

Skin tumor risk among atomic-bomb survivors in Japan

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(Received 16 December 1997; accepted in revised form 25 March 1998)

Objectives: Elevated risks of skin cancer following high doses of ionizing radiation have long been known. Recent reports on atomic-bomb survivors indicate that nonmelanoma skin cancer can be induced at low to medium doses. We studied atomic-bomb survivors to determine the effects of radiation on specific histologic types of skin cancer and to describe the dose-response relationship.

Methods: Cases of melanoma, nonmelanoma skin cancers, and Bowen's disease were ascertained between 1958 and 1987 for the 80,000 cohort members through the population-based Hiroshima and Nagasaki (Japan) tumor registries augmented by searches of other records.

Results: An excess of basal cell carcinoma ($n = 80$), with some suggestion of a non-linear dose-response, was observed. The excess risk decreased markedly as age at exposure increased, and there was no evidence for an interaction between ionizing and ultraviolet radiation. No dose-response was found for squamous cell carcinoma ($n = 69$). The excess relative risk point-estimates were large, but statistically nonsignificant for both melanoma ($n = 10$) and Bowen's disease ($n = 26$).

Conclusions: The basal layer of the epidermis appears to be quite sensitive to radiation carcinogenesis, particularly at a young age. The suprabasal layer seems to be more resistant, as shown by the lack of an association for squamous cell carcinomas. *Cancer Causes and Control* 1998, 9, 393–401

Key words: Atomic-bomb survivors, basal cell carcinoma, Japan, radiation dose, radiation effects, squamous cell carcinoma.

Introduction

The first study of skin cancer among atomic-bomb survivors in Japan¹ was conducted between 1964 and

1966 among the 20,000 members of the Adult Health Study (AHS), a clinically examined subset of the Life

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Span Study (LSS) cohort. Only five skin cancers were identified, with no evidence of radiation effect. Sadamori *et al*² investigated skin cancer incidence between 1958 and 1985 in 26,000 Nagasaki LSS subjects and reported a significant excess relative risk based on four melanoma and 43 nonmelanoma skin cancer cases. A correlation between skin cancer incidence and decreasing distance from the bombings also was reported among 66,276 Nagasaki survivors registered at the Nagasaki University School of Medicine.^{3,4} More recently, an increased risk of nonmelanoma skin cancer associated with radiation exposure was demonstrated in the entire LSS.^{5,6} Histologic type, skin cancer body location, and the effects of ultraviolet (UV) radiation were not considered in previous studies of skin cancer incidence in the LSS cohort, although these factors were considered in a recent report on the prevalence of skin neoplasms among 6,000 participants in the AHS.⁷ During a careful clinical examination between 1989 and 1992, only five skin cancers were detected, but a dose-response was observed for skin cancer and precancerous skin lesions combined.

Most other studies are of persons exposed to partial body irradiation, and none of them includes both children and adults.⁸⁻¹² Because of the relative lack of information on ionizing radiation exposure and skin neoplasia, we conducted a detailed epidemiologic and pathologic assessment of skin cancers, including *in situ* tumors, in the LSS cohort.

Materials and methods

As in the latest LSS incidence study,⁵ the present study population comprises 79,972 people with DS86 dose estimates who were residents of Hiroshima or Nagasaki at the time of the bombings and who were alive and not known to have cancer on 1 January 1958. Almost 60 percent of the cohort members are women, and 68 percent were in Hiroshima at the time of the bombings.

Skin cancers occurring between 1 January 1958 and 31 December 1987 were identified through the Hiroshima and Nagasaki tumor registries. For this study, follow-up ended in 1987 because of the five-year lag time in case registration in the Hiroshima and Nagasaki Tumor Registries and the time required for collecting tissue blocks for all cases as well as conducting the pathology slide review. To identify *in situ* tumors, the registry cases were augmented using the tissue registries (which were established in 1973), autopsy and surgical pathology records at major medical institutions in Hiroshima and Nagasaki, and records maintained at the Radiation Effects Research Foundation (RERF). To ensure complete ascertainment, tumor registry cases with ICD-9¹³ codes 140 (lip), 154.2 (anal canal), 154.3 (anus, not

otherwise specified [NOS]), and 171.0 (cartilage of eyelid or ear), which sometimes include misclassified skin cancers, were also reviewed.

Three study pathologists classified tumors by histologic type according to WHO¹⁴ criteria. Of the 343 tumors fitting the study pathology criteria, 301 (88 percent) tissue specimens were retrieved and examined by the study pathologists. For an additional 19 (six percent) cases, only pathology records were available for review. For the remaining 23 cases, either clinical records ($n = 11$) or death certificates ($n = 12$) were reviewed. Only the 299 first primary malignant and carcinoma *in situ* (including Bowen's disease) skin tumors with ICD codes 172, 173, 184.1, 184.4, 187.4, and 187.7 were studied because treatment for an earlier cancer could cause a subsequent cancer, and chances of detecting other cancers might be increased. After excluding tumors occurring before or after the study period ($n = 26$), those occurring among persons 'not in city' at the time of the bombings ($n = 39$), without DS86 dose estimates ($n = 22$), and not living in the Hiroshima and Nagasaki Tumor Registry catchment area ($n = 4$), 208 skin tumors remained for analysis.

Using the DS86,¹⁵ individual weighted dose-estimates were calculated as the sum of the γ -ray and 10 times the neutron kerma. Since this system does not include an organ dose estimate for skin, it was assumed that skin dose was equal to the DS86 kerma estimates. Approximately 40 percent of the study population had a DS86 weighted skin dose of less than 0.005 sievert (Sv), and almost three percent had dose estimates of one or more Sv.

Individual DS86 kerma estimates for survivors with estimates of less than four gray (Gy) actually may be between 30 and 50 percent higher or lower. Dose estimates in excess of four Gy are likely to be more uncertain¹⁶ and mostly are overestimated. To adjust for the impact of these errors, we set kerma estimates greater than four Gy equal to four Gy and used the method suggested by Pierce *et al*¹⁶ to produce bias-corrected risk estimates. These adjustments increase estimates of the slope of the dose-response function in linear models by 10 to 15 percent.

Data for the different types of skin tumors were cross-classified by age at exposure (13 categories), attained age (17 categories), calendar time (seven categories), dose (10 categories), gender, city, and membership in the AHS. Members of the AHS receive biennial clinical examinations, and, therefore, their likelihood for detection of a skin tumor is increased. For each stratum, person-years, tumor counts, person-year-weighted average values for dose, attained age, age at exposure, and time since exposure were computed. Person-years of observation were computed from 1 January 1958 until

the earliest of: (i) the date of diagnosis of the first primary cancer; (ii) the date of death; or (iii) 31 December 1987 (the end of follow-up). Because the tumor registries routinely obtain information on cancer diagnoses only for people who are resident in the registry catchment areas at the time diagnosis, we excluded cases diagnosed outside the catchment area and adjusted the person-years based on immigration and emigration information from the AHS cohort.^{5,17}

We used Poisson regression methods to compute maximum likelihood estimates for both relative and absolute excess risks.¹⁸ Parameter estimates, likelihood-ratio tests, and likelihood-based confidence intervals (CI)¹⁹ were computed with the AMFIT computer program.²⁰ We analyzed the data using general excess relative risk (ERR) models (the background rate times one plus the ERR) written as

$$\lambda(c, g, p, a, m)[1 + \rho(d)\varepsilon(c, g, a, e, t, m)],$$

and general excess absolute risk (EAR) model (the background rate plus the EAR) written as

$$\lambda(c, g, p, a, m) + \rho(d)\varepsilon(c, g, a, e, t, m).$$

In these models, $\lambda(\cdot)$ describes background skin cancer rates as a function of city (c), gender (g), time period (p), attained age (a), and membership in the AHS (m). The functions $\rho(\cdot)$ and $\varepsilon(\cdot)$ describe the dose-response function and effect modification, respectively. Potential effect modifiers included the covariates c , g , a , and m , as well as age at exposure (e) and time since exposure (t). The log of the background rates was modeled as a gender-specific linear function of log-attained age with additional effects for city, time period (1958-65, 1966-75, and 1976-87), and AHS membership. Time period was included to take into account temporal changes in skin cancer incidence. Effect modification was modeled as log-linear functions. We considered linear, linear-quadratic, linear-spline, and threshold dose-response models. The linear spline has the form:

$$\rho(d) = \begin{cases} \beta_1 d & d < d_0 \\ \beta_2(d-d_0) & d \geq d_0. \end{cases}$$

In the threshold model β_1 is set to equal to 0.

Results

Between 1958 and 1987, 208 first-primary skin tumors fitting the study criteria were diagnosed in Hiroshima and Nagasaki in LSS survivors with DS86 dose estimates. Ten malignant melanomas, 172 nonmelanoma skin cancers (80 basal cell, 69 squamous cell, 13 other epithelial, and 10 non-epithelial or unclassified), and 26 cases of Bowen's disease were identified (Table 1). Sixty-one (29.3 percent) tumors occurred on the face,

20 (9.6 percent) on the scalp and neck, 108 (51.9 percent) on the trunk and limbs, and 19 (9.1 percent) on the external genitals. The ratio of basal cell to squamous cell carcinoma was 1.2, and 45.0 percent of the basal cell compared with 18.8 percent of the squamous cell carcinomas occurred on the face.

For persons exposed to doses above one Sv, the crude rates for nonmelanoma skin cancer as a group, basal cell carcinoma, and Bowen's disease are high, but no difference was observed between persons exposed to less than 0.005 Sv compared with those exposed to 0.005-0.99 Sv (Table 2). Basal cell carcinoma occurred most frequently on body areas exposed to UV radiation (face and hands) in the survivors in the lowest dose group whereas the opposite distribution was seen in persons exposed to more than one Sv. For squamous cell carcinoma, the crude rates declined somewhat with increasing dose, and the distribution of cancers by body location also differed from that described for basal cell carcinoma.

Using a linear excess relative risk (ERR) model, a dose-response was demonstrated for nonmelanoma skin cancer as a group (ERR at one Sv [ERR_{1Sv}] = 0.62, 90 percent CI = 0.23-1.3). The ERR_{1Sv} was increased significantly for basal cell carcinomas (ERR_{1Sv} = 1.8, 90 percent CI = 0.83-3.3) and nonbasal, nonsquamous cell epithelial skin carcinomas (ERR_{1Sv} = 1.4, 90 percent CI = 0.02-5.8), but not for squamous cell carcinoma (ERR_{1Sv} = < -0.1, 90 percent CI = < -0.1-0.10). While the point estimates were high for malignant melanoma (ERR_{1Sv} = 2.1, 90 percent CI = < 0.1-12), nonepithelial skin cancer (ERR_{1Sv} = 0.5, 90 percent CI = < -0.1-6.7), and Bowen's tumor (ERR_{1Sv} = 0.86, 90 percent CI = -0.04-3.1), the CIs were extremely wide. Because of the small number of cases, no further analyses were conducted for melanoma, other epithelial carcinomas, and nonepithelial skin cancers.

Basal cell carcinoma

After allowance for radiation effects, the incidence of basal cell carcinoma increased substantially over time. Rates also increased rapidly with attained age. Women had about 25 percent less basal cell carcinoma than men, and in AHS members, the rate was between five and 15 percent higher than for other survivors. In Nagasaki, the rate of basal cell carcinoma was 63 percent higher than in Hiroshima ($P = 0.04$).

Over 75 percent of basal cell carcinomas seen among survivors with doses over one Sv appear to be associated with their radiation exposure (Table 3). A formal test for nonlinearity based on a linear-quadratic model in the full dataset with allowance for age-at-exposure effects provides no evidence ($P > 0.5$) of nonlinearity in the dose-response. Modeling the dose-response using a linear spline with a knot at one Sv improved the fit

Table 1. Distribution of histologic types of skin cancer by various factors; Atomic-bomb survivors (Japan)

	Person-years	Melanoma	BCC ^a	SCC ^b	Other epithelial	Other non-epithelial	Bowen's disease	Total
Gender								
Male	639,740	5	32	34	4	5	10	90
Female	1,055,630	5	48	35	9	5	16	118
City								
Hiroshima	1,175,658	5	51	49	10	6	21	142
Nagasaki	519,712	5	29	20	3	4	5	66
Age at diagnosis (yrs)								
< 50	853,041	2	6	11	0	2	0	21
50 < 60	319,576	0	11	8	0	1	2	22
60 < 70	276,237	3	17	15	2	3	3	43
70+	246,516	5	46	35	11	4	21	122
Age at exposure (yrs)								
< 10	399,850	0	3	3	0	1	0	7
10 < 20	400,148	2	8	9	0	1	0	20
20 < 40	550,043	3	28	18	4	3	9	65
40+	345,329	5	41	39	9	5	17	116
Year of diagnosis								
1958-65	550,531	2	9	17	3	2	3	36
1966-75	582,487	4	19	20	3	1	3	50
1976-87	562,352	4	52	32	7	7	20	122
Anatomical site								
Face		1	36	13	5	3	3	61
Scalp and neck		0	11	7	0	2	0	20
Trunk and limbs		9	29	36	6	5	23	108
External genitals		0	4	13	2	0	0	19
Total	1,695,370	10	80	69	13	10	26	208

^a BCC = basal cell carcinoma.^b SCC = squamous cell carcinoma.**Table 2.** Crude skin tumor incidence rates by histology and level of ultraviolet exposure, 1958-87; Atomic-bomb survivors (Japan)

Histology	Weighted skin dose (Sv ^a)					
	<0.005		0.005-0.99		1+	
	Cases	Rate ^b	Cases	Rate ^b	Cases	Rate ^b
Melanoma	3	0.4	6	0.6	1	1.2
Nonmelanoma skin cancer	67	10.0	83	8.8	22	27.5
BCC ^c	26	3.9	38	4.0	16	20.0
SCC ^d	33	4.9	34	3.6	2	2.5
Other epithelial	4	0.6	6	0.6	3	3.7
Nonepithelial and NOS ^e	4	0.6	5	0.5	1	1.2
Bowen's disease	11	1.6	11	1.1	4	5.0
Ultraviolet exposure						
High (face, hands)						
Nonmelanoma skin cancer	27	4.0	29	3.1	7	8.7
BCC ^c	17	2.5	16	1.7	4	5.0
SCC ^d	7	1.0	10	1.1	1	1.2
Low (rest of body)						
Nonmelanoma skin cancer	40	6.0	54	5.7	15	18.7
BCC ^c	9	1.3	22	2.3	12	15.0
SCC ^d	26	3.9	24	2.5	1	1.2
Migration-adjusted person-years		667,100		948,195		80,079

^a Sv = sievert.^b Rate per 10⁵ persons per year.^c BCC = basal cell carcinoma.^d SCC = squamous cell carcinoma.^e NOS = not otherwise specified.

Table 3. Observed (Obs) and excess skin cancers by dose and histologic type; Atomic-bomb survivors (Japan)

Dose (Sv) category	Subjects	All basal cell						Squamous cell		Bowen's disease	
		All UV ^a exposure ^b		High UV ^a exposure ^b		Low UV ^a exposure ^b		Obs	Excess ^c	Obs	Excess ^c
		Obs	Excess ^c	Obs	Excess ^c	Obs	Excess ^c				
< 0.005	31,708	26	0.1	17	2.4	9	-2.4	33	4.8	11	2.5
0.005 < 0.1	29,124	23	0.8	9	-2.3	14	3.6	21	-2.2	5	-2.3
0.1 < 0.2	5,740	7	2.6	3	0.8	4	1.8	8	2.7	3	1.2
0.2 < 0.5	6,088	6	1.0	3	0.2	3	0.7	3	-3.1	1	-1.1
0.5 < 1	3,633	2	-0.9	1	0.7	1	-0.3	2	-1.8	2	0.8
1 < 2	2,281	6	4.2	1	-0.2	5	4.3	2	-0.5	3	2.2
2 < 3	776	6	5.4	2	1.6	4	3.8	0	-0.9	0	-0.2
3+	799	4	3.5	1	0.7	3	2.8	0	-0.8	1	0.8
Total	80,149	80	16.7	37	3.9	43	14.3	69	-1.8	26	3.9

^a UV = ultraviolet.

^b Degree of UV exposure by body location. High UV exposure area includes the face and hands; low UV exposure area includes the rest of the body.

^c Excess = observed minus expected. Expected numbers of cases were determined on the basis of an internal analysis including a background rate model that allows for effects of age, calendar period, gender, and city. Observed to expected ratios (O/E) can be computed as (Observed/ [Observed-Excess]).

slightly ($P = 0.09$). This value for the knot was chosen *a priori* and we did not try to find the optimal value for the knot. Under the linear-spline model for a person age 30 at exposure, the ERR_{1Sv} is estimated to be 0.7 (90 percent CI = <0.1-2.8). For doses above one Sv, the change in the ERR is estimated to be four per Sv (90 percent CI = 1.9-9). The fit of a linear model with a one Sv threshold was marginally worse than the linear-spline model ($P = 0.12$). At doses less than approximately 1.5 Sv, risk estimates based on the non-linear models are lower than those predicted by the linear model while the opposite is true for higher doses. Figure 1 presents fitted curves for selected dose-response models.

Using a linear model with an age-at-exposure effect, the estimated ERR per Sv for basal cell carcinomas is 1.9

(90 percent CI = 0.6-4.3) for a person exposed to the bombings at age 30. Excess risks were strongly associated with age at exposure ($P < 0.001$), with the risk decreasing by about 11 percent (90 percent CI = 6%-16%) with each additional year of age at exposure. As indicated in Table 4, further adjustment for gender or time since exposure had little effect on the risk after allowing for an age-at-exposure trend. Attained age was found not to affect the ERR after allowance for age at exposure. The ERR for developing basal cell carcinoma in parts of the body not heavily exposed to UV rays is almost 10 times higher than in the face and hands. The ERR for Nagasaki is 1.3 times (90 percent CI = 0.4-4.0) the risk for Hiroshima, and the ERR for AHS members is 1.4 (90 percent CI = 0.4-5.0) times that for non-members. Without allowing for the effect of age at exposure, there is a significant ($P < 0.001$) decrease in the ERR with attained age. Adding age at exposure to this model leads to a significant improvement in the fit (χ^2 (1 df) = 4.46, $P = 0.04$) but the resulting model fits only slightly better (χ^2 (1 df) = 0.57, $P = 0.45$) than one in which the ERR depends only on age at exposure. On the basis of these analyses, a model including effect modification only by age at exposure provides the most parsimonious description of the current data.

Although interpretation of excess absolute risks (EAR) for nonmelanoma skin cancer is complicated by improvements in ascertainment and the dramatic increase in incidence during the last two decades, it is useful to note that the EAR increased rapidly with time. After allowing for the effect of improvements in ascertainment with calendar time period on both background and excess rates, this increase is proportional to time-since-exposure raised to the 3.5th power (95 percent CI

Figure 1. Basal cell carcinoma radiation dose-response curves for various excess relative risk models; Atomic-bomb survivors (Japan). The plot also includes fitted values and 90% confidence intervals for specific dose categories.

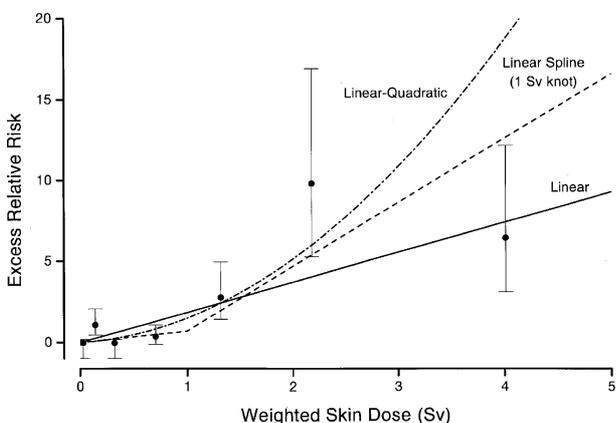


Table 4. Basal cell carcinoma fitted linear risk estimates by gender, time since exposure, and ultraviolet exposure; Atomic-bomb survivors (Japan)

Variable	Cancers	Person-years	ERR ^a per Sv ^b	(90% CI) ^c
Age at exposure (yrs)			Heterogeneity ^d $P = 0.03$; trend ^e $P < 0.001$	
0-9	3	399,850	21	(4.1-73)
10-19	8	400,150	6.7	(2.1-17)
20-39	28	550,040	1.7	(0.5-3.8)
40+	41	345,330	0.7	(-0.05-2.2)
Years since exposure ^f			Heterogeneity ^d $P > 0.17$; trend ^e $P > 0.5$	
13-20	9	550,530	< -0.1	(< -0.1-11)
21-30	19	582,490	6.0	(1.4-18)
31-42	52	562,350	1.6	(0.5-3.7)
Gender ^f			Heterogeneity ^d $P > 0.5$	
Female	48	1,055,630	1.6	(0.5-4.1)
Male	32	639,740	2.7	(0.5-9.1)
UV ^g exposure ^f			Heterogeneity ^d $P < 0.02$	
High (face and hands)	37	1,695,370	0.4	(< -0.1-2.1)
Low (rest of body)	43	1,695,370	4.7	(1.2-13)

^a ERR = excess relative risk.

^b Sv = sievert.

^c CI = confidence interval.

^d Test of the hypothesis that effects differ across categories.

^e Test for log-linear trend across categories.

^f Estimates are for a person exposed to the bombings at age 30. The estimates depend on age at exposure with larger risks for those exposed earlier and smaller risks for those exposed later in life. The risks change by about 11% for a one-year change in age at exposure. Trend tests are adjusted for age at exposure effects on the excess risk.

^g UV = ultraviolet.

= 0.9-7, $P = 0.008$). Under this model, 25 years after exposure, the EAR is 0.2 cases per 10,000 PYSv (95 percent CI = 0.05-0.5). There is no evidence of an additional effect of attained age on the EAR. The data do not suggest that the EAR varied with gender ($P = 0.2$) or with age at exposure ($P > 0.5$) after allowing for time-since-exposure. Without adjustment for time-since-exposure, the increase in the EAR is estimated to be proportional to attained age (*i.e.*, attained age raised to the first power) but this trend is not statistically significant (95 percent CI = -0.6-3.0). Adding either time-since-exposure or age-at-exposure to this model significantly improves the fit. Taken together, these results suggest that temporal changes in the EAR are best described in terms of time-since-exposure.

Squamous cell carcinoma

In contrast to the findings for basal cell carcinoma, no dose-response (linear or nonlinear) was seen for squamous cell carcinoma (Table 3). Further, we did not observe an effect of gender, attained age, age at exposure, or time since exposure on the ERR (P value > 0.5 for all factors). We also analyzed the data excluding the genital tumors but still no radiation effect was observed.

Bowen's Disease

While the point estimate of the ERR ($ERR_{1Sv} = 0.85$) suggested a dose-response relation for Bowen's disease,

the CI was wide (90 percent CI = -0.04-3.1), and the data are consistent with a broad range of risks. Unlike the results for basal cell carcinoma and most other solid cancers, risk appeared to increase with increasing age at exposure. There was no evidence against a hypothesis of linearity ($P > 0.5$ for linear-quadratic and linear-spline models).

Discussion

The relatively rare occurrence of skin cancer in Japan allows the Hiroshima and Nagasaki tumor registries to collect data on nonmelanoma skin cancer. While case ascertainment of nonmelanoma skin cancers is clearly not complete, particularly before the establishment of the tissue registries in 1973, we used multiple data sources to identify tumors – 80 percent of the skin cancers were identified from two or more sources – and made attempts to augment case ascertainment through additional record searches. We also compared the age-standardized incidence rates of melanoma and nonmelanoma skin cancers in the Hiroshima and Nagasaki population-based tumor registries with those reported from the other Japanese and Asian registries. Hiroshima and Nagasaki had the two highest incidence rates of the six Japanese registries and were the third and fourth highest of 17 Asian registries of Asian populations.²¹ The higher incidence of skin tumors in Nagasaki compared

with Hiroshima could be attributed, in part, to the routine reporting of 'tumor-like lesions' to the Nagasaki Registry.²² Since all of these lesions were reviewed by the study pathologists, there was more of a chance of identifying additional early-stage carcinomas in Nagasaki. The relatively low BCC:SCC ratio found in this study might indicate some underreporting of basal cell carcinomas, but it also could reflect a difference in the distribution of histologic types in a non-White population. For example, in some Asian populations, ratios of less than one have been reported,²³ and among Blacks in the United States, there is a predominance of squamous cell carcinoma.²⁴

By identifying cases from the tumor registries, we could prevent reporting bias, but case ascertainment could only begin in 1958, *i.e.*, 13 years after the bombings. Since skin cancer is a disease of older age, few cases would be expected to occur during these 13 years. Indeed, only nine cases were diagnosed between 1958-65. Shore *et al*¹¹ only found an excess risk 20 or more years after radiotherapy. This finding may be due to a long latency period, but, more likely, it is due to the young age of the study subjects.

The pathology review revealed errors in diagnoses taken directly from the tumor registries. Of the 181 skin cancers analyzed by Thompson *et al*,⁵ six (3.3 percent) were actually Bowen's disease; 26 (14.4 percent) were benign skin tumors; three were non-neoplastic skin diseases; two were non-skin neoplasms; and two were incorrectly identified as belonging to LSS cohort members. Because we used the WHO skin classification¹⁴ for this study, 19 genital skin cancers, four skin lymphomas, and two connective-tissue skin cancers were added to the study cases. Additional medical information obtained during this study allowed a final diagnosis for 10 previously pending cases, and five cancers previously coded to another cancer site were reclassified as skin cancers.

In this study, we found the risk of radiation-induced skin cancer varied markedly by histologic type. The ERR was almost three times higher for basal cell carcinoma than for nonmelanomas as a group. For basal cell carcinoma, age at exposure was the major factor in determining ERR; however, the lack of an age-at-exposure effect in the EAR suggests that high ERRs for those exposed as children are likely to decrease with time. In a skin cancer prevention trial,²⁵ the relative risk of BCC also increased with younger age at radiotherapy.

The A-bomb survivor data clearly indicate that basal cell carcinoma can be induced by acute exposure to ionizing radiation at doses in the range of one to four Sv. Results from the New York (USA)¹¹ and Israel⁹ tinea studies have demonstrated that ionizing radiation can

induce skin cancer at doses above four Gy, but other studies have not provided convincing direct evidence of excess risks following low doses.¹⁰ The tinea studies suggest a linear ERR_{1Gy} in the range of five to seven Gy following childhood exposure. Our linear estimates for children are 10 or more times these values (albeit with considerable uncertainty). Although we found some evidence of nonlinearity in the dose-response, precise characterization of the slope is difficult.

As in several,^{9,11,25} but not all,²⁶ studies of persons exposed to radiotherapy, we found no increased risk of squamous cell carcinoma. In rats, squamous cell carcinomas predominate at high doses.²⁷ Since almost all atomic-bomb survivors had skin doses below four Sv and close to 95 percent had doses below one Sv, an excess risk of squamous cell carcinoma might not be expected.

Experimental data suggest that about 70 percent of the proliferating stem cells are located in the basal layer of the epidermis, and they appear to proliferate faster than those in the suprabasal layer.²⁷ Since SCC usually occurs in the suprabasal cell layer and BCC develops in the basal layer,^{28,29} our findings for BCC and SCC are consistent with experimental studies suggesting that the basal layer of the epidermis is the most radio-sensitive skin tissue.

Although Bowen's disease is considered either a precursor lesion of squamous cell carcinoma²⁸ or squamous cell carcinoma *in situ*,²⁹ our results suggest an excess risk for Bowen's disease. While *in situ* carcinoma may become invasive, invasive squamous cell carcinoma can develop without going through this stage and can arise in association with pre-existing actinic keratosis or atypical epidermal hyperplasia.²⁹ It may be that actinic keratosis and atypical epidermal hyperplasia are less affected by radiation exposure than Bowen's disease and that many of the squamous cell carcinomas in this series may have developed from those conditions.

Based on the comparison of risk estimates from various studies as well as a lack of skin cancer excess in African-Americans (Blacks) treated with ionizing radiation for tinea capitis,¹¹ Shore¹⁰ has hypothesized an interaction between UV and ionizing radiation in skin cancer induction. Our data, however, do not support this hypothesis. We found an extremely high overall ERR of basal cell carcinoma associated with ionizing radiation in a population with low rates of UV-induced skin cancer. The ERR was significantly higher for parts of the body usually shielded from UV radiation compared with parts generally exposed to UV exposure. This finding does not indicate that UV-shielded skin is more sensitive to ionizing radiation, but rather that BCCs occur more uniformly over the body surface among heavily exposed survivors than they do among

survivors with little exposure. It is also possible that among people with a relatively high melanin content, any interaction between UV and ionizing radiation is minimized. A case report of an African-American patient with nevoid basal-cell-carcinoma syndrome suggests that while Blacks have considerable protection against developing UV-induced BCC, they do develop BCC following exposure to ionizing radiation.³⁰ The suggestion of an interaction between UV-exposure and radiation may also reflect a confounding effect of age at exposure. In atomic-bomb survivors, the relative risks declined sharply with age at exposure and the risk was no longer significant in people exposed after 40 years of age. The primary evidence for UV/ionizing-radiation interaction comes from the comparison of risks observed in studies of adults exposed to ionizing radiation in UV-shielded body sites with risks seen in studies of children or infants exposed to ionizing radiation in UV-exposed areas of the body.¹⁰ One exception is the study of uranium miners;³¹ however, the miners were exposed to high-linear energy transfer (LET) radiation and had special dermatologic examinations.

Because ascertainment and diagnosis of nonmelanoma skin cancer and, particularly, basal cell carcinoma, vary with calendar year, age, skin pigmentation, and possibly gender, the specific absolute risk estimates presented are difficult to generalize to populations other than the one studied. The rapid increase in the EAR with time is, however, consistent with the notion of a long latent period for radiation-induced nonmelanoma skin cancers. It is important to continue follow-up of this cohort to determine lifetime risks.

References

- Johnson MLT, Land CE, Gregory PB, Taura T, Milton, RC. *Effects of Ionizing Radiation on the Skin, Hiroshima and Nagasaki*. Hiroshima, Japan: Radiation Effects Research Foundation, 1969; RERF Technical Report Series TR 20-69.
- Sadamori N, Otake M, Honda T. *Study of Skin Cancer Incidence in Nagasaki Atomic Bomb Survivors, 1958-85*. Hiroshima, Japan: Radiation Effects Research Foundation, 1991; RERF Technical Report Series TR 10-91.
- Sadamori N, Mine M, Hori M. Skin cancer among atomic bomb survivors [Letter]. *Lancet* 1989; 1: 1267.
- Sadamori N, Mine M, Honda T. Incidence of skin cancer among Nagasaki atomic bomb survivors. *J Radiat Res* 1991; 32(Suppl 2): 217-25.
- Thompson DE, Mabuchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958-1987. *Radiat Res* 1994; 137: S17-S67 [based on RERF TR 5-92].
- Little MP, Charles MW. The risk of non-melanoma skin cancer incidence in the Japanese atomic bomb survivors. *Int J Radiat Biol* 1997; 71: 589-602.
- Yamada M, Kodama K, Fujita S, et al. Prevalence of skin neoplasms among the atomic bomb survivors. *Radiat Res* 1996; 146: 223-6.
- Hildreth NG, Shore RE, Hempelmann LH, Rosenstein M. Risk of extrathyroid tumors following radiation treatment in infancy for thymic enlargement. *Radiat Res* 1985; 102: 378-91.
- Ron E, Modan B, Preston DL, Alfandary E, Stovall M, Boice JD Jr. Radiation-induced skin carcinomas of the head and neck. *Radiat Res* 1991; 125: 318-25.
- Shore RE. Overview of radiation-induced skin cancer in humans. *Int J Radiat Biol* 1990; 57: 809-27.
- Shore RE, Albert RE, Reed M, Harley N, Pasternack BS. Skin cancer incidence among children irradiated for ringworm of the scalp. *Radiat Res* 1984; 100: 192-204.
- Van Vloten WA, Hermans J, Van Daal WAJ. Radiation-induced skin cancer and radiodermatitis of the head and neck. *Cancer* 1987; 59: 411-4.
- World Health Organization. *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (ICD-9)*. Geneva, Switzerland: World Health Organization, 1975.
- World Health Organization. *International Histological Classification of Tumours. No. 12, Histological Typing of Skin Tumours*. Geneva, Switzerland: World Health Organization, 1974.
- Roesch WC, ed. *Final Report on the Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki*. Hiroshima, Japan: Radiation Effects Research Foundation, 1987.
- 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 [based on RERF TR 2-89].
- Sposto R, Preston DL. *Correcting for Catchment Area Nonresidency in Studies Based on Tumor-Registry Data*. Hiroshima, Japan: Radiation Effects Research Foundation, 1992; RERF Commentary and Review Series CR 1-92.
- Breslow NE, Day NE. *Statistical Methods in Cancer Research. Vol. 2. The Design and Analysis of Cohort Studies*. Lyon, France: International Agency for Research on Cancer, 1987; IARC Sci. Pub. No. 82.
- Cox DR, Hinkley DV. *Theoretical Statistics*. London, UK: Chapman and Hall, 1974.
- Preston DL, Lubin JH, Pierce DA. *Epicure User's Guide*. Seattle, WA (USA): HiroSoft International Corporation, 1993.
- Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. *Cancer Incidence in Five Continents, Vol. VII*. Lyon, France: International Agency for Research on Cancer, 1997; IARC Sci. Pub. No. 143.
- Mabuchi K, Soda M, Ron E, et al. Cancer incidence in atomic bomb survivors. Part I: Use of the tumor registries in Hiroshima and Nagasaki for incidence studies. *Radiat Res* 1994; 137:S1-S16.
- Scotto J, Fears TR, Kraemer KH, Fraumeni JF Jr. Nonmelanoma skin cancer. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. New York, NY (USA): Oxford University Press, 1996: 1313-30.
- Gordon D, Silverstone H. Worldwide epidemiology of premalignant and malignant cutaneous lesions. In: Andrade R, Gumport S, Popkin G, Rees T, eds. *Cancer of the Skin: Biology-Diagnosis-Management, Vol. I*. Philadelphia, PA (USA): Saunders, 1976: 405-34.
- Karagas MR, McDonald JA, Greenberg ER, et al. Risk of basal cell and squamous cell skin cancers after ionizing radiation therapy. *J Natl Cancer Inst* 1996; 88: 1848-53.

26. Gallagher RP, Bajdik CD, Fincham S, *et al.* Chemical exposures, medical history, and risk of squamous and basal cell carcinoma of the skin. *Cancer Epidemiol Biomark Prev* 1996; **5**: 419-24.
27. International Commission on Radiation Protection. *The Biological Basis for Dose Limitation in the Skin*. Oxford, UK: Pergamon Press, 1991; Publication 59, Annals of the ICRP 22 (2).
28. Allen AC. Skin. In: Kissane JM, ed. *Anderson's Pathology*. Vol. 2. 9th Ed. St. Louis, MO (USA): C.V. Mosby Company, 1990: 1751-800.
29. Murphy GF, Elder DE. *Atlas of Tumor Pathology. Non-melanocytic Tumors of the Skin*. Washington, DC (USA): Armed Forces Institute of Pathology, 1991: 11-60.
30. Korczak JF, Brahim JS, DiGiovanna JJ, Kase RG, Wexler LH, Goldstein AM. Nevoid basal cell carcinoma syndrome with medulloblastoma in an African-American boy: A rare case illustrating gene-environment interaction. *Am J Med Genet* 1997; **69**: 309-14.
31. Sevcova M, Sevc J, Thomas J. Alpha irradiation of the skin and the possibility of late effects. *Health Phys* 1978; **35**: 803-6.