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Association of Acute Radiation Syndrome and Rain after the Bombings in Atomic Bomb Survivors

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Acute radiation-induced symptoms reported in survivors after the atomic bombings in Hiroshima and Nagasaki have been suspected to be associated with rain that fell after the explosions, but this association has not been evaluated in an epidemiological study that considers the effects of the direct dose from the atomic bombs and other factors. The aim of this study was to evaluate this association using information from a fixed cohort, comprised of 93,741 members of the Life Span Study who were in the city at the time of the bombing. Information on acute symptoms and exposure to rain was collected in surveys conducted by interviewers, primarily in the 1950s. The proportion of survivors developing severe epilation was around 60% at levels of direct radiation doses of 3 Gy or higher and less than 0.2% at levels <0.005 Gy regardless of reported rain exposure status. The low prevalence of acute symptoms at low direct doses indicates that the reported fallout rain was not homogeneously radioactive at a level sufficient to cause a substantial probability of acute symptoms. We observed that the proportion of reported acute symptoms was slightly higher among those who reported rain exposure in some subgroups, however, suggestions that rain was the cause of these reported symptoms are not supported by analyses specific to the known areas of radioactive fallout. Misclassification of exposure and outcome, including symptoms due to other causes and recall bias, appears to be a more plausible explanation. However, the insufficient and retrospective nature of the available data limited our ability to quantify the attribution to those possible causes.

INTRODUCTION

Acute radiation syndrome can occur after exposure to high doses of radiation (*1*) and has been reported among survivors of the atomic bombings in Hiroshima and Nagasaki, with a strong relationship to distance from the hypocenters and therefore, to the direct radiation dose from the bombs (*2*). After the bombings, rain fell over wide areas of Hiroshima and in reportedly limited areas of Nagasaki. The rain was thought to originate from the ascending air currents from the heat of the bombs and ensuing fires that consumed many of the cities' structures. Combined with the soot and ash from the fires, it came to be known as ''black rain'', and there is evidence that some of this was radioactive (*3*). Early survey measurements in the Koi-Takasu area in western Hiroshima and the Nishiyama area in eastern Nagasaki detected localized areas of residual radiation; both areas are distal from the hypocenter and the elevated measurements of radioactivity were thought to have been caused by fallout of radioactive bomb debris contained in rain (*4*). Some survivors who reported being exposed to the rain that fell shortly after the bombings, often during evacuation to areas outside the central parts of the cities, also reported acute radiation symptoms in interviews conducted by the Atomic Bomb Casualty Commission (ABCC) (*5, 6*). However, the association has not been evaluated in an epidemiological study that considers the effects of the direct dose from the atomic bombs, as well as other factors affecting the likelihood that a survivor reported particular symptoms in interviews conducted some time after the bombings. These factors may depend on both the existence and severity of the symptoms that occurred and the accuracy of survivor/surrogate responder recall.

The Life Span Study (LSS) is a prospective study of a fixed cohort of atomic bomb survivors followed since 1950 (*7*). The Atomic Bomb Casualty Commission collected surveys during the 1950s to early 1960s documenting rain exposure information along with the occurrence of acute symptoms and other data that could be used to estimate radiation dose received directly from the bombs, such as location and shielding. However, although information on acute symptoms was used for validation of estimated direct radiation from the atomic bomb explosions among high-

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dose survivors, in the 1950s prior to development of the first real dosimetry system, it was not evaluated for an association with exposure to rain. (*5, 6, 8–10*). This study is an examination of the association of exposure to rain with the occurrence of acute symptoms typically associated with radiation exposure, especially epilation.

RESEARCH COHORT AND METHODS

This study was comprised of 93,741 cohort members of the LSS whose locations at the time of bombings were less than 10 km from the hypocenters in Hiroshima and Nagasaki. Information on exposure to rain was collected primarily in two large-scale surveys across the LSS cohort with small numbers of reports from some provisional surveys, which were conducted by interview by ABCC personnel using the Migration Questionnaire (MQ, 1955–1956) and the Master Sample Questionnaire (MSQ, 1955–1961). The MQ questions were: ''Was person caught in Fallout Rain?'' (Yes or No) plus ''Where'' and ''Time'' with boxes for a free-form description. The MSQ questions were ''Was person caught in Fallout Rain?'' (Yes, No or Unknown) and ''Where'' with a box for a free-form description. Rain exposure status was classified as ''yes'', ''no'' or ''unknown.'' Blank answers were categorized as ''unknown.'' Survivor responses about their location at the time of rain exposure were recorded in a variety of ways, usually indicating some area such as the name of a town block. The distance and direction of the location from the hypocenter was determined by the geographic center of that area. If information was not sufficient to estimate that point (that is, the response was, for example, ''on the way from X to Y'' or ''along the river Z'', etc.), it was classified ''location unknown.'' A small number of answers that indicated a distant location from Hiroshima or Nagasaki city were also classified ''location unknown.'' The free-form information on exposure to rain was coded and computerized starting in 2008.

Information on the occurrence and severity of acute symptoms was also collected during the interviews. In addition to some provisional surveys, two large-scale surveys, the Radiation Questionnaire (RQ, conducted in 1953–1955) and the MSQ, included questions on acute symptoms. Symptom information included date of onset, severity (mild, moderate, severe, unknown or not stated and none) and a free-form response field for ''duration or comment.'' The types of symptoms included fever, malaise, vomiting, nausea, anorexia, diarrhea (bloody and non-bloody), sore throat, sore mouth, sore gums (gingivitis), bleeding gums, purpura, other bleeding and epilation. The MQ questions consisted of check boxes (Yes/No) for various symptoms, including sore throat, sore mouth, sore gums, bleeding gums, purpura and epilation.

For those with multiple questionnaires, discrepant answers were examined and the answer judged most reliable (usually based on an earlier response date and/or self-reported rather than surrogate-reported) was identified by ABCC personnel. Summary variables for epilation, bleeding and oropharyngeal lesions were coded from the questionnaires and an integrated database created from previous studies (*5, 6, 10*). As the LSS was expanded with individuals from the previous studies, the database was expanded in the same manner and was used in this study. Epilation that occurred within 60 days was classified by severity as: none, slight (loss of less than 1/4 of hair on the scalp), moderate (1/4 to less than 2/3), severe (2/3 or more), questionable (including unknown severity and unknown onset date) and no information (i.e., answer was left blank). Purpura or bleeding gums that occurred within 6 weeks after the bombings were summarized as ''bleeding'' (''Yes''/''No''/''Unknown or No Information''). Sore throat, sore mouth and sore gums that occurred within 6 weeks after the bombings were summarized as ''oropharyngeal lesions'' and were coded in the same manner as ''bleeding''.

Individual doses of direct radiation from the atomic bombs were estimated using the DS02 dosimetry system according to the established methods (*11, 12*). Weighted absorbed dose (neutron $\times$ 10 + gamma ray) to the skin was used for epilation in the analysis, and the dose to the bone marrow was used for bleeding and oropharyngeal lesions. Oropharyngeal lesions were thought to indicate severe inflammation of the mouth and throat mucosa due to lymphocytopenia (*2*).

The basic analysis strategy was to adjust for the contributions of direct radiation from the atomic bomb, along with variation by age and sex, to the likelihood of epilation or other acute symptoms. Analyses were performed separately by city because meteorological conditions and fallout materials contained in the rain were likely to have been different. First, the proportion of persons developing acute symptoms was tabulated by DS02 direct radiation dose. Next, associations of exposure to rain (yes vs. no) and occurrence of acute symptoms (occur vs. no symptoms) were examined by odds ratios (OR) using a conditional logistic regression matched for direct-dose band with cutoff points of 0.005, 0.1, 0.25 and every 0.25 Gy up to 4.0 Gy, and adjusted for sex and age at bombing using SAS® software (SAS Institute Inc., Cary, NC) (*13*). Survivors with unknown direct dose ($N = 7{,}070$) were excluded from odds ratio calculations.

Analyses were also conducted by distance and direction from the hypocenter because reported frequency of exposure to rain was different in different areas. Thus, areas were classified by quadrants from true north in Hiroshima and east and west semicircles in Nagasaki, based on the spatial distribution of the frequency of reported rain. In addition, specific effects of rain were investigated in the Koi-Takasu area in Hiroshima, which is a known area of high residual radiation around 3.5 km west-southwest of the hypocenter. Since the effects at Koi-Takasu might be attributable to either exposure to fallout in the rain or later integrated dose from fallout in the environment, the west-

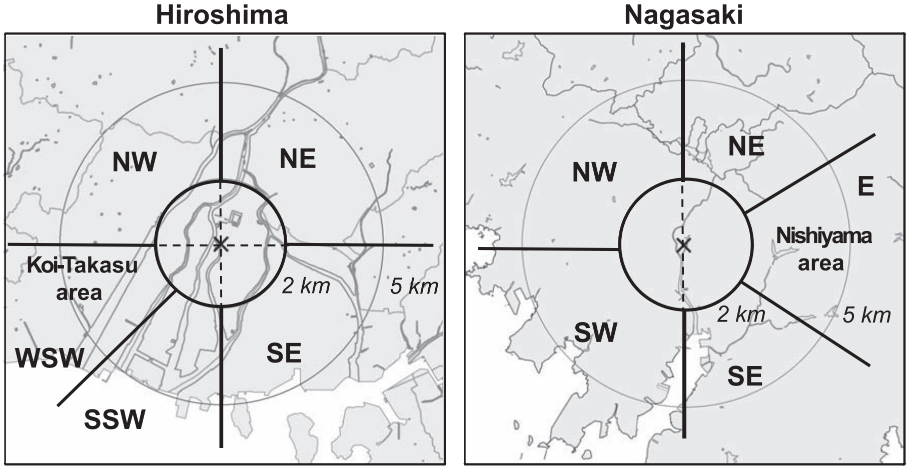

FIG. 1. Maps of Hiroshima and Nagasaki. "×" indicates hypocenters. N, E, S and W represent the compass directions from the hypocenter, respectively.

southwest octant 2 km or more distant from the hypocenter was analyzed as a separate area. In Nagasaki, the east sextant (between 60° and 120° clockwise from true north) 2 km or more distant was analyzed separately to provide a result specific to the Nishiyama area (around 3.0 km east of the hypocenter). Consequently, the distant areas beyond 2 km from the hypocenter were divided into five quadrants/octants in Hiroshima and five sextants/quadrants in Nagasaki [Fig. 1 and Table 1 (left column)].

Locations where persons encountered rain were only recorded for those who actually reported rain exposure, so effects of exposure to rain at a certain area were evaluated by the interaction between effects of exposure to rain and effects of area (*14, 15*). Therefore, coefficients in the conditional logistic regression model are described as:

$$\begin{aligned}\mathrm{logit[risk]} &= \ln[\mathrm{OR}]\\ &= \alpha \cdot sex + \sum \beta_i \cdot age_i + \sum \gamma_j \cdot rain \cdot area_j,\end{aligned}$$

TABLE 1
Distribution of Survivors Classified by Exposure to Rain and Location at the Time of the Bombings

Area[a]	Exposed to rain	Percentage (%)	Not exposed to rain	Unknown exposure to rain	Total
Hiroshima					
NE quadrant	2,418	20.7	5,247	4,004	11,669
SE quadrant	826	3.3	17,088	6,900	24,814
SW quadrant	3,708	24.8	6,610	4,632	14,950
NW quadrant	5,298	50.2	1,624	3,629	10,551
Total	12,250	19.8	30,569	19,165	61,984
Limited to 2+ km[b]					
NE quadrant	1,244	19.7	3,369	1,696	6,309
SE quadrant	339	2.1	12,216	3,328	15,883
SSW octant	276	7.5	2,458	946	3,680
WSW octant	1,551	31.6	2,170	1,184	4,905
NW quadrant	2,554	57.0	871	1,053	4,478
Nagasaki					
East semicircle	722	3.4	17,340	3,131	21,193
West semicircle	131	1.2	8,945	1,488	10,564
Total	853	2.7	26,285	4,619	31,757
Limited to 2+ km[b]					
NE sextant	86	12.7	506	85	677
E sextant	197	12.7	1,183	168	1,548
SE sextant	203	1.4	12,420	1,676	14,299
SW quadrant	62	0.9	5,866	652	6,580
NW quadrant	15	1.4	938	136	1,089

[a] Abbreviations indicate the direction from the hypocenter. N, E, S and W represent the compass directions, respectively.
[b] Numbers of these subareas are included in the above areas.

TABLE 2
Distribution of Survivors who were Exposed to Rain Classified by Location at the Time of the Bombings and at Exposure to Rain

Area[a]	At time of bombings	Percentage (%)	At exposure to rain	Percentage (%)
Hiroshima				
NE quadrant	2,418	19.8	2,397	19.6
SE quadrant	826	6.7	440	3.6
SW quadrant	3,708	30.3	4,783	39.0
NW quadrant	5,298	43.2	4,107	33.5
Unknown	-	-	523	4.3
Total	12,250	100	12,250	100
Limited to 2+ km[b]				
NE quadrant	1,244	20.9	1,630	19.8
SE quadrant	339	5.7	217	2.6
SSW octant	276	4.6	351	4.3
WSW octant	1,551	26.0	3,268	39.7
NW quadrant	2,554	42.8	2,772	33.6
Total	5,964	100	8,238	100
Nagasaki				
East semicircle	722	84.6	544	63.8
West semicircle	131	15.4	57	6.7
Unknown	-	-	252	29.5
Total	853	100	853	100
Limited to 2+ km				
NE sextant	86	15.3	36	10.3
E sextant	197	35.0	197	56.6
SE sextant	203	36.0	80	23.0
SW quadrant	62	11.0	24	6.9
NW quadrant	15	2.7	11	3.2
Total	563	100	348	100

[a] Abbreviations indicate the direction from the hypocenter. N, E, S and W represent the compass directions, respectively.
[b] Numbers of these subareas are included in the above areas.

α indicates a coefficient for effects of sex, β_i indicate that for age class with ten-year interval (0–9, 10–19, . . ., 60+) and age class of 40–49 was used for the reference and γ_j represents interaction of effects from exposure to rain and specific location of rain exposure, including the category of unknown location, respectively. Locations were known only for those individuals exposed to rain ($rain = 1$) and there was no information on areas occupied during and after evacuation at the times of the "fallout rain," for those who were not exposed to rain ($rain = 0$). Thus, there is no primary term for effects of rain or area and γ_j indicates area-specific effects of exposure to rain compared to nonexposure to rain anywhere. In addition, sex- and age class-adjusted odds ratios of the symptoms for direct radiation categories irrespective of rain exposure were estimated to evaluate the specificity of the symptoms with direct radiation exposure from the atomic bombs.

RESULTS

Table 1 shows the number of individuals exposed to rain and their location at the time of the bombings. A total of about 20% of survivors reported contact with "fallout" rain in Hiroshima (12,250/61,984), about half reported no exposure (30,569/61,984) and the remaining 30% (19,165/61,984) had unknown status. People located in the northwest (NW) quadrant at the time of the bombing reported the highest frequency of exposure to rain (50%), followed by those in the SW and NE quadrants, while those in the SE quadrant reported the lowest. Among those who reported exposure to rain, about 40% reported being in the SW quadrant at the time of exposure. Among those exposed who were located beyond 2 km (8,238), the highest concentration (40%) were exposed in the WSW octant, which includes the Koi-Takasu area (Table 2). In Nagasaki, only 3% (853/31,757) of individuals reported rain exposure, 83% (26,285/31,757) reported no exposure and 15% (4,619/31,757) had unknown exposure. People who were located in the east semicircle from the hypocenter at the bombing reported a higher frequency of exposure to rain than those in the other semicircle. About 64% of those exposed to rain reported being in the east semicircle. Beyond 2 km, 197 (50%) were exposed in the east sextant, which includes the Nishiyama area.

For those exposed to the Hiroshima bomb, the proportions and selected numbers of persons reporting acute symptoms by exposure to rain and radiation dose categories are shown in Table 3. The proportion of individuals reporting acute symptoms showed similar tendencies in each direct-dose category regardless of exposure to rain. Among those with no exposure to rain, the proportion of individuals who reported severe epilation was 57.4% in those with a direct radiation dose of 3.0 Gy or higher to the skin. This proportion decreased with lower doses of radiation to less than 1% at <0.1 Gy and decreased to 0.4% and 0.04% in the lowest two categories, respectively. Among those who were exposed to rain, the proportion was also large at the highest dose level (66.5%) and decreased with decreasing doses, to 0.4% and 0.2% in the lowest two, respectively. Individuals with unknown exposure to rain showed a similar tendency.

Table 4 shows the same information for those exposed in Nagasaki. The maximum values were smaller but the trends in the proportions by dose group were similar to those observed in Hiroshima. For those not exposed to rain, severe epilation was reported by 39.8% at the level of 3.0+ Gy, and also decreased in proportion to 0.2% and 0.1% at the lowest two dose categories, respectively. For those reporting rain exposures, the respective proportions were 33.3%, 0.9% and 0.3%. The proportions of individuals who reported moderate or slight epilation showed similar tendencies to those with severe epilation for all but the highest two dose categories (where values were consistently higher) in each city.

As for the bleeding category, the proportions were high at high doses and appeared to reach a plateau at 1.0 Gy or higher (43–48% at the highest three levels) and decreased to 0.9% at <0.005 Gy among those with no rain exposure in Hiroshima. The values ranged from 53–66% at the highest three levels and 2.3% at the lowest level among those

TABLE 3
Proportion of Hiroshima Bomb Survivors Developing Acute Symptoms, Classified by Exposure to Rain and DS02 Direct Radiation Dose

		Epilation					
		Severe[b]		Moderate[b]	Slight[b]	None	
Exposure to rain	Dose (Gy)[a]	No.[c]	Pecentage (%)	Pecentage (%)	Pecentage (%)	Pecentage (%)	Total
No	<0.005	5	0.04	0.2	0.4	99.2	12,944
	0.005–	41	0.4	0.9	1.3	96.9	10,568
	0.1–	42	1.1	2.2	2.5	92.4	3,706
	0.5–	20	1.8	4.8	4.9	86.1	1,099
	1.0–	69	12.0	8.5	9.9	65.9	574
	2.0–	73	38.6	13.8	5.8	38.6	189
	3+	109	57.4	13.2	1.6	24.2	190
	Unknown	44	3.4	3.3	2.9	89.3	1,299
	Total	403	1.3	1.3	1.4	95.2	30,569
Yes	<0.005	6	0.2	0.9	1.0	97.6	2,472
	0.005–	19	0.4	1.1	1.4	95.8	4,590
	0.1–	22	0.8	1.6	3.0	93.0	2,686
	0.5–	14	1.4	3.4	6.3	86.8	971
	1.0–	74	11.8	14.1	11.1	60.1	630
	2.0–	69	44.8	14.3	12.3	25.3	154
	3+	109	66.5	11.0	3.7	16.5	164
	Unknown	41	7.1	4.3	4.3	81.6	583
	Total	354	2.9	2.5	2.9	90.3	12,250
Unknown	<0.005	6	0.1	0.4	0.5	98.4	4,912
	0.005–	47	0.9	1.5	1.9	94.6	6,078
	0.1–	48	1.1	2.5	3.0	91.6	4,430
	0.5–	27	2.6	5.1	5.9	83.8	1,052
	1.0–	59	10.0	11.8	10.2	63.8	596
	2.0–	89	35.9	18.1	7.3	33.1	249
	3+	172	61.4	8.9	3.2	23.2	281
	Unknown	83	6.2	5.3	4.8	81.3	1,567
	Total	531	3.1	2.7	2.7	90.0	19,165

Note. The denominators of percentage (%) exclude respondents with ''no information'' on the symptoms from the total number.
[a] Weighted absorbed skin dose for epilation and bone marrow dose for bleeding and oropharyngeal lesions.
[b] Includes symptoms occurring within 60 days after the bombings for epilation and within 6 weeks for bleeding and oropharyngeal lesions.
[c] Number of respondents.

individuals with rain exposure. In Nagasaki, the values ranged from 39–54% at the highest three levels and 0.6% at the lowest level among those not reporting rain exposure, and 45.7% at 1.0 to <2.0 Gy and 63% at the combined level of 2.0 Gy or higher in those exposed to rain, and 2.6% at <0.005 Gy. Oropharyngeal lesions also showed similar values by dose category and exposure status to rain (Tables 3 and 4).

The point estimates of proportions of the cohort developing acute symptoms were higher in the rain-exposed group than the non-exposed group at many levels of direct radiation dose in both cities. Odds ratios of developing acute symptoms by location of rain exposure are shown in Fig. 2 and the cross tables for calculating the odds ratios are shown in Table 5. The odds ratio of severe epilation for the rain-exposed group was >1 but not statistically significant at the 0.05 level [1.20, 95% confidence interval (CI): 0.97, 1.47] in Hiroshima. The odds ratio in the SE quadrant and at unknown location were significantly higher than 1, but the odds ratio at WSW octant beyond 2 km (including the Koi-Takasu area which had measureable fallout) was not significantly higher. In Nagasaki, the odds ratio was 1.76 (95% CI: 0.86, 3.57), and the odds ratio for rain-exposed at the west semicircle was nominally higher than that at the east semicircle, but not statistically significant. The odds ratio for the east sextant at distances greater than 2 km (including the Nishiyama area which had considerable fallout) was not available because there were no reports of severe epilation in this area.

When the outcome of epilation included all grades (severe to slight), the odds ratio was 1.23 (95% CI: 1.11, 1.37) for all individuals in Hiroshima and 2.10 (95% CI: 1.54, 2.86) in Nagasaki. The odds ratio was significantly high for rain-exposed persons in the NE and SE quadrants of all distances and at unknown locations in Hiroshima, and was also high for those exposed in both semicircles and in some distant subareas in Nagasaki. However, for the WSW octant beyond 2 km in Hiroshima the odds ratio was not high, and at the east sextant beyond 2 km in Nagasaki it was comparatively low. (Fig. 2).

As for bleeding, the overall odds ratio after exposure to rain was 1.48 (95% CI: 1.33, 1.64) in Hiroshima and 2.01 (95% CI: 1.45, 2.78) in Nagasaki. The odds ratios were

TABLE 3
Extended.

Bleeding			Oropharyngeal lesions			
Occurrences[b]		None	Occurrences[b]		None	
No.	Pecentage (%)	Pecentage (%)	No.	Pecentage (%)	Pecentage (%)	Total
119	0.9	98.8	78	0.6	99.2	13,319
280	2.6	96.9	172	1.6	97.8	10,843
180	5.1	93.1	123	3.5	95.2	3,568
138	14.9	81.3	74	8.0	90.4	930
190	45.7	49.0	130	31.3	66.6	416
76	48.4	42.7	61	38.9	55.4	157
16	43.2	45.9	12	32.4	62.2	37
116	9.0	89.4	57	4.4	94.3	1,299
1,115	3.7	95.5	707	2.3	97.1	30,569
61	2.3	96.9	42	1.6	97.8	2,695
153	3.3	95.1	114	2.5	96.3	4,686
180	6.3	91.8	114	4.0	94.7	2,846
195	22.3	74.1	103	11.8	86.1	878
215	53.0	42.9	145	35.7	62.8	406
68	62.4	34.9	54	49.5	46.8	109
31	66.0	34.0	19	40.4	57.4	47
72	12.5	83.8	46	8.0	89.0	583
975	8.0	90.2	637	5.2	93.4	12,250
55	1.3	98.1	44	1.0	98.3	5,062
221	3.7	94.8	158	2.7	96.1	6,722
239	6.0	92.2	138	3.5	95.2	4,124
196	21.9	74.8	104	11.6	85.8	910
217	44.9	49.5	132	27.3	68.5	487
119	58.9	36.6	76	37.6	57.9	202
36	40.0	48.9	21	23.3	66.7	91
196	14.6	82.7	110	8.2	89.3	1,567
1,279	7.5	90.8	783	4.6	94.0	19,165

consistently high for all quadrants of rain exposure in Hiroshima and both semicircles in Nagasaki regardless of distance from the hypocenters, and also high in many of the distant subareas. The odds ratio was the highest for the SE quadrant at all distances and beyond 2 km in Hiroshima and higher for the west semicircle in Nagasaki in which rain was not frequently reported, except for location unknown, respectively. The odds ratio was significantly high for the WSW octant beyond 2 km in Hiroshima, but was not higher than the overall odds ratio or the odds ratios for other areas. The odds ratio was not high for the east sextant beyond 2 km in Nagasaki. The overall odds ratio of oropharyngeal lesions was 1.47 (95% CI: 1.29, 1.67) in Hiroshima and 2.46 (95% CI: 1.80, 3.36) in Nagasaki and the odds ratios showed similar tendencies to those for epilation or bleeding The odds ratios of those outcomes were heterogeneous between the areas and tended to be higher in areas where rain was not frequently reported (i.e., SE quadrant at all distances and beyond 2 km in Hiroshima and the west semicircle in Nagasaki). The odds ratios for the areas including Koi-Takasu and Nishiyama, which had known radioactive fallout, were not higher than the overall risks in Hiroshima or Nagasaki, respectively.

DISCUSSION

Exposure to high-dose radiation induces acute symptoms in various organs. Neurological, gastrointestinal and hematopoietic (bone marrow failure) syndromes are induced in a dose-dependent fashion. Acute tissue reactions also occur in skin (erythema, abnormal hair growth, epilation, desquamation, and vascular and dermal injury), mucous membranes in the mouth and throat (inflammation and swelling, with ulceration and necrosis), as well as in others at various levels of whole-body doses above approximately 1 Gy of X or gamma radiation (*1*). Unlike systemic exposure to direct radiation by neutrons and gamma rays from the atomic bombs, residual radioactivity would have involved radioactive material in the surrounding environment of the survivor and would have resulted in different exposure modalities. Examples include contact skin dose from fallout that may have been in rain, or beta dose to skin occurring after the end of rainfall from fallout on the ground or other surfaces in the environment, or external exposure from neutron-activated soil materials nearby or adhering to skin (*16, 17*).

Among the atomic bomb survivors exposed proximally to the explosion, epilation began abruptly about 2 weeks after the explosion, primarily at the frontal region and then the occipital and parietal areas, with temporal and neck areas

TABLE 4
Proportion of Nagasaki Bomb Survivors Developing Acute Symptoms, Classified by Exposure to Rain and DS02 Direct Radiation Dose

		Epilation					
		Severe[b]		Moderate[b]	Slight[b]	None	
Exposure to rain	Dose (Gy)[a]	No.[c]	Pecentage (%)	Pecentage (%)	Pecentage (%)	Pecentage (%)	Total no.
No	<0.005	13	0.1	0.1	0.3	99.4	13,882
	0.005–	13	0.2	1.0	1.3	96.7	6,605
	0.1–	15	0.9	2.8	3.4	91.4	1,636
	0.5–	9	1.4	5.4	6.1	83.3	658
	1.0–	49	7.7	11.5	11.8	65.9	637
	2.0–	41	26.3	16.7	10.9	44.2	157
	3+	41	39.8	10.7	7.8	38.8	103
	Unknown	56	2.2	3.3	4.9	87.5	2,607
	Total	237	0.9	1.4	1.7	95.3	26,285
Yes	<0.005	1	0.3	0.3	2.8	96.0	333
	0.005–	2	0.9	1.4	4.6	91.3	223
	0.1–	0	0.0	0.0	4.1	91.8	73
	0.5–	1	2.1	6.3	10.4	81.3	49
	1.0–	3	6.7	11.1	31.1	51.1	46
	2.0–	3	75.0	0.0	25.0	0.0	4
	3+	2	33.3	0.0	0.0	66.7	6
	Unknown	10	8.7	2.6	13.0	72.2	119
	Total	22	2.6	1.8	6.8	87.2	853
Unknown	<0.005	3	0.2	0.3	0.6	98.5	1,713
	0.005–	6	0.7	1.4	1.3	93.4	976
	0.1–	4	1.0	4.5	2.6	89.3	429
	0.5–	8	3.7	3.3	7.9	82.3	217
	1.0–	21	8.8	14.6	12.5	59.6	243
	2.0–	25	31.6	11.4	11.4	38.0	81
	3+	27	42.2	4.7	15.6	31.3	65
	Unknown	31	3.8	4.5	6.9	81.5	895
	Total	125	3.0	3.0	3.6	88.1	4,619

Note. The denominators of percentage (%) exclude respondens with ''no information'' on the symptoms from the total number.
[a] Weighted absorbed skin dose for epilation and bone marrow dose for bleeding and oropharyngeal lesions.
[b] Includes symptoms occurring within 60 days after the bombings for epilation and within 6 weeks for bleeding and oropharyngeal lesions.
[c] Number of respondents.

spared; very few of these individuals had total epilation. The onset was delayed as distance from the hypocenter increased (e.g., mean number of days was 28.1 at about 1.6–1.9 km in Hiroshima). Purpura occurred with a peak onset 20–30 days after the explosion and the mean time to onset was not greatly changed by the distance from the hypocenter. Oropharyngeal lesions occurred over a relatively wide time period after the explosion with a mean of 22 days (*2*). The periods for which we chose to analyze the occurrence of acute symptoms (60 days for epilation and 6 weeks for bleeding and oropharyngeal lesions) were consistent with those findings.

The list of acute symptoms in the ABCC surveys included prodromal gastrointestinal symptoms, hemorrhagic diathesis (purpura and oropharyngeal lesions) and epilation. Since gastrointestinal symptoms could be induced by many causes and are therefore not considered to be specific to radiation exposure (*2*), survey data categorization did not use gastrointestinal symptoms but focused on epilation, bleeding and oropharyngeal lesions, as in previously published studies (*5–10*).

Two major findings were observed in this study. First, the proportion of those developing acute symptoms was large at high DS02 dose levels and lower with decreasing doses, with the lowest level reached in the lowest dose category in all groups regardless of rain exposure. If the reported rain had been homogenous and highly radioactive, those exposed to rain should have uniformly higher frequencies of reported acute effects regardless of their direct radiation dose category. For example, if rain exposure was equivalent to 0.1 Gy or higher, the proportion of those exposed to rain developing severe epilation should be similarly high as those with direct dose of 0.1–0.5 Gy and no rain exposure (1.1%, 95% CI of 0.8–1.5% based on normal distribution, Hiroshima). Yet, among those with direct exposures of <0.005 Gy and rain exposure, the proportion was 0.2% (95% CI: 0.05%, 0.4%). Similar findings were observed for bleeding and oropharyngeal lesions, except for severe epilation in Nagasaki because of the small number of the individuals exposed to rain. Therefore, it is unlikely that the rain was uniformly highly radioactive.

The second finding was that rain exposure was associated with increased frequency of acute symptoms, especially in

TABLE 4
Extended.

Bleeding			Oropharyngeal lesions			
Occurrences[b]		None	Occurrences[b]		None	
No.	Pecentage (%)	Pecentage (%)	No.	Pecentage (%)	Pecentage (%)	Total no.
85	0.6	99.2	104	0.7	99.1	14,247
142	2.2	96.9	159	2.5	97.0	6,393
92	5.5	93.3	76	4.5	94.4	1,675
136	19.4	77.9	87	12.4	85.6	703
202	39.2	53.6	145	28.2	65.6	517
63	53.8	41.9	44	37.6	59.0	117
12	46.2	53.8	5	19.2	76.9	26
242	9.3	88.7	203	7.8	90.8	2,607
974	3.7	95.5	823	3.1	96.3	26,285
9	2.6	96.5	17	5.0	93.3	348
11	5.3	94.3	12	5.7	93.3	213
5	6.5	89.6	5	6.5	90.9	77
14	27.5	66.7	8	15.7	84.3	53
16	45.7	45.7	11	31.4	65.7	35
5	83.3	16.7	5	83.3	16.7	6
0	0.0	100.0	0	0.0	100.0	2
27	23.3	72.4	18	15.7	78.3	119
87	10.4	87.5	76	9.1	88.8	853
15	1.0	98.1	19	1.2	98.1	1,757
31	3.5	93.6	39	4.4	93.1	976
28	6.5	90.4	23	5.4	92.3	440
48	18.5	78.0	34	13.1	82.7	264
83	40.5	50.7	59	28.8	63.4	207
32	49.2	43.1	29	45.3	42.2	67
2	15.4	69.2	3	23.1	69.2	13
105	13.0	83.6	94	11.8	85.2	895
344	8.2	89.1	300	7.2	90.4	4,619

the survivors who were exposed to rain in distal areas and in the areas in which rain was not frequently reported. This finding appears to support the deleterious nature of the rain. There were localized areas of high residual radiation in the Koi-Takasu area in Hiroshima and the Nishiyama area in Nagasaki; both areas are distal from the hypocenter and thought to be caused by fallout rain (*4*). While the increased odds ratios for acute symptoms among those who were exposed to rain appeared to be consistent with the effects of radioactive fallout in the rain, the odds ratio for the west-southwest octant beyond 2 km in Hiroshima (including the Koi-Takasu area) did not exceed the odds ratios for the other areas. No individuals developed severe epilation in the east sextant beyond 2 km in Nagasaki (which includes the Nishiyama area) and the odds ratios for other acute symptoms were generally smaller in the east sextant compared to other sextants. Thus, there was no further increased risk of exposure to rain for developing acute symptoms in the areas where radioactive fallout was actually detected. Therefore, the increased odds ratios of rain exposure for acute symptoms in distal areas and in the areas in which rain was not frequently reported were not thought to be due to radioactive fallout.

The symptoms recorded in the ABCC surveys were not directly observed by the investigators but were reported by the individuals in interviews approximately ten years after the bombings, probably reducing the reliability of the information for several reasons. First, not all questionnaires were answered directly by the responder but instead could have been answered by a surrogate who may not have had firsthand information on either the exposure or the outcome. Second, individuals could have misjudged the symptoms since they were not medical specialists. For some elicited exposure symptoms such as severe epilation, misclassification would be unlikely as the symptoms were pathognomonic for radiation exposure and easily apparent. However, other symptoms were less specific to radiation and might have been misreported as radiation related, such as ''sore throat'' and ''other bleeding.'' Third, memories of occurrence could be lost or confused in the years after the bombing. Finally, both the exposure (rain) and the outcome (acute effects) were asked retrospectively and on the same survey or on two surveys that occurred within a short interval. This situation often can induce the occurrence of ''recall bias'' where individuals who have experienced a disease or adverse health outcome tend to think about the possible ''causes'' of their illness and are likely to remember their exposure histories differently from those unaffected by the disease, or more frequently report exposures that did not actually

TABLE 5
Cross Tables Calculating Fig. 1

	Total	Severe epilation		Severe to slight epilation		Bleeding		Oropharyngeal lesions	
		Occurences	None	Occurences	None	Occurences	None	Occurences	None
Hiroshima									
Exposed to rain at any location	11,667	313	10,527	914	10,527	903	10,490	591	10,860
NE[a] quadrant	2,248	54	2,023	177	2,023	172	2,022	98	2,111
SE quadrant	398	27	315	58	315	56	323	42	332
SW quadrant	4,621	96	4,259	303	4,259	312	4,224	206	4,350
NW quadrant	3,922	109	3,535	322	3,535	307	3,536	212	3,659
2+ km, all directions	7,968	110	7,449	396	7,449	407	7,410	275	7,574
2+ km, NE quadrant	1,575	22	1,462	85	1,462	92	1,448	51	1,498
2+ km, SE quadrant	213	5	184	13	184	14	187	12	189
2+ km, SWS octant	340	8	308	29	308	33	301	16	319
2+ km, WSW octant	3,166	39	2,992	136	2,992	140	2,977	107	3,020
2+ km, NW quadrant	2,674	36	2,503	133	2,503	128	2,497	89	2,548
Location unknown	478	27	386	54	386	56	385	33	408
Non-exposed to rain	29,270	359	27,827	1,112	27,827	999	27,914	650	28,326
Nagasaki									
Exposed to rain at any location	734	12	647	66	647	60	650	58	652
East semicircle	465	6	425	32	425	32	420	26	428
West semicircle	50	2	34	13	34	10	39	8	40
2+ km, all directions	329	2	312	10	312	12	311	13	307
2+ km, NE sextant	34	0	34	0	34	1	33	2	32
2+ km, E sextant	192	0	189	1	189	3	187	2	186
2+ km, SE sextant	71	0	65	3	65	4	64	5	62
2+ km, SW quadrant	23	2	18	4	18	3	19	2	20
2+ km, NW quadrant	9	0	6	2	6	1	8	2	7
Location unknown	219	4	188	21	188	18	191	24	184
Non-exposed to rain	23,678	181	22,714	772	22,714	732	22,746	620	22,892

[a] Abbreviations indicate the direction from the hypocenter. N, E, S and W represent the compass directions, respectively.

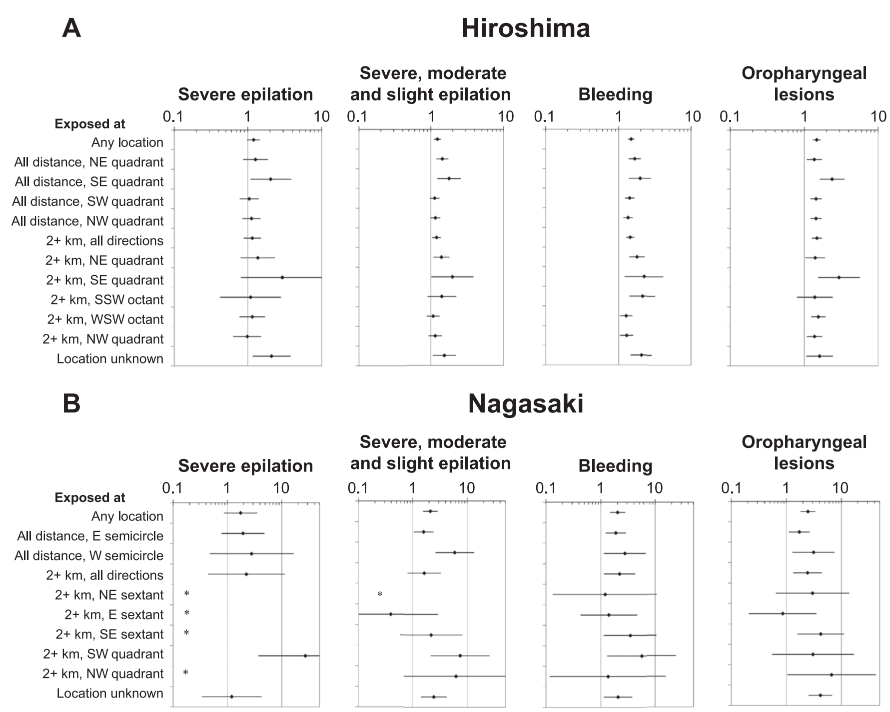

FIG. 2. Odds ratios and 95% confidence intervals of exposure to rain for acute symptoms by city and location at exposure to rain. Odds ratios of exposure to rain (vs. non-exposure) for acute symptoms (vs. no symptoms) matched for dose (weighted absorbed skin dose for epilation and bone marrow dose for bleeding and oropharyngeal lesions) and adjusted for sex and age at the time of bombing. *Asterisk indicates no odds ratio because of null cell. (For point values see supplementary materials, http://dx.doi.org/10.1667.RR14038.S1.)

TABLE 6
Odds Ratios of Acute Symptoms for Direct Dose Adjusted for Sex and Age at Exposure

	Weighted skin dose				Weighted bone marrow dose			
City	Dose band (mean dose, Gy)	No. of individuals	Odds ratio of severe epilation	Odds ratio of all grade (severe to slight) epilation	Dose band (mean dose, Gy)	No. of individuals	Odds ratio of bleeding	Odds ratio of oropharyngeal lesions
Hiroshima	<0.005 (<0.001)	20,328	1 (ref.)	1 (ref.)	<0.005 (<0.001)	21,076	1 (ref.)	1 (ref.)
	1 to 2 (1.38)	1,800	209	59	1 to 2 (1.38)	1,309	91	59
	2 to 3 (2.44)	592	>999	225	2 to 3 (2.44)	468	131	93
Nagasaki	<0.005 (0.0013)	15,928	1 (ref.)	1 (ref.)	<0.005 (0.0012)	16,352	1 (ref.)	1 (ref.)
	1 to 2 (1.39)	926	119	81	1 to 2 (1.34)	759	103	46
	2 to 3 (2.32)	242	707	216	2 to 3 (2.55)	190	180	85

Note. Results of other dose bands are omitted.

occur (*18, 19*). The responses from surrogates are thought to have similar tendency although there was no information on surrogate response in the database used in this study.

During the surveys, survivors who had some symptoms similar to acute radiation syndrome may have sought tangible causes associated with radiation exposure (such as ''black rain'') because direct radiation from the bomb was invisible and people could not estimate the dose. The inverse is also true: people who experienced rain exposure may have been more likely to think that their symptoms were caused by radiation. There was no difference in odds ratios of exposure to rain between the areas in which radioactive fallout was detected shortly after the bombings and the other areas. This finding suggests that the increased frequency of reporting acute symptoms was not associated with actual radioactivity, but with exposure to any rain regardless of radioactivity level. Increased odds ratios for the answer category of ''location unknown'' suggests uncertain memory of rain and symptoms, which is likely to be affected by recall bias. Increased odds ratios were also observed in the southeast quadrant in Hiroshima and the west semicircle in Nagasaki where rain exposure was less frequently reported. It would be difficult to conclude that strong radioactive fallout rain had fallen on a limited number of people in those areas, especially since there was no evidence of residual radiation in early surveys of those areas with radiation-measuring instruments (*20*). Instead, it is more plausible that recall bias occurred in a small group of people who reported exposure to rain and produced a higher odds ratio. A follow-up study indicated no increase in mortality of all cause, cancer or leukemia, or in cancer or leukemia incidence among the survivors who were exposed to rain (*21*). Because cause of death in the vital statistics and cancer incidence collected by population-based registries is more valid in quality of information compared to self-reported symptoms used in this study, the results of this follow-up study are consistent with the interpretation that increased frequencies of acute symptoms among those exposed to rain were derived from some systematic misclassification such as recall bias.

When epilation is defined using any grade of occurrence (severe to slight), it is less specific to radiation exposure than severe epilation because low-grade epilation is difficult to recognize and easily misreported. This is evident in the smaller odds ratios of all-grade epilation compared to those for severe epilation at a given dose level irrespective of rain exposure (Table 6). Bleeding and oropharyngeal lesions were thought to be even less specific. However, the odds ratios of fallout rain were not smaller for those less radiation-specific symptoms. This inconsistency suggests that the association of exposure to fallout rain and acute symptoms was influenced by other factors in addition to radiation effects.

Fission products of nuclear weapons were thought to produce much more beta dose to exposed skin than gamma-ray dose to the skin and deeper tissues. For example, beta-to-gamma dose ratio for bare skin exposure to mixed fission products in some nuclear tests were around 10 for a height of 1 m above the source plane and more than 3 times that value at a height of 1 cm (*22*). Since beta rays originating outside the body do not penetrate to deep organs through the human body (their range in tissue is typically <1 cm), radiation dose due to external exposure or skin contact exposure to fallout rain should be much higher to the skin than to bone marrow. Nevertheless, odds ratios of epilation (due to skin exposure) and those of bleeding and oropharyngeal lesions (due to bone marrow exposure) after exposure to rain were quite similar. Although we do not know how high or different the doses to skin and bone marrow were (beta doses were added to the skin) or how similar the dose responses of radiation for epilation and bone marrow symptoms were, the similarity seems too coincidental for the associations to be true. Thus, it suggested that the association of exposure to fallout rain and acute symptoms was influenced by other factors.

Radiation dose of external exposure from radioactive fallout was estimated as 200–400 mGy in the Nishiyama area in Nagasaki and 10–30 mGy in the Koi-Takasu area in Hiroshima, but early measurements of soil and air indicated essentially no fallout in other areas of the cities (*4, 20*). Fallout doses in the Nishiyama district of Nagasaki were high enough to cause blood disorders among some of the

600 residents who lived in areas with the highest contamination in the months after exposure. A peak in leukocytosis occurred within a few months of the bombing and then regressed (*23*). Also, a small sample of Nishiyama and non-exposed residents were tested for radiological body burdens in 1970 and higher ^{137}Cs counts were observed among the Nishiyama residents.

Radiation dose to the skin from fission fallout and neutron-activated soil has been previously estimated based on the following assumptions in Hiroshima (*16, 17*). Endo *et al.* calculated that if the skin was covered with a 26 μm thick layer of soil contaminated with a fallout radionuclide inventory corresponding to an initial ground deposition of 1 kBq/m^2–^{137}Cs, the total beta dose to skin would be about 0.5 Sv for continuous exposure over the one-month period after the explosion (*16*). Therefore, for the highest initial ground deposition estimated for the Koi-Takasu area in Hiroshima (0.49 kBq/m^2), Shizuma *et al.* (*24*) expected the skin dose of 0.25 Sv. As for induced radiation, a thickness on the skin of about 1 mm of the neutron-activated soil at the hypocenter, continuously present throughout the first 7 days from the detonation, would result in a skin exposure of about 0.8 Gy, but such an exposure condition was not plausible (*17*).

The findings that distal survivors were not exposed to high-dose residual radiation are also supported by studies using biodosimetry. The frequency of stable chromosome aberrations among the survivors with individual dose estimates of $<$0.005 Gy was thought to be similar to that in the general population and the not-in-city group (*26*). Another published study, on electron spin resonance of tooth enamel, did not support claims that a large fraction of distally-exposed survivors received a large dose (e.g., 1 Gy) of external penetrating radiation resulting from residual radiation (*27*).

Using DS02 dose estimates, our data clearly indicate some increase in severe epilation at doses less than 1 Gy, shown in Tables 3 and 4 and by Stram, *et al.* (*6*), in contrast to the threshold of 3 Gy suggested by the ICRP (*25*). Consideration of dose error based on existing RERF models would not suggest that this corresponds to a true dose much above 1 Gy. These considerations are supported by studies using multiple end points in addition to epilation, including chromosomal aberrations and leukemia (*28, 29*). On the other hand, even doses on the order of 1 Gy are considerably in excess of those that could plausibly result from known fallout levels, as discussed above. Although very small rates of epilation on the order of a few percentages are observed at longer distances where DS02 doses are vanishingly small, these are not spatially localized to the Nishiyama or Koi-Takasu areas or to any other particular distal area for that matter, and we consider them to be artifacts due to non-radiation effects, such as trauma, poor nutrition and hygiene conditions after the bombings or other unknown causes, including exceptional instances of high radioactive fallout or high radiosensitive persons, or misreported locations at the time of the bombings or symptoms.

The number of individuals who reported acute symptoms in distant areas from the hypocenter (2.0+ km) was small, but the proportion developing acute symptoms in the lowest direct dose categories was not nil, although those levels of exposure were below that required to induce such symptoms (*1*). There were no conclusive explanations about whether those symptoms were genuine acute radiation syndromes or about any misclassifications of location at the time of the bombings or reported symptoms. Another unresolved issue is the higher proportion of individuals who reported epilation in Hiroshima compared to Nagasaki (but not for bleeding or oropharyngeal legions). This was previously observed in reports documenting atomic bomb dosimetry systems, but no consensus was reached to explain this (*5, 6*).

The proportion of survivors with no records of rain (unknown exposure) was higher in Hiroshima than in Nagasaki, and higher in proximal survivors than in distal survivors in both cities, but there were no substantial differences by direction from the hypocenter (Table 1). The reasons for the city-specific differences in the survey results are unknown, as no field documentation for survey methods has been found. The unbalanced proportions between proximal and distal survivors were adjusted for by matching on direct dose. Frequencies of occurrence of acute symptoms among those with unknown rain exposure generally fell between those of exposed and unexposed individuals (Tables 3 and 4). It has been suggested that the group with unknown exposure was a mixture of exposed and unexposed individuals. The intermediate values imply that the considerable proportion of the those with unknown exposure to rain did not induce a serious systematic bias on the analysis comparing exposed and unexposed individuals but likely did decrease the study's statistical power.

In conclusion, there is no consistent evidence to support the notion that the reported rain was generally and homogeneously radioactive at a considerable level, such that it would have resulted in cumulative doses over time of several hundred mGy or higher from integrated external exposure. This accords with ground measurements made soon after the bombings showing that radioactive fallout occurred only in a localized area in each city. Only the small and sparsely populated area just west of the reservoir in Nishiyama had estimated doses from fallout that approached several hundred mGy. The observed infrequent associations between reported exposure to rain and reported development of acute symptoms observed in distant areas from the hypocenter may have occurred due to various but exceptional reasons. First is the possibility of exposure to highly radioactive fallout or direct exposures among highly radiosensitive persons, or an interaction of radiation and poor health. The second is due to misclassifications or misreporting of exposure and outcome, such as incorrect memory of the location at the time of bombing, reporting symptoms due to other causes or reporting that suffers from recall bias that produces an apparent association between exposures and outcomes. Although there may have been some individual cases consistent with rare circumstances, recall bias is a more plausible explanation of the association between reported exposure to rain and development of acute symptoms based on this group analysis. However, the insufficient and retrospective nature of the available data limits our ability to differentiate attribution of acute effects to the several possible causes.

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