Radiation Exposure and the Risk of Mortality from Noncancer Respiratory Diseases in the Life Span Study, 1950–2005

Authors: Pham, Truong-Minh, Sakata, Ritsu, Grant, Eric J., Shimizu, Yukiko, Furukawa, Kyoji, et al.

Source: Radiation Research, 180(5) : 539-545

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR13421.1

RADIATION RESEARCH **180**, 539–545 (2013)
0033-7587/13 $15.00

DOI: 10.1667/RR13421.1

Radiation Exposure and the Risk of Mortality from Noncancer Respiratory Diseases in the Life Span Study, 1950–2005

Truong-Minh Pham,[a] Ritsu Sakata,[a] Eric J. Grant,[a] Yukiko Shimizu,[a] Kyoji Furukawa,[b] Ikuno Takahashi,[a] Hiromi Sugiyama,[a] Fumiyoshi Kasagi,[c] Midori Soda,[d] Akihiko Suyama,[d] Roy E. Shore[e] and Kotaro Ozasa[a,1]

Departments of [a] Epidemiology and [b] Statistics, and [e] Vice Chairman and Chief of Research, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732-0815, Japan; [d] Department of Epidemiology, Radiation Effects Research Foundation, 1-8-6 Nakagawa, Nagasaki, 850-0013, Japan; and [c] Institute of Radiation Epidemiology, Radiation Effects Association, 1-9-16, Kaji-cho, Chiyodaku, Tokyo, 101-0044, Japan

Pham, T-M., Sakata, R., Grant, E. J., Shimizu, Y., Furukawa, K., Takahashi, I., Sugiyama, H., Kasagi, F., Soda, M., Suyama, A., Shore, R. E. and Ozasa. K. Radiation Exposure and the Risk of Mortality from Noncancer Respiratory Diseases in the Life Span Study, 1950–2005. 180, 539–545 (2013).

An apparent association between radiation exposure and noncancer respiratory diseases (NCRD) in the Life Span Study (LSS) of atomic bomb survivors has been reported, but the biological validity of that observation is uncertain. This study investigated the possibility of radiation causation of noncancer respiratory diseases in detail by examining subtypes of noncancer respiratory diseases, temporal associations, and the potential for misdiagnosis and other confounding factors. A total of 5,515 NCRD diagnoses listed as the underlying cause of death on the death certificate were observed among the 86,611 LSS subjects with estimated weighted absorbed lung doses. Radiation dose-response analyses were conducted using Cox proportional hazard regression for pneumonia/influenza, other acute respiratory infections, chronic obstructive pulmonary disease and asthma. The linear excess relative risks (ERR) per gray (Gy) were 0.17 (95% CI 0.08, 0.27) for all NCRD and 0.20 (CI 0.09, 0.34) for pneumonia/influenza, which accounted for 63% of noncancer respiratory disease deaths. Adjustments for lifestyle and sociodemographic variations had almost no impact on the risk estimates. However, adjustments for indications of cancer and/or cardiovascular disease decreased the risk estimates, with ERR for total noncancer respiratory diseases declined by 35% from 0.17 to 0.11. Although it was impossible to fully adjust for the misdiagnosis of other diseases as noncancer respiratory diseases deaths in this study because of limitations of available data, nevertheless, the associations were reduced or eliminated by the adjustment that could be made. This helps demonstrates that the association between noncancer respiratory diseases and radiation exposure in previous reports could be in part be attributed to coincident cancer and/or cardiovascular diseases. © 2013 by Radiation Research Society

[1]Address for correspondence: Department of Epidemiology, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima, 732-0815, Japan; e-mail: ozasa@rerf.or.jp.

INTRODUCTION

The Life Span Study (LSS) cohort of survivors of the atomic bombings in Hiroshima and Nagasaki has provided comprehensive evaluations of the health risks of exposure to ionizing radiation (*1*). Excess risks of both cancer incidence and mortality have been documented (*2–4*). In recent years, there has been increasing interest in examining possible associations of radiation exposure and subsequent noncancer diseases (*5–7*). Recent LSS mortality studies have shown associations of radiation exposure with several noncancer diseases, including elevated risks of both stroke and heart disease (*8*). Further, associations of radiation with other noncancer conditions, such as benign thyroid neoplasms, chronic liver disease, cataract, uterine myoma and calculus of the kidney have also been reported (*9*).

With regard to noncancer respiratory diseases (NCRD), significant excess relative risks of respiratory deaths have been reported in the LSS cohort (*3–6*), however these analyses were based on all subtypes combined and did not examine the possibility of artifactual associations. Results from other radiation-exposed cohorts (*7, 10–18*) have been inconclusive, as summarized in the Discussion section of this article.

The fact that subtypes of noncancer respiratory diseases differ in their risk factors and in their etiology and pathogenesis suggested the need for an in-depth examination of the risks of radiation exposure by subgroups. Since some types of noncancer respiratory diseases (e.g., pneumonia) are often the end-of-life condition caused by other disease processes (cancer or cardiovascular disease, for instance), we will examine the impact upon the radiation-noncancer respiratory diseases associations of potential death certificate misdiagnosis. The potential for confounding by lifestyle and sociodemographic variations will also be examined, as will temporal variations in the associations.

In the current study, we examined the risks of radiation exposure associated with finer categories of noncancer respiratory diseases among atomic-bomb survivors in Hiroshima and Nagasaki, from 1950–2005. We also

TABLE 1
Description of Codes for Noncancer Respiratory Diseases from the ICD-7 to ICD-10 Revisions

Causes of death	ICD-7 codes	ICD-8 codes	ICD-9 codes	ICD-10 codes
All noncancer respiratory diseases	470–527, 241	460–519	460–519	J00–J99
Acute respiratory infections	470–475, 500	460–466	460–466	J00–J06, J20–J22
Pneumonia/Influenza	480–483, 490–493	470–474, 480–486	480–487	J10–J18
Chronic obstructive pulmonary disease	501–502, 526, 527	490–492, 518	490–492, 494, 496	J40–J44, J47
Asthma	241	493	493, 495	J45–J46
Other respiratory diseases	510–525	500–517, 519	470–478, 500–519	J30–J39, J60–J99

considered the effects of potential confounding factors as well as misdiagnoses of coexistent cancer and cardiovascular disease (CVD) on the radiation risks. Cardiovascular disease was added as a potential misdiagnostic factor because cardiovascular disease mortality is apparently associated with radiation exposure in the LSS (*8*) although the detailed dose-response or causal nature of the relationship has not been fully elucidated.

MATERIALS AND METHODS

Study Subjects

The study subjects were members of the LSS cohort (*1*), which was originally defined on the basis of the 1950 Japanese National Census and associated surveys between 1950–1953. The present analyses were based on 86,611 atomic bomb survivors whose estimated lung doses were available. This study was approved by the Human Investigation Committee of the Radiation Effects Research Foundation and the collection of vital status and cause of death of the subjects was approved by the Ministry of Justice and the Ministry of Health, Labour and Welfare of Japan.

Outcome Determination

Mortality follow-up from 1950 until the end of 2005 used the Japanese national family registration system (*koseki*). Cause of death was ascertained from the death certificates. Underlying causes of death were coded using the International Classification of Diseases and Injuries (ICD), 7th Revision (ICD-7) for deaths in 1950–1968, ICD-8 in 1969–1978, ICD-9 in 1979–1997 and ICD-10 in 1998–2005. Table 1 shows the detailed descriptions of noncancer respiratory diseases according to several ICD Revisions. In the ICD-10 Revision, the codes for all noncancer respiratory diseases were defined as J00–J99.

TABLE 2
Characteristics of 86,611 Study Subjects and Numbers of Deaths from Noncancer Respiratory Diseases, 1950–2005

			Number of deaths (death rate per 10,000 person-years)					
Characteristics	Number of subjects	Person-years	All noncancer respiratory diseases	Acute respiratory infection	Pneumonia/ Influenza	Chronic obstructive pulmonary disease	Asthma	Other respiratory diseases
Sex								
Men	35,687	1,307,515	2547 (19.48)	84 (0.64)	1501 (11.48)	377 (2.88)	260 (1.99)	325 (2.49)
Women	50,924	2,058,466	2968 (14.42)	117 (0.57)	1970 (9.57)	299 (1.45)	215 (1.04)	367 (1.78)
City								
Hiroshima	58,495	2,242,073	3770 (16.81)	149 (0.66)	2333 (10.41)	463 (2.07)	336 (1.50)	489 (2.18)
Nagasaki	28,116	1,123,908	1745 (15.53)	52 (0.46)	1138 (10.13)	213 (1.90)	139 (1.24)	203 (1.81)
Age at the time of bombings								
<10	17,832	942,026	102 (1.08)	4 (0.04)	50 (0.53)	5 (0.05)	14 (0.15)	29 (0.31)
10–	17,564	874,356	372 (4.25)	5 (0.06)	219 (2.50)	34 (0.39)	23 (0.26)	91 (1.04)
20–	10,891	505,188	618 (12.23)	10 (0.20)	385 (7.62)	74 (1.46)	40 (0.79)	109 (2.16)
30–	12,270	465,949	1487 (31.91)	30 (0.64)	978 (20.99)	173 (3.71)	76 (1.63)	230 (4.94)
40–	13,504	365,383	1532 (41.93)	47 (1.29)	1036 (28.35)	179 (4.90)	105 (2.87)	165 (4.52)
50+	14,550	213,079	1404 (65.89)	105 (4.93)	803 (37.69)	211 (9.90)	217 (10.18)	68 (3.19)
Weighted absorbed lung dose								
<0.005	37,713	1,468,898	2,353 (16.02)	82 (0.56)	1,478 (10.06)	274 (1.87)	209 (1.42)	310 (2.11)
0.005–	29,695	1,158,582	1,917 (16.55)	79 (0.68)	1,200 (10.36)	261 (2.25)	151 (1.30)	226 (1.95)
0.1–	6,232	242,122	418 (17.26)	16 (0.66)	262 (10.82)	50 (2.07)	44 (1.82)	46 (1.90)
0.2–	6,418	246,070	411 (16.70)	12 (0.49)	260 (10.57)	40 (1.63)	38 (1.54)	61 (2.48)
0.5–	3,696	141,733	215 (15.17)	8 (0.56)	147 (10.37)	24 (1.69)	14 (0.99)	22 (1.55)
1.0–	2,029	77,732	141 (18.14)	4 (0.51)	88 (11.32)	23 (2.96)	12 (1.54)	14 (1.80)
2.0+	828	30,844	60 (19.45)	0 (0.00)	36 (11.67)	4 (1.30)	7 (2.27)	13 (4.21)

TABLE 3
Excess Relative Risk (ERR[a]) Estimates per Gy and 95% Confidence Interval (95% CI) for Noncancer Respiratory Disease Deaths, 1950–2005

	For both sexes			For men			For women		
Causes of death	Deaths	ERR (95% CI)	*P*	Deaths	ERR (95% CI)	*P*	Deaths	ERR (95% CI)	*P*
All noncancer respiratory diseases	5515	0.17 (0.08; 0.27)	<0.01	2547	0.14 (0.03; 0.27)	0.01	2968	0.22 (0.08; 0.37)	<0.01
Acute respiratory infections	201	–0.16 (<0;[b] 0.40)	0.38	84	0.10 (<0;[b] 1.18)	>0.50	117	–0.22 (<0;[b] 0.35)	0.27
Pneumonia/Influenza	3471	0.20 (0.09; 0.34)	<0.01	1501	0.14 (−0.01; 0.31)	0.06	1970	0.30 (0.11; 0.51)	<0.01
Chronic obstructive pulmonary disease	676	0.08 (−0.14; 0.37)	>0.50	377	0.20 (−0.09; 0.60)	0.2	299	–0.12 (<0;[b] 0.33)	>0.50
Asthma	475	0.16 (−0.10; 0.52)	0.27	260	0.22 (−0.11; 0.71)	0.23	215	0.05 (<0;[b] 0.66)	>0.50
Other respiratory	692	0.20 (−0.01; 0.48)	0.07	325	0.06 (−0.18; 0.41)	>0.50	367	0.37 (0.02; 0.85)	0.04

[a] ERR was estimated using the linear-dose model without effect modifiers, in which the background rates included sex, city, age at exposure, but sex was not included for sex-specific risk estimates.

[b] Less than zero (<0) was designated for the lower confidence bounds, when these could not be estimated (see Materials and Methods).

Among these, subtypes included acute upper respiratory infections and acute bronchitis (J00–J06, J20–J22); pneumonia/influenza (J10–J18); chronic obstructive pulmonary disease (COPD, J40–J44, J47); asthma (J45–J46); and other diseases of the respiratory system (J30–J39; J60–J99). The risk of noncancer respiratory disease was estimated by the follow-up period of 1950–1964, 1965–1979 and 1980–2005.

Radiation Exposure and Other Variables

We used weighted absorbed lung dose (gamma dose plus ten times the neutron dose) in Gy according to DS02 (*4*). The cohort covered a large range of doses, however more than 90% of subjects were exposed to less than 0.5 Gy of absorbed lung dose. To consider confounding factors, information on sociodemographic and lifestyle factors was collected through four mail surveys carried out between 1965–1991, and through clinical interviews performed in the 1960s among members of the Adult Health Study (AHS), a clinical study of a subset of the LSS. About 60% of the study subjects (n = 55,132) had provided information for assessing potential confounding variables, which were determined as follows: smoking habits were identified as last known smoking status with categories of never smoker, past smoker and current smoker. Alcohol consumption was documented as grams of ethanol per week. Body mass index was computed as weight in kilograms divided by the square of height in meters (kg/m^2). Educational level was classified as primary school or less, secondary school and college/university. Diabetes mellitus was a yes/no variable. Occupational histories were classified as professional/technical, clerical/sales, farmer/craftsman, transportation/service and other occupation categories. Those variables were included in an analysis that adjusted for potential confounding factors.

Statistical Analysis

Partial-likelihood survival analyses (*19*) were conducted using a variant form of the Cox model to estimate the excess relative risk (ERR) for mortality from noncancer respiratory diseases. Age at risk (i.e., attained age) was used as the primary time scale in the models (*20*). We used the PEANUTS program in the Epicure software package (*19*) to estimate the ERR per gray of radiation. The model for the expected hazard took the form:

$$\lambda_0(c,s,b)[1+\mathrm{ERR}(d,s,e)]$$

where $\lambda_0(.)$ is the background death rate, depending on city (c), sex (s) and birth year (b). The ERR(.) is described as a function of the form $\rho(d)\omega(s,e)$, in which $\rho(d)$ is a radiation dose-response function, and $\omega(s,e)$ is an exponential function of the effect modifier terms for sex (s) and age at exposure (e). Confidence intervals (CIs) for the risk estimates were based on the maximum likelihood profile. Because the relative risk [1 + ERR(.)] should not be negative, the dose parameters in this linear model should be larger than −1/maximum dose. Due to this restriction, negative lower confidence bounds could sometimes not be estimated, which were then designated as ''<0'' (see for example in Table 3). To examine the linearity or curvature of the ERR function, we used the following models:

$$\rho(d) = \beta d \quad \text{linear model}$$

$$\rho(d) = \beta d + \gamma d^2 \quad \text{linear} - \text{quadratic model}$$

To examine the effects of potential misdiagnosis and/or misclassification of other major causes of death (cancer and cardiovascular disease) with noncancer respiratory diseases, we performed an analysis that censored persons who had previously been diagnosed with cancer from tumor registry data as of the date of cancer diagnosis. Those with diagnoses of cancer and/or cardiovascular disease listed anywhere on the death certificate also were censored at two years prior to the date of death.

We used Stata (version 9.2) to estimate the radiation risk when performing the analysis adjusting for potential confounders among the subset of 55,132 subjects with information available from mail surveys or clinical interviews. Adjustments for the potential effect of cancer and/or cardiovascular disease were also conducted in this subanalysis. For these analyses, person-years were counted from the time of a subject's first mail survey. We identified some proportions of missing variables among the respondents of surveys/interviews, ranging from 1.5% for smoking habit to 8.6% for drinking habit. To account for such missing data in the analyses, we applied a multiple imputation approach (*21*) in Stata (*ice* command for multiple imputation by chained equations). Then the Cox proportional hazard regression was used to estimate the hazard ratio (HR) of radiation risk and mortality of noncancer respiratory diseases, adjusted for the potential confounding factors.

RESULTS

Over the course of more than 50 years of follow-up among 86,611 subjects, we observed 5,515 people whose primary cause of death was listed as some form of noncancer respiratory disease. Table 2 shows the numbers of subjects, persons-years of follow-up, number of deaths

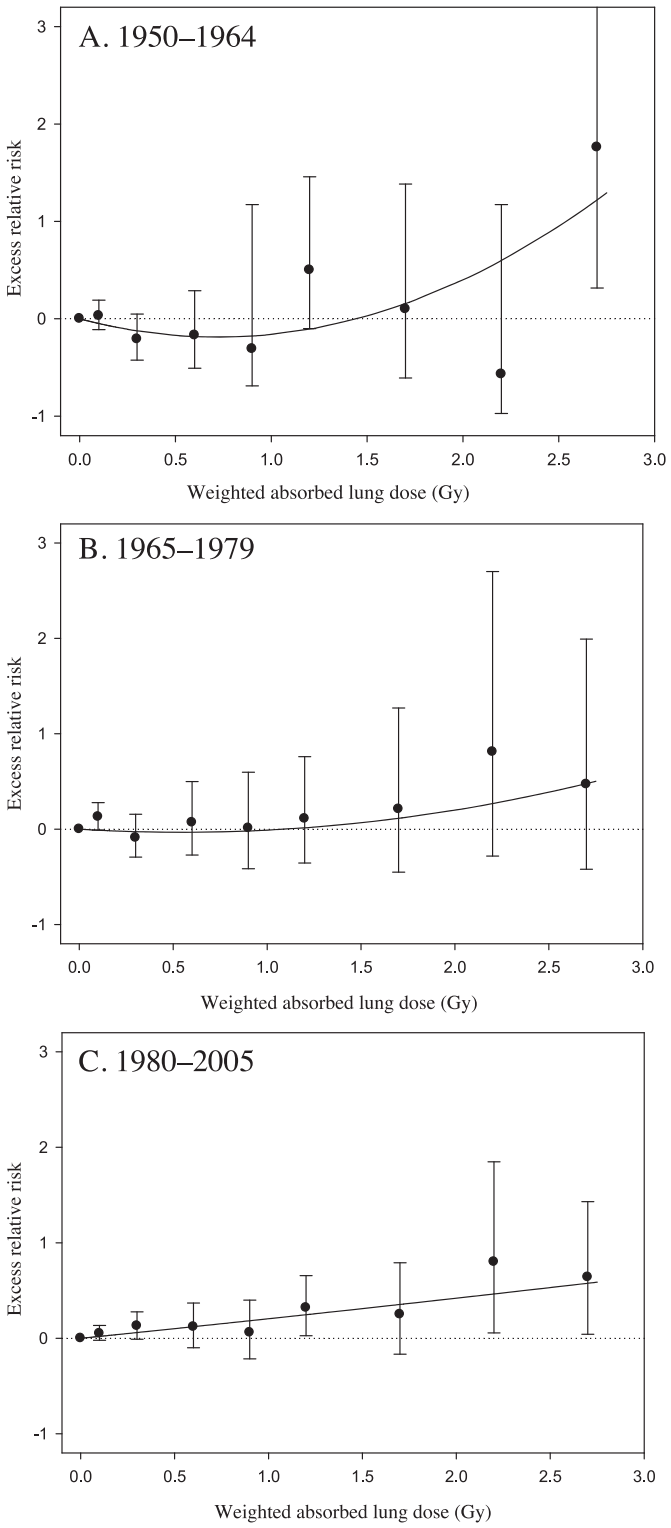

FIG. 1. Dose response of excess relative risk for all noncancer respiratory diseases by periods based on the changes in disease structure of noncancer respiratory disease in Japan. The closed circles and bars represent point estimates of ERR and 95% confidence intervals for the dose categories without effect modifiers, in which the background rates included sex, city and age at exposure. Solid line shows dose-response curve based on the linear-quadratic model.

and death rates per 10,000 person-years by sex, city, age at the time of the bombings and weighted absorbed lung dose categories. The most common subtype was pneumonia/influenza, accounting for about two thirds of all noncancer respiratory disease deaths, followed by COPD and asthma. The category ''other respiratory disease'' represents a large variety of diseases, many of which are rare. For example, diffuse interstitial lung diseases represent many different entities including interstitial pneumonia (*22*).

Table 3 shows the ERR/Gy estimates of noncancer respiratory disease associated with lung dose for the entire follow-up period. The ERR estimates were 0.17 (95% CI: 0.08; 0.27) for all NCRD and 0.20 (0.09; 0.34) for the pneumonia/influenza subtype. The ERR estimates of total noncancer respiratory diseases were significant for both men and women, and those for pneumonia/influenza also were significant for women but were marginal for men.

Table 4 shows radiation risks by follow-up periods. Increased ERR estimates were apparent in the late periods (1980–2005), while ERR estimates for the early (1950–1964) and the middle period (1965–1979) were smaller and did not reach statistical significance. Figure 1 graphically depicts period-specific dose-responses for all noncancer respiratory diseases using linear-quadratic models and by categorical estimates. In the early period, a linear-quadratic model fit better than a linear model ($P < 0.01$), but not for the middle and late periods. No increased risks among low-dose survivors were observed in the early and middle periods, but a mostly linear increase in risk appeared in the late period.

One major question was the degree to which the apparent association between radiation and noncancer respiratory disease may be due to cancer or cardiovascular disease being misdiagnosed as noncancer respiratory disease on the death certificate. About 10% of noncancer respiratory disease cases also had been diagnosed with any cancer and about another 20% with cardiovascular disease. When adjusting for the records of cancer by censoring those with cancer incidence and/or cancer comorbidity on the death certificate, the radiation risk estimates were decreased by about 35% for all noncancer respiratory diseases, by about 15% for pneumonia/influenza and by about 56% for asthma but the statistical significance did not change (Table 5). However, further adjustment for cardiovascular disease comorbidity did not substantially change the ERR estimates (Table 5).

Table 6 shows radiation risks adjusted for potential confounding factors, and additionally adjusted for comorbidity due to cancer and/or cardiovascular disease in the subset of 55,132 subjects with information on lifestyle factor. Hazard ratio estimates that were adjusted for the six potential confounding factors related to lifestyle or sociodemographics tended to be slightly lower for most of the noncancer respiratory disease subtypes compared with estimates that were not adjusted, but the patterns of the associations remained. For instance, the HR for all noncancer respiratory diseases decreased slightly from

TABLE 4
Excess Relative Risk (ERR[a]) Estimates per Gy and 95% Confidence Interval (95% CI) for Noncancer Respiratory Disease Deaths by Calendar Year Periods

	Calendar years 1950–1964			Calendar years 1965–1979			Calendar years 1980–2005		
Cause of death	Deaths	ERR (95% CI)	*P*	Deaths	ERR (95% CI)	*P*	Deaths	ERR (95% CI)	*P*
All noncancer respiratory disease	849	0.11 (−0.08; 0.36)	0.30	1149	0.08 (−0.09; 0.29)	0.39	3517	0.21 (0.10; 0.34)	<0.01
Acute respiratory infections	59	–0.24 (<0;[b] 1.28)	>0.50	70	0.26 (<0;[b] 1.59)	>0.50	72	–0.22 (<0;[b] 0.36)	0.25
Pneumonia/Influenza	407	0.20 (−0.09; 0.61)	0.20	697	0.09 (−0.12; 0.37)	0.42	2367	0.23 (0.08; 0.40)	<0.01
Chronic obstructive pulmonary disease	116	0.29 (−0.22; 1.24)	0.36	183	–0.15 (<0;[b] 0.44)	>0.50	377	0.09 (−0.17; 0.47)	>0.50
Asthma	211	–0.01 (<0;[b] 0.44)	>0.50	124	0.13 (<0;[b] 0.91)	>0.50	140	0.76 (0.04; 1.90)	0.04
Other respiratory disease	56	–0.18 (<0;[b] 0.96)	>0.50	75	0.14 (<0;[b] 1.14)	>0.50	561	0.23 (−0.01; 0.55)	0.07

[a] ERR was estimated using the linear-dose model without effect modifiers, in which sex, city, age at exposure were included in the background rates.
[b] Less than zero (<0) was designated for the lower confidence bounds, when these could not be estimated (see Materials and Methods).

1.22 (95% CI: 1.13; 1.33) to 1.19 (1.09; 1.29) after adjustment for confounding factors. Similarly, the HR estimates for subtypes such as pneumonia/influenza, asthma and other respiratory disease groups were reduced after adjustment but remained significant.

However, the radiation risks were remarkably reduced when additionally adjusted for the records of cancer and cardiovascular disease using the same method as in shown Table 5. Consequently, the HR for all NCRD fell to 1.12 (1.00; 1.25) after performing those adjustments (Table 6). The risk for only pneumonia/influenza remained significant with a HR estimate of 1.18 (1.04; 1.35), while the risks for the remaining subtypes lost their significance.

DISCUSSION

In the current study we examined the association between radiation and the mortality risks from noncancer respiratory diseases among the LSS survivors up to 60 years after the detonation of the atomic bombs. For the whole period, the results showed a significant dose-response association for total noncancer respiratory diseases when there was no adjustment for cancer or cardiovascular disease comorbidity. However, the radiation association appeared to vary by finer disease subtypes as well as by gender and follow-up periods.

The patterns of associations of ionizing radiation with noncancer respiratory disease mortality were different by calendar periods (see Table 4 and Fig. 1). Noncancer respiratory disease as a whole and most subtypes showed stronger unadjusted associations in the late period, during which both pneumonia/influenza and asthma appeared to be associated with significant risks, although those associations were greatly attenuated or eliminated when adjustments for cancer and cardiovascular disease were made. The lesser associations in the earlier time period might reflect a healthy survivor effect, which others have indicated may have been more operative in the early years after the bombings (*23*).

Over the long follow-up period, the background disease structure of respiratory diseases has changed due to factors such as aging, hygiene, socioeconomic status and medical care availability. The national trend of mortality rates from noncancer respiratory diseases based on the vital statistics for all of Japan (*24*) between 1950–2005 suggested two distinct causal pathways, especially for pneumonia/influenza. The high rates in the early decades are probably associated predominantly with influenza epidemics and with other respiratory infections that could not be adequately treated in that era and no association with radiation would

TABLE 5
Excess Relative Risk (ERR[a]) Estimates per Gy Adjusted for the Records of Cancer and Cardiovascular Disease (CVD)

	Not adjusted for cancer or CVD			Adjusted for cancer[b]			Adjusted for cancer and/or CVD[c]		
	3,365,981 person-years			3,273,363 person-years			3,260,476 person-years		
Cause of death	Deaths	ERR (95% CI)	*P*	Deaths	ERR (95% CI)	*P*	Deaths	ERR (95% CI)	*P*
All noncancer respiratory diseases	5515	0.17 (0.08; 0.27)	<0.01	4935	0.11 (0.02; 0.21)	0.01	3978	0.11 (0.01; 0.22)	0.04
Pneumonia/Influenza	3471	0.20 (0.09; 0.34)	<0.01	3115	0.17 (0.04; 0.30)	<0.01	2439	0.17 (0.04; 0.33)	0.01
Asthma	475	0.16 (−0.10; 0.52)	0.27	455	0.07 (−0.17; 0.42)	>0.50	411	0.05 (−0.19; 0.40)	>0.50

[a] ERR was estimated using the linear-dose model without effect modifiers, in which the background rates included sex, city and age at exposure.
[b] Subjects with the records of incidence/comorbidity of cancer were censored (see Materials and Methods).
[c] Subjects with the records of incidence/comorbidity of cancer and/or comorbidity of CVD were censored (see Materials and Methods).

TABLE 6
Hazard Ratios (HR) at 1 Gy and 95% Confidence Intervals (95% CI) for Noncancer Respiratory Disease Deaths Adjusted for Both Potential Confounding Factors and The Records of Cancer and Cardiovascular Disease (CVD)

	Not adjusted for cancer or CVD[a]					Adjusted for cancer[a,b]			Adjusted for cancer and/or CVD[a,c]		
	1,252,159 person-years					1,182,124 person-years			1,172,628 person-years		
Cause of death	Deaths	HR1 (95% CI)	*P*	HR2 (95% CI)	*P*	Deaths	HR2 (95% CI)	*P*	Deaths	HR2 (95% CI)	*P*
All noncancer respiratory diseases	3292	1.22 (1.13; 1.33)	<0.01	1.19 (1.09; 1.29)	<0.01	2850	1.12 (1.02; 1.24)	0.02	2216	1.12 (1.00; 1.25)	0.05
Acute respiratory infections	78	0.65 (0.27; 1.56)	0.34	0.64 (0.27; 1.57)	0.34	68	0.53 (0.18; 1.56)	0.25	41	0.93 (0.35; 2.42)	0.88
Pneumonia/ Influenza	2157	1.23 (1.11; 1.37)	<0.01	1.19 (1.07; 1.33)	<0.01	1882	1.17 (1.04; 1.31)	0.01	1445	1.18 (1.01; 1.35)	0.01
Chronic obstructive pulmonary disease	379	1.06 (0.81; 1.39)	0.67	1.00 (0.76; 1.31)	0.98	322	0.92 (0.66; 1.28)	0.62	266	0.93 (0.64; 1.33)	0.68
Asthma	161	1.47 (1.08; 2.00)	0.01	1.43 (1.04; 1.96)	0.03	147	1.30 (0.90; 1.87)	0.16	120	1.28 (0.86; 1.88)	0.23
Other respiratory disease	517	1.31 (1.07; 1.60)	<0.01	1.28 (1.04; 1.57)	0.02	431	1.08 (0.83; 1.40)	0.56	344	0.92 (0.66; 1.28)	0.61

Notes. HR1 was adjusted for sex, city and birth year. HR2 was adjusted for the variables for HR1 plus 6 potential confounding factors (smoking, alcohol consumption, body mass index, education, diabetes and occupation).

[a] Analyses were conducted among a subset of 55,132 subjects with the information of lifestyle factor.

[b] Subjects with the records of incidence/comorbidity of cancer were censored (see Table 5).

[c] Subjects with the records of incidence/comorbidity of cancer and/or comorbidity of CVD were censored (see Table 5).

be evident. In more recent decades, as acute respiratory infections became more treatable and deaths from pneumonia among the elderly increased, deaths designated as noncancer respiratory disease often represent the terminal stage of other lethal conditions such as cancer and cardiovascular disease. As such, the association of radiation with death-certificate diagnoses of noncancer respiratory disease may be attributed to death certificate misdiagnosis.

Coexistent cancer or cardiovascular disease that was misclassified or misdiagnosed as noncancer respiratory disease apparently increased the nominal noncancer respiratory disease radiation risk estimates. A previous comparison of death certificates and autopsy reports among LSS subjects showed a large amount of diagnostic misclassification, such that only 28% of death certificates with noncancer respiratory disease listed as the underlying cause were attributed to noncancer respiratory disease at autopsy (*25*). These figures, based on deaths primarily before the mid-1970s, indicate that death certificate attribution of noncancer respiratory disease was both erroneous and incomplete; however, death certificates may be more accurate in recent decades. In this study, the association with radiation decreased appreciably by adjusting for indications of concomitant cancer and/or cardiovascular disease on the death certificate or for a prior incident cancer recorded in the tumor registry. The censoring that might have eliminated the radiation effect on cancer/cardiovascular disease cases, might subsequently lower the power of detecting radiation effects for noncancer respiratory disease. The risk of pneumonia/influenza was also reduced, although it was the sole subtype whose risk remained significant after such adjustment (see Tables 5 and 6).

However, the misdiagnosis adjustment that was possible to perform may have been an under-adjustment for several reasons: (1) the recording of contributing causes of death on death certificates by physicians is irregular and incomplete: some death certificates list no contributing causes while others list several; (2) there may be other conditions besides cancer and cardiovascular disease which are misdiagnosed as noncancer respiratory disease on the death certificate and which were not investigated; (3) the cancer incidence data are incomplete because such data did not begin until 1958, whereas mortality data began in 1950, and the incidence data do not cover cancer diagnoses occurring outside of Hiroshima or Nagasaki prefectures. If those missed due to the intrinsic methodological limitations could be ascertained, they might further reduce the noncancer respiratory disease radiation risk estimates. Hence, it is unclear whether there would still be an association of radiation with pneumonia/influenza if ascertainment of other potential underlying causes of death were complete, so the results of the present study require some caution in interpretation. In contrast, other lifestyle risk factors for noncancer respiratory disease had little impact as confounders of the radiation risks (see Table 6).

Subtypes of noncancer respiratory diseases have different physiological and pathological features. Our results indicate that noncancer respiratory diseases subtypes do not share the same degree of association with radiation. Once adjustment was made for cancer misdiagnosis, the categories acute respiratory infections, chronic obstructive pulmonary disease, asthma, and other respiratory disease were not associated with radiation (see Table 6). However, the most common subtype, pneumonia/influenza, was still statistically significant. The

nature of diseases in this category was thought to change from acute infectious diseases in the earlier years to mostly the terminal conditions in the elderly in recent decades, which might imply a different potential for association with radiation over time. Given the limitations of the comorbidity data (above) this association may not be genuine. But, if it is, it may reflect infections associated with diminished immune competence as a function of radiation dose (*26, 27*).

With regard to studies among other radiation-exposed cohorts that examined noncancer radiation risks, study subjects were mostly workers at nuclear facilities (*7, 10–18*) who were typically exposed at chronic low-dose levels. Most studies have shown no association of noncancer respiratory disease with radiation (*7, 10, 12–18*), although a study of UK radiation workers reported an elevated ERR of 0.8 (90% CI: 0.04; 1.8) with respiratory diseases not related to smoking (*11*).

ACKNOWLEDGMENTS

We would like to thank the Hiroshima and Nagasaki cancer registries for use of the cancer incidence data. We are also grateful to the Department of Clinical Studies for offering the information of lifestyle in the Adult Health Study, the staff of the Master File Section for their diligent efforts to provide accurate data on mortality in the Life Span Study and Ms. Mikiko Hayashi for the dataset preparation. The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW) and the U.S. Department of Energy (DOE). The research was also funded in part through DOE award DE-HS0000031 to the National Academy of Sciences. This publication was supported by RERF Research Protocols 1–75 and A-1-11. The views of the authors do not necessarily reflect those of the two governments.

Received: June 4, 2013; accepted: August 5, 2013; published online: October 23, 2013

REFERENCES

1. Kodama K, Mabuchi K, Shigematsu I. A long-term cohort study of the atomic-bomb survivors. J Epidemiol 1996; 6:S95–105.
2. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat Res 2007; 168:1–64.
3. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. Radiat Res 2003; 160:381–407.
4. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. Radiat Res 2012; 177:229–43.
5. Shimizu Y, Kato H, Schull WJ, Hoel DG. Studies of the mortality of A-bomb survivors. 9. Mortality, 1950–1985: Part 3. Noncancer mortality based on the revised doses (DS86). Radiat Res 1992; 130:249–66.
6. Shimizu Y, Pierce DA, Preston DL, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, part II. Noncancer mortality: 1950–1990. Radiat Res 1999; 152:374–89.
7. McGeoghegan D, Binks K, Gillies M, Jones S, Whaley S. The non-cancer mortality experience of male workers at British Nuclear Fuels plc, 1946–2005. Int J Epidemiol 2008; 37:506–18.
8. Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ 2010; 340:b5349.
9. Yamada M, Wong FL, Fujiwara S, Akahoshi M, Suzuki G. Noncancer disease incidence in atomic bomb survivors, 1958–1998. Radiat Res 2004; 161:622–32.
10. Vrijheid M, Cardis E, Ashmore P, Auvinen A, Bae JM, Engels H, et al. Mortality from diseases other than cancer following low doses of ionizing radiation: results from the 15-Country Study of nuclear industry workers. Int J Epidemiol 2007; 36:1126–35.
11. Muirhead CR, O'Hagan JA, Haylock RG, Phillipson MA, Willcock T, Berridge GL, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br J Cancer 2009; 100:206–12.
12. Boice JD, Jr., Cohen SS, Mumma MT, Chadda B, Blot WJ. A cohort study of uranium millers and miners of Grants, New Mexico, 1979–2005. J Radiol Prot 2008; 28:303–25.
13. Berrington A, Darby SC, Weiss HA, Doll R. 100 years of observation on British radiologists: mortality from cancer and other causes 1897–1997. Br J Radiol 2001; 74:507–19.
14. Silver SR, Daniels RD, Taulbee TD, Zaebst DD, Kinnes GM, Couch JR, et al. Differences in mortality by radiation monitoring status in an expanded cohort of Portsmouth Naval Shipyard workers. J Occup Environ Med 2004; 46:677–90.
15. Wiggs LD, Cox-DeVore CA, Wilkinson GS, Reyes M. Mortality among workers exposed to external ionizing radiation at a nuclear facility in Ohio. J Occup Med 1991; 33:632–7.
16. Wiggs LD, Johnson ER, Cox-DeVore CA, Voelz GL. Mortality through 1990 among white male workers at the Los Alamos National Laboratory: considering exposures to plutonium and external ionizing radiation. Health Phys 1994; 67:577–88.
17. Loomis DP, Wolf SH. Mortality of workers at a nuclear materials production plant at Oak Ridge, Tennessee, 1947–1990. Am J Ind Med 1996; 29:131–41.
18. Matanoski GM. Health Effects of Low-Level Radiation in Shipyard Workers, Final Report, DOE Contract: DE-AC02-79EV10095. Baltimore, MD: Johns Hopkins University; 1991.
19. Preston DL, Lubin J, Pierce DA. Epicure: Risk regression and data analysis software. Seatle: Hirosoft International Corporation; 1991.
20. Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol 1997; 145:72–80.
21. van der Heijden GJ, Donders AR, Stijnen T, Moons KG. Imputation of missing values is superior to complete case analysis and the missing-indicator method in multivariable diagnostic research: a clinical example. J Clin Epidemiol 2006; 59:1102–9.
22. Demedts M, Wells AU, Anto JM, Costabel U, Hubbard R, Cullinan P, et al. Interstitial lung diseases: an epidemiological overview. Eur Respir J Suppl 2001; 32:2s–16s.
23. Pierce DA, Vaeth M, Shimizu Y. Selection bias in cancer risk estimation from A-bomb survivors. Radiat Res 2007; 167:735–41.
24. Ministry of Health Labour and Welfare, Vital Statistics of Japan, 1950–2005. Tokyo: Health, Labor, and Welfare Statistics Association; 1953–2007.
25. Ron E, Carter R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. Epidemiology 1994; 5:48–56.
26. Kusunoki Y, Hayashi T. Long-lasting alterations of the immune system by ionizing radiation exposure: implications for disease development among atomic bomb survivors. Int J Radiat Biol 2008; 84:1–14.
27. Kusunoki Y, Yamaoka M, Kubo Y, Hayashi T, Kasagi F, Douple EB, et al. T-cell immunosenescence and inflammatory response in atomic bomb survivors. Radiat Res 2010; 174:870–6.