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Radiation Dose Associated with Renal Failure Mortality: A Potential Pathway to Partially Explain Increased Cardiovascular Disease Mortality Observed after Whole-Body Irradiation

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Whole-body and thoracic ionizing radiation exposure are associated with increased cardiovascular disease (CVD) risk. In atomic bomb survivors, radiation dose is also associated with increased hypertension incidence, suggesting that radiation dose may be associated with chronic renal failure (CRF), thus explaining part of the mechanism for increased CVD. Multivariate Poisson regression was used to evaluate the association of radiation dose with various definitions of chronic kidney disease (CKD) mortality in the Life Span Study (LSS) of atomic bomb survivors. A secondary analysis was performed using a subsample for whom self-reported information on hypertension and diabetes, the two biggest risk factors for CRF, had been collected. We found a significant association between radiation dose and only our broadest definition of CRF among the full cohort. A quadratic dose excess relative risk model [ERR/Gy^2 = 0.091 (95% CI: 0.05, 0.198)] fit minimally better than a linear model. Within the subsample, association was also observed only with the broadest CRF definition [ERR/Gy^2 = 0.15 (95% CI: 0.02, 0.32)]. Adjustment for hypertension and diabetes improved model fit but did not substantially change the ERR/Gy^2 estimate, which was 0.17 (95% CI: 0.04, 0.35). We found a significant quadratic dose relationship between radiation dose and possible chronic renal disease mortality that is similar in shape to that observed between radiation and incidence of hypertension in this population. Our results suggest that renal dysfunction could be part of the mechanism causing increased CVD risk after whole-body irradiation, a hypothesis that deserves further study.

INTRODUCTION

Numerous studies of various populations exposed to whole-body and chest irradiation have demonstrated that they are at increased risk of fatal cardiovascular disease (CVD) primarily due to increased myocardial infarction mortality (*1*). These populations include patients treated with radiotherapy for Hodgkin's disease (*2–4*), breast cancer (*5–8*), and peptic ulcer disease (9), as well as some but not all occupational cohorts (*10–12*), and atomic bomb survivors (*13–16*). After 40 years of follow-up, evidence began to emerge within the Adult Health Study (AHS), the longitudinal clinical follow-up of atomic bomb survivors, that radiation dose was associated with increased incidence of myocardial infarction (not just CVD mortality) among those less than 40 years of age at the time of the bombing (*17–19*).

Recent work by the Radiation Effects Research Foundation has also demonstrated that radiation dose is associated with increased hypertensive heart disease mortality[2] and with increased systolic and diastolic blood pressure (*20*). Studies of total-body irradiated (TBI) bone marrow transplant survivors demonstrate that a linear relationship exists between biologically effective radiation dose and risk of renal (kidney) failure (dysfunction) (*21*). These findings suggest that the risk of cardiovascular disease in those exposed to whole-body radiation may be mediated in part by damage to the kidney. The kidney is a key organ involved with blood pressure regulation, and hypertension is a well-known risk factor for myocardial infarction. Chronic renal failure, regardless of the presence of hypertension, is thought to add the same risk of future myocardial infarction as having had a prior myocardial infarction (*22*).

Thus we sought to evaluate whether the increased risk of cardiovascular disease in those exposed to whole-body

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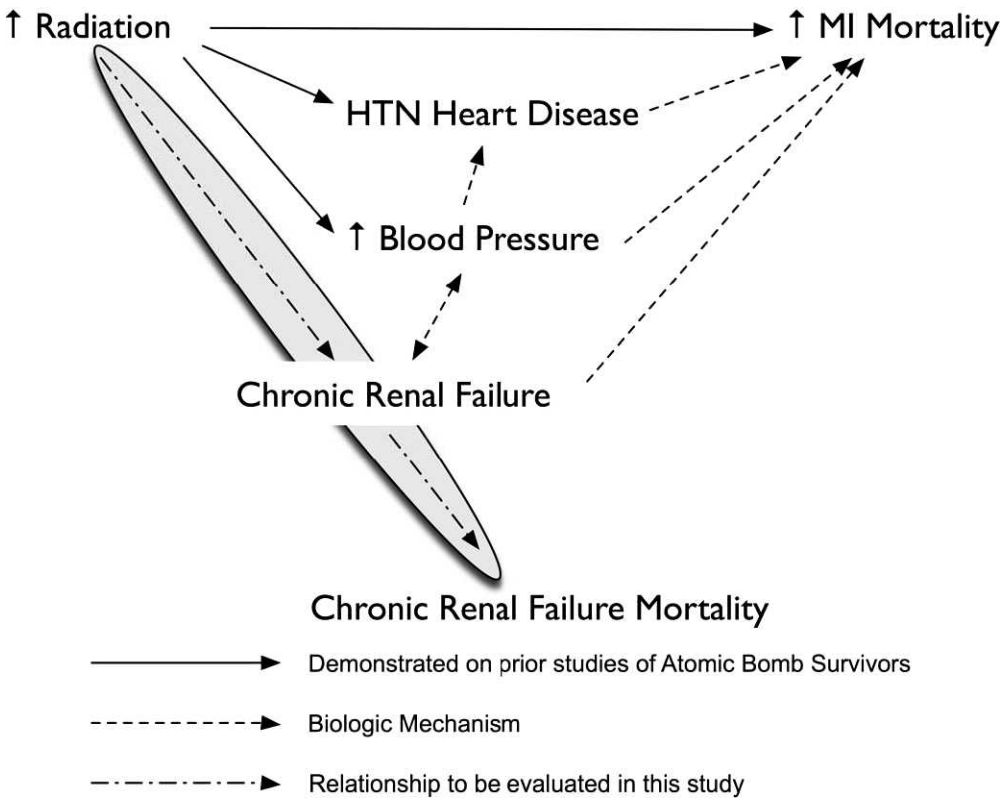

FIG. 1. Relationship between radiation and heart disease in atomic bomb survivors (solid lines) and potential biological mechanisms explaining the relationships (dashed lines). Also shown is the relationship that we hoped to demonstrate in this study (dash/dotted lines).

radiation might be mediated at least in part through chronic renal dysfunction. We indirectly explored this main hypothesis by evaluating the association between radiation exposure from the atomic bomb and kidney disease mortality, in particular chronic renal failure mortality.

Figure 1 illustrates the relationship between radiation and heart disease as demonstrated in the atomic bomb survivors (solid lines) and potential biological mechanisms explaining the relationships (dashed lines). This figure also illustrates the relationship (dash/dotted arrows) that we hope to demonstrate in this research study. If radiation exposure increases the incidence of chronic renal failure, this should lead to higher chronic renal failure mortality and increased mortality from both hypertensive heart disease and myocardial infarction, as previously observed in atomic bomb survivors. However, the relationship is not as simple as a one-way relationship from kidney disease to myocardial infarction risk, because there are many overlapping risk factors for myocardial infarction and chronic kidney disease (CKD). Thus our secondary aim was to evaluate whether overlapping risk factors potentially explained or confounded the relationship between radiation and kidney disease mortality.

The most significant overlapping modifiable risk factors for myocardial infarction and kidney disease are hypertension and diabetes mellitus (*23*). In fact, Yamada *et al.* demonstrated a significant quadratic dose–response relationship between radiation dose and hypertension as well as myocardial infarction incidence in atomic bomb survivors clinically followed between 1958 and 1998 (*19*). Although other overlapping risk factors exist such as dyslipidemia, they are much less important than hypertension and diabetes in terms of kidney disease risk (*22, 23*). Therefore, we concentrated on adjusting our analysis on the two most important modifiable risk factors for kidney disease as well as age.

METHODS

Study Population

The Life Span Study (LSS) cohort consists of 120,321 registered residents of Nagasaki and Hiroshima at the time of the atomic bombings and who were still residents of these two cities when the cohort was established between 1950 and 1953 (*24*). It contains a vast majority of the survivors who were within 2.5 km of the hypocenters at the time of the bombings, a random sample of age- and sex-matched controls who were 2.5 to 10 km from the hypocenter who received small to negligible radiation doses, and 26,580 residents who were out of the city at the time of bombing (*24*). Like other recent reports on non-cancer mortality, our analyses used only the cohort members with estimated radiation doses and who were within 10 km of the hypocenter of the bombs (*16*).

Subjects in the LSS were never formally recruited for participation, and therefore a formal informed consent was not initially acquired. Mail survey subjects agree to their inclusion by returning the questionnaire. Any subject can withdraw from the overall study via

TABLE 1
Definition of Renal Failure Codes By Increasing Sensitivity/Decreasing Specificity

Disease	ICD-10 (1998–2003)	ICD-9 (1979–1997)
Definite chronic renal failure	**N18**	**585**
Chronic renal failure + hypertensive kidney disease	N18, **I12, I13**	585, **403, 404**
Probable chronic renal failure[a]	N18, I12, I13, **N03, N04, N11**	585, 403, 404**, 581, 582**
Possible chronic renal failure[b]	N18, I12, I13, N03, N04, N11, **N05, N12, N19**	585, 403, 404, 581, 82, **583, 586**

Notes. Corresponding 4-digit codes for subcategories used when appropriate. Bolded codes represent the conditions that are added on top of the stricter conditions from the stricter categories above.

[a] Also includes other chronic kidney disease conditions.

[b] Also includes kidney disease and renal failure of unspecified length.

written request. The study design, analysis and procedures performed for this paper were approved by the Radiation Research Effects Foundation Independent Review Board, the Human Investigation Committee.

Individual doses to multiple organs have been carefully estimated using the improved DS02 dosimetry system, primarily on the basis of people's location and shielding at the time of the bombings (*25*). We estimated risks by using the weighted DS02 dose estimate of exposure to the urinary system. Weighted doses sum the γ-ray dose plus 10 times the smaller neutron dose to allow for the greater biological effectiveness of neutrons.

In summary, for atomic bomb survivors to be eligible for inclusion in this analysis, they had to be in the LSS cohort, had to have a urinary system DS02 dose estimate, and had to be within one of the cities at the time of the bombing.

Data Sources and Variables

Data on demographics, dosimetry, mortality status and causes of death were obtained from the LSS database. Follow-up of vital status for this analysis began October 1, 1950 and ended December 31, 2003. Mortality data, including causes of death, were collected from the nationwide obligatory family registration system in Japan (koseki), a system that is virtually 100% complete. Underlying and contributing causes of death were classified according to the ICD-7 (International Classification of Diseases, 7th revision) through ICD-10 as appropriate for year of death.

The strongest correlation between heart disease and kidney disease is between coronary heart disease and chronic renal failure. Although not well defined today, we choose to call our outcome of interest chronic renal failure (CRF), because we believe the association between disease processes in the kidney and CVD is due primarily to effects on the kidney's filtering function and to distinguish our outcome from the strict definition of chronic kidney disease (CKD) as defined in 2002. In that year, U.S. national guidelines defined CKD as abnormal kidney/renal function for 3 months or greater below a certain threshold of normal that results from a chronic disease process (*23*). The condition then called chronic renal failure or end stage kidney disease was defined as stage 5 CKD in these guidelines, but it should be reemphasized that our use of the term ''CRF'' refers to the whole spectrum of non-acute renal dysfunction. In addition, for most of the period of follow-up, there was no standard test to screen for renal dysfunction, let alone a standard cut-off level to define renal failure. Therefore, there may be significant misclassification of chronic renal failure with other types of kidney disease. As a result we defined CRF using four different definitions of increasing sensitivity and decreasing specificity. Table 1 illustrates how we defined these outcomes by ICD revision period: chronic renal failure, chronic renal failure + hypertensive kidney disease, probable chronic renal failure, and possible chronic renal failure, with this last category also including kidney pathologies of indeterminate length. Additionally, cardiovascular disease is the leading cause of death in individuals with chronic renal failure (*26*), which is often asymptomatic until its end stages. Thus cardiovascular disease may often have been coded mistakenly as the underlying cause of death. Therefore, we performed secondary analyses to evaluate all causes of death listed on the death certificate as well as for each definition of our outcome.

Covariate Data

Hypertension and diabetes status information was obtained from questionnaires sent to different but overlapping subsets of LSS subjects in 1965, 1978 and 1991 (*27, 28*). For the first survey, a categorical yes/no variable was created from the text answer for each of these conditions. For the last two surveys, the presence of a condition was queried using a checkbox; we considered a blank checkbox as a negative answer. Once positive for a risk factor, an individual was coded as having the risk factor until death or censoring, unless the subject reported not having the risk factor on two subsequent surveys after the first positive response in which case they were coded as never having the risk factor.

Statistical Analysis

We constructed detailed summary tables of number of deaths and person-years stratified by dose, city, sex and 5-year intervals of age at exposure, attained age and follow-up time. We divided subjects into urinary system weighted dose categories of 0–, 0.005–, 0.01–, 0.02–, 0.04–, 0.06–, 0.08–, 0.10–, 0.15–, 0.20–, 0.25–, 0.30–, 0.50–, 0.75–, 1.00–, 1.50–, 2.00–, 2.50–, 3.00– and $\geq$3.50 Gy. We created separate tables for each of the four definitions of our outcome. We also created a second set of four tables to evaluate whether diabetes and hypertension affected the relationship between radiation dose and kidney disease mortality, because data on these factors were available only in the subset of the entire LSS cohort that returned at least one of the above questionnaires.

We used Poisson regression methods for grouped survival data to describe the dependence of risk on radiation dose and to evaluate the variation of dose–response effects with respect to city, sex, age at exposure, time since exposure and attained age (*29*), essentially the same methods used previously to examine mortality from cancer in this cohort (*24*). Time at risk was calculated for each subject starting at the initiation of the LSS and ending at loss of follow-up or death. We used SAS version 9.1 and the Epicure software package (*30*) (Datab and Amfit modules) to create the summary tables and perform statistical analysis. We based significance tests on a two-sided alpha of <0.05 and calculated 95% confidence intervals for excess relative risk estimates, when P values were <0.10.

The primary models evaluated are excess relative risk (ERR) models of the form

$$\lambda_0(c, s, a, \text{age\_atb})[1 + \text{ERR}(d, s, \text{age\_atb}, \text{age}]],$$

where $\lambda_0(*)$ is a log-linear parametric model of the baseline renal

TABLE 1
Extended

ICD-8 (1969–1978)	ICD-7 (1950–1968)
792	792
792, **403, 404**	792, **446, 442**
792, 403, 404**, 581, 582**,	792, 446, 442, **592,**
792, 403, 404, 581, 582, **583**	592, 792, 446, 442, 592, **591, 593**

disease mortality rate, in the absence of radiation exposure, depending upon city (c), sex (s), attained age (age) and age at time of bombing (age_atb). The excess rate depends upon dose, allowing for the effect of city (c), sex (s), attained age (age) and age at time of bombing (age_atb).

We compared the relative fitness of several different models of the ERR term. These included a linear model of dose [$\rho(d) = \beta d$] with and without thresholds, a linear-quadratic model [$\rho(d) = \beta d + \gamma d^2$], and a purely quadratic model [$\rho(d) = \gamma d^{2'}$] using likelihood ratio tests for nested models and the Akaike information criterion for non-nested models (*31*).

A similar analytic approach was taken to evaluate whether radiation dose was independently associated with cause-specific kidney disease mortality after also adjusting for hypertension and diabetes in the LSS. Terms were included to evaluate both the direct association of each on kidney disease mortality and whether each modified the association of radiation dose on kidney disease mortality. If either factor appeared to be significant at $P < 0.10$, we performed stratified analysis based on that factor. This may be particularly important for hypertension, because it is both a cause and consequence of chronic renal failure. Thus, if dose was only significantly associated with kidney disease mortality in those with hypertension, this would potentially suggest that hypertension is somewhere in the pathway between radiation exposure and kidney disease mortality. If stratified analyses were not significantly different by strata, then only multivariate analyses were reported. Finally, the demographic information of the subsample of the LSS included in this analysis was also compared to those not included to evaluate whether the subsample was representative of the cohort as a whole.

RESULTS

A total of 86,609 survivors with a total of 3,296,595 person-years of follow-up were included in the analysis of our first aim, the evaluation of the association between the estimated atomic bomb radiation dose and CRF mortality. Of the survivors, 41.2% were male (Table 2); 67.5% were from Hiroshima. The median urinary weighted dose was 7.81 mGy (range: 0–3860 mGy), while the mean was 117.56 mGy (SD 315.5 mGy). As Table 3 illustrates, 214 deaths had an underlying cause of death of chronic renal failure for a rate of 6.5 per 100,000 person-years, and 908 deaths had CRF listed anywhere on the death certificate for a rate of 27.5 per 100,000 person-years. After adjusting for city, sex, attained age and age at time of bombing, the excess relative risk per Gy (ERR/Gy) estimate for CRF as the underlying cause was 0.38 ($P = 0.33$) and as any cause of death was 0.26 ($P = 0.19$), so neither was statistically significant. Neither the quadratic nor the linear-quadratic dose models fit the data better than the linear models.

TABLE 2
Characteristics of 86,609 LSS Survivors Analyzed in Aim 1: Overall CRF Mortality

	Subjects (%) ($N = 86,609$)	Person-years[a] (%) (PY = 3,296,595)
Gender		
Male	35,687 (41.2)	1,281,734 (38.9)
Female	50,922 (58.8)	2,014,861 (61.1)
City		
Hiroshima	58493 (67.5)	2,197,930 (66.7)
Nagasaki	28116 (32.5)	1,098,665 (33.3)
Age at time of bombing	Median: 27.37 years	Range: 0–91.5 years
Urinary dose (mGy)	Median: 7.81	Range: 0–3860

[a] Follow-up from 01/01/1950 until 12/31/2003.

Table 3 also illustrates similar data for the three other secondary definitions of our outcome. Only the broadest category, possible CRF listed as an underlying or a contributory cause of death (number of events = 2436), approached significance in the adjusted model, with an ERR/Gy of 0.135 (95% CI: −0.008–0.30). The quadratic dose multivariate model fit the data as well [Akaike information criterion (AIC) difference = 0.891] with ERR/Gy^2 term of 0.091 (95% CI: 0.05–0.198).

A total of 49,970 unique subjects (57.7% of the LSS cohort) provided information on hypertension and diabetes through the three self-report surveys. They make up our sample for aim 2, the evaluation of the association between the estimated atomic bomb radiation dose and CRF mortality including adjustment for hypertension and diabetes. This sample provides 2,372,139 person-years of follow-up (72% of entire cohort). For each alternative definition of our outcome, Table 4 shows the number of deaths, the mortality rate per 100,000 person-years, the ERR/Gy estimates from the adjusted linear model, and the *P* value of whether the estimate was significantly different from zero. Models were adjusted for city*sex (a combined variable of sex and city with four categories), age at time of the bombing, attained age, hypertension and diabetes. Number of deaths (and rates) ranged from 140 with an underlying cause of CRF (5.9 per 100,000 person-years) and 466 deaths with CRF listed anywhere on the death certificate (19.6 per 100,000 person-years) to 417 deaths with an underlying cause of possible CRF (rate 17.6. per 100,000 person-years) and 1171 with possible CRF anywhere on the death certificate (rate 49.4. per 100,000 person-years). Only the outcome of possible CRF as any cause of death demonstrated a significant dose effect. The adjusted linear model revealed an ERR/Gy of 0.27 ($P = 0.033$), though the quadratic dose–effect model fit the data nonsignificantly better (AIC difference = 0.896), with an ERR/Gy^2 of 0.17 ($P = 0.031$) (Table 4, Fig. 2). The linear model explains 34 excess deaths (2.98%) of the 1171 possible CRF deaths, while the quadratic dose model explains only 18 excess deaths (1.55%). The addition of the

TABLE 3
Aim 1: CRF Mortality: Number of Events, Rate and Adjusted Excess Relative Risk Estimates

	Underlying cause of death				All listed causes of death			
	Number	Rate (per 100K PY)	ERR/Gy	*P* value	Number	Rate (per 100K PY)	ERR/Gy	*P* value
Chronic renal failure	214	6.5	0.13	>0.50	908	27.5	0.075	>0.50
CRF or HKD	448	13.5	0.22	0.27	1137	34.5	0.126	0.27
Probable CRF	765	23.2	0.10	0.50	1456	44.2	0.096	0.34
Possible CRF	1105	33.5	0.09	0.46	2436	73.9	*D*: 0.135	(−0.008–0.30)
							D^2: .091	(0.005–0.198)

Notes. $N = 86{,}609$ survivors (100% of cohort); PY = 3,296,595 (100% of cohort). CRF: chronic renal failure; HKD: hypertensive kidney disease. Baseline models adjust for city*sex, attained age and age_at time of bombing (latter two variables continuous), using the estimated, weighted radiation dose to urinary system from the atomic bomb. All models linear regression except where noted. D = ERR/Gy estimate from adjusted linear model; D^2 = ERR/Gy estimate from adjusted model of quadratic dose.

TABLE 4
Aim 2: CRF Mortality Adjusted for Hypertension and Diabetes: Number of Events, Rate and Adjusted Excess Relative Risk Estimate

	Underlying cause of death				All listed causes of death			
	Number	Rate (per 100K PY)	ERR/Gy	*P* value	Number	Rate (per 100K PY)	ERR/Gy	*P* value
Chronic renal failure	140	5.9	0.38	0.33	466	19.6	0.26	0.19
CRF or HKD	195	8.2	0.28	0.28	514	21.7	0.29	0.13
Probable CRF	255	10.8	0.30	0.28	590	24.9	0.24	0.16
Possible CRF	417	17.6	0.08	>0.50	1171	49.4	*D*: 0.27	0.033
							D^2: 0.17	0.031

Notes. $N = 49{,}970$ survivors (57.7% of cohort); PYR = 2,372,139 (71.96% of cohort). CRF: chronic renal failure; HKD: hypertensive kidney disease; CKD: chronic kidney disease. Baseline models adjust for city*sex, hypertension, diabetes, attained age and age_at time of bombing (latter two variables continuous), using the estimated, weighted radiation dose to urinary system from the atomic bomb. All models linear regression except where noted. D = ERR/Gy estimate from adjusted linear model; D^2 = ERR/Gy estimate from adjusted model of quadratic dose.

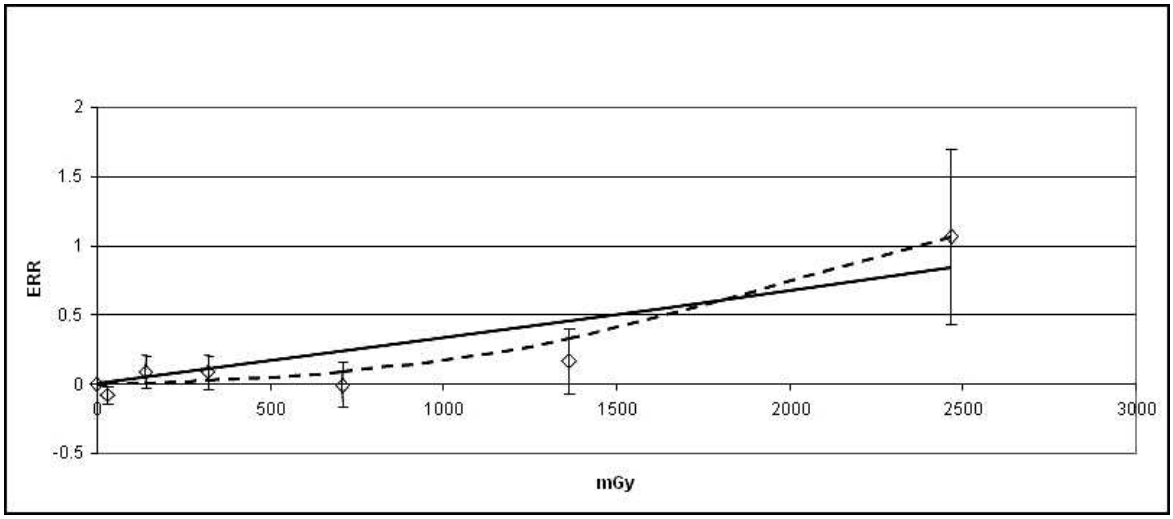

FIG. 2. Excess relative risk of possible chronic renal failure by dose. Black line is the linear model; dashed line is the quadratic model. Models adjusted for city*sex, age_atb, attained age, HTN and diabetes. City*sex is a single combined variable of city and sex with 4 categories (males in Hiroshima is the baseline group). Age_atb = age at time of bombing = age at exposure

quadratic term to the linear model did not improve the statistical fit by the AIC.

The parameter estimates and their 95% confidence intervals for all variables in both the linear and quadratic dose multivariate models of possible CRF as a cause of death are shown in Table 5. As expected, diabetes and hypertension each nearly doubled the risk of possible CRF mortality in both models. Male sex also nearly doubled the risk, though city had little effect. Each decade of aging increased the risk of possible CRF death by 4.25 times. These parameter estimates remained remarkably steady no

TABLE 5
Results Aim 2: Multivariate Model Parameters for Possible CRF All Listed Causes of Death

	Linear		Quadratic	
	RR	95% CI	RR	95% CI
Baseline risk		0.066 per million PY		0.067 per million PY
City*sex[a]				
Hiroshima*female	0.54	0.47–0.62	0.55	0.47–0.63
Nagasaki*male	0.89	0.72–1.08	0.89	0.72–1.09
Nagasaki*female	0.43	0.35–0.52	0.43	0.35–0.52
Age at time of bombing (per decade)	0.73	0.69–0.79	0.74	0.69–0.79
Age (per decade)	4.25	3.98–4.57	4.26	3.98–4.57
Diabetes	1.91	1.65–2.19	1.91	1.65–2.19
Hypertension	1.96	1.74–2.21	1.96	1.74–2.21
Dose (ERR/Gy)	0.27	0.05–0.54	0.17	0.03–0.35

[a] Baseline group for comparison is males in Hiroshima.

matter which definition of kidney failure or disease we modeled (data not shown).

Unfortunately, the subcohort for aim 2 is less male (57.6% compared to 60.4%, $P < 0.001$), contains a higher percentage of Hiroshima survivors (69.5% compared to 64.9%, $P < 0.001$), had lower median age at time of bombing (18.4 compared to 43.9 years, $P < 0.001$), and had a higher median urinary dose (8.74 mGy compared to 6.37 mGy) than those who were not included in the survey (Supplementary Table A, http://dx.doi.org/10.1667/RR2746.1.S1). Thus this subcohort is not representative of the LSS cohort as whole. As the earliest survey occurred in 1965, it is not surprising that those who participated would have been younger than the overall population of the two cities at the time of the bombings. We sought to evaluate the potential for selection bias in our results by comparing our results in just those who were less than 30 years of age at the time of the bombing (Table 6a). In the same multivariate linear model adjusting for city*sex, attained age and age at time of bombing, the ERR/Gy estimate was 0.28 (95% CI: 0.02–0.61) in those younger than 30 in the full LSS and 0.55 (95% CI: 0.15–1.06) in those younger than 30 in the subcohort analyzed for aim 2. Adjusting for hypertension and diabetes slightly increases the ERR/Gy by about 12% to 0.62 (95% CI: 0.20–1.16). Similarly, when using the multivariate quadratic dose model, the ERR/Gy estimate nearly doubles in the aim 2 subsample and increases by about 12% when adjusted for hypertension and diabetes. Similar results are also seen when we do not restrict the analysis by age at exposure (Table 6b).

DISCUSSION

We found evidence that radiation dose is associated with increasing chronic renal disease mortality even though estimated exposure in all individuals was less than 4 Gy and the median dose was 7.81 mGy. The strongest evidence for a radiation effect came from the subsample of the LSS cohort who also answered survey questions. Their ERR/Gy based on the linear model prior to adjusting for known chronic renal disease risk factors equaled 0.237 (95% CI: 0.02, 0.49) compared to 0.135 (95% CI: −0.008, 0.30) in the LSS as a whole. A quadratic dose model fit the data as well, if not minimally better, in both the subsample and the LSS as a whole and gave statistically significant ERR/Gy^2 estimates of 0.15 (95% CI: 0.02, 0.32) and 0.09 (95% CI: 0.005, 0.20), respectively.

TABLE 6
Excess Relative Risk Dose Parameters for Possible CRF: All Listed Causes

	Linear (dose)		Quadratic (dose)^2	
	ERR/Gy	95% CI	ERR/Gy	95% CI
a: Age < 30 at time of bombing				
Full LSS (n = 86, 609) adjusted for city*sex, attained age, age_at time of bombing	**0.28**	**0.02–0.60**	0.14	−0.009–0.341
Aim 2 sample (n = 49,970) adjusted for city*sex, attained age, age at time of bombing	**0.55**	**0.15–1.06**	**0.26**	**0.04–0.59**
Aim 2 sample (n = 49,970) adjusted for hypertension and diabetes as well	**0.62**	**0.20–1.16**	**0.29**	**0.05–0.63**
b: All ages at time of bombing				
Full LSS (n = 86,609) adjusted for city*sex, attained age, age_at time of bombing	0.135	−0.008–0.30	**0.09**	**0.005–0.20**
Aim 2 sample (n = 49,970) adjusted for city*sex, attained age, age_at time of bombing	**0.237**	**0.02–0.49**	**0.15**	**0.02–0.32**
Aim 2 sample (n = 49,970) adjusted for hypertension and diabetes as well	**0.271**	**0.05–0.54**	**0.17**	**0.04–0.35**

Note. Bolded ERR/Gy estimates are significantly different than no radiation effect.

A dose-associated increased risk of kidney failure mortality has not been reported previously in the LSS cohort. However, a significant radiation-associated increase in kidney and ureteral stones was first observed in men but not women with the follow-up of the AHS ending in 1998 (*19*). Frequent stone formation may be a sign of decreased kidney function and may also increase the risk of kidney failure, as shown by Gillen *et al*. (*32*). Yamada *et al*. also noted a significant quadratic dose relationship for hypertension and for myocardial infarction incidence in those less than 40 years of age at the time of the bombing (*19*). In fact, Sasaki *et al*. first reported significant relationships between radiation dose and rise in both systolic and diastolic blood pressure, potentially quadratic in nature, even after accounting for aging and smoking (*20*). There is an interesting similarity between our finding of a quadratic dose relationship between radiation and kidney disease and their findings. Our study results and prior results from the RERF cited above suggest that there truly is a relationship between radiation dose and kidney function and that part of the effect of radiation on cardiovascular health is via kidney function. Although we attempted to validate that by looking at the radiation dose relationship with deaths caused by both cardiovascular and renal failure, there were far too few events to do this ($n = 416$).

We are aware of only a limited number of studies that attempted to evaluate the association between radiation dose and kidney health, and none that analyzed the association between dose and chronic renal failure mortality. A recent review of 14 studies, including all the studies we found independently, evaluating bone marrow transplant (BMT) survivors treated with total-body irradiation and renal failure as measured by serum creatinine, proteinuria, anemia and hypertension found a significant linear relationship between biologically effective radiation doses above 16 Gy and kidney failure (*20*). Unfortunately, it is difficult to compare the BMT population to atomic bomb survivors. First, biologically effective doses are used to measure radiation exposure in cancer patients while weighted doses were used in the atomic bomb survivors. Cancer patients also receive a cumulative dose that is usually at least 10 times greater than those of the atomic bomb survivors, and the dose received is fractionated over multiple treatments. In addition, cancer survivors are often treated with various other therapies toxic to the kidneys, which may confound the association between radiation and renal failure.

Admittedly, the evidence for an association between radiation dose and kidney disease mortality is limited to the least specific definition of possible CRF listed anywhere on the death certificate. This most sensitive category of possible CRF actually includes kidney disease and renal failure of unspecified length (but not acute conditions) as well as a variety of chronic kidney conditions, only one of which is chronic renal failure. However, the ability to detect renal failure, especially chronic renal failure, has changed drastically over the years this cohort has been followed. In fact, a consensus definition of CKD and its diagnosis was not reached until 2002 (*23*). Thus the use of CKD or CRF as a cause of death on the death certificate in our cohort was likely not consistent throughout time and does not correspond with this current consensus definition. Nevertheless, it is unlikely that there is bias associated with exposure level since personal physicians diagnosing this condition, or others filing out the death certificate, were unlikely to have known an individual's dose from the atomic bomb.

The finding that ERR/Gy estimates increased when we adjusted for hypertension and diabetes was somewhat surprising and should be interpreted in light of the large confidence intervals around these estimates. We would have expected that as independent risk factors for kidney disease they would have explained some of the absolute risk in this population. In addition, prior findings from atomic bomb survivors between radiation dose and increased risk of hypertension, hypertensive heart disease mortality, CVD incidence and mortality, and known associations in the general public between blood pressure, kidney failure and heart disease suggest that hypertension is part of the mechanism between radiation and kidney disease mortality. For both reasons, we would have expected that adjusting for hypertension would have decreased the size of association between radiation and kidney disease mortality as it would reflect only that part truly independent of blood pressure.

One limitation of our study that could possibly explain this odd finding is that we relied on self-report. However, when we evaluated the association between hypertension and diabetes on kidney disease mortality, they each increased the risk as expected. Furthermore, when we validated the self-reported conditions against the most recent clinic visits in those who participated in both the clinically followed AHS and the questionnaires, the positive predictive value of self-reported hypertension for truly having diastolic blood pressure and/or systolic blood pressure in the hypertensive range was 82.5% and the negative predictive value was 72%. Data were not available to validate self-reported diabetes. Another limitation of our study is the reliance on death certificate data that may not be accurate, especially for contributing causes of death and diseases that tend to be asymptomatic like kidney disease until their end stages. And as mentioned previously, the definitions and diagnosis of CKD and CRF have changed over time, although they were likely to be similar amongst physicians within each community at a particular time. All of these limitations would have likely affected all survivors the same regardless of dose, which would have led to non-differential bias and decreased our ability to find a significant association when one was truly present rather than increase the risk of finding an association when one was not really present.

In conclusion, our results suggest, but do not prove, that there is a positive association between radiation dose and kidney disease mortality at doses under 3 Gy. The

relationship is likely mediated through blood pressure, but there also appears to be a component independent of blood pressure. While our study cannot address this independent component, it may be related to inflammation, which is one of the mechanisms of atherosclerotic cardiovascular in the general population (*33*) and has been noted to be elevated in a dose-dependent manner among atomic bomb survivors (*34*). As relationships between radiation dose and blood pressure, presence of hypertension, cardiovascular disease mortality and incidence of myocardial infarction in those $<$40 years old at exposure have already been reported, our findings further suggest that part of the risk of cardiovascular disease, particularly myocardial infarction risk, is mediated by renal dysfunction. Given the importance of cardiovascular disease as a cause of mortality in those exposed to whole-body radiation and therapeutic radiation to the chest, our results suggest that future studies should seek to better measure kidney function over time and evaluate its association with the incidence and mortality of cardiovascular events, especially myocardial infarction.

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