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Skin Cancer Incidence among Atomic Bomb Survivors from 1958 to 1996

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The radiation risk of skin cancer by histological types has been evaluated in the atomic bomb survivors. We examined 80,158 of the 120,321 cohort members who had their radiation dose estimated by the latest dosimetry system (DS02). Potential skin tumors diagnosed from 1958 to 1996 were reviewed by a panel of pathologists, and radiation risk of the first primary skin cancer was analyzed by histological types using a Poisson regression model. A significant excess relative risk (ERR) of basal cell carcinoma (BCC) (n = 123) was estimated at 1 Gy (0.74, 95% confidence interval (CI): 0.26, 1.6) for those age 30 at exposure and age 70 at observation based on a linear-threshold model with a threshold dose of 0.63 Gy (95% CI: 0.32, 0.89) and a slope of 2.0 (95% CI: 0.69, 4.3). The estimated risks were 15, 5.7, 1.3 and 0.9 for age at exposure of 0–9, 10–19, 20–39, over 40 years, respectively, and the risk increased 11% with each one-year decrease in age at exposure. The ERR for squamous cell carcinoma (SCC) *in situ* (n = 64) using a linear model was estimated as 0.71 (95% CI: 0.063, 1.9). However, there were no significant dose responses for malignant melanoma (n = 10), SCC (n = 114), Paget disease (n = 10) or other skin cancers (n = 15). The significant linear radiation risk for BCC with a threshold at 0.63 Gy suggested that the basal cells of the epidermis had a threshold sensitivity to ionizing radiation, especially for young persons at the time of exposure.

INTRODUCTION

An increased risk of skin cancer associated with exposure to ionizing radiation has been reported in various exposed populations, including the atomic bomb (A-bomb) survivors (*1–3*), uranium miners (*4*), radiologists and individuals treated with radiation in childhood for tinea capitis (*5, 6*) and malignant tumors (*7, 8*). The first report among the A-bomb survivors in Hiroshima and Nagasaki by the Atomic Bomb Casualty Committee (ABCC) was 26 years after the A-bombs were dropped. Johnson *et al*. (*9*) reported that malignancy of the skin was observed in only one of the 10,650 subjects of the Adult Health Study (AHS), a subcohort of the Life Span Study (LSS) that were clinically followed since 1958. An increased risk of skin cancer associated with A-bomb radiation exposure was first reported by Sadamori *et al*. who found a significant linear dose-response relationship among the LSS cohort members who resided in Nagasaki using the Nagasaki Tumor Registry for the period 1958–1985 (*10*). Subsequently, Ron *et al*. reported a significant radiation-related excess risk of incident basal cell carcinoma (BCC), but not squamous cell carcinoma (SCC), in both Hiroshima and Nagasaki subjects of the LSS cohort for the period 1958–1987 with a suggestion of a nonlinear dose response (*1*). Analyzing the same data, Kishikawa *et al*. reported that the excess absolute risk of BCC attributable to radiation exposure, expressed per unit skin surface area, did not significantly differ between ultraviolet (UV) radiation exposed and shielded parts of the body (*2*). This finding was consistent with the uniform distribution of the radiation-related excess risk over the body, implying an additive nature of the radiation-related risk above the background BCC rate. However the risk estimates had wide statistical confidence intervals due to the small number of BCC cases. These findings motivated us to update the skin cancer incidence data.

The current analysis was based on pathologically reviewed skin cancer incidence data through 1996, adding 10 years of follow up. Age at exposure is one of the most

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significant modifiers of dose response for skin and many other cancers (*1, 5, 7*). The LSS subjects who were exposed in childhood have now reached cancer-prone ages. The updated data allow us to examine the effects of age at exposure and temporal patterns of the radiation-related risk for skin cancer up to 50 years after exposure to A-bomb radiation.

MATERIALS AND METHODS

Study Cohort

The LSS cohort comprises 120,321 people who were selected from the 1950 National Census that had a supplementary questionnaire about A-bomb radiation exposure along with 26,000 persons who were not in either city (NIC) at the time of the bombing. The detailed sampling methods were previously described by Preston *et al*. (*11*). The current study population comprises 80,158 LSS subjects with known individual dose estimates based on the Dosimetry System 2002 (DS02) (*12, 13*), who were alive and not known to have had cancer as of January 1, 1958, when both the Hiroshima and Nagasaki Cancer Registries began operations. NIC people were excluded because of concerns about the comparability of their baseline cancer rates to those for other zero-dose cohort members, likely due to sociodemographic (urban/rural) or other differences (*14–16*). The distributions of total subjects by city and gender were 32,399 men (40.4%) and 47,759 women (59.6%) and 54,159 in Hiroshima (67.6%) and 26,002 in Nagasaki (32.4%).

Individual radiation dose to the skin was estimated as the DS02 shielded kerma dose (*12*). To correct for dose uncertainties due to random measurement error, unadjusted DS02 estimates were replaced by expected survivor dose estimates using the method developed by Pierce *et al*. (*17*) and assuming 35% measurement error in individual doses. Weighted skin dose was given as the sum of gamma dose plus 10 times the neutron dose. Estimated doses above 4 Gy were truncated to 4 Gy.

Case Ascertainment

Potential cancer cases of the skin and related sites that occurred after 1958 were identified from the Hiroshima City Cancer Registry, Hiroshima Prefecture Tumor Registry, Nagasaki Prefecture Cancer Registry including Tissue Registries, as well as autopsy and surgical pathology records at Radiation Effects Research Foundation (RERF) and other medical institutions. One of the study pathologists (SY) reviewed the records of all potential skin tumor cases, including benign tumor and tumor with uncertain malignancy cases from the following sources: tumor registry records (3,070 reports); pathology reports (1,097); autopsy reports (46); surgical pathology reports (133); and death certificates (283). After the first screening, a total of 896 tumor cases (820 persons) were identified as skin cancers, including *in situ* cancers. Using the same protocol, three pathologists (MK, MI and SY) then reviewed the pathology reports, slides and available clinical records that were not rejected by the first screening. When a pathology slide was not available or in poor condition, the tissue block was collected and a new slide was prepared. As a last step, the three original pathologists along with an additional pathologist (TH) examined the slides together to reach a final diagnosis. All tumors were coded using ICD-O-2 topography code (C44.0-C44.9, C510, C51.9, C60.9 and C63.2) and the World Health Organization, Histological Typing of Skin Tumors, second edition (*18*). Finally, 642 individuals with 700 tumors were diagnosed as having skin cancers. The percentage of death certificate only (DCO) cases was 3.4% (24 cases among 700 cases).

Tumors diagnosed before 1958 and after 1997 were excluded from the initial 700 tumors (130 cases) identified. Those occurring among persons who were not living in the catchment area of the Hiroshima or Nagasaki cancer registry (9 cases) were also excluded. Out of the remaining 561 cases, secondary cancers were excluded as treatment for a preceding cancer could cause a subsequent cancer or increase the chances of detecting other cancers, leaving 451 cases of first primary cancer and carcinoma *in situ* (including SCC *in situ*). Finally, 39 cases for which individual doses were not available and 76 cases that occurred among NIC cohort members were excluded leaving 336 first primary skin cancer cases diagnosed from 1958 to 1996 for analyses.

Statistical Analysis

Excess relative risk (ERR) and excess absolute risk (EAR) were estimated using the Poisson regression method. The general ERR model was written as:

$$\text{Expected rate} = \text{background rate}[1 + \text{ERR}]$$

$$\text{Expected rate} = \lambda_0(c, s, p, a, pa)[1 + \boldsymbol{\rho}(\mathrm{d})\varepsilon(c, s, a, pa, e, t)],$$

and the general EAR model was written as:

$$\text{Expected rate} = \text{background rate} + \text{EAR}$$

$$\text{Expected rate} = \lambda_0(c, s, p, a, pa) + \boldsymbol{\rho}(\mathrm{d})\varepsilon(c, s, a, pa, e, t).$$

In these models, λ_0 (.) represents the background rate of skin cancer as a logarithmic function of potential determinant variables, including city (c), sex (s), period at diagnosis (p), attained age (a) and an indicator of participating in the biennial health examination of the AHS at least once or not (pa). City, sex and attained age were routinely included in the background function, but birth year was not included in this study because it is co-linear with p and a. Period at diagnosis was included to evaluate the temporal trend of skin cancer incidence. The AHS is a subset of the LSS cohort that has been followed by biennial clinical examinations at RERF. AHS subjects may have had a higher chance of skin cancer detection due to the biennial exams. Potential variables were included in the functions if they were found to be significant ($P < 0.1$), and the background models of each histological type were compared with the nonparametric models consisting of the categorical variables of potential variables to check the model fit. The functions ρ(.) and ε(.) described the dose-response function and effect modification, respectively, and ε(.) was modeled as log-linear functions. Potential effect modifiers included c, s, a and pa, as well as age at exposure (e) and time since exposure (t).

Model assessments of the radiation dose-response were carried out as follows. First, a linear ERR model with potential background parameters was estimated for all skin cancer cases and then for each histological type. If there was a significant response, effect modifiers were included as potential variables. Once the background parameters and effect modifiers were determined, the shape of dose response was explored. The best-fit dose-response curves were selected using the Akaike's information criteria (AIC) from among linear, linear-quadratic, linear-spline, threshold and pure quadratic dose-response models with the selected background function and effect modifiers. The linear spline model was described as:

$$\boldsymbol{\rho}(d) = \begin{cases} \beta_1 d(d < d_0), \\ \beta_2 d(d - d_0)(d >= d_0). \end{cases}$$

In the threshold model β_1 was set to be equal to 0 and d_0 is the dose at threshold. Appropriate knots in linear spline and threshold models were determined using the selected background parameters and effect modifiers. The best-fit threshold and the 95% confidence bounds were empirically determined from the likelihood profile.

To examine the interaction between radiation and UV radiation exposures, ERRs and EARs were adjusted for the nominal areas of skin surface that were likely or unlikely to be exposed to the sunlight. The skin areas that were likely to be exposed to UV radiation were defined by the ICD-2nd topography codes of C44.0 (lip), C44.1 (eyelid), C44.3 (face), C44.6 (arm and shoulder: only hand), C44.2 (external ear) and C44.4 (scalp and neck). Areas that were unlikely to be exposed to UV radiation included C44.5 (trunk), C44.6 (arm and shoulder other than hand), C44.7 (leg and hip) and C44.8 (overlapping lesion of skin)(*2*). We assumed the total skin surface area for the average Japanese to be 1.6 m^2 (*19*), with proportions of UV radiation likely to be exposed and unlikely to be exposed areas being 0.12 m^2 (7.5%) and 1.48 m^2 (92.5%) , respectively (*20*). Adjustment was made to the incidence rate denominator by multiplying the observed person-time by the nominal surface area (m^2) (*2*).

The analytical data file consisted of tabulation of person–time and numbers of cases by city (Hiroshima or Nagasaki), gender (male or female), age at exposure (14 five-year categories from 0 to 69 and $\geq$70 to $<$100), attained age (17 five-year categories from 0 to 84 and the other of $\geq$85 to $<$110), time period of cancer diagnosis (9 categories: 1958–1960, 1961–1965, 1966–1970, 1971–1975, 1976–1980, 1981–1985, 1986–1987, 1988–1990 and 1991–1996), DS02 adjusted shielded kerma dose (23 categories including cut points and larger: 0, 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 Gy, and another category of unknown dose) and AHS (participant or not).

Person-years (PYs) of observation were computed from January 1, 1958, until the earliest date of diagnosis of any tumor, date of death or December 31, 1996, whichever occurred first. Since tumors that were diagnosed outside the catchment area were excluded from the analysis, PYs were adjusted for the estimated migration rates in and out of the area based on the AHS migration data.(*21*) Estimated parameters, likelihood ratio tests, and likelihood-based 95% confidence intervals (CI) were computed with the AMFIT computer program from the Epicure risk regression software.(*22*) CIs for attributable fractions were based on an asymptotic variance estimators based on a delta method.

This study was approved by the Human Investigation Committee of Radiation Effects Research Foundation (RERF).

RESULTS

Distribution of Histological Types of Skin Cancer by Various Factors

We analyzed 336 eligible cases with first primary skin cancer, adding 128 new cases to the previous 1958–1986 series. Of these, 320 cases (95.2%) were diagnosed by pathological review, 8 (2.4%) based on clinical records and 8 (2.4%) were based on death certificates only.

There were 10 malignant melanomas, 301 epidermal tumors (123 BCCs, 114 SCCs and 64 SCC *in situ*), 10 Paget disease tumors and 15 other tumors (5 adnexal tumors, 3 cutaneous lymphoproliferative tumors, 3 vascular tumors, 3 cutaneous fibrohistiocytic tumors and 1 miscellaneous tumor) (Table 1). There were more female than male cases for skin cancers combined, largely due to the higher female frequency of cases with SCC *in situ*, BCC and SCC. The higher proportion of Hiroshima cases (72.9% vs. 35.1% for Nagasaki) reflected the larger number of Hiroshima subjects in the cohort. The ratio of BCC to SCC was 1.08, which was slightly lower than the previous study (1.2) (*1*).

Crude Incidence Rates of Skin Cancer

Crude incidence rates of skin cancer were calculated by histological types (Table 2). The crude incidence rates for BCC and SCC *in situ* were high in the highest dose category ($>$1 Gy) but were similarly low in the two lower dose categories. The rates for SCC and Paget disease were similar for the three dose categories. There was no difference of crude incidence rates of BCC between males and females exposed to less than 1 Gy. However, the crude incidence rate for males exposed to more than 1 Gy (35.7 per 10^5 person-years) is 1.8 times higher than that for females (20.1 per 10^5 person-years).

Dose Response by Histological Types

A significant dose response was found for total skin cancer based on a linear ERR model without effect modifiers, with an ERR at 1 Gy (ERR_{1Gy}) of 0.74, 95% confidence interval (CI): 0.37, 1.2. A significant dose-response was observed for non-melanoma skin cancer as a group ($ERR_{1Gy} = 0.72$, 95% CI: 0.36, 1.2), and especially for BCC ($ERR_{1Gy} = 2.2$, 95% CI: 0.78, 2.9) and SCC *in situ* ($ERR_{1Gy} = 0.71$, 95% CI: 0.063, 1.9). There was no association for melanoma ($ERR_{1Gy} = 0.86$, 95% CI: -1.4, 7.3) and for Paget disease ($ERR_{1Gy} = 1.3$, 95% CI: < -1.3, 9.2). SCC showed a negative point estimate that was not statistically significant ($ERR_{1Gy} = -0.12$, 95% CI: < -0.12, 0.25). Because of the small number of the cases, further analyses were not conducted for either melanoma or Paget disease.

Basal Cell Carcinoma

ERR Model

Several possible modifiers of the ERR for BCC were examined (Table 3). The ERRs of age at exposure group of 0–9, 10–19, 20–39 and over 40 years were 15 (95% CI: 4.2, 43), 5.7 (95% CI: 2.2, 13), 1.3 (95% CI: 0.35, 2.9), 0.19 (95% CI: $<$–0.32, 1.2), respectively, and age at exposure was the most significant modifier with a coefficient estimate $= -0.11$ (95% CI: -0.17, -0.070). That is, the ERR decreased 11% (95% CI: 6.7%, 15%, $P < 0.001$) with each one year increase in age at exposure. Attained age did not significantly modify the ERR after allowance for the effect of age at exposure. With the exception of the earliest calendar period (1958–1965), the ERR remained stable through the last follow-up period, with no significant temporal trend. The ERR was estimated to be 1.3 (95% CI: 0.44, 2.8, $P = 0.046$) for people who were exposed to 1 Gy of radiation at age 30.

The shape of the dose response was examined using five models with effect modification. First, was a linear spline function with a knot between 0.5–1.5 Gy (incrementing 0.01 Gy with each iteration) with effect modification by age at exposure (fixed to age at exposure of 30). A model with a

TABLE 1
Distribution of Histological Type of Skin Cancer among Atomic-Bomb Survivors, 1958–1996

		Melanoma		BCC[a]		SCC[b]		SCC[b] *in situ*		Paget disease		Other		Total	
	Person-years	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)	No. of cases	Percentage (%)
Gender															
Male	756,536	5	(50.0)	49	(39.8)	46	(40.4)	14	(21.9)	3	(30.0)	7	(46.7)	124	(36.9)
Female	1,265,140	5	(50.0)	74	(60.2)	68	(59.6)	50	(78.1)	7	(70.0)	8	(53.3)	212	(63.1)
City															
Hiroshima	1,398,540	5	(50.0)	83	(67.5)	83	(72.8)	56	(87.5)	7	(70.0)	11	(73.3)	245	(72.9)
Nagasaki	623,128	5	(50.0)	40	(32.5)	31	(27.2)	8	(12.5)	3	(30.0)	4	(26.7)	91	(27.1)
AHS[c]															
Participants	329,788	1	(10.0)	42	(34.1)	30	(26.3)	18	(28.1)	1	(10.0)	2	(13.3)	94	(28.0)
Non-participants	1,691,890	9	(90.0)	81	(65.9)	84	(73.7)	46	(71.9)	9	(90.0)	13	(86.7)	242	(72.0)
Age at diagnosis (years)															
<50	891,417	2	(20.0)	6	(4.9)	11	(9.6)	0	(0.0)	0	(0.0)	1	(6.7)	20	(6.0)
50 < 60	417,829	0	(0.0)	17	(13.8)	11	(9.6)	3	(4.7)	2	(20.0)	1	(6.7)	34	(10.1)
60 < 70	368,268	4	(40.0)	27	(22.0)	19	(16.7)	14	(21.9)	1	(10.0)	2	(13.3)	67	(19.9)
70 < 80	240,742	2	(20.0)	40	(32.5)	29	(25.4)	22	(34.4)	5	(50.0)	7	(46.7)	105	(31.3)
80+	103,415	2	(20.0)	33	(26.8)	44	(38.6)	25	(39.1)	2	(20.0)	4	(26.7)	110	(32.7)
Age at exposure (years)															
<10	505,421	0	(0.0)	6	(4.9)	3	(2.6)	1	(1.6)	1	(10.0)	1	(6.7)	12	(3.6)
10 < 20	502,253	2	(20.0)	18	(14.6)	12	(10.5)	6	(9.4)	1	(10.0)	1	(6.7)	40	(11.9)
20 < 40	655,076	3	(30.0)	52	(42.3)	40	(35.1)	34	(53.1)	3	(30.0)	8	(53.3)	140	(41.7)
40+	358,922	5	(50.0)	47	(38.2)	59	(51.8)	23	(35.9)	5	(50.0)	5	(33.3)	144	(42.9)
Year of diagnosis															
1958–1965	550,583	2	(20.0)	9	(7.3)	20	(17.5)	3	(4.7)	1	(10.0)	2	(13.3)	37	(11.0)
1966–1975	582,368	4	(40.0)	19	(15.4)	21	(18.4)	4	(6.3)	1	(10.0)	2	(13.3)	51	(15.2)
1976–1987	561,855	4	(40.0)	55	(44.7)	35	(30.7)	23	(35.9)	2	(20.0)	5	(33.3)	124	(36.9)
1988–1996	326,865	0	(0.0)	40	(32.5)	38	(33.3)	34	(53.1)	6	(60.0)	6	(40.0)	124	(36.9)
Anatomical site															
Face		1	(10.0)	67	(54.5)	32	(28.1)	12	(18.8)	0	(0.0)	6	(40.0)	118	(35.1)
Scalp and neck		0	(0.0)	15	(12.2)	12	(10.5)	0	(0.0)	0	(0.0)	2	(13.3)	29	(8.6)
Trunk, limbs and other		9	(90.0)	33	(26.8)	54	(47.4)	51	(79.7)	1	(10.0)	7	(46.7)	155	(46.1)
External genitals		0	(0.0)	8	(6.5)	16	(14.0)	1	(1.6)	9	(90.0)	0	(0.0)	34	(10.1)
Total	2,021,670	10		123		114		64		10		15		336	
(%)		(3%)		(37%)		(34%)		(19%)		(3%)		(4%)		(100%)	

[a] Basal cell carcinoma.
[b] Squamous cell carcinoma.
[c] Adult Health Study.

TABLE 2
Crude Skin Cancer Incidence Rates by Histological Types, Radiation Dose and Gender

	Male						Female						Both sexes					
	Weighted skin dose (DS02, Gy)						Weighted skin dose (DS02, Gy)						Weighted skin dose (DS02, Gy)					
	<0.005		0.005-0.99		1+		<0.005		0.005-0.99		1+		<0.005		0.005-0.99		1+	
	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]	Case	Rate[a]
Melanoma	1	0.3	3	0.7	1	2.6	2	0.4	3	0.4	1	0.0	3	0.4	6	0.6	1	1.0
Nonmelanoma skin cancer	44	13.9	57	14.2	18	45.9	84	16.1	99	14.5	24	40.3	128	15.3	156	14.4	42	42.5
BCC[b]	13	4.1	22	5.5	14	35.7	27	5.2	35	5.1	12	20.1	40	4.8	57	5.3	26	26.3
SCC[c]	22	7.0	22	5.5	2	5.1	30	5.7	35	5.1	3	5.0	52	6.2	57	5.3	5	5.1
SCC[c] *in situ*	5	1.6	7	1.7	2	5.1	24	4.6	20	2.9	6	10.1	29	3.5	27	2.5	8	8.1
Paget disease	3	0.9	0	0.0	0	0.0	1	0.2	5	0.7	1	1.7	4	0.5	5	0.5	1	1.0
Other	1	0.3	6	1.5	0	0.0	2	0.4	4	1.5	2	3.4	3	0.4	10	0.9	2	2.0
Migration-adjusted person-years	316,032		401,308		39,196		522,793		682,725		59,617		838,825		1,084,030		98,813	

[a] Rate per 10^5 persons per year.
[b] Basal cell carcinoma.
[c] Squamous cell carcinoma.

TABLE 3
Basal Cell Carcinoma Fitted Linear Risk Estimates by Age at Exposure, Age at Diagnosis, Period at Diagnosis, City, Gender and AHS Participant; Atomic-Bomb Survivors

Variables	No. of cases	Person-years	ERR_{1Gy}[a]	95% CI[b]	Heterogeneity[c] *P*	Trend[d] *P*
Age at exposure (years)						
0–9	6	505,421	15	(4.2, 43)	<0.001	<0.001
10–19	18	502,253	5.7	(2.2, 13)		
20–39	52	655,076	1.3	(0.35, 2.9)		
40+	47	358,922	0.19	(<–0.32,[e] 1.2)		
Age at diagnosis (years)						
<50	6	891,417	11	(2.3, 36)	<0.001	<0.001
50 < 60	17	417,829	7.5	(3.1, 17)		
60 < 70	27	368,268	1.6	(0.28, 4.2)		
70 < 80	40	240,742	0.7	(0.014, 2.1)		
80+	33	103,415	0.02	(<–0.49,[e] 1.1)		
Period at diagnosis						
1958–1965	9	550,582	< 0	(<0.1,[e] 2.1)	0.11	0.21
1966–1975	19	582,368	2.2	(0.40, 6.8)		
1976–1987	55	561,855	1.3	(0.41, 3.0)		
1988–1996	40	326,865	2.5	(0.83, 6.2)		
City						
Hiroshima	83	1,398,540	1.2	(0.48, 2.9)	0.054	
Nagasaki	40	623,128	3.0	(1.2, 6.2)		
Gender						
Male	49	756,536	2.4	(0.97, 5.5)	0.17	
Female	74	1,265,140	1.1	(0.33, 2.5)		
AHS						
Participant	42	329,788	2.3	(0.93, 5.3)	0.22	
Non-participant	81	1,691,890	0.9	(0.35, 2.6)		

[a] Excess relative risk at 1 Gy.
[b] Confidence interval.
[c] Test of hypothesis that effects differ across categories.
[d] Test of log-linear trend across categories.
[e] The lower confidence bounds were described as the limit to be estimated.

knot at 0.63 (95% CI: 0.3, 0.9) was selected as the best (AIC = 1,086.0). The slope was estimated to be 2.0 (95% CI: <0, 4.3) at doses over 0.63 Gy and −0.05 (95% CI: <–0.05, 1.2) below the knot of 0.63 Gy. Second, among linear threshold models with a knot in the same range, a model with a knot at 0.63 Gy fit best (95% CI: 0.3, 0.9, AIC = 1,084.3). The slope over 0.63 Gy was estimated to be 2.0 (95% CI: 0.69, 4.3). Third, the best-fit linear model estimated an ERR_{1Gy} of 1.3 (95% CI: 0.44, 2.8, AIC = 1,089.6). Fourth, the best-fit linear quadratic model (AIC = 1,088.8) showed that the coefficient estimate of the linear term was 0.40 (95% CI: <0, 2.0) and that the quadratic term was 0.31 (95% CI: −0.059, 0.87). The best-fit quadratic model (AIC = 1,087.8) showed a coefficient estimate of 0.43 (95% CI: 0.14, 0.97). Comparing those five models based on the AIC, the best-fit model was the threshold model and a slope over the threshold of 2.0 (95% CI: 0.69, 4.3), with an 11% increase of effect modification with a one-year decrease in age at exposure (95% CI: 6.9%, 16%) (Figs. 1 and 2).

EAR Model

The excess absolute risk (EAR) of radiation effects was estimated using the selected variables in the linear threshold ERR model with a knot at 0.63. When effect modification by age at exposure, time since exposure and attained age were examined simultaneously, the effect of time since exposure was found to be significant ($P < 0.001$), but not age at exposure or attained age. The EAR_{1Gy} was estimated to be 0.059 cases per 10^4 PYs (95% CI: <0, 0.30). The background cases, excess cases and attributable fractions of radiation were estimated for each category of radiation dose based on the above ERR model. The attributable fraction was 19.9% (95% CI: 13.6, 26.2) for total BCC (Table 4). While there were no excess cases under the threshold of 0.63 Gy, the attributable fraction rapidly increased in the dose category of 0.5 Gy or higher.

Interaction Between UV Radiation and Radiation

The number of BCC cases observed on the face or neck (likely to be exposed to UV radiation) was 65, and with an ERR_{1Gy} of 0.6 (95% CI: <0, 2.1) based on the linear model including background parameters of city, period of diagnosis and attained age, with age at exposure as an effect modifier. The number of the BCC cases observed on the rest of body (unlikely to be exposed to UV radiation) was 58 with in an ERR_{1Gy} of 2.3 (95% CI: 0.61, 6.7). The difference in ERRs was not statistically significant (likeli-

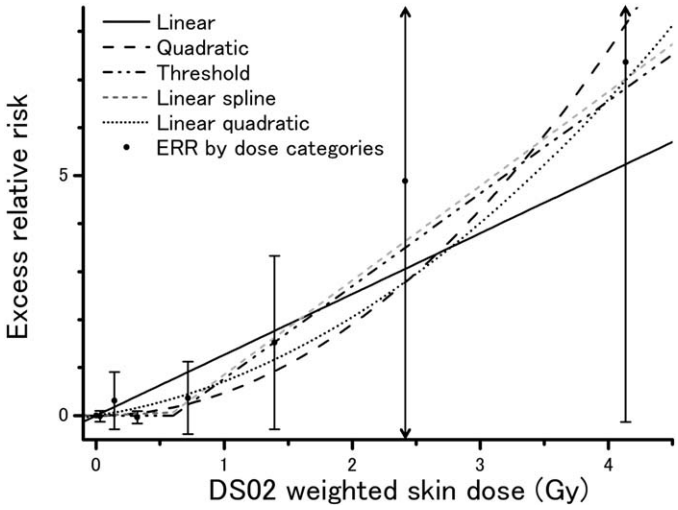

FIG. 1. Basal cell carcinoma radiation dose-response curves for various excess relative models; Atomic bomb survivors (Japan) diagnosed between 1958 and 1996. The excess relative models include variables; gender, period at diagnosis and log age 70 as the background parameters, and age at the time of bombing as the effect modifier. The 95% Wald confidence bounds were also estimated.

FIG. 2. Solid line shows excess relative risk at 1 Gy with age at exposure modification for basal cell carcinoma based on the linear model with a threshold at 0.63 Gy. Dots show excess relative risk point estimates by age at exposure categories, 0–9, 10–19, 20–39, over 40 years old at the time of bombing and the 95% confidence bounds were also estimated.

hood ratio test, $P = 0.15$) based on the joint analysis proposed by Pierce and Preston (*17, 23*). For BCC in the area likely to be exposed to UV radiation, the background rate and the EAR (cases per m^2 10^5 years Gy) were estimated to be 23 and 40 (95% CI: <0, 106), respectively. The comparable rates in the area unlikely to be exposed to UV radiation were estimated to be 1.0 and 5.7 (95% CI: 1.9, 11), respectively. These were based on a linear model with background parameters (city, gender, period at diagnosis and attained age) and effect modifier (age at exposure and attained age).

SCC In Situ

There was a significant dose response for SCC *in situ* using a linear model ($ERR_{1Gy} = 0.71$, 95% CI: 0.063, 1.9). Also, there was a statistically significant city difference in dose-response slopes between Hiroshima and Nagasaki (likelihood ratio test, $P < 0.001$). The ERR_{1Gy} in Hiroshima was 0.28 (95% CI: <0, 1.9), which was not statistically significant, while that in Nagasaki was 17.6 (95% CI: 3.0, 149), which was statistically significant. Although the ERR slope for Nagasaki was steep, the 95% CI was extremely wide and the number of cases in Nagasaki was only 8, which included no cases with high radiation dose (more than 2 Gy).

DISCUSSION

We extended the follow-up period by 10 years since the previous study of skin cancer incidence among the LSS adding 128 new cases, which is a 60% increase. As in the previous study, we found a significant dose relationship for BCC but not for invasive SCC. The updated BCC data strengthened the results of the previous 1958–1987 results (*1*), and the trend indicates that elevated risks of radiation for BCC remains more than 50 years after exposure. The number of melanoma cases oddly remained the same and was quite small with no evidence of a dose response. The significantly elevated ERR for SCC *in situ*, an intra-epidermal lesion of SCC, was surprising, but the evidence of radiation causality is uncertain, as discussed below.

Skin cancer is rare among Asian populations, for instance, incidence rates of melanoma were highest in the Oceania region (range 41.1 to 55.8 per 100,000 population, age standardized by Segi's world standard population), while they were 0.5 in Hiroshima in 1995–2000 as well as Nagasaki in 1997–2002 (*24*). The rates of non-melanoma skin cancer were high in Central and South America and in Europe (range 12.6 to 19.8 per 100,000 population, age standardized by above population), while they were 6.2 and 5.9 in Hiroshima and Nagasaki, respectively (*24*). As the number of skin cancer cases is so small in Japan with a variety in histological types and good prognoses, cancer incidence data with pathological review are crucial for skin cancer studies. Both the Hiroshima and Nagasaki cancer registries include data from tumor and tissue registries, which record histological diagnoses directly from pathologists. These independent reports were major sources for the histological diagnoses in our study.

The estimates of $ERRs_{1Gy}$ for different age-at-exposure strata (Table 3) were almost 10 times greater than the estimates that were reported for medical radiation exposures (*5–7, 25*). The ERR/Gy estimates for LSS subjects exposed at ages 0–9 years, 10–19 years, 20–39 years and more than

TABLE 4
Observed and Fitted Cases of Basal Cell Carcinoma by Dose Category with Attributable Fraction Estimates

Dose category[a]	Subjects	Cases	Background[b]	Excess[b]	Attributable fraction[c]
<0.005	33,456	40	40.6	0.0	0%
0.005–0.1	26,879	31	31.6	0.0	0%
0.1–0.2	5,618	10	7.2	0.0	0%
0.2–0.5	6,412	10	8.7	0.0	0%
0.5–1	3,757	6	5.1	1.5	22.7%
1–2	2,540	8	3.5	8.1	69.7%
2–3	766	8	1.0	5.3	84.6%
3+	730	10	0.8	9.6	92.6%
Total	80,158	123	98.5	24.5	19.9%

[a] Weighted skin dose (shielded kerma) in Gy.
[b] Estimates of background and fitted excess cases are based on an ERR model with threshold dose response and a knot at 0.63, effect modification by time since exposure.
[c] Attributale fraction among cohort members.

40 years were estimated to be 15, 5.7, 1.3 and 0.19, respectively, while the corresponding estimates among patients with total body irradiation (TBI) for hematopoietic cell transplantation were 1.49, 0.55, 0.11 and 0.02, respectively (*7*). Also the EAR_{1Gy} of 0.053 cases per 10^4 PYs for LSS subjects was much lower than the estimates that were reported among medical exposures, such as 55.6 cases per 10^4 PYs for TBI exposure patients (*7*), 1.1 cases per 10^4 PYs for New York tinea capitis study series (*5*) and 0.31 cases per 10^4 PYs for Israel tinea capitis study(*6*). This may be partially explained by three reasons. First, the A-bomb survivors had acute whole-body radiation exposure whereas most of the medical exposures were fractionated and more localized. Second, the TBI cohort members didn't include any patients with doses less than 7.5 Gy. Schwartz *et al*. hypothesized that the dose responses, which are much steeper at the lower doses received by A-bomb survivors, may flatten out at the much higher doses received by TBI-conditioned patients. Third, the LSS cohort only included Japanese whose background rate of skin cancer is lower than rates among Caucasians, and pigmentation characteristics might have modified the radiation risk of BCC as reported in either the Israel or New York tinea capitis study or the U.S. radiologic technologists study (*26*).

In the tinea capitis study, the skin cancer radiation risk was 10 times lower among African-Americans than among Caucasians.(*5*) The difference in the magnitude of radiation risk estimates may be due to the lower background risk of skin cancer in the Japanese population compared with Caucasian populations. Although the radiation risk estimates for the different age-at-exposure categories among the A-bomb survivors were greater than those of medical exposure, the magnitude of effect modification by age at exposure was similar [11% increase with each one-year decrease in age at exposure among A-bomb survivors vs. 10.9% increase among patients who were irradiated for medical reasons (*7*)].

Using an ERR model, the best-fit knot for a threshold dose was determined to be 0.63 Gy according to the AIC. Previous studies have reported that the threshold may be as high as 1 Gy for BCC (*1, 3*). A significant dose response at doses greater than 1 Gy and nonsignificant at doses less than 1 Gy were reported in a case-control study of childhood cancer survivors who has received radiotherapy in the U.S. (*27*). The current study provides data with doses comparable to those observed in radiotherapy (<1 Gy) and allows for an analysis to estimate a threshold dose for radiation-induced skin cancer. Additional data that will be collected in later years will be valuable for this and other purposes in the future.

In regards to the interaction between UV radiation and radiation for BCC, the ERR estimated for skin areas unlikely to be exposed to UV radiation was 2.3, but was 0.6 in skin areas likely to be exposed to UV radiation. A skin cancer case-control study among New Hampshire residents found that radiotherapy risk was statistically high in the subjects who had not experience sunburn and the risk in those who had experience sunburn did not increase, although the difference in the risks between those two groups was not significant (*28*). These two reports suggested that radiation effects were stronger on skin that was unlikely to be exposed to UV radiation.

On an absolute risk scale, the New York tinea capitis study reported higher risks for excess BCC on the sun-exposed margin of the scalp (EAR = 21/100 cm^2 Gy) compared with the relatively sun-shielded scalp (EAR = 4.7/100 cm^2 Gy). In the previous report by Kishikawa *et al*. the BCC EAR/10^5 m^2 years Sv for skin areas likely to be exposed to UV radiation was slightly, but not significantly, higher than those for areas unlikely to be exposed to UV radiation, suggesting that the uniform distribution of the radiation risks are additive to the background rates. A different pattern is observed in the current study where the EAR was 40/10^5 m^2 years Gy for areas likely to be exposed to UV radiation compared with 5.7/10^5 m^2 years Gy for areas unlikely to be exposed to UV radiation. The current EAR was markedly higher than the previous report from this cohort (9.1/10^5 m^2 years Gy). Given that the baseline

BCC rates were more than 20 times higher in UV radiation-exposed areas than in UV radiation-shielded areas and all estimates had wide confidence intervals due to the small number of cases, the present EAR estimate for BCC on UV radiation-exposed body parts cannot rule out either an additive or multiplicative interaction between ionizing radiation and UV radiation exposure. Therefore, a further follow-up is needed to assess the nature of the UV radiation and ionizing radiation interaction more precisely.

BCC is rarely metastatic or fatal (*29–31*), but can be invasive and prone to multiple lesions (*32*). Among 123 patients, 8.1% (10 cases) had a second skin cancer (SCC = 3, BCC = 6 and SCC *in situ* = 1) after having suffered a first primary BCC. This proportion was lower than that observed among Caucasian subjects in the tinea capitis treatment study [38% of the irradiated cases and 24% of the control BCC cases (*5*)]. However, people who were exposed at a young age have reached a cancer-prone age and are also at a higher risk for skin cancer due to their radiation exposure. Thus, second skin cancers may occur with greater frequency in the subsequent follow-up period. The city difference in the dose-response relationship for SCC *in situ* was large. To further explore this finding, we calculated the ERR including NIC people to increase the number of persons in the reference group. However, the city difference persisted after this analysis. We then calculated the age-standardized incidence rates of SCC *in situ* in Hiroshima and Nagasaki City based on the population-based cancer registries. The rates were nearly the same (1.2 and 1.0 per 100,000 population, respectively). Finally, since the number of cases in Nagasaki was very small, we reviewed the tissue registry reports of the LSS cases in Nagasaki who had been diagnosed as ''Bowen type of actinic keratosis'', which is similar to SCC *in situ* (Bowen's disease). Out of 65 actinic keratosis cases, 11 cases were found to be similar to SCC *in situ* but were not registered in the Nagasaki Cancer Registry because actinic keratosis was not considered a cancer and were therefore not included in this study. Thus, there may be city differences in diagnoses and reporting. In light of these difficulties, it is hard to determine the dose-response relationship for SCC *in situ*.

There may be a concern for our choice of a relative biological effectiveness (RBE) of 10 for the neutron dose. A publication by Preston *et al*. stated the purpose of an RBE assumption for analysis of the LSS data was to adjust for neutron effects at higher doses where the cancer risks are substantial, which is the reason that the assumption of RBE = 10 is ordinarily used for the LSS data (*13*). They also compared the results of solid cancer ERR to consider the confidence of the RBE assumption. If a dose constant RBE of 20 was assumed, the solid cancer ERR estimate decreased from 0.41/Sv (RBE = 10) to 0.39/Sv. Finally they concluded that the neutron component accounted for only a small fraction of the total dose received by LSS cohort members, (especially for the organ doses most relevant to risk estimation in the LSS) and this fraction will be virtually impossible to make useful inference about the effect of neutron exposure on LSS cancer risks directly from the LSS data. To examine the effect of the RBE assumption for BCC threshold estimation in this study, we performed a sensitivity analysis. When the RBE was assumed to be 5 and 20, the threshold was estimated to be 0.63 (95% confidence interval: 0.35, 0.84) and 0.80 (95% CI: 0.32, 1.1), respectively. Therefore the neutron RBE fraction played only a small role on the BCC risk estimation on the LSS members.

In conclusion, the current analysis showed a significant linear dose-response with a threshold association between BCC and exposure to A-bomb radiation. Significant effect modification by age at exposure was observed and the radiation-related risk of BCC persisted throughout the follow-up period, 50 years after the bombs. These findings suggested that the response of the basal cells of the epidermis to ionizing radiation had a threshold shape and the overall risks were especially high for those who were young at the age of exposure. No association was observed for malignant melanoma, SCC or Paget disease. An association of SCC *in situ* with radiation was implied but the unusual results in Nagasaki and significant city difference make the finding difficult to interpret.

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