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Cancer Mortality in Nagasaki Atomic Bomb Survivors with Epilation

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To elucidate the association between epilation and cancer mortality in Nagasaki atomic bomb survivors, cancer mortality was determined for a total of 9,356 survivors (3,591 males and 5,765 females) from 1 January 1970 to 31 December 1997. The subjects included individuals other than those in the Life Span Study (LSS) cohort of ABCC-RERF. Information on acute injury was obtained from a survey that was conducted at the time of application for a health handbook. The association between epilation and cancer mortality was evaluated by the Cox proportional hazards model, including factors such as gender, age at the time of the bombing, attained age, radiation dose and epilation. Epilation was found in 81 (2.3%) males and 148 (2.6%) females. No significant difference in the frequency of epilation was observed by gender or age at the time of the bombing. The hazard ratio of cancer mortality in those with epilation compared to those without epilation was 1.06 (95% confidence interval: 0.72-1.54). Similar to the study of the LSS cohort, no significant effects of epilation on cancer mortality were observed in the present study. The results indicated that the cancer mortality was significantly higher in those exposed to atomic bombing younger as was reported by LSS studies. However, the effects of radiation dose on cancer mortality have not been observed in the present study.

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Introduction

Association between acute radiation injury, such as epilation, and cancer mortality in atomic bomb survivors has still been in controversy. Stewart and Kneale[1-3] demonstrated an association between acute radiation injury and cancer mortality. They also reported an association between epilation and leukemia- or neoplasm-related mortality and pointed out the selection effects of early death. On the other hand, Neriishi et al.[4] reported, on the basis of the Life Span Study (LSS) cohort,[5] that a significant association observed between acute radiation outcomes, especially epilation and leukemia mortality, became insignificant after adjustment for dosimetric errors. Furthermore, Little[6] re-analyzed the LSS mortality data and found no significant difference between the groups with and without acute radiation injury with respect to cancer or non-cancer mortality, except for leukemia. Little also showed that a statistically significant difference observed in the dose-response for leukemia between the groups with and without epilation or burns was no longer significant after adjustment for dosimetric errors.

The objective of the present study was to elucidate the association between epilation and cancer mortality in a cohort different from the LSS cohort, i.e., Nagasaki atomic bomb survivors registered in the database of the Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Sciences.[7]

The present study was reviewed and approved by the institutional ethical committee of Nagasaki University Graduate School of Biomedical Sciences.

Methods and Subjects

Study subjects

The Atomic Bomb Disease Institute of the Nagasaki University Graduate School of Biomedical Sciences has been following up atomic bomb survivors with Atomic Bomb Survivor's Handbook issued by Nagasaki city since 1970. As of 1 January 1970, there were 21,666 survivors in Nagasaki city who were directly exposed to the Nagasaki atomic bomb within 2.6 km from the hypocenter and were issued

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Atomic Bomb Survivor's Handbook by Nagasaki city. The study subjects were those atomic survivors who further satisfied the following conditions: (1) information on acute radiation injury was available; (2) radiation dose was available; and (3) exposed to the atomic bomb at the age under 50 years. A total of 9,356 individuals (3,591 males and 5,765 females) remained for the present study.

We note that the subjects of the present study are not necessarily included in the LSS cohort. Indeed, we confirmed that among 11,911 Nagasaki atomic bomb survivors including all subjects of the present study, 5,004 (42.0%) were in the LSS cohort (data not published). Research Institute for Radiation Biology and Medicine of Hiroshima University, which has been following up Hiroshima atomic bomb survivors with Atomic Bomb Survivor's Handbook, reported that among 10,000 subjects randomly selected from their database, 5,615 (56.2%) were in the LSS cohort.[8]

Information on acute radiation injury

Information on acute injury was obtained at the time of the survivor's application for the Atomic Bomb Survivor's Handbook. The subjects completed a self-reporting questionnaire that included questions about symptoms of acute radiation injury (vomiting, diarrhea, fever, epilation, purpura, nasal bleeding, gingival bleeding, stomatitis and oropharyngeal lesions) that appeared within 6 months after the bombing. Our study focused on epilation. We used the information on the time when the epilation occurred and the degree of epilation. The latter was divided into 2 groups: (1) slight or moderate (less than half of hair lost) and (2) severe (loss of half or more). We considered a survivor to have epilation if he or she reported severe epilation that had occurred by 30 September 1945.

Dose estimation

We estimated individual radiation doses[9] using the Atomic Bomb Survivor 1993 Dose (ABS93D) developed at Hiroshima University[10] on the basis of DS86.[11] From the questionnaires, we also obtained information on the distance of the exposed from the hypocenter and any shielding conditions. We used estimates of shielded kerma and truncated them at 6 Gy.

Mortality information

We collected the subjects' death certificates and classified the underlying cause of death on the basis of the International Statistical Classification of Diseases and Related Health Problems (ICD). We used ICD-9 and ICD-10 codes for the deaths from 1 January 1970 to 31 December 1994 and for those from 1 January 1995 onward, respectively. We defined the underlying cause of death coded 140-208 by ICD-9 or C00-C97 by ICD-10 as cancer.

Statistical analysis

We evaluated the effects of gender, age at the time of the bombing (ATB) and radiation dose on the frequency of epilation on the basis of the following linear logistic regression model:

$$\text{logit}\ (p) \equiv \log\,[p/(1-p)] = ß_0 + ß_1 G + ß_2 A + ß_3 D,$$

where p denotes the frequency of epilation; G=1 or 0 for males and females, respectively; A denotes the age ATB (years); D denotes the radiation dose (Gy); and ßs are unknown parameters to be estimated.

We evaluated the effects of epilation, gender, age ATB, attained age and radiation dose on the cancer mortality on the basis of the following Cox proportional hazards model:

$$\log \lambda(t) = \log \lambda_0(t) + ß_1 E + ß_2 G + ß_3 A + ß_4 A^*(t) + ß_5 D,$$

where t denotes the time since the commencement of the follow-up; $\lambda(t)$ and $\lambda_0(t)$ denote the hazard rate and baseline hazard rate at t, respectively; E=1 or 0 according to whether the subject had epilation; G, A and D are as defined above; $A^*(t)$ denotes the attained age at t; and ßs are unknown parameters to be estimated. We treated non-cancer disease deaths, survival to the end of the study period (31 December 1997) and the first migration out of Nagasaki city as censoring.

FREQ, LOGISTIC and PHREG in the SAS® system[12] were used for the calculations.

Results

Frequency of epilation

Table 1 shows the frequency of epilation by gender, age ATB and radiation dose. Epilation was observed in 229 individuals (81 males and 148 females) among 9,356 subjects. The frequency of epilation was 2.3% (81/3,591) in males and 2.6% (148/5,765) in females, and there was no significant difference by gender (p=0.343, chi-square test). There was a significant increase of epilation with radiation dose after adjustment for 2 other factors; odds ratio was 2.07 (95% confidence interval, 1.92-2.22) with every 1 Gy increase in radiation dose.

Table 1. Frequency of epilation by gender, age at the time of bombing (ATB) and radiation dose

Factor		Male	Female	Total
Age ATB (years)	0-9	24/1,348 (1.8)[a]	23/1,313 (1.8)	47/2,661 (1.8)
	10-19	24/1,071 (2.2)	56/1,429 (3.9)	80/2,500 (3.2)
	20-29	12/305 (3.9)	30/1,262 (2.4)	42/1,567 (2.7)
	30-39	14/420 (3.3)	23/979 (2.3)	37/1,399 (2.6)
	40-49	7/447 (1.6)	16/782 (2.0)	23/1,229 (1.9)
Radiation dose (Gy)	0-0.09	11/2,546 (0.4)	29/4,190 (0.7)	40/6,736 (0.6)
	0.1-0.9	18/727 (2.5)	30/1,100 (2.7)	48/1,827 (2.6)
	1.0-2.4	27/207 (13.0)	40/306 (13.1)	67/513 (13.1)
	2.5-3.9	11/52 (21.2)	25/79 (31.6)	36/131 (27.5)
	4.0-6.0	14/59 (23.7)	24/90 (26.7)	38/149 (25.5)
Total		81/3,591 (2.3)	148/5,765 (2.6)	229/9,356 (2.4)

[a]Denominator and numerator denote the number of subjects and the number of subjects with epilation, respectively. Parenthetic entries refer to the percentage of subjects with epilation.

Cancer mortality

Out of 9,356 subjects, 4,396 (47%) were alive as of 31 December 1997, while 2,717 (29%) had died and 2,243 (24%) had migrated out of Nagasaki city. Of the 2,717 deaths, 774 were due to cancer, 398 to cerebrovascular disease, 458 to heart disease and 917 to other diseases. Also, there were 74 deaths due to external causes and 96 deaths could not be classified. The 774 cancers were classified by site: stomach—157, lung—134, liver—106, colon—67, pancreas—44, gallbladder—43, uterus—37, leukemia—30, breast—19 and others—137.

Table 2 shows the cancer mortality by gender, radiation dose and epilation. There was the appearance of an increase in cancer mortality with radiation dose in those without epilation under 4Gy. It was noted that cancer mortality in males was higher in those with epilation than in those without epilation, whereas no such difference was observed in females.

Table 2. Cancer mortality observed in 1970-1997 by gender, epilation and dose

Gender	Epilation	Radiation dose(Gy)	No. of Subjects	No. of Deaths	Person-years	Mortality[a]
Male	Yes	0-0.09	11	0	199	0
		0.1-0.9	18	5	247	2,024
		1.0-2.4	27	5	468	1,068
		2.5-3.9	11	7	248	2,823
		4.0-6.0	14	5	263	1,901
	No	0-0.09	2,535	196	44,671	439
		0.1-0.9	709	72	13,079	551
		1.0-2.4	180	27	3,045	887
		2.5-3.9	41	11	632	1,741
		4.0-6.0	45	4	807	496
Female	Yes	0-0.09	29	1	565	177
		0.1-0.9	30	4	656	610
		1.0-2.4	40	4	857	467
		2.5-3.9	25	2	491	407
		4.0-6.0	24	3	470	638
	No	0-0.09	4,161	301	81,763	368
		0.1-0.9	1,070	88	21,583	408
		1.0-2.4	266	28	4,802	583
		2.5-3.9	54	6	989	607
		4.0-6.0	66	5	1,232	406

[a]Number of deaths per 100,000 person-years

Table 3 presents the effects of epilation, gender, age ATB, attained age and radiation dose on the cancer mortality. No factors other than age ATB and attained age showed significant effects on cancer mortality.

Table 3. Effects of epilation, gender, age at the time of bombing (ATB), attained age and radiation dose on cancer mortality

Factor		Hazard ratio	95% CI[a]	*p*-value
Epilation	yes vs. no	1.06	0.72-1.54	0.780
Gender	male vs. female	1.11	0.96-1.28	0.155
Age ATB	1 year increase	0.98	0.97-0.98	<0.001
Attained Age	1 year increase	1.08	1.07-1.08	<0.001
Radiation dose	1Gy increase	0.98	0.91-1.07	0.679

[a]CI=confidence interval.

Discussion

Acute radiation injury includes not only epilation but also vomiting, diarrhea, fever, purpura, nasal bleeding, gingival bleeding, stomatitis and oropharyngeal lesions. However, epilation has been used to assess the estimated radiation dose in previous studies.[13-15] We also focused on epilation in the present study because it was observed most frequently in atomic bomb survivors shortly after the bombing[16,17] and because it is considered the most objective and least prone to influence by other factors. It is also the symptom that tends to be remembered most clearly.[18]

The accuracy of the information on epilation may have been affected by the fact that it was gathered more than 12 years after the bombing. Furthermore, the epilation that some survivors experienced may have been caused by factors other than radiation exposure due to their distance from the hypocenter.[14] Some epilation may have been a physiological response to the change in seasons from summer to autumn, or it may have been caused by undernourishment or psychological stress.

In Table 2, a monotone increase in the cancer mortality with radiation dose (under 4 Gy) was observed in both males and females without epilation, while the cancer mortality varied irregularly with radiation dose in those with epilation. This may be due to errors in dose estimation and smallness in the subjects with epilation.

Since recent analysis of the LSS cohort usually excludes those who received 4 Gy or more,[6] we re-analyzed the data excluding such subjects. The results, however, changed little; the hazard of cancer mortality in males with epilation was 1.09 (95% confidence interval: 0.96-1.24)-fold higher than in those without epilation, while no significant effects of epilation were observed in females.

The findings of the present study clearly show that the effects of acute radiation injury are complex and further investigations are needed.

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