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Study of Skin Cancer Incidence in Nagasaki Atomic Bomb Survivors, 1958–85

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業績報告書シリーズ

長崎原爆被爆生存者の皮膚癌発生率調査，1958−85年[§]

Study of Skin Cancer Incidence in Nagasaki Atomic Bomb Survivors, 1958–85

貞森直樹[a]　大竹正徳[b]　本田武夫[c]

要　約

長崎寿命調査拡大集団（LSS-E85）の被爆者コホートの皮膚癌発生に関する電離放射線被曝の影響をDS86線量を用いて検討した。DS86線量が付与された25,942人の被爆者のうち，1958年4月1日から1985年12月31日までの期間に悪性黒色腫を含めて47の皮膚癌症例が長崎腫瘍登録で確認された。 加算的相対リスクモデルに基づいた皮膚癌についての線量−反応関係はしきい値のない線形であり，線形−二次曲線形ではなかった。LSS-E85集団の過剰相対リスクはグレイ当たり2.2で，95％信頼区間グレイ当たり0.5−5.0の範囲で高い有意性が認められた。更に，AHS集団の過剰相対リスクはグレイ当たり3.1で，95％信頼区間グレイ当たり0.6−20.3の範囲で有意であった。中性子RBEを10として線量当量を用いると，LSS-E85集団の過剰相対リスクはシーベルト当たり2.0（95％信頼区間0.7−4.5）に，また，AHS集団の過剰相対リスクも同様にシーベルト当たり2.7（95％信頼区間0.6−17.8）に減少した。LSS-E85及びAHS両集団において男女間の過剰相対リスクに有意差はなかったが，被爆時年齢及び被爆からの時間的変化についての過剰相対リスクに有意に高い増加を認めた。悪性黒色腫の4症例を含む場合と含まない場合の皮膚癌症例における過剰相対リスクは，LSS-E85集団においてほとんど同じ線形線量−反応を示した（AHS集団では悪性黒色腫症例はなかった）。これは原爆被爆と皮膚癌に有意性の高い線量−反応が証明された初めての報告である。

[§]本業績報告書は研究計画書RP 2-85に基づく。本報告にはこの要約以外に訳文はない。承認1991年8月12日。印刷1993年3月。

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Technical Report Series

Study of Skin Cancer Incidence in Nagasaki Atomic Bomb Survivors, 1958–85§

Naoki Sadamori, M.D.[a]; Masanori Otake, Ph.D.[b]; Takeo Honda, D.Sc.[c]

Summary

The effects of exposure to ionizing radiation on skin cancer incidence in a cohort of atomic bomb (A-bomb) survivors in the Nagasaki Extended Life Span Study (LSS-E85) sample have been investigated. Among 25,942 exposed survivors at risk whose DS86 dose estimates were available, 47 cases of skin cancer including malignant melanoma were confirmed in the Nagasaki Tumor Registry during the period from 1 April 1958 to 31 December 1985. The dose-response relationship of skin cancer based on an additive relative risk model showed linearity without threshold, not a linear-quadratic curve. The excess relative risk (ERR) of 2.2 per gray in the LSS-E85 sample was highly significant (95% confidence limits: 0.5 to 5.0). In addition, the ERR of 3.1 per gray in the Adult Health Study (AHS) sample was also significant (95% confidence limits: 0.6 to 20.3). When dose equivalents based on a relative biological effectiveness of neutrons of 10 were used, the ERR in the former sample decreased to 2.0 per sievert (95% confidence limits: 0.7–4.5), and the risk in the latter group also declined, to 2.7 per sievert (95% confidence limits: 0.6–17.8). The ERRs did not differ significantly between males and females in the LSS-E85 and AHS samples, but a highly significant increase was observed for the ERR of age at exposure and time trend since exposure. The ERR of skin cancer cases including and excluding 4 malignant melanoma cases for the LSS-E85 sample (there were no malignant melanoma cases in the AHS sample) showed almost the same linear dose response. This is the first report to demonstrate a highly significant dose-response relationship between A-bomb exposure and skin cancer incidence.

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Introduction

The effects of radiation-induced carcinogenesis seen to date in the long-term follow-up studies of the Japanese atomic bomb (A-bomb) survivors have been the significantly increased occurrence of leukemia, multiple myeloma, and cancers of the thyroid, lung, stomach, esophagus, female breast, urinary tract, and colon.[1,2] Chromosomal aberrations caused by ionizing radiation are still being observed in cultured skin fibroblasts derived from A-bomb survivors. However, because cancer development in the scar tissue of survivors is extremely rare, the incidence and developmental mechanism of cicatricial cancer in A-bomb survivors have not been studied. The median latent period of cicatricial cancer developing at the sites of heat burns is reported to be 35–48 years.[3,4]

In 1969, Johnson et al[5] carried out an extensive study of skin cancer in A-bomb survivors but they found no evidence of increased incidence. Because the latent period from therapeutic irradiation to the occurrence of skin cancer is very long, long-term observations are necessary to determine if the occurrence of skin cancer is increased in A-bomb survivors. Thus the purpose of this study is to evaluate the risk of skin cancer from exposure to ionizing radiation among Nagasaki A-bomb survivors from 1958–85 and to examine, to the extent these data allow, the temporal pattern and effect modification in the excess risk of skin cancer from whole-body exposure to radiation.

Materials and Methods

In the Extended Life Span Study (LSS-E85) sample in Nagasaki, composed of 31,757 persons who were proximally or distally exposed to the A-bomb, there

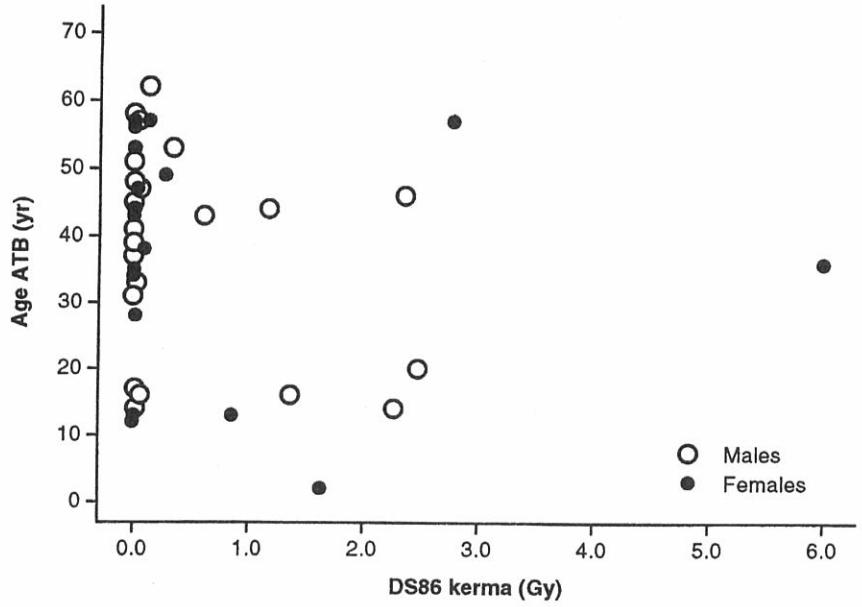

Figure 1. Distribution by sex and age at the time of the bombing (ATB) of 47 cases of skin cancer based on the Dosimetry System 1986 (DS86). Of the 47 cases, 28 persons (15 males and 13 females) were exposed to ≥0.01 Gy.

were 16 subjects whose family register (*koseki*) or life status could not be identified, 17 subjects who were lost due to migration from Japan, and 3625 subjects whose DS86 dose estimates[6] were not available. Furthermore, because the Nagasaki Tumor Registry was established on 1 April 1958,[7] the 2157 deaths prior to that date were excluded from the study sample. The present analysis is based on the experiences of 25,942 A-bomb survivors during the period from 1 April 1958 to 31 December 1985. Seventy-seven cases of benign, malignant, and metastatic skin tumor in the LSS-E85 were identified from the tumor registry data. Of the 77 skin tumor cases, 13 were DS86 dose-unknown cases and 5 were not-in-city (NIC) at the time of the bombing (ATB). One case (Master File No. [redacted]) was excluded from this study because the onset of skin cancer occurred in September 1955. Medical records and histological reports were reviewed for all the selected cases. When the diagnosis in a pathology report was questionable, pathological specimens were obtained and dermatologists were consulted. Of the 58 remaining cases, 9 were excluded because they were either non-skin cancer or Bowen's disease (a precancerous state of skin cancer) and 2 were excluded due to the loss of their clinical charts and pathological preparations (see Appendix A). Of 58 cases of skin tumor, 47 cases of skin cancer including malignant melanomas were detected during the 28-year period reviewed. Their clinical and histological findings, sample classification, sex, age ATB, and DS86 dose estimates are shown in Appendix B. Of the 47 skin cancer cases with DS86 dose estimates, 28 (15 males and 13 females) were exposed to 0.01 Gy or more. The 47 cases included 25 cases of basal cell epithelioma, 16 cases of squamous cell carcinoma, one case of basosquamous cell carcinoma, 4 cases of malignant melanomas, and one case of sweat gland carcinoma. Figure 1 shows the relationship between the age ATB and dose of the 47 skin cancer cases.

Dosimetry and neutron RBE

DS86 dose estimates[8] for individual survivors were computed in one of two ways.[6] For survivors exposed within 2000 m of the hypocenter in Nagasaki, whenever detailed shielding histories existed, dose estimates were obtained by modeling directly the circumstances attending an individual's exposure including his or her posture and orientation toward the burst point; fixed transmission coefficients were not used. These estimates are termed "direct." At distances beyond 2000 m, individual doses were assigned by computing average transmission factors from unshielded individuals exposed between 1000 m and 2000 m and by using regression equations from DS86 dosimetry data. Such estimates are said to be "indirect." However, it should be noted that even when detailed shielding histories were available for exposures beyond 2000 m, direct computations were only possible for exposures at <2500 m. If the total (gamma + neutron) kerma exceeded 6 Gy it was truncated to 6 Gy. Table 1 gives the mean gamma and neutron DS86 doses by dose category.

Generally, the neutron relative biological effectiveness (RBE) is estimated from cancer incidence or mortality among the A-bomb survivors by comparing the dose response as a function of neutron and gamma components. A-bomb radiation dose equivalents in Nagasaki are almost totally accounted for by gamma rays, but the neutron dose is not zero, as is shown in Table 1 and

Table 1. Crude annual incidence rate of skin cancer among atomic bomb survivors in Nagasaki, 1958–85, based on the Dosimetry System 1986

	Extended Life Span Study (LSS-E85) sample						Adult Health Study (AHS) cohort					
	Mean dose (Gy)		Number of				Mean dose (Gy)		Number of			
Dose category (Gy)	Gamma	Neutron	Person-years	Cases of skin cancer	Rate per 100,000		Gamma	Neutron	Person-years	Cases of skin cancer	Rate per 100,000	
≥3.00	4.64	0.07	2907 (1436)*	1 (0)	34.4 (0.0)	71.6 (91.4)	4.53	0.07	2438 (1232)	1 (0)	41.0 (0.0)	83.1 (104.3)
2.00–2.99	2.34	0.03	4072 (1847)	4 (3)	98.2 (162.4)		2.34	0.03	3576 (1643)	4 (3)	111.9 (182.6)	
1.00–1.99	1.35	0.02	19,699 (8541)	3 (2)	15.2 (23.4)		1.35	0.02	17,564 (7496)	2 (1)	11.4 (13.3)	
0.50–0.99	0.71	0.01	21,448 (8603)	2 (1)	9.3 (11.6)		0.73	0.01	15,927 (6263)	2 (1)	12.6 (16.7)	
0.10–0.49	0.24	0.00	48,225 (19,106)	4 (2)	8.3 (10.5)		0.27	0.00	12,427 (4591)	1 (0)	8.0 (0.0)	
0.01–0.09	0.02	0.00	212,635 (79,229)	14 (7)	6.6 (8.8)		0.06	0.00	3731 (1245)	1 (0)	26.8 (0.0)	
0.00	0.00	0.00	303,726 (126,468)	19 (9)	6.3 (7.1)		0.00	0.00	51,091 (22,371)	2 (2)	3.9 (8.9)	
Total	0.13	0.00	612,711 (245,229)	47 (24)	7.6 (9.8)		0.55	0.01	106,754 (44,841)	13 (7)	12.2 (15.6)	

NOTE: The numbers of subjects corresponding to the seven dose categories from 0.00 to ≥3.00 Gy are 12,858, 9054, 2040, 879, 822, 167, and 122 for the LSS-E85 and 2010, 150, 514, 631, 708, 146, and 98 for the AHS cohort.

*The values in parentheses are the person-years at risk for males or the number of males.

Appendix B. From this fact, a constant neutron RBE value for skin cancer in Nagasaki based on DS86 dosimetry would be of interest. Recently, Otake and Schull[9] investigated the quantitative relationship of ionizing radiation to the occurrence of posterior lenticular opacities among the A-bomb survivors in both cities, and they suggest a constant neutron RBE of 12. The BEIR III report[10] suggests that the RBE for high-linear energy transfer (LET) radiation for a single cataractogenic exposure is in the range of 2–9. The International Commission on Radiological Protection[11] also gives a table of RBE values for the production of lens opacities with single exposures to X or gamma rays or fission neutrons. These values range from 2 to 20. Some studies of experimental cataractogenesis[12,13] suggest an RBE of approximately 9 for the induction of mild opacities in mice exposed to fast neutrons of 2- to 3-MeV mean energy. A constant neutron RBE of 10 was therefore assumed for our analysis of skin cancer incidence.

Statistical model

We shall consider some models that permit assessments of the risk for radiation-induced skin cancer in order to compare it with the incidence of spontaneously occurring skin cancer. The relationship of radiation exposure to skin cancer incidence can be evaluated by an additive relative risk model: This model includes situations in which the effects increase linearly or linear-quadratically with dose.

Let a hazard function $\lambda_i(t:h)$ for data analysis of relative risks be constant in time $t = 1, 2, \ldots$ within each interval of that grouping. We shall assume that the number of observed skin cancer cases, $Y_i(t)$, for the ith stratum or cell ($i = 1, 2, \ldots, k$) has independently a Poisson distribution with mean $R_i(t)\lambda_i(t;h)$, where $R_i(t)$ denotes the number of person-years (PY) at risk depending on t in the ith cell, and k strata are classified by sex, age ATB (<20, 20–29, 30–39, 40–49 and ≥50), dose (<0.01, 0.01–0.09, 0.10–0.49, 0.50–0.99, 1.00–1.99, and ≥2.00 Gy), and t is time since exposure (1958–61, 1962–65, 1966–69, 1970–73, 1974–77, 1978–81, and 1982–85). The incidence data are classified into 420 groups for skin cancer cases composed of group cuts of five variables such as sex (2) × age ATB (5) × time (7) × dose (6). Appendix C gives the results of linear dose-response and linear-quadratic dose-response relationships of the additive relative risk models to skin cancer data. As is evident from Appendix C, the deviance statistics suggest that Model 1 is linear for skin cancer. Figure 2 shows the excess deaths per 100,000 PY at risk and 95% confidence limits by DS86 kerma (in gray) and sample. A significant excess of skin cancer cases was evident with a linear dose-response pattern for both the LSS-E85 and the Adult Health Study (AHS) samples.

Results

In the LSS-E85 fixed cohorts, comparing 13,084 exposed (≥0.01 Gy) and 12,858 control (<0.01 Gy) survivors whose DS86 doses were available, 47 skin cancer cases (13 in the AHS fixed cohort) were observed in the period from 1 April 1958 to 31 December 1985. The exposed survivor group consists of 5173 males and 7911 females, and the control group is composed of 5496 males and 7362 females. The crude annual incidence rates of skin cancer per 100,000 PY at risk by sex and sample over the period 1958–85 and the average DS86 gamma-ray and

neutron kerma in the dose groups are given in Table 1 and Figure 3. The crude annual incidence rates of skin cancer, ignoring confounding factors such as age ATB and time since exposure, increase markedly with increasing DS86 dose, especially for doses ≥ 2.0 Gy, with average kermas of 3.36 and 3.27 in the LSS-E85 and AHS survivors, respectively.

Dose-response relationship and relative or excess risk

The dose-response pattern of skin cancer risk in Nagasaki suggests a linear trend without threshold for DS86 dosimetry as the best fit to the data, but other models are not excluded because of the limited data (Appendix C). Table 2 gives the dose-response relationship of linear regression coefficients per DS86 gray kerma and per DS86 sievert dose equivalents based on an assumed neutron RBE of 10 for skin cancer incidence data. A highly significant excess relative risk (ERR) was manifestly observed in the linear dose-response trend. The ERRs of 2.2 per gray and 2.0 per sievert in the LSS-E85 sample were highly significant (95% confidence limits: 0.5 to 5.0 per gray and 0.7 to 4.5 per sievert, respectively), and the ERRs of 3.1 per gray and 2.7 per sievert in the AHS sample were also significant (95% confidence limits: 0.6 to 20.3 per gray and 0.6 to 17.8 per sievert, respectively). A significant relationship was also noted for males and females (Table 2). When we compare the risks between males and females, the ERRs were in the ranges of 2.1–2.4 per gray (95% confidence limits: 0.3 to 7.6) and 1.9–2.2 per sievert (95% confidence limits: 0.4 to 6.9), respectively, in the LSS-E85 sample. No significant difference in ERR by sex was noted in the LSS-E85 and the AHS samples (Table 3).

Significant excesses of cases per 100,000 person-year-gray (PYGy) and 95% confidence limits were evidently observed with a linear dose-response pattern for both the LSS-E85 and the AHS samples (Figure 2). The similar pattern of excess cases per 100,000 person-year-sievert (PYSv) based on a neutron RBE of 10 was examined for age ATB (attained age) groups and periods (Figures 4 and 5). A

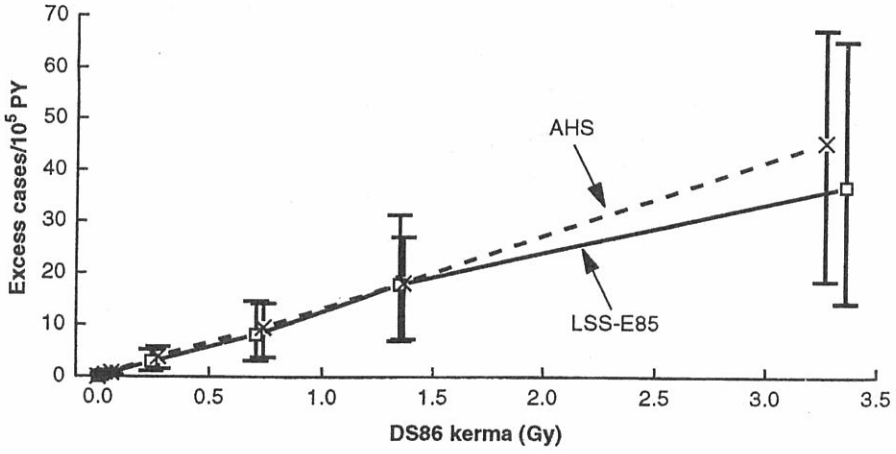

Figure 2. Excess cases of skin cancer per 10^5 person-years (PY) and 95% confidence limits by sample. AHS = Adult Health Study; LSS-E85 = Extended Life Span Study sample.

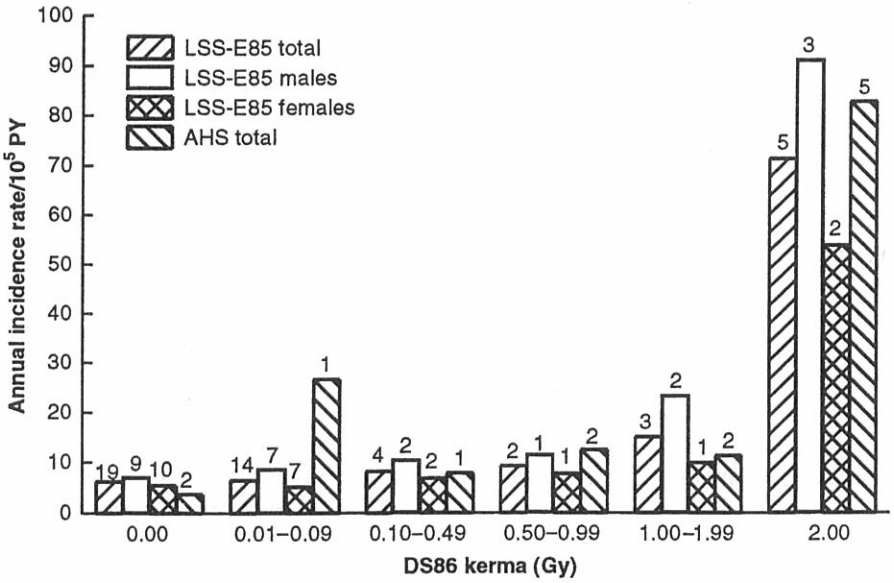

Figure 3. Crude annual incidence rate of skin cancer per 10^5 person-year (PY) among exposed survivors in the Nagasaki Extended Life Span Study sample (LSS-E85) and Adult Health Study (AHS), 1958–85. The number of skin cancer cases is indicated above each bar.

significant number of excess cases per 100,000 PYSv was noted with increasing age in both samples, and the number of excess cases per 100,000 PYSv fluctuated widely with period for the AHS sample, but not for the LSS-E85 sample. As is summarized in Table 3, a highly significant ERR was observed with increasing age at exposure and time since exposure. The ERRs of skin cancer cases including and excluding 4 malignant melanoma cases (there were none in the AHS sample) were of almost the same magnitude.

It is of interest to examine the years exhibiting no excess risk in the period from A-bomb exposure to the development of skin cancer. Risk may be defined as an evaluation of the relative excess difference between background and radiogenic effects. Let us consider the approximate period from exposure to clinical onset of skin cancer when significant radiogenic excess risks are observed. Figure 6 gives variations of the relative risk of skin cancer per sievert with the 95% lower confidence limit based on DS86 dose equivalents assuming a neutron RBE of 10. A significant risk was noted after the period 1958–69 for the LSS-E85 sample and after 1958–77 for the AHS sample, but not for earlier sampling periods. The relative risk for the significant excess periods was roughly threefold per sievert higher than the background level.

Discussion

Exposure to A-bomb radiation is significantly related to the increased occurrence of leukemia, multiple myeloma, and cancers of the thyroid, female breast, lung, and stomach.[1,2] There have been many reports of skin cancer induced by

medical irradiation, including one case of squamous cell carcinoma reported by Frieben[14] in 1902. In 1984 Hood and Young[15] pointed out first, that superficial irradiation results in well-recognized late sequelae including not only sclerosis and atrophy of the skin and subcutaneous tissue, but also the development of benign and malignant tumors of the skin and adjacent structures, and second, that the long latency between irradiation and its late effects allowed the early uncontrolled use of radiation treatment for benign conditions. However, in 1969 Johnson et al.[5] reported that no increase in the incidence of skin cancer was observed in A-bomb survivors, and no specific studies on this matter were conducted thereafter.

The incidence of skin cancer during the period 1958–85 was examined using the LSS-E85 and AHS samples based on data from the Nagasaki Tumor Registry

Table 2. Excess relative risk (ERR) of skin cancer and 95% confidence limits based on Dosimetry System 1986 (DS86) kerma and dose equivalents

Item	No. of skin cancer cases	ERR per Gy or per Sv	No. of excess cases/10^5 PYGy or 10^5 PYSv
		DS86 kerma (Gy)	
		LSS-E85 sample	
All	47 (28)*	2.19 (0.53, 4.98)**	12.08 (4.74, 21.45)
Males	24 (15)	2.08 (0.41, 6.14)	16.07 (3.91, 32.22)
Females	23 (13)	2.36 (0.31, 7.56)	9.12 (1.46, 20.64)
		AHS sample	
All	13 (11)	3.09 (0.62, 20.26)	13.68 (5.51, 20.13)
Males	7 (5)	2.83 (0.29, 24.13)	16.14 (3.48, 25.33)
Females	6 (6)	3.29 (no est., no est.)	11.66 (no est., no est.)
		DS86 dose equivalent (Sv) based on an RBE of 10	
		LSS-E85 sample	
All	47 (28)*	1.98 (0.66, 4.51)**	10.97 (4.30, 19.51)
Males	24 (15)	1.88 (0.37, 5.53)	14.55 (3.54, 29.24)
Females	23 (13)	2.15 (0.29, 6.89)	8.33 (1.34, 18.82)
		AHS sample	
All	13 (11)	2.71 (0.56, 17.81)	12.26 (4.98, 18.23)
Males	7 (5)	2.57 (0.26, 21.81)	14.61 (3.18, 22.94)
Females	6 (6)	2.92 (0.15, no est.)	10.51 (1.36, no est.)

NOTE: AHS = Adult Health Study; est. = estimate; LSS-E85 = Extended Life Span Study sample; and RBE = relative biological effectiveness.

*The number of persons exposed to ≥0.01 Gy or ≥0.01 Sv is shown in parentheses.

**In parentheses are the lower and upper confidence limits.

Table 3. Results of tests on the effects of Dosimetry System 1986 dose, sex, age at exposure, and time trend based on dose equivalents of relative biological effectiveness = 10

Item	Estimate (per Sv)	Deviance (*df* = 1)	*p* value
LSS-E85 sample (including 4 malignant melanoma cases)			
Linear term			
Dose	1.98	16.29	<.001
Log-linear terms			
Sex[a] (male, female)	0.86	1.29	.35
Age at exposure[b]	1.23	18.81	<.001
Time trend[c] (log time)	2.44	7.09	.008
LSS-E85: Skin cancer (excluding 4 malignant melanoma cases)			
Linear term			
Dose	1.97	15.13	<.001
Log-linear terms			
Sex[a] (male, female)	0.65	0.70	.40
Age at exposure[b]	1.14	14.93	<.001
Time trend[c] (log time)	2.50	6.15	<.013
AHS sample (no malignant melanoma cases)			
Linear term			
Dose	2.92	12.64	<.001
Log-linear terms			
Sex[a] (male, female)	0.52	0.44	.51
Age at exposure[b]	0.75	6.53	.011
Time trend[c] (log time)	1.30	2.64	.104

NOTE: AHS = Adult Health Study; LSS-E85 = Extended Life Span Study sample.
[a]Adjusting for age at the time of exposure and time trends.
[b]Adjusting for sex and time trends.
[c]Adjusting for sex and age at the time of exposure.

and 47 cases were confirmed among 25,942 A-bomb survivors with known DS86 doses. In our analysis, we have selected an additive model for the ERR of skin cancer. Models of this type seem to fit the data reasonably well and are often used in studies of radiation effects. A highly significant linear trend was noted for the incidence of skin cancer in Nagasaki during 1958–85. This finding should be emphasized because this is the first report to indicate a highly significant dose-response relationship between A-bomb exposure and the incidence of skin cancer.

In order to stress the risk of exposure to ionizing radiation, therefore, we must examine the likelihood of skin cancer cases obtained from the Nagasaki Tumor

Registry in the LSS-E85 sample. The LSS-E85 sample comprises the AHS sample and the non-AHS sample. The AHS subjects have received detailed clinical examinations every 2 years since 1959 in Nagasaki, and the records of these careful examinations contain valuable information. In 1977 the AHS was extended to include survivors exposed within 2500 m of the hypocenter, who were called the "Reserve Part." Details concerning the 47 cases of skin cancer among persons with available DS86 doses are given in Appendix B. Of the 47 skin cancer cases in the period from 1958 to 1985, 13 occurred in the AHS extended sample and 34 in the non-AHS extended sample. As is evident from Appendix B, most of the persons with high dose estimates are members of the AHS sample. Of the 10 persons with skin cancer exposed to 0.50 Gy or more, 9 belonged to the AHS sample. Eighty percent (1583/1990) of the survivors exposed to ≥0.50 Gy belonged to the AHS sample, and the crude annual incidence rates per 10^5 PY at risk were 20.1 and 22.8 in the LSS-E85 and AHS samples (11.6 in the non-AHS sample), respectively. Of the survivors exposed to 0.01–0.49 Gy, only 6% (664/11,094) belonged to the AHS sample, and the annual incidence rates per 10^5 PY at risk were 6.8 in the LSS-E85 sample and 12.4 in the AHS sample (only 2 skin cancer cases; 6.5 cases in the non-AHS sample), whereas the annual incidence rates per 10^5 PY at risk were 6.3 and 3.9 for the LSS-E85 and AHS (6.7 in the non-AHS) sample control survivors, respectively. The number of skin cancer cases in the AHS sample was very limited. The difference in the number of cases between the LSS-E85 and AHS samples is not large and the results were parallel, but the

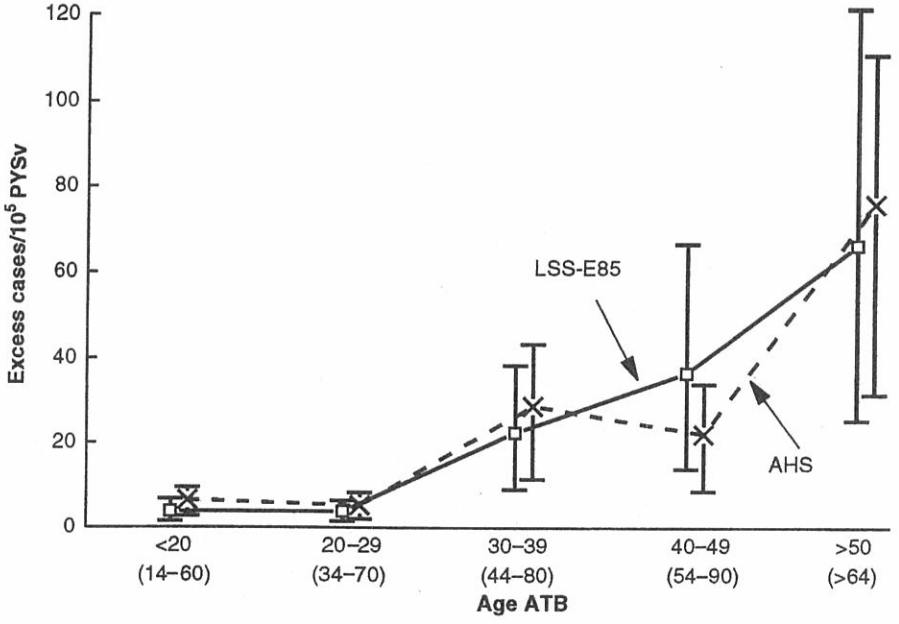

Figure 4. Excess cases of skin cancer per 10^5 person-year-sievert (PYSv) (relative biological effectiveness = 10) and 95% confidence limits by sample and age at the time of the bombing (ATB). The values in parentheses express attained age in relation to age ATB. AHS = Adult Health Study; LSS-E85 = Extended Life Span Study sample.

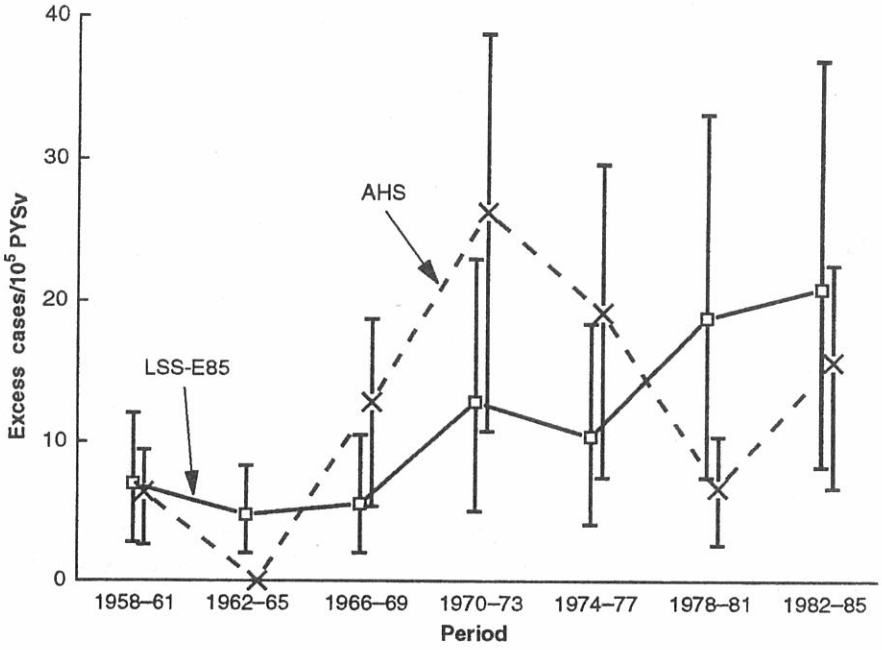

Figure 5. Excess cases of skin cancer per 10^5 person-year-sievert (PYSv) (relative biological effectiveness = 10) and 95% confidence limits by period. AHS = Adult Health Study; LSS-E85 = Extended Life Span Study sample.

detection rate for non-AHS distal survivors is a little higher than that for the AHS. No significant dose-response relationship was observed in the non-AHS data.

The ERR and excess cases of skin cancer were noted to be significant at 2.2 per gray and $12.1/10^5$ PYGy, respectively, in the LSS-E85 sample, and 3.1 per gray and $13.7/10^5$ PYGy, respectively, in the AHS sample. When DS86 dose equivalents based on a neutron RBE of 10 were used, these estimates decreased to 2.0 per sievert and $11.0/10^5$ PYSv, respectively, in the former sample, and 2.7 per sievert and $12.3/10^5$ PYSv, respectively, in the latter sample. These risk estimates are seemingly conservative. In a recent report on radiation-induced skin cancer of the head and neck, Ron et al.[16] reported that the estimated excess relative risk of skin cancer was 0.7 per gray and the average excess risk was $3.1/10^5$ PYGy. Their results were derived from people who had received X-ray therapy for tinea capitis between 1948 and 1960 and who were much younger (≤15 years old) at the time of their exposure than were the A-bomb survivors in this study. Their skin cancer cases were diagnosed between 1950 and 1980. Our findings are based on follow-up observations between 1958 and 1985 after a single exposure to A-bomb radiation in 1945. The average follow-up period of the former was roughly 25 years whereas that of the latter was 40 years. As is evident from Figure 5, the number of excess cases of skin cancer in the LSS-E85 sample shows a significant increase with time.

It is known that the incidence and site of skin cancer in general, not restricted to skin cancer induced by medical irradiation, differ greatly by race, geographical area, and sex.[17,18] In this respect, Nagasaki A-bomb survivors are of the same race and reside in the same area, thus this population is advantageous for an examination of the incidence of skin cancer. The Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF), have operated a tumor registry in Nagasaki for the last 28 years since its establishment in 1958 by the Nagasaki Medical Association and a tissue registry for the last 13 years since it was established in 1973 by the Nagasaki City Medical Association.[19] These registries have served as important data sources in the assessment of cancer incidence among the A-bomb survivors as well as in geographically defined populations. Incidence data offer an advantage over mortality data in that the former provide a direct measure of cancer risk. The skin cancer detection rate is considered to be higher compared to the rates for lung cancer and cancer of the internal organs because skin cancer is visible even to those with poor medical knowledge. Of 77 cases of skin tumors detected from these registries, 19 were excluded from this study—13 cases whose DS86 doses were unknown, 5 NIC cases, and one case with onset outside the 1958–85 study period. Furthermore, 11 cases were excluded because they were non-skin cancer or Bowen's disease, a precancerous state of skin cancer, or because of the loss of their clinical charts and pathological preparations (2 cases; see Appendix A). The rate of histological diagnosis is high in cases of skin cancer. In fact, histological examinations had been performed for all 47 cases in this study. One of the

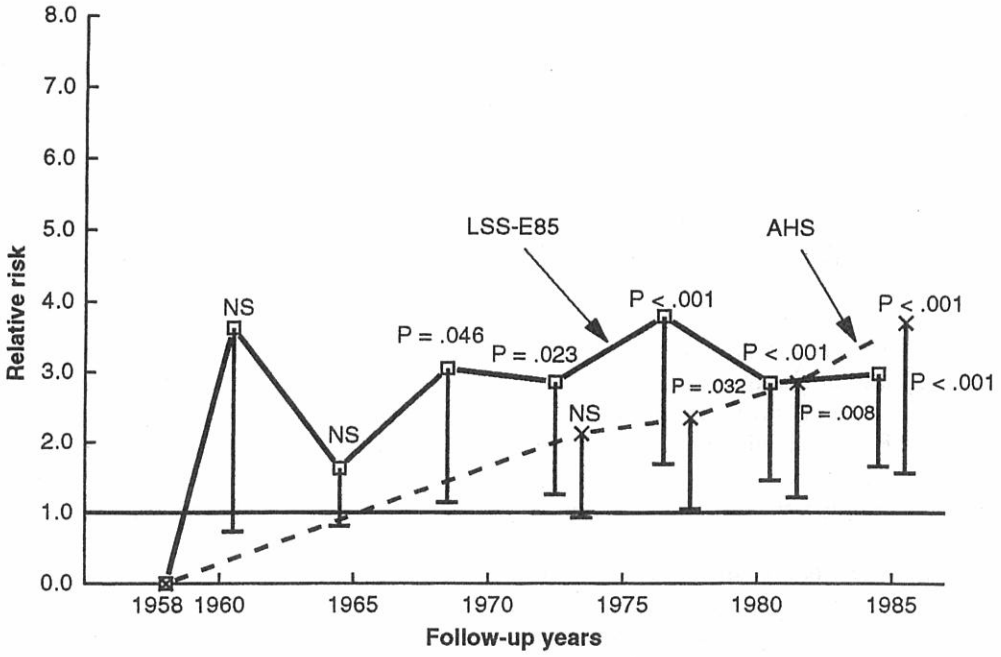

Figure 6. Relative risk of skin cancer and 95% lower bound between 1958 and follow-up years. AHS = Adult Health Study; LSS-E85 = Extended Life Span Study sample; NS = not significant.

characteristics of A-bomb exposure is that the systemic skin was relatively evenly exposed to radiation, unlike medical irradiation of a restricted region. This is important when studying whether the incidence of radiation-induced skin cancer varies by site.

Keeping these points in mind, the 28 cases exposed to 0.01 Gy or more based on the DS86 system were reviewed from various points of interest. The ratio of males to females was 15:13 and the mean age at onset was around 68 years (Appendix B). This sex ratio and mean age are similar to those for the occurrence of skin cancer in the general population in Japan that is not associated with medical irradiation.[18] This indicates that, at least within the range of A-bomb radiation doses received by the skin cancer cases of this study, the incidence by sex and age at onset resembles that in the general population.

The histological types of the 28 skin cancer cases in persons exposed to 0.01 Gy or more were 16 basal cell epitheliomas, 7 squamous cell carcinomas, 1 basosquamous cell carcinoma, 3 malignant melanomas, and 1 sweat gland carcinoma. Among the histological types of radiation-induced skin cancer, basal cell epithelioma has been considered to be predominant in western countries[20–26] and squamous cell carcinoma in Japan.[27,28] The reason for this difference is not known, but it may be related to the fact that skin cancer in western countries is frequently observed on the faces of persons irradiated for hirsuteness or acne,[25] whereas in Japan it is frequently observed on the hands of radiologists and X-ray technicians who neglected proper radiation-protection measures.[28] This suggests that the frequency of the histological type of skin cancer varies by the site of irradiation. As far as skin cancer cases in A-bomb survivors are concerned, basal cell epithelioma was predominant in the same manner as reported in western countries. Martin et al.[29] and Basso-Ricci and Bartoli[30] report that the occurrence of multiple lesions is characteristic of radiation-induced skin cancer. In our study, cases 21 and 27 (Appendix B) developed another histological type of skin cancer at a later date. Case 17 had squamous cell carcinoma arising at the site of heat burn caused by A-bomb exposure. It is well known that most cicatricial cancers are squamous cell carcinoma.[31,32]

One of the issues of interest and importance is the latent period from radiation exposure to the development of skin cancer. The BEIR V report[33] summarizes current views on latency for skin cancer as follows: With respect to excess risk of cancer from whole-body exposure to radiation, solid tumors are now known to be of greater numerical significance than leukemia. Solid cancers characteristically have long latent periods; they seldom appear before 10 years after radiation exposure and may continue to appear for 30 years or more after radiation exposure; in contrast, the excess risk of leukemia appears within a few years after radiation exposure and largely disappears within 30 years after exposure. Although there have been many reports that describe the latent period of skin cancer caused by radiation therapy,[18,21,26,30,34–36] their median latent period varied from 18 to 37 years. These differences are ascribed to various factors in the samples, such as sex, age, race, number of cases, irradiated site, dose, type of skin cancer, and follow-up period. It is essential, therefore, to study skin cancers in A-bomb survivors, because the incidence and latent period of radiation-induced skin cancer in a single race residing in the same area can be better understood. Based on the present study, the radiogenic excess period from

A-bomb exposure to development of skin cancer appears to be 25 years or more with a significant increase in risk as time passes.

In 1969, when Johnson et al.[5] reported the incidence of skin cancer in A-bomb survivors in Hiroshima and Nagasaki, the number of skin cancer cases in the survivors was small, especially for the AHS sample, but it gradually increased thereafter (Figure 5). The trend of excess deaths after 1970 linearly increased in the LSS-E85 A-bomb survivors. A large-scale surveillance of individual LSS-E85 A-bomb survivors in Hiroshima and Nagasaki in relation to skin cancer is now underway.[37]

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List of clinical, radiological, and histological findings of the 11 cases who were excluded from this study

Case no.	Master File no.	Member of AHS	Sex	Age ATB (yr)	Age at onset (yr)	Latent age* (yr)	Date of diagnosis (yr-mo)	Date of birth (yr-mo)	DS86 kerma (mGy) Total	Neutron	Gamma	Histology	Tumor site	Comments
1	[redacted]	No	F	57	79	22	1967-08	1888-07	0	0	0	Comedocarcinoma	Breast	
2		No	F	62	85	23	1968-09	1882-10	5	0	5	Unk.	Eyelid	Loss of clinical chart and pathological preparations
3		Yes	M	36	70	34	1979-10	1909-05	1243	13	1230	Nodular hyperplasia	Prostate	
4		No	M	51	90	39	1984-09	1894-03	10	0	10	Bowen's disease	Unk.	
5		Yes	F	44	81	37	1982-09	1901-01	641	5	636	Bowen's disease	Thigh	
6		Yes	F	42	Unk.	Unk.	Unk.	1902-10	1180	10	1170	Unk.	Unk.	Loss of clinical chart and pathological preparations
7		Yes	M	13	49	36	1982-03	1932-07	0	0	0	*Mycosis fungoides* (T-cell malignancy)	General skin	
8		No	M	49	65	16	1961-11	1895-11	169	0	169	Bowen's disease	Abdomen	
9		Yes	F	39	77	38	1983-10	1906-04	1639	15	1624	Pannuclitis	Breast	
10		Yes	F	35	69	34	1979-08	1910-02	1479	16	1463	Lymphocytic lymphosarcoma	Hip	
11		No	M	61	91	29	1974-11	1883-09	4	0	4	Merkel cell carcinoma	Head	

NOTE: AHS = Adult Health Study; ATB = at the time of the bombing; DS86 = Dosimetry System 1986; and Unk. = unknown.
*"Latent age" means the period from age ATB to age at diagnosis.

Appendix B

The table below and the table on the facing page list the clinical, radiological, and histological findings of the 47 skin cancer cases in this study.

Case no.	Master File no.	Member of AHS	Sex	Age ATB (yr)	Age at onset (yr)	Latent age* (yr)	Date of diagnosis (yr-mo)	Date of death (yr-mo)	Date of birth (yr-mo)
1	[redacted]	No	M	41	80	41	1985-03	1986-08	1904-01
2		No	M	45	65	20	1965-05	1965-11	1899-09
3		No	M	33	68	35	1980-06		1912-01
4		No	F	53	75	22	1967-02	1969-02	1891-12
5		No	M	37	77	40	1985-10		1908-06
6		No	F	44	66	22	1967-07		1900-12
7		Yes	M	43	74	31	1975-04	1980-06	1902-04
8		No	F	35	63	28	1973-11		1910-04
9		No	M	44	74	30	1975-04	1977-03	1901-03
10		No	F	44	77	33	1978-07		1901-07
11		No	M	62	77	15	1960-10	1961-06	1883-06
12		No	M	58	94	36	1981-05	1984-02	1887-02
13		No	F	43	80	37	1982-12	1983-10	1902-06
14		No	M	17	56	39	1984-07		1928-03
15		No	M	47	87	40	1985-05		1897-09
16		No	M	14	43	28	1973-09		1930-09
17		No	M	16	49	33	1978-07		1929-01
18		No	F	49	87	38	1983-06	1989-09	1895-10
19		Yes	F	13	39	26	1971-06		1931-08
20		No	M	31	45	14	1959-01		1913-08
21		Yes	F	36	74	38	1985-04	1985-04	1909-03
22		Yes	F	57	80	23	1980-05	1980-05	1888-03
23		Yes	M	46	76	30	1975-11	1976-12	1899-04
24		No	M	53	93	40	1985-07	1987-17	1892-07
25		Yes	M	16	43	27	1973-04	1984-01	1929-07
26		No	F	12	27	15	1960-04	1960-07	1932-08
27		Yes	M	39	65	26	1971-06	1974-11	1905-10
28		No	F	28	62	34	1978-10		1916-10
29		No	F	43	73	33	1975-04	1978-12	1902-01
30		No	F	56	79	23	1968-10	1978-01	1889-02
31		No	F	44	79	35	1980-09	1983-11	1901-03
32		No	F	53	70	18	1963-06	1967-03	1892-07
33		Yes	M	39	71	32	1977-12		1906-03
34		No	F	57	83	26	1971-10	1985-02	1888-05
35		Yes	F	57	80	23	1968-03	1970-04	1887-09
36		No	M	57	84	27	1972-10	1974-03	1888-01
37		No	F	47	79	32	1977-11	1979-11	1898-06
38		Yes	F	38	66	28	1974-01	1983-01	1907-02
39		No	F	44	84	40	1985-03	1987-11	1901-03
40		Yes	M	14	53	39	1983-10		1930-10
41		No	M	39	59	20	1966-01		1906-03
42		No	M	51	85	34	1979-12	1980-04	1894-01
43		No	F	34	70	36	1981-06		1910-11
44		No	M	48	84	36	1982-02	1985-02	1897-06
45		No	F	13	48	35	1980-07		1932-04
46		Yes	M	20	53	33	1978-03		1924-12
47		Yes	F	2	16	14	1959-11		1943-07

NOTE: AHS = Adult Health Study; ATB = at the time of the bombing; BCE = basal cell epithelioma; BSCC = basosquamous cell carcinoma; MM = malignant melanoma; SCC = squamous cell carcinoma; and SGC = sweat gland carcinoma.

*"Latent age" means the period from age ATB to age at diagnosis.

Case no.	Master File no.	DS86 kerma (mGy) Total	Neutron	Gamma	Histology	Site	Comments
1	[redacted]	0	0	0	BCE	Hand	
2		0	0	0	SCC	Scalp	
3		30	0	30	SCC	Scalp	
4		7	0	7	BCE	Abdomen	
5		0	0	0	SCC	Leg	
6		11	0	11	BCE	Nose	
7		611	4	607	BSCC	Hand	
8		6	0	6	BCE	Axilla	
9		1180	13	1167	MM	Sole	
10		0	0	0	SCC	Head	
11		126	0	126	SCC	Foot	Rectal cancer at age 78
12		0	0	0	SCC	Sole	
13		0	0	0	BCE	Abdomen	
14		19	0	19	BCE	Eyelid	
15		57	0	57	BCE	Leg	
16		26	0	26	BCE	Sole	
17		68	0	68	SCC	Back	SCC arising from keloid
18		270	1	269	BCE	Breast	
19		861	7	854	BCE	Thigh	
20		0	0	0	SCC	Head	
21		6000	94	5906	SGC	Chest	SCC at age 75
22		2779	32	2747	BCE	Cheek	
23		2364	33	2331	BCE	Axillar	
24		336	1	335	BCE	Face	
25		1376	25	1351	BCE	Eyelid	
26		0	0	0	SCC	Jaw	
27		0	0	0	BCE	Forehead	SCC at age 65
28		20	0	20	BCE	Eyelid	
29		0	0	0	BCE	Nose	
30		0	0	0	SCC	Arm	
31		0	0	0	BCE	Nose	
32		0	0	0	SCC	Leg	
33		0	0	0	BCE	Cheek	
34		0	0	0	BCE	Nose	
35		128	1	127	SCC	Foot	
36		38	0	38	MM	Sole	
37		30	0	30	SCC	Cheek	Gastric cancer at age 81
38		92	0	92	SCC	Foot	Gastric cancer at age 75
39		0	0	0	BCE	Abdomen	
40		2275	24	2251	BCE	Eyelid	
41		0	0	0	BCE	Nose	
42		0	0	0	SCC	Cheek	
43		0	0	0	MM	Sole	
44		7	0	7	BCE	Back	
45		9	0	9	MM	Sole	
46		2485	32	2453	BCE	Scalp	
47		1641	43	1598	SCC	Scalp	

Appendix C

Deviance of additive hazard models to skin cancer data

Item	LSS-E85 sample		AHS sample		Non-AHS sample	
	Deviance	*df*	Deviance	*df*	Deviance	*df*
Model 1: $\lambda(t,z)$ = Background(1 + $\beta_1$dose and $\beta_2$dose^2)						
Background	117.4	384	48.5	337	60.3	333
Linear	101.3	347	36.0	336	60.1	332
Linear-quadratic	99.2	346	34.3	335	59.5	331
Model 2: $\lambda(t,z)$ = Background[1 + $\beta_1$dose exp($\beta_s$sex + $\beta_a$age)]						
Linear	100.6	345	35.6	334	59.7	330

NOTE: The 70 strata in background effects are composed of sex (2) × age (5) × time (7); AHS = Adult Health Study; and LSS-E85 = Extended Life Span Study.