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Source: Radiation Research, 173(6):837-842.
Published By: Radiation Research Society
DOI: http://dx.doi.org/10.1667/RR2096.1
URL: http://www.bioone.org/doi/full/10.1667/RR2096.1

RADIATION RESEARCH 173, 837–842 (2010)
0033-7587/10 $15.00

DOI: 10.1667/RR2096.1

Ionizing Radiation and Kidney Cancer among Japanese Atomic Bomb Survivors

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Richardson, D. B. and Hamra, G. Ionizing Radiation and Kidney Cancer among Japanese Atomic Bomb Survivors. *Radiat. Res.* 173, 837–842 (2010).

Understanding of the role of radiation as a cause of kidney cancer remains limited. The most common types of kidney cancer are renal cell carcinoma and renal pelvis carcinoma. It has been posited that these entities differ in their degree of radiogenicity. Recent analyses of cancer incidence and mortality in the Life Span Study (LSS) of Japanese atomic bomb survivors have examined associations between ionizing radiation and renal cell carcinoma, but these analyses have not reported results for cancer of the renal pelvis and ureters. This paper reports the results of analyses of kidney cancer incidence during the period 1958–1998 among 105,427 atomic bomb survivors. Poisson regression methods were used to derive estimates of associations between radiation dose (in sievert, Sv) and cancer of the renal parenchyma ($n = 167$), and cancer of the renal pelvis and ureter ($n = 80$). Heterogeneity by cancer site was tested by joint modeling of cancer risks. Radiation dose was positively associated with cancers of the renal pelvis and ureter [excess relative rate (ERR)/Sv = 1.65; 90% confidence interval (CI): 0.37, 3.78]. The magnitude of this association was larger than the estimated association between radiation dose and cancer of the renal parenchyma (ERR/Sv = 0.27; 90% CI = −0.19, 0.98). While the association between radiation and cancer of the renal parenchyma was of greater magnitude at ages <55 years (ERR/Sv = 2.82; 90% CI = 0.45, 8.89) than at older attained ages (ERR/Sv = −0.11; 90% CI = nd, 0.53), the association between radiation and cancers of the renal pelvis and ureter varied minimally across these categories of attained age. A test of heterogeneity of type-specific risks provides modest support for the conclusion that risks vary by kidney cancer site (LRT = 2.34, 1 *d.f.*, $P = 0.13$). Since some studies of radiation-exposed populations examine these sites in aggregate, results were also derived for the combined category of cancer of the renal parenchyma, renal pelvis and ureters. Overall, there was a positive association between radiation and the combined category of cancer of the renal parenchyma, renal pelvis and ureters (ERR/Sv = 0.60, 90% CI: 0.09, 1.30). Updated follow-up of the LSS cohort provides substantial additional information on the association between radiation and cancer of the renal pelvis and ureter, a site not examined in recent reports on analyses of these data. The results are suggestive of differences between the different regions of the kidney in sensitivity to the carcinogenic effects of ionizing radiation. © 2010 by Radiation Research Society

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INTRODUCTION

Kidney cancer refers to any cancer that forms in the tissues of the kidney. The most common types of kidney cancer are renal cell carcinoma, which arises in the small tubes in the kidney, and renal pelvis carcinoma, which forms in the center of the kidney where urine collects (*1*). While a variety of workplace and environmental hazards have been investigated in relation to kidney cancer, there are few established occupational or environmental causes of this disease (*1*). Even ionizing radiation, an established carcinogen, has been considered to exhibit only weak evidence of an association with kidney cancer (*2*). The strongest evidence to date comes from studies of cancer after radiotherapy, where the radiation doses to the kidney tended to be very high (*3, 4*). Boice *et al.* noted that cancers of the renal pelvis and ureter appeared to be more strongly associated with radiation than cancer of the renal parenchyma in their study of second cancer risk in patients treated by radiotherapy for cancer of the cervix (*5*). Given that the transitional cells that predominate in the renal pelvis and ureters are like those in the bladder, it has been posited that transitional cell carcinomas arising in the renal pelvis and ureters may be more strongly associated with radiation exposure than cancer of the renal parenchyma (*5*). There was very limited support for this supposition in the first comprehensive report on solid cancer incidence in the LSS cohort. A positive radiation dose–response association was reported for cancers of the renal parenchyma [excess relative rate (ERR)/Sv = 0.71; 95% CI: −0.11, 2.25], and a somewhat larger positive association was reported for cancers of the renal pelvis and ureter (ERR/Sv = 1.66; 95% CI: −0.21, 6.57) (*6*). However, the 95% confidence bounds were extremely wide for these estimated associations; therefore, the results offered, at most, suggestive evidence of differ-

ences in the magnitude of radiation dose–kidney cancer associations by site.

This issue has not been clarified by recent analyses of solid cancer mortality or cancer incidence among members of the LSS. With vital status follow-up through 2000, Preston *et al.* reported a negative dose–response association for renal cell cancer mortality among males (ERR/Sv = −0.02; 90% CI: <−0.3, 1.1) and a positive dose–response association among females (ERR/Sv = 0.97; 90% CI: <−0.3, 3.8); however, radiation risk estimates were not reported for cancers of the renal pelvis and ureters (*7*). Similarly, in recent analyses of cancer incidence in the LSS, Preston *et al.* reported that the radiation dose–response association for renal cell carcinoma was small in magnitude and imprecisely estimated (ERR/Sv = 0.13; 90% CI: −0.25, 0.75); radiation risk estimates were not reported for cancers of the renal pelvis and ureters (*8*).

The recent update of the LSS cancer incidence data provides an opportunity to examine these associations further. In this paper we report on estimated associations between radiation dose and the incidence of cancer of the renal parenchyma and of cancer of the renal pelvis and ureter among members of the Life Span Study cohort of Japanese atomic bomb survivors.

MATERIALS AND METHODS

The Life Span Study cohort includes 105,427 survivors of the atomic bombings of Hiroshima and Nagasaki who were registered residents of the cities at the times of bombings, were residents of Hiroshima or Nagasaki at the time of the 1950 census, have radiation dose estimates based on the Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagaski Dosimetry System 2002 (DS02) dosimetry system, and were alive and had not been diagnosed with cancer as of 1958 (*9*). As in recent analyses of cancer incidence in this cohort (*8*), these analyses include residents who were temporarily not in either Hiroshima or Nagasaki or were more than 10 km from the hypocenter in either city at the time of the bombings [referred to as not in city (NIC)]. These people subsequently returned to Hiroshima or Nagasaki and responded to special A-bomb surveys conducted between 1950 and 1953.

In this analysis, follow-up commenced on 1 January 1958 and continued until 31 December 1998. Cancer cases were ascertained through searches of the Hiroshima and Nagasaki tumor registries, established in 1957 and 1958, respectively. Cases are identified by abstractors in the large hospitals in Hiroshima city and Nagasaki prefecture. These data are supplemented with information on cancer deaths obtained from death certificates as well as information from the Hiroshima and Nagasaki tissue registries and from RERF records from the clinic, autopsy and surgery programs. Tumors were classified and coded according to the International Classification of Diseases for Oncology (ICD). Information on cancer incidence is ascertained systematically only for those survivors residing in the catchment areas for the Hiroshima and Nagasaki cancer registries (Hiroshima prefecture and Nagasaki prefecture, respectively). Therefore, as in prior LSS cancer incidence analyses, we indirectly account for the effect of migration out of the catchment areas on the completeness of case ascertainment by adjustment of person-years of follow-up by means of city-, sex-, age- and period-specific estimates of migration probabilities (*10*). The adjustment involves multiplying person-time in a given sex, birth cohort, time and city by stratum-specific estimates of the probability of residence in the catchment area for that stratum (*11*). The residence probability estimates were based on information obtained from the Adult Health Study (AHS), a long-term clinical follow-up study conducted by RERF on a subset of the LSS cohort.

Analyses are conducted for cancers of the renal parenchyma (ICD-10 code C64) and for cancers of the renal pelvis (ICD-10 code C65) and ureter (ICD-10 code C66). The available data do not permit subdivision of the renal pelvis and ureter. The epidemiological literature includes studies of a number of other radiation-exposed populations in which associations between radiation and kidney cancer have been examined. In some previous analyses of cancer in irradiated populations, cancers of renal parenchyma, renal pelvis and ureter have been examined in aggregate (*3, 5, 12*). To facilitate comparisons of radiation risk estimates derived in this paper with findings from these studies of other important radiation-exposed populations, the present paper also reports radiation risk estimates for the combined category of cancers of renal parenchyma, renal pelvis and ureter.

Similar to prior analyses of the LSS incidence data, we take the bladder as the target organ for dose estimation. The primary exposure of interest was defined as weighted DS02 bladder dose estimates adjusted for dosimetry errors. Weighted DS02 dose estimates represent the sum of the γ-radiation dose plus 10 times the neutron dose to allow for the greater biological effectiveness of neutron doses. Uncertainties about survivor location and shielding are an important potential source of error in individual dose estimates. Adjusted dose estimates have been developed to compensate for attenuation bias due to random errors in these dose estimates (*13*). This report makes use of downloadable data obtained from the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan.

Statistical Methods

Poisson regression methods were used to analyze these cohort data. The analytical data file for these analyses is a cross-tabulation of person-time and cancer cases by city (Hiroshima or Nagasaki), sex, age at exposure (in 5-year intervals), attained age (in 5-year intervals), calendar time (1958–1960, then in 5-year intervals up to 1985, the final categories being 1986–1987, 1988–1990, 1991–1995 and 1996–1998), distance from the hypocenter (proximal: 0–3000 m, distal: 3000–10,000 m, or not in city), and dose (in categories defined by cutpoints of 0.005, 0.02, 0.04, 0.06, 0.08, 0.1, 0.125, 0.150, 0.175, 0.2, 0.25, 0.3, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5 and 3 Sv). For each cell of the cross-classification, the number of observed cancers, the number of person-years, and person-year weighted average values for dose, attained age and age at exposure were computed.

Control for potential confounding by covariates was achieved by stratification of regression models on sex, city, attained age, age at exposure and location. City was included as a covariate to adjust for potential differences between Hiroshima and Nagasaki in baseline cancer rates. Sex, attained age and age at exposure were included as covariates to adjust for sex, age and birth cohort variation in cancer rates. Prior research suggests that LSS cohort members who were in the cites at the time of the bombings tended to be more highly educated and less likely to work in occupations such as agriculture and fishing, than survivors who were at distal locations at the time of the bombings (*14, 15*). If risk factors for kidney cancer that were associated with education, residence or occupation were correlated with dose then the true effect of radiation may be obscured or exaggerated. Therefore, we have included a binary indicator of distal location as a covariate in these analyses.

Radiation dose–cancer associations were estimated using an ERR model of the form $\lambda(c, s, a, e, l, d) = e^{\alpha_i}(1 + \delta d)$, where c, s, a, e, l and d denote city, sex, attained age, age at exposure, location and dose, respectively. The baseline cancer rate is described in this model by the parameters α_i for the stratum-specific disease rate in the absence of

radiation exposure (the strata defined by the categories of covariates in which person-time and events are tabulated). The parameter estimate $\hat{\delta}$ describes the estimated excess relative risk per 1-Sv increase in dose. A piecewise constant model for the dose–response function was estimated by defining binary indicator variables for dose categories at cutpoints of 0.005, 0.10, 0.20, 0.50 and 1 Sv; the associated vector of parameters describes the estimated rate ratio (RR) for each dose category relative to the referent category (<0.005 Sv). Modification of the excess relative risk was evaluated by fitting a regression model of the form $\lambda(c, s, a, e, l, d) = e^{\alpha_i}(1 + \delta_1 dz_1 + \delta_2 dz_2)$, where the effect measure modifier, z, has categories indexed via binary indicator variables z_1 and z_2. The δ values provide estimates of the ERR per Gy for the categories of the modifying factor. Associations were estimated for categories of sex and, following prior findings by Preston *et al.* (*8*), attained age (in categories of <55 and 55+ years); a finer categorization of attained age was not possible because it resulted in failure of model convergence.

To evaluate the sensitivity of findings to inclusion in these analyses of not-in-city cohort members (who contribute to estimation of baseline incidence rates), we also report analyses excluding not-in-city cohort members. Last, we employed the approach described by Pierce and Preston (*16*) for joint analysis of site-specific cancer risks to statistically compare risk estimates for cancers of the renal parenchyma and renal pelvis. Briefly, we incorporated cancer site as another factor of the multi-way tabulation of data for analysis. This permitted testing of interactions between radiation dose effects and cancer site (*16*).

Parameter estimation was performed using the AMFIT program in the EPICURE statistical package (*17*). For consistency with other epidemiological studies of radiation-exposed populations, 90% confidence intervals were generated for estimated parameters via the likelihood method (*18*). In some analyses confidence bounds for an estimated parameter could not be determined; these are designated as "nd". To aid interpretation of model fittings, we also report likelihood ratio test (LRT) statistics and associated P values derived by comparing the goodness of fit of nested models.

RESULTS

The study population included 42,902 men and 62,525 women. This analysis includes 247 cases of kidney cancer; 167 (67.6%) of the cases were cancer of the renal parenchyma and 80 (32.4%) are cancers of the renal pelvis and ureter. Table 1 describes the numbers of cases by city, sex, location and categories of attained age and age at exposure. Sixty-one cases of kidney cancer were observed among residents of Nagasaki. Fifty-three cases were observed among the subgroup of people who were NIC at the time of bombings. Cancer of the renal parenchyma was more common among males than females; no cases of cancer of the renal parenchyma were observed at ages less than 30 years. Eighty cases of cancers of the renal pelvis and ureter were observed; similar numbers of cases were observed males and females.

Table 2 reports estimated RRs for kidney cancer by category of radiation dose. For cancer of the renal parenchyma the estimated RR was close to unity when contrasting those exposed to 0.005–<0.1, 0.1–<0.2 and 0.2–<0.5 Sv with those people exposed to less than 0.005 Sv. The estimated trend in cancer of the renal parenchyma with radiation dose obtained by fitting of an ERR model was of small magnitude and highly imprecise (Table 2); inclusion of a term for radiation dose in the baseline regression model for cancer of the renal parenchyma led to minimal improvement in model fit (LRT = 0.74, 1 *d.f.*, P = 0.39). For cancers of the renal pelvis and ureter the estimated RRs exceeded unity when contrasting those exposed to 0.1–<0.2, 0.2–<0.5, 0.5–<1 and 1.0+ Sv with those exposed to less than 0.005 Sv; estimated RRs exceeded 2.0 when contrasting those exposed to 0.2–<0.5, 0.5–<1 and 1.0+ Sv with those exposed to less than 0.005 Sv. When estimating the trend in cancers of the renal pelvis and ureter with radiation dose via an ERR model, inclusion of a term

TABLE 1
Distribution of Person-Time and Observed Cases of Kidney Cancer, Cancer of the Renal Parenchyma, and Cancer of the Renal Pelvis and Ureter by Sex, Attained Age, Age at Exposure, City and Location, Japanese Atomic Bomb Survivors, 1958–1998

	Person-years	Kidney	Renal parenchyma	Renal pelvis
Attained age (years)				
<15	7,037	0	0	0
15–<20	57,254	0	0	0
20–<25	93,547	0	0	0
25–<30	134,199	0	0	0
30–<35	178,490	1	1	0
35–<40	206,884	3	2	1
40–<45	233,948	6	6	0
45–<50	263,823	4	2	2
50–<55	294,104	11	7	4
55–<60	289,838	24	17	7
60–<65	274,478	42	30	12
65–<70	245,500	43	29	14
70–<75	193,763	41	25	16
75–<80	142,677	36	27	9
80–<85	89,835	25	13	12
≥85	59,360	11	8	3
Age at exposure (years)				
<10	680,293	18	13	5
10–<30	1,170,060	94	58	36
30–<50	769,596	108	74	34
≥50	144,789	27	22	5
Sex				
Male	1,040,280	129	91	38
Female	1,724,450	118	76	42
City				
Hiroshima	1,967,600	186	126	60
Nagasaki	797,133	61	41	20
Location				
<3 km	1,475,230	137	92	45
3 km–<10 km	608,757	57	38	19
NIC[a]	680,774	53	37	16
Total	2,764,730	247	167	80

[a] Not in city. Life Span Study cohort members who were temporarily not in Hiroshima or Nagasaki or were more than 10 km from the hypocenter at the time of the bombings.

TABLE 2
Estimated Relative Rate of Kidney Cancer, Cancer of the Renal Parenchyma, and Cancer of the Renal Pelvis and Ureter by Categories of External Ionizing Radiation Dose to the Bladder for Japanese A-Bomb Survivors, 1958–1998

	Dose category (Sv)						
	<0.005	0.005–<0.10	0.10–<0.20	0.20–<0.50	0.50–<1	≥1	Trend[a]
	RR (90% CI)	RR (90% CI)	RR (90% CI)	RR (90% CI)	RR (90% CI)	RR (90% CI)	ERR per Sv (90% CI)
	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths	Deaths
Renal parenchyma	1	1.05	0.94	1.01	0.64	1.96	0.27
(ICD-10 code C64)	(referent)	(0.75, 1.47)	(0.48, 1.67)	(0.53, 1.76)	(0.20, 1.51)	(0.90, 3.75)	(−0.19, 0.98)
	97	44	8	9	3	6	167
Renal pelvis and ureter	1	0.99	1.44	2.52	2.73	2.35	1.65
(ICD-10 code	(referent)	(0.57, 1.70)	(0.59, 3.08)	(1.27, 4.72)	(1.11, 5.82)	(0.73, 5.82)	(0.37, 3.78)
C65–C66)	42	16	5	9	5	3	80
Total (ICD-10 codes	1	1.04	1.08	1.44	1.23	2.07	0.60
C64–C66)	(referent)	(0.78, 1.37)	(0.64, 1.73)	(0.92, 2.18)	(0.63, 2.17)	(1.11, 3.55)	(0.09, 1.30)
	139	60	13	18	8	9	247

Note. All rate ratio estimates are adjusted for city, sex, attained age, age at exposure (i.e., birth cohort), and location via background stratification.

[a] Excess relative rate per Sv, calculated as the parameter estimate obtained via fitting of a linear relative rate model with a linear term for dose.

for radiation dose led to a substantial improvement in model fit (LRT = 5.73, 1 *d.f.*, $P = 0.02$). For cancer of the renal parenchyma, renal pelvis and ureters considered in aggregate, the estimated RR was greater than unity when contrasting those exposed to 0.005–<0.1, 0.1–<0.2, 0.2–<0.5, 0.5–<1 and 1.0+ Sv with those exposed to less than 0.005 Sv, and estimated RRs tended to increase in magnitude with increasing dose (although the pattern is not entirely monotonic). The estimated trend with radiation dose obtained via fitting of an ERR model was 0.60 (90% confidence interval = 0.09, 1.30); inclusion of a term for radiation dose in the baseline regression model led to a modest improvement in model fit (LRT = 4.13, 1 *d.f.*, $P = 0.04$).

Similar results were obtained after exclusion of the NIC cohort members. The estimated trend in all kidney cancers combined with radiation dose obtained via fitting of a linear ERR model was 0.50 (90% CI = 0.02, 1.21); the estimated trends in cancer of the renal parenchyma and cancers of the renal pelvis and ureter with radiation dose obtained after exclusion of the NIC cohort members were 0.21 (90% CI = −0.22, 0.92) and 1.47 (90% CI = 0.22, 3.87), respectively.

Risk estimates for cancer of the renal pelvis among males (ERR/Sv = 0.74, 90% CI: nd, 3.10) are smaller in magnitude that risk estimates for cancer of the renal pelvis among females (ERR/Sv = 3.07, 90% CI: 0.65, 8.08). However, these sex-specific point estimates are estimated imprecisely, and there was little statistical support for a conclusion of heterogeneity in the radiation dose–renal pelvis cancer association by sex (LRT = 1.27, 1 *d.f.*, $P = 0.26$). Cancer of renal parenchyma is highly imprecise among males (ERR/Sv = −0.08, 90% CI: nd, 0.65) and positive but imprecise among females (ERR/Sv = 1.00, 90% CI: −0.00, 2.73).

Table 3 presents analyses of heterogeneity with attained age in the dose–response association for renal parenchyma (Table 3); the magnitude of the dose–response association for renal parenchyma is smaller among those with greater attained ages. In contrast, the dose–response association for cancers of the renal pelvis and ureter exhibits very minimal evidence of variation with attained age.

Last, we fitted a joint model for cancer of the renal parenchyma and cancer of the renal pelvis and ureters. In addition to adjustment for the other model covariates (sex, city, attained age, age at exposure and location), the baseline model for the joint analysis was stratified by an indicator of cancer type, thereby allowing separate covariate effects for each cancer site. We compared a model with a single parameter for radiation dose effects on all kidney cancers combined to a model that included an additional parameter allowing the radiation risk coefficients to vary by cancer site. There was modest evidence of heterogeneity by cancer site (LRT = 2.34, 1 *d.f.*, $P = 0.13$).

DISCUSSION

This paper examines the association between ionizing radiation dose and cancer of the renal pelvis and ureters and cancer of the renal parenchyma using cancer incidence data from the Life Span Study of atomic bomb survivors and DS02 dosimetry estimates. We observe that incidence of cancer of the renal pelvis and ureters is positively associated with estimated ionizing radiation dose among members of the Life Span Study. This finding is consistent with a prior analysis of cancer incidence through 1987 in the LSS (*6*). With updated follow-up of the LSS cohort, the magnitude of the excess

TABLE 3
Estimated ERR per Sievert of Cancer of the Renal Parenchyma, and Cancers of the Renal Pelvis and Ureter, by Attained Age for Japanese A-Bomb Survivors, 1958–1998

	Renal parenchyma ERR/Sv (90% CI)	Renal pelvis ERR/Sv (90% CI)
Attained age <55 years	2.82 (0.45, 8.89)	1.55 (nd, 14.12)
Attained age >=55 years	−0.11 (nd, 0.53)	1.66 (0.34, 3.94)
Likelihood ratio test for heterogeneity by attained age group	4.64, 1 *d.f.*, $P = 0.03$	0.00, 1 *d.f.*, $P = 0.99$

relative risk for cancers of the renal pelvis and ureter (ERR/Sv = 1.65, 90% CI: 0.37, 3.78) is similar in magnitude to the point estimate reported in analyses of cancer incidence through 1987 (ERR = 1.66; 95% CI: −0.21, 6.57). While the findings for the previous analysis were highly imprecise, with confidence bounds spanning the null, the current analysis has tighter confidence bounds for site-specific risk estimates, includes nearly three times as many cases of cancer of the renal pelvis and ureters as the previous analysis by Thompson *et al.* (*6*) and incorporates the most recent DS02 radiation dosimetry estimates for this cohort. The estimate of the ERR/Sv for cancer of the renal parenchyma is relatively small and is highly imprecise, with the exception of risk estimates at attained ages <55 years. The point estimate for cancer of the renal parenchyma is consistent with the point estimate reported by Preston *et al.* (*1*).

We noted that the estimated ERR/Sv for cancer of the renal parenchyma is larger in magnitude at younger attained ages (<55 years) than it is at older attained ages (Table 3). This observation is consistent with prior analyses by Preston *et al.*, who observed that inclusion of attained age as an effect modifier led to a substantial improvement in model fit. While the current paper has focused solely on fitting excess relative rate models, Preston *et al.* noted that under an excess absolute risk model there was a positive association between radiation dose and cancer of the renal parenchyma (*8*).

Questions have been raised about limitations of the data for this cohort study of Japanese atomic bomb survivors, including concerns about errors in dosimetry, selection and other potential sources of bias. However, most plausible scenarios of exposure measurement error and selection discussed in the literature imply attenuation or masking of effects rather than sources of bias leading to spurious positive associations (*13, 19*). Consequently, the observation of positive associations between radiation dose and kidney cancer incidence in this cohort contributes important epidemiological evidence in support of the conclusion that kidney cancer risk increases after exposure to ionizing radiation. Aside from the LSS, the strongest evidence of an association between radiation dose and kidney cancer comes from studies of patients receiving radiotherapy treatment. Given evidence in the current study of variation in the magnitude and temporality of radiation dose–response associations for cancers of the renal parenchyma and renal pelvis and ureters, it is worth noting that many of these prior studies of kidney cancer after radiotherapy examined these diseases in aggregate. Weiss *et al.* reported that among patients with ankylosing spondylitis who were treated X radiation, mortality due to kidney cancer was significantly increased (*3*). Kleinerman *et al.* reported that women with cervical cancer treated with radiotherapy experienced an increased risk of kidney cancer (*4*), and Travis *et al.* reported that men treated for testicular cancer had an increased risk of kidney cancer (*20*).

The results of these analyses suggest differences in the magnitude of radiation dose–response associations for cancers of the renal parenchyma and renal pelvis and ureters. We observed a positive association between radiation dose and cancer of the renal pelvis and ureters similar in magnitude to estimates from prior follow-up of the LSS cohort through 1987. Given the updated follow-up of the LSS cohort, the current analysis provides substantial additional information on the association between radiation and cancer of the renal pelvis and ureter.

ACKNOWLEDGMENTS

This report makes use of data obtained from the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private, nonprofit foundation funded by the Japanese Ministry of Health, Labour and Welfare and the U.S. Department of Energy, the latter through the National Academy of Sciences. The conclusions in this report are those of the authors and do not necessarily reflect the scientific judgment of RERF or its funding agencies.

Received: November 23, 2009; accepted: January 4, 2010; published online: March 22, 2010

REFERENCES

1. J. K. McLaughlin, L. Lipworth, R. E. Tarone and W. J. Blot, Renal cancer. In *Cancer Epidemiology and Prevention: Third Edition* (D. Schottenfeld and and J. F. Fraumeni, Jr., Eds.). Oxford University Press, Oxford, 2006.
2. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources and Effects of Ionizing Radiation*. United Nations, New York, 2006.
3. H. A. Weiss, S. C. Darby and R. Doll, Cancer mortality following X-ray treatment for ankylosing spondylitis. *Int. J. Cancer* **59**, 327–338 (1994).
4. R. A. Kleinerman, J. D. Boice, Jr., H. H. Storm, P. Sparen, A. Andersen, E. Pukkala, C. F. Lynch, B. F. Hankey and J. T.

Flannery, Second primary cancer after treatment for cervical cancer. An international cancer registries study. *Cancer* **76**, 442–452 (1995).

5. J. D. Boice, Jr., G. Engholm, R. A. Kleinerman, M. Blettner, M. Stovall, H. Lisco, W. C. Moloney, D. F. Austin, A. Bosch and B. McMahon, Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat. Res.* **116**, 3–55 (1988).
6. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ochikubo, S. Sugimoto, T. Ikeda, M. Terasaki and D. L. Preston, Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat. Res.* **137** (Suppl.), S17–S67 (1994).
7. D. L. Preston, Y. Shimizu, D. A. Pierce, A. Suyama and K. Mabuchi, Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat. Res.* **160**, 381–407 (2003).
8. D. L. Preston, E. Ron, S. Tokuoka, S. Funamoto, N. Nishi, M. Soda, K. Mabuchi and K. Kodama, Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat. Res.* **168**, 1–64 (2007).
9. D. L. Preston, D. A. Pierce, Y. Shimizu, H. M. Cullings, S. Fujita, S. Funamoto and K. Kodama, Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. *Radiat. Res.* **162**, 377–389 (2004).
10. D. L. Preston, S. Kusumi, M. Tomonaga, S. Izumi, E. Ron, A. Kuramoto, N. Kamada, H. Dohy, T. Matsuo and K. Mabuchi, Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987. *Radiat. Res.* **137** (Suppl.), , S68–S97 (1994); Erratum, *Radiat. Res.* 139, 129 (1994).
11. R. Sposto and D. L. Preston, *Correcting for Catchment Area Non-residency in Studies Based on Tumor Registry Data*. Radiation Effects Research Foundation, Hiroshima, 1992.
12. C. R. Muirhead, J. A. O'Hagan, R. G. Haylock, M. A. Phillipson, T. Willcock, G. L. Berridge and W. Zhang, Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br. J. Cancer* **100**, 206–212 (2009).
13. D. A. Pierce, D. O. Stram and M. Vaeth, Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat. Res.* **123**, 275–284 (1990).
14. G. W. Beebe, M. Ishida and S. Jablon, *Life Span Study Report Number 1: Description of study. Mortality in the medical subsample, October 1950–June 1958*. Atomic Bomb Casualty Commission, Hiroshima, 1961.
15. N. Nishi, H. Sugiyama, W. L. Hsu, M. Soda, F. Kasagi, K. Mabuchi and K. Kodama, Differences in mortality and incidence for major sites of cancer by education level in a Japanese population. *Ann. Epidemiol.* **18**, 584–591 (2008).
16. D. A. Pierce and D. L. Preston, Joint analysis of site-specific cancer risks for the atomic bomb survivors. *Radiat. Res.* **134**, 134–142 (1993).
17. D. L. Preston, J. H. Lubin, D. A. Pierce and M. E. McConney, *Epicure: User's Guide*. Hirosoft International Corporation, Seattle, WA, 1993.
18. United Nations Scientific Committee on the Effects of Atomic Radiation, *Sources, Effects, and Risks of Ionizing Radiation*. United Nations, New York, 2000.
19. D. A. Pierce, M. Vaeth and Y. Shimizu, Selection bias in cancer risk estimation from A-bomb survivors. *Radiat. Res.* **167**, 735–741 (2007).
20. L. B. Travis, R. E. Curtis, H. Storm, P. Hall, E. Holowaty, F. E. Van Leeuwen, B. A. Kohler, E. Pukkala, C. F. Lynch and J. D. Boice, Jr., Risk of second malignant neoplasms among long-term survivors of testicular cancer. *J. Natl. Cancer Inst.* **89**, 1429–1439 (1997).