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Source: Radiation Research, 179(1) : 46-52

Published By: Radiation Research Society

URL: https://doi.org/10.1667/RR2863.1

RADIATION RESEARCH **179**, 46–52 (2013)
0033-7587/13 $15.00

DOI: 10.1667/RR2863.1

The Association Between Chronic Kidney Disease and Cardiovascular Disease Risk Factors in Atomic Bomb Survivors

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Sera, N., Hida, A., Imaizumi, M., Nakashima, E. and Akahoshi, M. The Association Between Chronic Kidney Disease and Cardiovascular Disease Risk Factors in Atomic Bomb Survivors. *Radiat. Res*. 179, 46–52 (2013).

Atomic bomb (A-bomb) radiation is associated with cardiovascular disease (CVD) and metabolic CVD risk factors. Chronic kidney disease (CKD) is also known to be a risk factor for CVD and little is known whether CKD is associated with A-bomb radiation. To examine whether CKD is associated with CVD risk factors or with A-bomb radiation in A-bomb survivors, we classified renal dysfunction in 1,040 A-bomb survivors who were examined in 2004–2007 as normal [$n = 121$; estimated glomerular filtration rate (eGFR) $\geq$90 ml/min/1.73 m^2]; mild ($n = 686$; eGFR 60–89 ml/min/1.73 m^2); moderate ($n = 217$; eGFR 30–59 ml/min/1.73 m^2); or severe ($n = 16$; eGFR $<$30 ml/min/1.73 m^2). Also, we diagnosed subjects in the moderate and severe renal dysfunction groups as having CKD ($n = 233$; eGFR $<$59 ml/min/1.73 m^2). After adjusting for age, gender, and smoking and drinking habits, we looked for an association between renal dysfunction and hypertension, diabetes mellitus (DM), hyperlipidemia, and metabolic syndrome (MetS), and between renal dysfunction and A-bomb radiation. Hypertension [odds ratio (OR), 1.57; 95% confidence interval (CI), 1.12–2.20, $P = 0.009$]; DM (OR, 1.79; 95% CI, 1.23–2.61, $P = 0.002$); hyperlipidemia (OR, 1.55; 95% CI, 1.12–2.14, $P = 0.008$); and MetS (OR, 1.86; 95% CI, 1.32–2.63, $P < 0.001$) were associated with CKD (moderate/severe renal dysfunction), and hyperlipidemia and MetS were also associated with mild renal dysfunction. CKD (OR/Gy, 1.29; 95% CI, 1.01–1.63, $P = 0.038$) and severe renal dysfunction (OR/Gy, 3.19; 95% CI, 1.63–6.25, $P < 0.001$) were significantly associated with radiation dose. CKD associated with radiation may have played a role in the development of CVD among A-bomb survivors.

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INTRODUCTION

High-dose radiation therapy to the chest or neck has been shown to induce ischemic heart disease (IHD) (*1, 2*) and stroke (*3, 4*), but the effect of low-dose radiation on heart disease is controversial (*5, 6*). Atomic bomb (A-bomb) radiation increases both cardiovascular disease (CVD) mortality (*7*) and the incidence of myocardial infarction (*8*). It is also associated with aortic calcification (*9*) and retinal arteriosclerosis (*10*), suggesting that general atherosclerosis is involved in the connection between A-bomb radiation and CVD.

Atomic bomb radiation is associated with systolic and diastolic blood pressure trends of the younger exposed subjects (*7*) and cholesterol trends of all exposed subjects shifted upward in the growth-curve analysis (*11*). Also, it has been reported that A-bomb radiation was associated with increased risk of hypertension in a longitudinal follow-up study from 1958–1998 (*12*) and prevalence of dyslipidemia in a cross-sectional study (*13*). In addition, it is associated with an increase in many inflammatory markers, including C-reactive protein (CRP), interleukin-6, and interferon-γ, as well as the erythrocyte sedimentation rate (*14, 15*) and may be associated with diabetes mellitus (DM) (*11*). Thus, A-bomb survivors show an increase in metabolic CVD risk factors and inflammatory markers in much the same way as people with metabolic syndrome (MetS), suggesting the possibility that MetS plays a role in the development of CVD in A-bomb survivors. Indeed, fatty liver, a surrogate marker for MetS, is associated with A-bomb radiation dose (*13*) and CVD risk factors (*16*), and it predicts IHD (*17*).

Chronic kidney disease (CKD) as a clinical entity has started to draw attention only recently, with its categorization advocated by the U.S. National Kidney Foundation in 2002 (*18*): it is a risk factor for CVD (*19, 20*). The MetS and the increase of MetS components (obesity, high blood pressure, dyslipidemia and impaired glucose tolerance) predicted the development of CKD in a longitudinal follow-up study (*21*), and the cumulative incidence of CKD was significantly higher in subjects with MetS (*22*). The aforementioned findings in A-bomb survivors suggest that CKD may also have a role in the development of CVD.

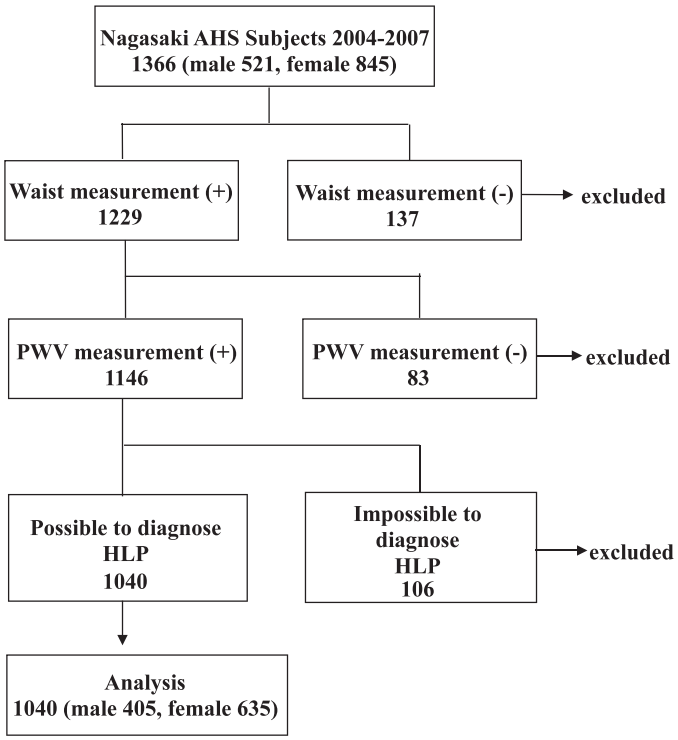

FIG. 1. Flow of Adult Health Study (AHS) subjects into analysis. Subjects who did not have their waist circumference or pulse wave velocity (PWV) measured were excluded. Subjects who were not taking medication for hyperlipidemia, but were post prandially hypertriglyceridemic, were excluded because it was impossible to determine whether they had hyperlipidemia (HLP).

Therefore, we examined here whether CKD is associated with MetS with its individual components, and with radiation dose in A-bomb survivors.

METHODS

Participants

The Adult Health Study (AHS) was established in 1958 by the Atomic Bomb Casualty Commission, now the Radiation Effect Research Foundation (RERF), to study the late effects of radiation in Hiroshima and Nagasaki A-bomb survivors. The AHS conducts biennial health examinations whose clinical information complements death and tumor registry data. A detailed description of the program has been published elsewhere (*23*).

From 2004 through 2007, 1,366 people (521 men and 845 women) in the Nagasaki AHS cohort underwent clinical examinations, and hematological, biochemical, electrocardiogram and pulse wave velocity (PWV) measurements. They were excluded from the study if they had not undergone waist circumferences or PWV measurements or if they were not taking medication for hyperlipidemia but had postprandial hypertriglyceridemia (because we could not determine whether they had hyperlipidemia), leaving 1,040 participants (Fig. 1), all providing written informed consent. There were two subjects with severe renal dysfunction without undergoing extracorporeal dialysis among 83 AHS subjects who did not undertake PWV measurement. Fasting blood (more than 10 h after last meal) was drawn in 585 participants among 1,040 study participants.

Out of the 1,040 potential participants, we analyzed the relationship between CKD and radiation dose for 746 participants whose A-bomb radiation dose was estimated.

Clinical Examination and Laboratory Methods

Participants visited RERF's Nagasaki Laboratory for a clinical examination every 2 years. A trained nurse recorded information on current and past disease and medications. We used both current smoking/alcohol information on the health examination and questionnaires from mail surveys taken before each visit and divided participants into three categories: never, past and current smokers/drinkers. Three category variables were used to complete the analysis.

Standing height (m) and body weight (kg) were measured without socks and outer clothing. Body mass index (BMI) was calculated as body weight divided by the square of the standing height (kg/m^2). Sitting blood pressure (mmHg) was measured on the left arm after an adequate sedentary period using the first Korotkoff phase for systolic blood pressure and the fourth or fifth for diastolic blood pressure. Waist circumference was measured at navel level with the participant standing.

Blood samples were drawn for biochemical measurements, and serum blood urea nitrogen (mg/dl), creatinine (mg/dl), uric acid (mg/dl), total cholesterol (mg/dl), high-density lipoprotein cholesterol (HDL-cholesterol, mg/dl), low-density lipoprotein cholesterol (LDL-cholesterol, mg/dl), triglycerides (mg/dl), and blood glucose (mg/dl) were measured by an automated procedure (Hitachi 7170S, Hitachi Ltd, Tokyo) with quality control monitored in accordance with the College of American Pathologists (Northfield, IL). We measured adiponectin by ELISA (Otsuka, Osaka, Japan), hemoglobin A1c (HbA1c value, Japan Diabetes Society) by HPLC (HA-8150, Arcray, Tokyo), insulin by a chemiluminescent ELISA (Lumipulse f, Fujirebio Diagnostics, Tokyo), high sensitivity C-reactive protein (hs-CRP) by a chemiluminescent ELISA (Nissui, Tokyo), and hemoglobin (Hb) by an automated procedure (Sysmex XE-2100, Sysmex, Kobe, Japan). We expressed HbA1c as the U.S. National Glycohemoglobin Standarization Program HbA1c value by adding 0.4% to the measured Japan Diabetes Society value (*24*).

Insulin resistance was evaluated on the basis of a homeostasis model assessment of insulin resistance (HOMA-IR), which is used widely in epidemiological research, with the following formula: HOMA-IR = fasting insulin (μU/ml) × fasting blood glucose (mg/dl)/405. Analyses for blood glucose, triglyceride, insulin and HOMA-IR were conducted in 585 participants, whose fasting blood (more than 10 h after last meal) were drawn, because the effect that blood glucose, triglyceride and insulin have are strongly affected by eating, and obviously increase in individuals after a meal, in comparison with the time when they are in a fasting state. Brachial-ankle pulse wave velocity (ba-PWV) was measured to assess arterial stiffness using BP-203RPEII (Omron, Kyoto, Japan).

Radiation Dose

As the renal dose for individual subjects is not available, for our statistical analysis we used a shielded total kerma dose based on Dosimetry System 2002 (DS02) (*25*) with adjustment of the γ and neutron doses for 35% dose error, truncating them at 4 Gy, to reduce radiation effect estimation bias (*26*). We thought shielded total kerma dose would be appropriate for analysis of CKD, which seems to be more of a secondary condition caused by the systemic vascular pathology that is attributable to DM and hypertension, as evidenced by the breakdown of patients who started undergoing dialysis for end-stage renal disease in Japan. As this tendency is seemingly more pronounced in CKD, we think radiation effects on the overall vascular system play a more important role in CKD, and thus used a shielded total kerma dose.

TABLE 1
Clinical and Biochemical Profile of the Study Subjects by Renal Dysfunction

Factor	Renal dysfunction level (eGFR)					
	Normal (≥90) $n = 121$	Mild (60–89) $n = 686$	Moderate (30–59) $n = 217$	Severe (<29) $n = 16$	P for trend	P^a for trend
eGFR (ml/min/1.73 m^2)	99.4 ± 9.4	73.6 ± 8.8	49.7 ± 7.1	23.8 ± 4.7	0.010	-
Age (year)	67.5 ± 6.0	72.5 ± 6.7	76.1 ± 6.6	77.1 ± 6.2	<0.001	-
Male *n* (%)	35 (28.9)	263 (38.3)	102 (47.0)	5 (31.3)	0.002	-
Past smokers (%)	25 (20.7)	179 (26.1)	79 (36.4)	4 (25.0)	0.6073	-
Current smokers (%)	23 (19.0)	72 (10.5)	23 (10.0)	2 (12.5)		
Past drinkers (%)	35 (28.9)	226 (32.9)	92 (42.4)	3 (18.8)	0.4648	-
Current drinkers (%)	46 (38.0)	237 (34.5)	65 (30.0)	3 (18.8)		
Weight (kg)	52.0 ± 8.8	54.8 ± 10.5*	56.0 ± 10.2*	55.6 ± 9.9*	0.002	<0.001
Waist (cm)	81.7 ± 8.7	84.8 ± 9.8*	85.5 ± 9.5*	89.3 ± 10.0*	<0.001	<0.001
BMI (kg/m^2)	22.0 ± 3.2	23.0 ± 3.3*	23.0 ± 3.3*	24.7 ± 3.3*	0.004	<0.001
SBP (mm Hg)	132.9 ± 20.0	130.6 ± 17.1	129.2 ± 18.7*	137.3 ± 16.8*	0.159	0.088
BUN (mg/dL)	13.0 ± 2.9	14.9 ± 3.4*	19.1 ± 5.1*	32.9 ± 9.2*	<0.001	<0.001
Cre (mg/dL)	0.51 ± 0.07	0.68 ± 0.11*	0.99 ± 0.19*	1.92 ± 0.66*	<0.001	<0.001
Uric acid (mg/dL)	4.43 ± 1.02	5.02 ± 1.21*	5.91 ± 1.31*	6.65 ± 3.29*	<0.001	<0.001
T-cho (mg/dL)	205.3 ± 34.0	204.6 ± 31.7	202.3 ± 32.2	224.4 ± 57.9*	0.765	0.071
HDL-cho (mg/dL)	59.4 ± 15.2	57.1 ± 14.4	52.8 ± 12.5*	56.6 ± 19.0	<0.001	0.002
LDL-cho (mg/dL)	113.5 ± 29.6	115.4 ± 27.5	116.8 ± 26.5*	113.6 ± 43.3	0.351	0.048
TG (mg/dL)	122.3 ± 100.9	111.9 ± 58.9	116.9 ± 53.0	162.3 ± 159.0	0.247	0.205
HbA1c (%)	6.08 ± 1.11	5.89 ± 0.73*	6.01± 0.80	6.57 ± 1.17*	0.134	0.124
Insulin (μU/mL)	6.98 ± 4.03	7.40 ± 4.65	7.91 ±4.893*	18.33 ± 28.13*	0.006	<0.001
Glucose (mg/dL)	101.5 ± 17.6	100.2 ± 14.1	98.1 ± 12.5	116.7 ± 44.0*	0.301	0.147
HOMA-IR	1.83 ± 1.39	1.86 ± 1.34	1.96 ± 1.29	7.78 ± 14.9*	0.003	<0.001
Hemoglobin (g/dL)	13.5 ± 1.2	13.4 ± 1.4	13.1 ± 1.6	11.4 ± 1.5*	<0.001	<0.001
Adiponectin (μg/mL)	9.51 ± 5.03	10.52 ± 5.64	10.31 ± 5.37	13.77 ± 5.56*	0.157	0.797
HS-CRP (mg/dL)	0.24 ± 0.74	0.16 ± 0.612	0.19 ± 0.43	0.16 ± 0.17	0.029	0.331
ba-PWV (cm/sec)	1781.3 ± 419.0	1831.6 ± 404.9*	1919.3 ± 434.5*	2017.0 ± 45.8*	0.006	<0.001

Notes. Values are mean ± SD unless otherwise indicated. P for trend test was performed without adjustment. P^a for trend test adjusted for age, gender, and smoking and drinking habits. TG, Insulin, Glucose and HOMA-IR are values of 585 subjects whose fasting blood are collected. eGFR, estimated glomerular filtration rate; BMI, body mass index; SBP, systolic blood pressure; BUN, blood urea nitrogen; Cre, creatinine; T-cho, total cholesterol; HDL-cho, high-density lipoprotein cholesterol; LDL-cho, low-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; HS-CRP, highly sensitive C-reactive protein; ba-PWV, brachial-ankle pulse wave velocity.

*$P < 0.05$ vs. normal group adjusted for age, gender, and smoking and drinking habits.

Diagnostic Criteria

1. CKD and renal dysfunction level. We calculated estimated glomerular filtration rate (eGFR) using an equation adjusted for the Japanese: eGFR (ml/min/1.73 m^2) = 194 × age$^{-0.287}$ × creatinine$^{-1.094}$ (for women, the eGFR was multiplied by 0.739) (*27*). Subjects were grouped by renal function according to their eGFR as follows: ≥90 ml/min/1.73 m^2 as normal, 60–89 ml/min/1.73 m^2 as mildly dysfunctional, 30–59 ml/min/1.73 m^2 as moderately dysfunctional, and <30 ml/min/1.73 m^2 as severely dysfunctional.

Also, we diagnosed subjects in the moderate and severe renal dysfunction groups as having CKD according to the CKD guideline of the U.S. National Kidney Foundation (*18*). The group with severe renal dysfunction had a more serious form of CKD.

2. Hypertension. Subjects were diagnosed as hypertensive if they had a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or were taking anti-hypertensive medication.

3. Diabetes mellitus. Subjects were diagnosed as having DM if they had a fasting blood glucose ≥126 mg/dl, a postprandial glucose ≥200 mg/dl, HbA1c ≥6.5%, a blood glucose ≥200 mg/dl at 2 h in a 75-g oral glucose tolerance test, if they were under treatment for DM, or had a history of DM.

4. Hyperlipidemia. We diagnosed subjects as having hyperlipidemia if they had a total cholesterol level ≥220 mg/dl, an LDL cholesterol level ≥140 mg/dl, a fasting triglyceride level ≥150 mg/dl, or if they were taking a lipid-lowering medication. A total of 106 subjects were not taking medication for hyperlipidemia, but had postprandial hypertriglyceridemia. These subjects were excluded in this study because we could not determine whether or not they had hyperlipidemia (Fig. 1).

5. MetS. We used the modified criteria on the MetS guidelines in Japan (*28*) and diagnosed MetS when waist circumference was ≥85 cm in men or ≥90 cm in women and subjects showed 2 of the following 3 features: (1) serum triglyceride ≥150 mg/dl; HDL cholesterol ≥140 mg/dl, or the subject was being treated for hyperlipidemia; (2) systolic blood pressure ≥130 mmHg,d iastolic blood pressure ≥85 mmHg, or subject was being treated for hypertension; (3) fasting blood glucose ≥100 mg/dl or subject was being treated for DM.

The definition of hypertension, DM and hyperlipidemia were restricted to current medication use but not to past medication use.

Statistical Analysis

All statistical analyses were performed with the Statistical Analysis System package for personal computers (SAS, Cary, NC). Baseline covariate values were compared between the normal subjects and the subjects with renal dysfunction using general linear model (GLM) analysis adjusted for age, gender, and smoking and drinking habits. Several factors (SBP, HDL cholesterol, triglyceride, HbA1c, HS-CRP), which tend to be right-skewed, log transformation for statistical testing was used (Table 1). Ordinal logistic regression analysis was

TABLE 2
Prevalence and Odds Ratio (95% Confidence Interval) of Cardiovascular Disease (CVD) Risk Factors by Renal Dysfunction

	Renal dysfunction				
	Number (%)				
	Odds ratio (95% confidence interval)				
CVD risk factor	Normal ($n = 121$)	Mild ($n = 686$)	Moderate ($n = 217$)	Severe ($n = 16$)	P for trend
Hypertension	73 (60.3)	419 (61.1)	153 (70.5)	15 (93.8)	
	1	0.96 (0.63–1.46)	1.39 (0.83–2.32)	8.20 (1.03–66.67)*	0.041
Diabetes mellitus	26 (21.5)	101 (14.7)	48 (22.1)	7 (43.8)	
	1	0.64 (0.39–1.06)	1.08 (0.60–1.94)	3.10 (1.02–9.43)*	0.100
Hyperlipidemia	57 (47.1)	379 (55.2)	128 (59.0)	13 (81.2)	
	1	1.75 (1.16–2.66)*	2.34 (1.42–3.88)*	6.37 (1.65–24.39)*	<0.001
Metabolic syndrome	16 (13.2)	140 (20.4)	60 (27.6)	11 (68.8)	
	1	1.85 (1.04–3.29)*	2.76 (1.44–5.26)*	17.24 (5.13–58.82)*	<0.001

Note. P for trend was analyzed with ordinal logistic regression model adjusted for age, gender, and smoking and drinking habits.
*$P < 0.05$ vs. normal group ($n = 121$) adjusted for age, gender, and smoking and drinking habits.

used with adjustment for age, gender, and smoking and drinking habits to evaluate the association between renal dysfunction and CVD risk factors (Table 2) We used logistic regression analysis was used with adjustment for age, gender, and smoking and drinking habits to evaluate the association between CKD and CVD risk factors (Table 3). We used GLM analysis with adjustment to evaluate the association between renal dysfunction and radiation dose (Table 4) and used logistic or ordinal logistic regression analysis to evaluate the association between renal dysfunction/CKD and radiation dose (Table 5). We considered $P < 0.05$ as significant.

RESULTS

Table 1 shows the distribution of risk factors in the 4 renal dysfunction groups and in the anthropometric indexes and variables relating to renal dysfunction. Almost all the CVD risk factors relating to blood pressure, lipid metabolism, and glucose metabolism deteriorated with renal dysfunction but medication history was not taken into account, which could have led to some measurement error. The Hb level was low in the severe renal dysfunction group, while the adiponectin level was high. HOMA-IR was significantly high in the severe renal dysfunction group. Additionally, ba-PWV increased with renal dysfunction, while ba-PWV significantly decreased with renal dysfunction when age, gender, and smoking and drinking habits were incorporated into the analysis (data not shown).

Serum adiponectin levels were low in subjects with DM (8.94 ± 4.81 μg/mL) vs. those without DM (10.72 ± 5.63 μg/mL) ($P < 0.001$), in subjects with hyperlipidemia (9.95 ± 5.41 μg/mL) vs. subjects without hyperlipidemia (10.97 ± 5.63 μg/mL) ($P < 0.001$), and in subjects with MetS (8.37 ± 5.05 μg/mL) vs. those without MetS (10.98 ± 5.53 μg/mL) ($P < 0.001$), while they tended to increase with renal dysfunction and were significantly elevated in subjects with severe renal dysfunction.

Table 2 shows the prevalence and odds ratio of hypertension, DM, hyperlipidemia, and MetS by renal dysfunction. Prevalence of hypertension, hyperlipidemia, and MetS increased with renal dysfunction. Odds ratios of hypertension, DM, hyperlipidemia, and MetS are shown for the mild, moderate, and severe renal dysfunction groups using the normal group as a reference. Hypertension and DM were associated with only severe renal dysfunction, while hyperlipidemia and MetS were associated with mild-to-severe renal dysfunction.

The odds ratios of hypertension, DM, hyperlipidemia and MetS, with the combined normal and mild renal dysfunction

TABLE 3
Odds Ratio (95% Confidence Interval) of Cardiovascular Disease (CVD) Risk Factors for Chronic Kidney Disease

CVD risk factor	Odds ratio (95% CI)	P
Hypertension	1.57 (1.12–2.20)	0.009
Diabetes mellitus	1.79 (1.23–2.61)	0.002
Hyperlipidemia	1.55 (1.12–-2.14)	0.008
Metabolic syndrome	1.86 (1.32–2.63)	<0.001

Note. P, compared with combined normal and mild renal dysfunction groups ($n = 807$) adjusted for age, gender, and smoking and drinking habits.

TABLE 4
Mean Radiation Doses for Three Levels of Renal Dysfunction

Renal dysfunction	n	mGy (mean ± SD)	P	P^a
Normal–mild	584	503.2 ± 720.7		
Moderate	149	572.8 ± 769.6	0.279	0.278
Severe	13	1199.3 ± 1034.4	<0.001	<0.001

P; v.s. combined normal and mild renal dysfunction groups ($n = 584$) adjusted for age, gender, and smoking and drinking habits.
P^a; v.s. combined normal and mild renal dysfunction groups adjusted for age, gender, and smoking and drinking habits, hypertension, diabetes mellitus, hyperlipidemia and metabolic syndrome.

TABLE 5
Odds Ratio (95% Confidence Interval) of Radiation Dose for Chronic Kidney Disease (CKD)

Renal dysfunction	*n*	Not adjusted OR/Gy (95%CI)	*P*	Adjusted[a] OR/Gy (95%CI)	*P*[a]
Normal–mild	584	1		1	
Moderate	149	1.13 (0.90–1.44)	0.295	1.15 (0.89–1.48)	0.293
Severe	13	2.25 (1.36–3.78)	0.002	3.19 (1.63–6.25)	<0.001
CKD (moderate + severe)	162	1.26 (1.01–1.57)	0.040*	1.29 (1.01–1.63)	0.038*

Notes. Reference was the combined normal and mild renal dysfunction group. CKD; chronic kidney disease.
[a]Adjusted for age, gender, and smoking and drinking habits, hypertension, diabetes mellitus, hyperlipidemia and metabolic syndrome.
*Analyzed with ordinal logistic regression model.

groups used as the reference, show that all 4 conditions were significantly associated with CKD (Table 3).

Compared with combined normal and mild renal dysfunction groups, the severe renal dysfunction group had received a significantly higher dose of A-bomb radiation (Table 4), and radiation dose was significantly associated with both CKD and severe renal dysfunction with or without adjustment for age, gender, and smoking and drinking habits, hypertension, DM, hyperlipidemia and MetS (Table 5).

DISCUSSION

In this study, we found radiation dose to be significantly associated with CKD (moderate/severe renal dysfunction) and with severe renal dysfunction in A-bomb survivors, with or without adjustment for age, gender, and smoking and drinking habits, hypertension, DM, hyperlipidemia and MetS. Our findings suggest that CKD is involved in the mechanism(s) linking radiation exposure with CVD risk factors.

When we assessed the association of hypertension, DM, hyperlipidemia and MetS with renal dysfunction, odds ratios representing these associations increased along with the deterioration of renal functions from mild to severe dysfunctions, although significance was not observed for DM. However, when we compared the clinical setting of CKD, including moderate and severe, to the reference group including normal and mild, hypertension, DM, hyperlipidemia and MetS were significantly associated with CKD, which was the same as that reported for non A-bomb survivors (*21,*).

PWV, a marker of aortic wall stiffness, predicts cardiovascular events (*29*), and vascular function and arterial compliance are impaired in patients with CKD (*30*). Thus, PWV is associated inversely with GFR in patients with non-dialysis-dependent renal insufficiency (*31, 32*). Also, in hypertensive patients, GFR >60 ml/min/1.73 m^2 correlates inversely with aortic PWV (*33*). In the present study, ba-PWV was inversely associated with eGFR and it increased with renal dysfunction when no adjustment was made. Our finding that both PWV and eGFR were closely related to age, and that the association between ba-PWV and renal dysfunction disappeared when age was incorporated into the analysis (data not shown) was in agreement with a previous study (*34*).

Serum adiponectin levels reportedly decrease in patients with hypertension (*35*), DM (*36*), dyslipidemia (*37, 38*), or MetS (*39*), which is in agreement with the results of the present study. On the other hand, we also found that elevated serum adiponectin levels are seen in patients with moderate renal dysfunction (*17, 40*). Further studies are necessary to explain the association we found between elevated serum adiponectin level and severe renal dysfunction.

The prevalence of systemic CVD risk factors such as hypertension, DM and hyperlipidemia, as well as the level of inflammatory markers, increases with radiation dose in A-bomb survivors (*7, 11, 14, 15*). The clustering of systemic CVD risk factors suggests the possibility that MetS plays a role. In line with this, we previously reported that fatty liver, a surrogate marker of MetS, clusters with CVD risk factors (*16*), predicts IHD (*17*), and is associated with A-bomb radiation dose (*13*). Since aortic calcification and retinal arteriosclerosis also increase with radiation dose (*9*), it is reasonable to think that a general rather than a regional atherosclerotic process is involved in the development of CVD in A-bomb survivors. Thus, we think that the mechanism(s) that induces MetS is stimulated, leading to the clustered systemic CVD risk factors, general atherosclerosis, and CVD, although that mechanism(s) has yet to be clarified.

High-dose radiation therapy induces renal injury, leading to renovascular hypertension (*41*), and high levels of A-bomb radiation induce ureter and renal calculi in men (*12*), but the effect of low-to-moderate dose radiation on the kidney has not been elucidated. In the present study, low-dose radiation was significantly associated with CKD and severe renal dysfunction independently of hypertension, DM, hyperlipidemia and MetS, suggesting that A-bomb radiation affects the kidney directly. Prospective studies are needed to clarify how the association between low-dose radiation and CVD may be mediated by CKD.

ACKNOWLEDGMENTS

The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan, is a private, nonprofit foundation funded by the Japanese Ministry of Health, Labour and Welfare (MHLW), and the U.S. Department of Energy (DOE), the latter in part through DOE Award DE-HS0000031 to the National Academy of Sciences. The present study was supported by grant number 15590570 from the Japanese Ministry of Education, Culture, Sports, Science and Technology. This publication was

based on RERF Research Protocol RP 2–75. The views of the authors do not necessarily reflect those of the two governments.

Received: November 11, 2011; accepted: July 29, 2012; published online: November 13, 2012

REFERENCES

1. Boivin JF, Hutchison GB, Lubin JH, Mauch P. Coronary artery disease mortality in patients treated for Hodgkin's disease. Cancer 1992; 69:1241–7.
2. Paszat LF, Mackillop WJ, Groome PA, Schulze K, Holowaty E. Mortality from myocardial infarction following postlumpectomy radiotherapy for breast cancer: a population-based study in Ontario, Canada. Int J Radiat Oncol Biol Phys 1999; 43:755–62.
3. Cheng SW, Ting AC, Lam LK, Wei WI. Carotid stenosis after radiotherapy for nasopharyngeal carcinoma. Arch Otolaryngol Head Neck Surg 2000; 126:517–21.
4. 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.
5. Darby SC, Doll R, Gill SK, Smith PG. Long term mortality after a single treatment course with X-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987; 55:179–90.
6. Carr ZA, Land CE, Kleinerman RA, Weinstock RW, Stovall M, Griem ML, et al. Coronary heart disease after radiotherapy for peptic ulcer disease. Int J Radiat Oncol Biol Phys 2005; 61:842–50.
7. Sasaki H, Wong FL, Yamada M, Kodama K. The effects of aging and radiation exposure on blood pressure levels of atomic bomb survivors. J Clin Epidemiol 2002; 55:974–81.
8. Katsuda S, Hasegawa M, Kusanagi M, Shimizu T. Comparison of pulse-wave velocity in different aortic regions in relation to the extent and severity of atherosclerosis between young and older Kurosawa and Kusanagi-hypercholesterolemic (KHC) rabbits. Clin Sci 2000; 99:393–404.
9. Yamada M, Naito K, Kasagi F, Masunari N, Suzuki G. Prevalence of atherosclerosis in relation to atomic bomb radiation exposure: an RERF Adult Health Study. Int J Radiat Biol 2005; 81:821–6.
10. Minamoto A, Taniguchi H, Yoshitani N, Mukai S, Yokoyama T, Kumagami T, et al. Cataract in atomic bomb survivors. Int J Radiat Biol 2004; 80:339–45.
11. Wong FL, Yamada M, Sasaki H, Kodama K, Hosoda Y. Effects of radiation on the longitudinal trends of total serum cholesterol levels in the atomic bomb survivors. Radiat Res 1999;151:736–46.
12. 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.
13. Akahoshi M, Amasaki Y, Soda M, Hida A, Imaizumi M, Nakashima E, et al. Effects of radiation on fatty liver and metabolic coronary risk factors among atomic bomb survivors in Nagasaki. Hypertens Res 2003; 26:965–70.
14. Hayashi T, Kusunoki Y, Hakoda M, Morishita Y, Kubo Y, Maki M, et al. Radiation dose-dependent increases in inflammatory response markers in A-bomb survivors. Int J Radiat Biol 2003; 79:129–36.
15. Hayashi T, Morishita Y, Kubo Y, Kusunoki Y, Hayashi I, Kasagi F, et al. Long-term effects of radiation dose on inflammatory markers in atomic bomb survivors. Am J Med 2005; 118:83–6.
16. Akahoshi M, Amasaki Y, Soda M, Tominaga T, Ichimaru S, Nakashima E, et al. Correlation between fatty liver and coronary risk factors: a population study of elderly men and women in Nagasaki, Japan. Hypertens Res 2001; 24:337–43.
17. Baba T, Amasaki Y, Soda M, Hida A, Imaizumi M, Ichimaru S, et al. Fatty liver and uric acid levels predict incident coronary heart disease but not stroke among atomic bomb survivors in Nagasaki. Hypertens Res 2007; 30:823–9.
18. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39:S1–266.
19. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004; 351:1296–305.
20. Muntner P, He J, Hamm L, Loria C, Whelton PK. Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. J Am Soc Nephrol 2002; 13:745–53.
21. Tozawa M, Iseki C, Tokashiki K, Chinen S, Kohagura K, Kinjo K, et al. Metabolic syndrome and risk of developing chronic kidney disease in Japanese adults. Hypertens Res 2007; 30:937–43.
22. Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, et al. Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. Am J Kidney Dis 2006; 48:383–91.
23. *23*. Commission ABC. Research plan for joint ABCC-NIH Adult Health Study in Hiroshoima and Nagasaki in ABCC. Technical Reports; 1962. P. 11–62.
24. Seino YN, Tajima N, Kadowaki N, Kashiwagi A, Araki E, Ito C, et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetol Int; 2010.
25. Young RK, G. . Reassessment of the Atomic Bomb Radiation Dosimetry for Hiroshima and Nagasaki-Dosimetry System 2002. Hiroshima: Radiation Effects Research Foundation. 2005.
26. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. Radiat Res 1990; 123:275–84.
27. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009; 53:982–92.
28. *28*. Examination committee of criteria for diagnosis of metabolic syndrome in Japan. Definition and criteria for the diagnosis of metabolic syndrome. J Jpn Soc Int Med 2005; 94:794–809.
29. Espinola-Klein C, Rupprecht HJ, Bickel C, Lackner K, Savvidis S, Messow CM, et al. Different calculations of ankle-brachial index and their impact on cardiovascular risk prediction. Circulation 2008; 118:961–7.
30. Dogra G, Irish A, Chan D, Watts G. Insulin resistance, inflammation, and blood pressure determine vascular dysfunction in CKD. Am J Kidney Dis 2006; 48:926–34.
31. Wang MC, Tsai WC, Chen JY, Huang JJ. Stepwise increase in arterial stiffness corresponding with the stages of chronic kidney disease. Am J Kidney Dis 2005; 45:494–501.
32. Briet M, Bozec E, Laurent S, Fassot C, London GM, Jacquot C, et al. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. Kidney Int 2006; 69:350–7.
33. Schillaci G, Pirro M, Mannarino MR, Pucci G, Savarese G, Franklin SS, et al. Relation between renal function within the normal range and central and peripheral arterial stiffness in hypertension. Hypertension 2006; 48:616–21.
34. Peralta CA, Katz R, Madero M, Sarnak M, Kramer H, Criqui MH, et al. The differential association of kidney dysfunction with small and large arterial elasticity: the multiethnic study of atherosclerosis. Am J Epidemiol 2009; 169:740–8.
35. Iwashima Y, Katsuya T, Ishikawa K, Ouchi N, Ohishi M, Sugimoto K, et al. Hypoadiponectinemia is an independent risk factor for hypertension. Hypertension 2004; 43:1318–23.
36. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001; 86:1930–5.
37. Matsubara M, Maruoka S, Katayose S. Decreased plasma adiponectin concentrations in women with dyslipidemia. J Clin Endocrinol Metab 2002; 87:2764–9.
38. Kazumi T, Kawaguchi A, Hirano T, Yoshino G. Serum

adiponectin is associated with high-density lipoprotein cholesterol, triglycerides, and low-density lipoprotein particle size in young healthy men. Metabolism 2004; 53:589–93.

39. Mohan V, Deepa R, Pradeepa R, Vimaleswaran KS, Mohan A, Velmurugan K, et al. Association of low adiponectin levels with the metabolic syndrome–the Chennai Urban Rural Epidemiology Study (CURES-4). Metabolism 2005; 54:476–81.

40. Tentolouris N, Doulgerakis D, Moyssakis I, Kyriaki D, Makrilakis K, Kosmadakis G, et al. Plasma adiponectin concentrations in patients with chronic renal failure: relationship with metabolic risk factors and ischemic heart disease. Horm Metab Res 2004; 36:721–7.

41. Fakhouri F, La Batide Alanore A, Rerolle JP, Guery B, Raynaud A, Plouin PF. Presentation and revascularization outcomes in patients with radiation-induced renal artery stenosis. Am J Kidney Dis 2001; 38:302–9.