exposure (Table 3). Like all solid cancers, the ERR/Gy decreases with attained age but the EAR/Gy increases as background rates increase with age (Fig. 4). There was little evidence to suggest a relationship between radiation exposure and risk of laryngeal cancer, but a nonsignificantly elevated risk of other respiratory cancers was observed.

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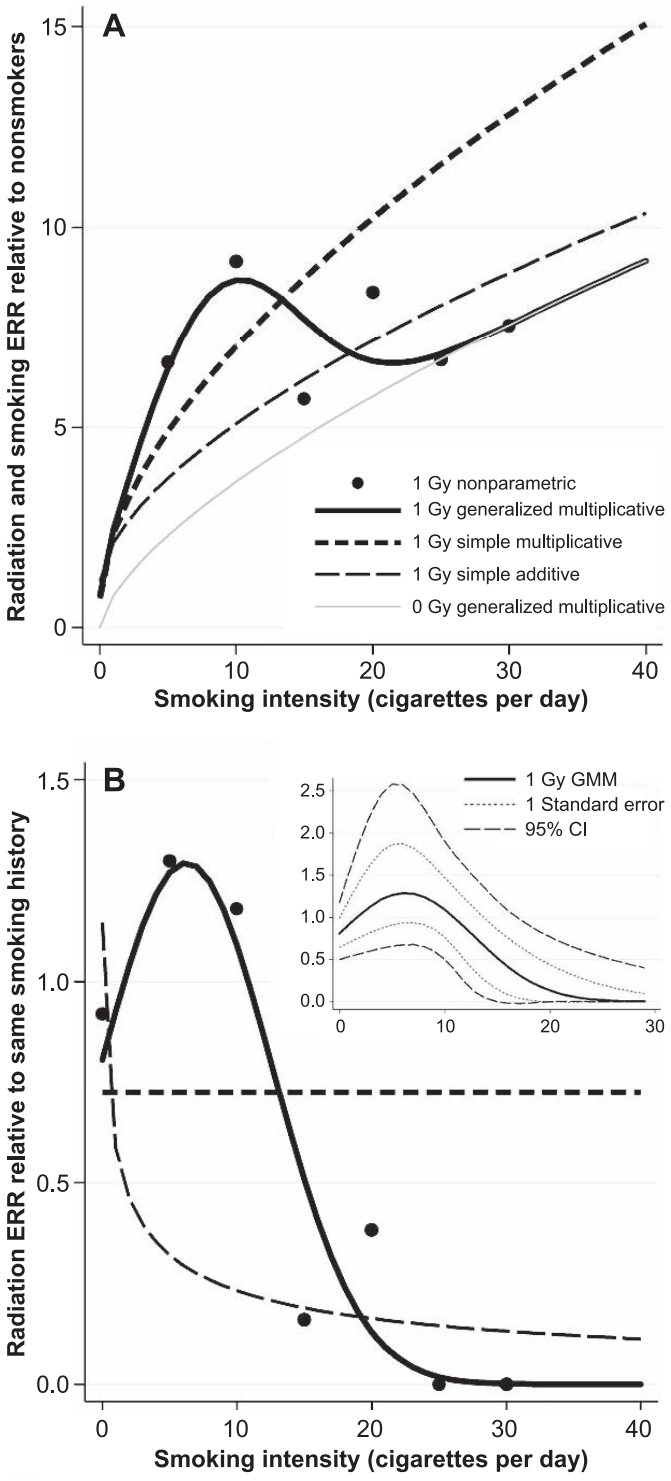


FIG. 5. Excess relative risk (ERR) of lung cancer according to cigarettes smoked per day relative to an unexposed never-smoker (panel A) and a person with the same smoking history (panel B) among Japanese atomic bomb survivors from 1958 to 2009. The sex-averaged ERR estimates are for a person age 70 years with radiation exposure at age 30. Smoking duration was set at 50 years with smoking assumed to start at age 20. Panel A: Joint effect of radiation and smoking relative to the baseline rate for an unexposed nonsmoker. The thin long-dashed line is the fitted ERR for a person with no radiation exposure using the best fitting generalized multiplicative model. 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 cigarettes smoked per day categories replaced the linear-quadratic function of cigarettes smoked per day used in the generalized multiplicative model. Panel B: Radiation-associated excess risks for a 1 Gy radiation exposure relative to the risk of an unexposed person with the same smoking history (i.e., duration of smoking and time since quitting) under various interaction models considered. The inset (panel B) portrays the degree of uncertainty for the ERR/Gy curve using the best fitting model. Values for panel B nonparametric estimates with 95% confidence intervals are shown in Supplementary Table S2 (http://dx.doi.org/10.1667/RR14583.1.S1). GMM = generalized multiplicative model.

For lung cancer, the ERR/Gy increases with smoking up to approximately 10 cigarettes per day and then decreases, approaching no radiation-associated excess risk for subjects who smoke 20 or more cigarettes per day, a similar pattern was found in previously reported work (*1, 2, 8*). In the moderate smoking intensity range near 10 cigarettes per day, smoking could promote radiation-initiated cells by causing inflammation in the tissue microenvironment (*9*). Experimental data in rats supports the proposition that smoking after exposure could elevate lung cancer risk, possibly by promoting cellular proliferation (*10–12*). Another explanation is that the radiation effect in heavy smokers may be difficult to detect using an epidemiological approach because of the overwhelming effect of smoking on lung cancer risk in this group.

In contrast to smoking intensity, a longer duration of smoking significantly increased risk of lung cancer for the same cumulative exposure to smoking (Fig. 1). The reduction of the smoking effect at higher cigarettes per day could be related to heavy smokers receiving fewer carcinogenic compounds per cigarette-smoked than lower intensity smokers, as suggested by dose-response patterns relating smoking intensity and cotinine levels (*13*). Figure 2 shows a decline in lung cancer risk over time after smoking cessation. With 10 additional years of follow-up, the relative risk of smoking-related lung cancer in Japan continues to be lower than what is reported in populations from Europe (*14*) or the U.S. (*15*). Several factors have been proposed to play important roles in these differences including genetic predisposition, higher efficiency filters and lower concentrations of carcinogens in Japanese cigarettes and lower consumption of alcohol and dietary fat (*16*). Unlike Furukawa *et al.*, we did not find a significant sex difference in the smoking effect (*1*). A sensitivity analysis restricting follow-up through 1999 suggested this was largely due to the additional 10 years of follow-up rather than relatively small changes in the coding of smoking data or radiation dose estimates (Supplementary Table S1; http://dx.doi.org/10.1667/RR14583.1.S1).

There was little evidence of a radiation effect for laryngeal cancer and an elevated, but nonsignificant radiation-related risk for other respiratory cancers. To our

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TABLE 4
Observed and Fitted Respiratory Cancer Cases among Japanese Atomic Bomb Survivors from 1958 to 2009

			Excess cases						
Dose (Gy)	Cases	Baseline (no smoking)	Radiation only	Radiation and smoking	Smoking only	Unknown smoking	Total	Total radiation	Total smoking
Lung cancer[a]									
0 (NIC)	600	262.7	0.0	0.0	189.8	147.5	337.3	0.0	189.8
0–0.005	773	356.3	0.3	0.1	279.8	123.0	403.2	0.4	279.9
0.005–0.1	580	268.3	7.7	1.7	227.3	84.4	321.1	9.3	229.0
0.1–0.2	133	55.8	7.4	2.0	50.3	17.5	77.2	9.4	52.3
0.2–0.5	154	58.6	17.6	5.5	56.1	19.1	98.3	23.1	61.6
0.5–1	96	33.0	21.7	6.9	31.1	13.4	73.1	28.6	38.0
1–2	79	16.2	19.7	6.5	19.3	8.5	54.0	26.2	25.8
2–3.55	31	5.1	12.3	3.3	6.0	4.2	25.8	15.6	9.3
Total	2,446	1,056.0	86.7	25.8	859.8	417.6	1,390.0	112.5	885.6
Laryngeal cancer[b]									
Total	180	21.3	0.1	0.6	97.3	60.5	158.7	0.7	97.9
Other respiratory cancers[b]									
Total	115	80.8	6.5	1.3	13.3	12.4	34.2	7.8	14.6

Note. NIC = Not in either city of Hiroshima or Nagasaki at the time of bombing.
[a] Based on the generalized multiplicative model.
[b] Based on the simple multiplicative model.

knowledge, this report represents the first examination of radiation related to incidence of laryngeal or other respiratory cancers in the LSS. Previous analyses of these cases combined them into a larger group that included a number of relatively rare cancer sites (*3*). Our findings, of no association between radiation risk and laryngeal cancer, are consistent with a case-control study of German uranium miners, in which no relationship was observed between external gamma radiation and risk of laryngeal cancer (*17*) and a large pooled analysis of uranium miners (*18*). However, smoking was significantly related to higher risk for both laryngeal and other respiratory cancers.

Our findings should be interpreted in the context of several limitations. History of smoking at diagnosis was unknown for approximately 40% of the cases and approximately 60% of the follow-up time. A multiple imputations method, based on conditional imputation of smoking history applied to the earlier data on smoking, radiation and lung cancer risks in the LSS, resulted in relatively small changes in the radiation and smoking effect parameters or on the nature of the radiation-smoking joint effect (*8*). Our analyses assumed that the subjects' smoking habits remained the same since the last time they provided information on smoking (1992 at the latest). In view of the age of the cohort members, it is unlikely that many had begun to smoke in recent years. However, if those who reported quitting on their last survey then resumed their smoking habits, the effect of quitting could be underestimated. On the other hand, a likely scenario is that many people who reported smoking at the time of their last survey response have since quit smoking. As a result, the effect of smoking in more recent years of follow-up could be underestimated. This may contribute to a somewhat less pronounced increased risk in moderate-intensity smokers than seen in the previously reported study (an ERR as high as 1.3 at approximately 10 cigarettes per day (Fig. 5B) compared to approximately 2.1 found previously). However, a sensitivity analyses, which discounted smoking duration over the period of follow-up when smoking was unknown, suggests that the radiation effect and smoking-radiation effect modification were not particularly sensitive to the incompleteness of the smoking history data. In the current analysis, we considered all lung cancer types together, while smoking and radiation have different effects on different subtypes of lung cancer (*2*). However, it should be noted that the nature of the joint effects of smoking and radiation showed a similar pattern for different types of lung cancer (*2*). In

TABLE 5
Laryngeal and Other Respiratory Cancers Parameter Estimates and 95% Likelihood-Based Confidence Intervals for Smoking and Radiation Effects among Japanese Atomic Bomb Survivors from 1958 to 2009

	Laryngeal cancer		Other respiratory cancers	
	Radiation only	Simple multiplicative	Radiation only	Simple multiplicative
Smoking parameter				
ERR per 50 pack-years, e^{λ_1}		23.52 (8.44, 71.05)		1.21 (0.10, 3.25)
Radiation parameter				
ERR per Gy, β	0.06 (–0.25, 0.66)	0.05 (–0.25, 0.65)	0.81 (–0.02, 2.19)	0.82 (–0.02, 2.23)
Akaike information criterion	1966.6	1904.6	1410.8	1407.5

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addition, ''other respiratory cancers'' represents a heterogeneous grouping of several different cancer sites. Due to sample size limitations, we were only able to explore a limited series of models for examining laryngeal and other respiratory cancers.

We believe that the data from this study continue to provide the most detailed characterization of the joint effects of low-dose radiation and smoking on lung cancer risk, and contribute important information to the sparse data available for laryngeal and other respiratory cancer risks. Future studies of radiation exposure, smoking and respiratory cancer risk could consider subtype-specific lung cancer analyses and development of multiple imputation methods for missing risk factor data.

SUPPLEMENTARY INFORMATION

Table S1. Lung cancer parameter estimates and 95% likelihood-based confidence intervals for smoking and radiation effects among Japanese atomic bomb survivors using current generalized multiplicative model and updated doses from 1958 to 1999.

Table S2. Excess relative risks of lung cancer associated with exposure to 1 Gy radiation (ERR/Gy) by categories of cigarettes smoked per day among Japanese atomic bomb survivors from 1958 to 2009.

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