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Survival Analyses of Atomic Bomb Survivors in Hiroshima Prefecture, Japan, 1968–1982. – Cancer Mortality Risk among Early Entrants –

Masaaki MATSUURA, Norihiko HAYAKAWA and Hiroshi SHIMOKATA

Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, Japan

ABSTRACT

We examined the mortality risk due to all causes of death and due to malignant neoplasms during 1968–82 among 204,209 atomic bomb survivors, including 49,215 early entrants. We used data compiled by the Research Institute for Radiation Biology and Medicine at Hiroshima University, which conducts mortality surveillance of these survivors in Hiroshima Prefecture, Japan. The purposes of this study were to investigate whether there was any relationship between exposure status and mortality risk among survivors, not altered by adjustment for confounding factors, and whether there were any differences among early entrants to the region within 2 km of the hypocenter after the bombing in mortality risk associated with date of entry and duration of stay. The mortality risk in directly exposed survivors decreased with distance from the hypocenter, even after adjustment for confounding factors. Entrants who entered the region on the day of the bombing had a significantly higher risk of mortality due to malignant neoplasm than those who entered thereafter, even after adjustment for the length of stay. The same results were obtained throughout the study period.

Key words: *Atomic Bomb Survivors, Early entrants, Mortality, Dynamic population*

The Research Institute for Radiation Biology and Medicine (RIRBM) at Hiroshima University has conducted mortality surveillance of the entire population of atomic bomb (A-bomb) survivors residing in Hiroshima Prefecture since 1968[6,10]. The surveillance conducted by RIRBM has the unique merit of identifying the difference between the A-bomb survivor population and the general population in mortality, because the institute has been examining the mortality statistics of A-bomb survivors in Hiroshima Prefecture in comparison with those of non-exposed residents there. The most recent report by Hayakawa et al[6] indicated that the standardized mortality ratio (SMR) for all causes of death in A-bomb survivors was lower than that in the non-exposed, but that the mortality risk among those directly exposed within about 1 km from the hypocenter was higher than that in the non-exposed. The SMR for malignant neoplasms was higher in A-bomb survivors than in the non-exposed. The shorter the exposure distance from the hypocenter, the higher was the mortality risk.

However, the SMR results could not reflect many important confounding factors simultaneously, because the calculation of SMR is based on stratified data. These confounding factors include place of residence, level of family destruction, time of issuance of Health Handbook, and age at bombing. Whether the SMR results remain valid after adjustment for these factors has not yet been ascertained. The first purpose of the present research was to investigate this point. We examined the relationship between exposure status and mortality risk among about 200,000 A-bomb survivors in Hiroshima Prefecture with simultaneous adjustment for confounding factors. We also thought out a method for statistical analyses and described the characteristics of the method because, as noted in a later section, the study population is not a fixed cohort but a dynamic population[9,17].

While many of the reports published to date on the mortality statistics of A-bomb survivors have been confined to survivors who were directly exposed at the time of the bombing, 8:15 a.m. on August 6, 1945, we focused special attention on the early entrants to the area within about 2 km of the hypocenter between August 6 and 20, 1945, and investigated the mortality risk accord-

Send all correspondence to: Masaaki Matsuura Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734, JAPAN

ing to the date of entry between August 6 to 9.

Finally, the results presented herein are discussed in relation with those reported previously by RIRBM, the Scientific Data Center of Atomic Bomb Disaster at Nagasaki University[11–14], and the Radiation Effects Research Foundation (RERF)[2,8,15,18,19].

MATERIALS AND METHODS

Our institute has conducted a "Survey for a comprehensive picture of A-bomb damages (Reconstruction Survey)" in cooperation with Hiroshima City since 1968[20], and prepared an Atomic Bomb Survivors (ABS) File based on this survey. The ABS File has been updated several times, and includes all recipients of the A-Bomb Survivors' Health Handbook (herein referred to as Health Handbook) in Hiroshima Prefecture.

A-bomb survivors are administratively defined as individuals who have received Health Handbooks, and are classified, according to their various conditions at the time of the bombing, as directly exposed survivors, early entrants, persons engaged in the relief and care of the sufferers and in burying corpses, and in-utero exposed survivors. Health Handbooks have been issued to survivors since the enforcement of the Atomic Bomb Survivors Medical Treatment Law in 1957. These Health Handbooks are issued to survivors after administrative verification of their personal declaration as A-bomb survivors. Health Handbook holders are provided free medical care for certain designated diseases, allowances and welfare benefits. Because of the availability of these services and a change in the attitudes of survivors, their number has been increasing in Hiroshima Prefecture. These newly recognized survivors include individuals who left the prefecture after the bombing and then returned, and individuals who had been living in Hiroshima since the bombing but waited until long afterwards to declare themselves survivors. Even after 1968, several thousand survivors were newly recognized every year. These survivors are called left truncated in statistical terminology, and are added annually to the ABS File. Furthermore, survivors who re-immigrated after emigration during the study period (herein called interval dropout) also exist in the population. Therefore, it should be noted that the study population treated herein is different from a fixed cohort such as the Life Span Study (LSS) sample used by the RERF.

In the ABS File, the exposure status of the directly exposed survivors was classified according to their distance from the hypocenter. However, the distance was formerly based on the "machi", a Japanese administrative district, where the individual was at the time of the bombing. To define more precisely the exposure status of the directly exposed within 2km, we used the results of the distance-confirmation working which has been conducted since 1983. In this confirmation working, the distance from the hypocenter reported by Woodbury and Mizuki[21] was calculated for the 33,292 survivors with detailed information of exposed position. A previous report by Hayakawa et al[6] used the distance based on the administrative district, since the results of the working was not available on the computer file at that time.

Early entrants are classified in the ABS File by the date of first entry and the exposure distance. "Early entrants within 3 days after the bombing" are thus defined as persons who entered within about 2 km from the hypocenter between August 6 and 9, while "early entrants after 3 days" are defined as persons who entered this zone between August 10 and 20. These early entrants include those who were directly exposed beyond 2 km from the hypocenter and those who were not. The in-utero exposed are classified according to the exposure status of their mothers.

Death information is based on Vital Statistics Death Schedules permitted by the Prime Minister's Office. As ascertainment of the cause of death for all of the survivors in Hiroshima Prefecture was complete for the duration from 1968 to 1982, we set this duration for the study period.

Study Subjects

We prepared two sets of study populations. One is for the analyses of all atomic bomb survivors and the other is for the analyses of early entrants. The latter constitutes a part of the former. Survivors exposed at Nagasaki and foreign survivors were excluded from both of them.

To form the study population for the analyses of all atomic bomb survivors, we selected directly exposed survivors and early entrants with a history of residence in Hiroshima Prefecture during the period between 1968 and 1982. The total study population was 204,207 (97,045 males and 107,162 females). The numbers of deaths due to all causes and due to malignant neoplasm by exposure status are shown in Table 1, and those by calendar year are shown in Table 2.

For the analyses of early entrants, the study population included the entrants for whom information regarding the initial date of entry and the length of stay in the region within 2 km from the hypocenter was available, and excluded the entrants for whom information of length of stay was unavailable. In the analyses, adjustment was made for the length of the entrants' stay in the region, because the length of stay may differ for each subject even though the date of first entry into the region was the same. Furthermore, although there are early entrants who were

Table 1. Numbers of subjects and deaths by exposure status

Exposure Status	Number of Subjects		Number of deaths			
			All causes of death		Malignant neoplasm	
	Male	Female	Male	Female	Male	Female
Directly exposed within about 1 km from the hypocenter	3,895	3,757	1,098	613	302	198
Directly exposed about 1 to 1.5 km from the hypocenter	8,931	13,374	2,177	2,284	558	529
Directly exposed about 1.5 to 2 km from the hypocenter	13,171	15,265	2,822	2,349	690	531
Early entrants within 3 days, directly exposed beyond 2 km	9,670	9,573	2,366	1,469	594	328
Early entrants within 3 days, not directly exposed	30,698	22,622	10,251	3,524	2,190	776
Early entrants after 3 days, directly exposed beyond 2 km	642	1,016	111	122	19	35
Early entrants after 3 days, not directly exposed	6,588	8,029	1,216	604	291	157
Directly exposed beyond 2 km, not entering the city†	23,450	33,526	4,214	4,722	993	938
Total	97,045	107,162	24,255	15,687	5,637	3,492

†: The city is defined herein as the region within about 2 km of the hypocenter.

Table 2. Number of subjects each year by sex and number of deaths per year from all causes and from malignant neoplasm

Beginning of follow-up	Number of subjects		Number of deaths			
			All causes of death		Malignant neoplasm	
	Male	Female	Male	Female	Male	Female
1968	72,716	80,176	1,304	796	306	185
1969	74,037	81,944	1,439	834	311	172
1970	74,402	83,108	1,525	915	326	192
1971	74,673	84,048	1,404	916	338	198
1972	74,831	84,967	1,488	918	342	195
1973	75,573	87,203	1,665	1,017	415	228
1974	75,090	87,540	1,641	1,071	338	241
1975	75,191	88,404	1,651	1,106	371	248
1976	75,941	89,832	1,714	1,090	385	247
1977	75,206	89,748	1,720	1,099	421	254
1978	74,428	89,553	1,716	1,085	399	247
1979	73,658	89,505	1,728	1,155	423	267
1980	72,864	89,310	1,781	1,239	437	258
1981	72,180	89,084	1,748	1,223	402	290
1982	71,341	88,646	1,731	1,223	423	270
Total			24,255	15,637	5,637	3,492

Table 3. Number of subjects and deaths by date of first entry during 1968–1982 for the analyses of early entrants

Date	Number of subjects		Number of deaths during 1968–82	
	First Entry	Staying in city†*	All causes of death	Malignant neoplasm
August 6	7,033	7,033	2,140	498
7	18,102	22,736	5,507	1,118
8	11,044	25,517	3,135	651
9	4,428	19,661	1,153	238
10–20	8,606	20,356	1,275	293
Total	49,213		13,210	2,798

†: The city is defined herein as the region within about 2 km of the hypocenter.

*: The number of subjects staying in the city by date was obtained from individual information regarding the date of first entry and the length of stay. For example, 7,033 subjects entered the city on August 6, but 2,399 of them left on the same day. Therefore, the remaining 4,634 subjects and 18,102 new entrants, 22,736 subjects in total, stayed in the city on August 7. After August 10, new 8,606 subjects entered the city and a total 20,356 of subjects stayed in the region between August 10 and 20.

exposed directly beyond 2 km from the hypocenter, only the early entrants not directly exposed were included in the study population, to exclude the effects of direct exposure. Table 3 shows the numbers of early entrant subjects and deaths during 1968–82 by date of first entry. The number of subjects staying in the region by date, which was obtained from individual information regarding the date of first entry and the length of stay, is also indicated in Table 3. The total early entrant study population was 49,213, of which 13,210 entrants died during the observation period due to all causes of death, and 2,798 died due to malignant neoplasms.

Statistical methods

(a) Data-reconstruction method

To take into consideration newly recognized survivors and interval dropout in the framework of the theory of survival analysis, we reconstructed sub-populations of the entire study population with different starting dates of observation. The starting date is the time origin for calculation of the survival times of subjects in a given sub-population. The starting date of January 1 was used for each year from 1968 to 1982, because the ABS File was revised by calendar year. Thus, fifteen sub-populations with different starting dates of observation were obtained. For all sub-populations, the end of follow-up was December 31, 1982. If a subject moved and then returned during the study period, the final date of return was regarded as the date of registry in the ABS File to avoid the case of interval dropout. Each sub-population included subjects who had already been recognized as survivors before the defined starting date and excluded those who had died or had not been recognized as survivors before this starting date. For example, an individual who had been recognized as a survivor before January 1, 1968, and had lived in Hiroshima Prefecture until December 31, 1982, was included in all the sub-populations. On January 1, 1968, 72,716 males and 80,176 females were still alive and residing in Hiroshima Prefecture (Table 2). For the analyses of early entrants, the numbers of subjects were obtained in a similar manner.

Since death information was available only in Hiroshima Prefecture, survivors who moved away from the prefecture after a given starting date and did not return were treated as censored cases at the time of exit. Because deaths and censored events were recorded with the calendar date, the survival time for each subject in a given sub-population could be obtained by calculating the number of days from the time origin to the death date, censored date, or date at the end of follow-up, according to the subject's final follow-up condition.

Having its own starting date of observation as the beginning of follow-up, each sub-population becomes equivalent to a fixed cohort including survivors recognized before the starting date.

(b) Cox model and covariates

As each sub-population can be considered as a fixed cohort, we can use the standard survival analysis technique. To treat many confounding factors (or covariates), we can thus use Cox's proportional hazards regression models[3]. The model is given by the form of $h(t;z)=h_0(t)exp(b'z)$, where $h(t;z)$ is the hazard rate at time t for an individual with covariate vector z, b is a column vector of unknown regression coefficients and $h_0(t)$ is an unknown hazard function for an individual with covariate vector $z=(0, 0,...,0)'$: column vector. We applied the models to each respective sub-population in sequence throughout the study period.

Estimated regression coefficients in a Cox model are invariant and not changed, even if a certain past date is substituted for the starting date of observation. The reason is that the starting date is common for all members in a given sub-population, and this substitution of time origin is a monotonic transformation of survival time. Therefore, if we regard the past date as the date of bombing for all sub-populations, the relative risks obtained from any sub-population can be interpreted as the risks after the date of bombing, on condition that all members of a given sub-population were still alive at the starting date of observation.

In the examination of the relationship between exposure status and mortality risk among the entire study group of A-bomb survivors, we used such covariates as exposure status, family destruction, place of residence, time of issuance of Health Handbook, and age at the time of the bombing.

The eight kinds of exposure status indicated in Table 1 can be expressed by the following six dummy (or indicator) variables: Directly exposed within 1 km, 1–1.5 km, 1.5–2 km, and beyond 2 km, and early entry within 3 days or after 3 days. For example, if an individual has the exposure status of early entrant within 3 days and exposed directly beyond 2 km, the variable of early entry within 3 days was coded one and the variable of directly exposed beyond 2 km was also coded one. In this manner, the risk of the directly exposed beyond 2 km and that of early entry within 3 days can be estimated separately. Hereafter we call these six variables exposure level to distinguish them from exposure status. The mortality risk by exposure level was calculated relative to that of early entry after 3 days.

The level of family destruction was classified as severe, slight or unknown as described in detail elsewhere[6]. For these three levels, two dummy variables were used. The place of residence was coded with two dummy variables. The first variable was coded one if the individual lived in Hiroshima City, and the second variable was coded one if the individual lived elsewhere. If an individual had a history of residence in both, both variables were coded. The dummy variable for the time of issuance of the Health Handbook was coded as one if the date of issuance was within 5 years before the time origin for the given sub-population, and zero if otherwise, for each sub-population. For the age at the time of the bombing, six categories of age decades, of which the last includes all those more than 50 years old, were used.

In the investigation of the relationship between the initial date of entry and the mortality risk in early entrants, dummy variables were used for each entry date from August 6 to 9 and for those after August 10. For the subsequent analysis of mortality risk by date of staying, these variables were replaced by four covariates for dates of stay from August 6 to 9, which were coded one if an individual stayed in the region within 2 km, or zero if otherwise, for each date, respectively. In the analyses for early entrants, dummy variables were also used for sex, age at time of bombing, and time of issuance of the Health Handbook. Because most of the early entrants lived in places other than Hiroshima City and the level of family destruction, which is strongly influenced by the bombing, can be considered as not important in the analysis for them, the variables of place of residence and family destruction were not applied in these analyses.

These statistical analyses were performed using BMDP statistical software[4].

RESULTS

Analyses of all atomic bomb survivors

The results for consecutive years were almost the same throughout the study period; therefore results for every third year are shown. The relative risk of death due to all causes by exposure level compared to that for early entry after 3 days is shown in Table 4. Each relative risk was estimated after adjustment for confounding factors. The risk for the directly exposed was significantly higher than that for entry after 3 days at a 5% significance level throughout almost the entire study period. For both sexes, the risk decreased as the distance from the hypocenter increased throughout the study period. The relative risk for early entry within 3 days was lower than that for directly exposed beyond 2 km. The risk for females who entered within 3 days was significantly higher than that for those who entered after 3 days throughout almost the entire study period, while this result for males was observed only during the first half of the study period. The relative risk for females was higher than that for males at all exposure levels.

The relative risk of mortality from malignant neoplasm is shown in Table 5. The overall pattern of relative risk was almost the same as that of death due to all causes. However, the numerical values of relative risk for mortality from malignant neoplasm were greater than those for death due to all causes, for all exposure levels and for both sexes, particularly females, throughout the study period. Furthermore, the relative risk of mortality from malignant neoplasm was extremely high for females directly exposed within 1 km, even in the later half of the study period. The relative risk in females was 2.87 (95%CI=2.21–3.73) in the sub-population followed

Table 4. Relative risk† of all causes of death by exposure level

Beginning of follow-up	Directly exposed				Early entry within 3 days
	Within 1 km	1–1.5 km	1.5–2 km	Beyond 2 km	
Male					
1968	1.35 (1.22–1.49)	1.42 (1.32–1.54)	1.33 (1.24–1.44)	1.33 (1.23–1.43)	1.07 (1.00–1.15)
1971	1.28 (1.15–1.42)	1.33 (1.22–1.44)	1.27 (1.17–1.37)	1.26 (1.17–1.37)	1.10 (1.02–1.18)
1974	1.14 (1.01–1.28)	1.17 (1.07–1.28)	1.12 (1.02–1.22)	1.13 (1.03–1.22)	1.07 (0.99–1.16)
1977	1.15 (1.00–1.33)	1.17 (1.05–1.30)	1.12 (1.02–1.24)	1.11 (1.01–1.23)	1.10 (1.01–1.20)
1980	1.20 (0.98–1.45)	1.12 (0.96–1.30)	1.15 (1.00–1.31)	1.12 (0.98–1.27)	1.11 (0.99–1.25)
Female					
1968	1.83 (1.59–2.10)	1.61 (1.45–1.78)	1.42 (1.28–1.56)	1.41 (1.28–1.55)	1.17 (1.07–1.29)
1971	1.73 (1.49–2.01)	1.45 (1.31–1.61)	1.32 (1.19–1.46)	1.30 (1.18–1.43)	1.15 (1.05–1.27)
1974	1.57 (1.33–1.85)	1.27 (1.14–1.42)	1.18 (1.06–1.31)	1.16 (1.04–1.28)	1.09 (0.99–1.20)
1977	1.56 (1.28–1.90)	1.28 (1.12–1.46)	1.19 (1.05–1.35)	1.18 (1.05–1.33)	1.16 (1.04–1.30)
1980	1.56 (1.20–2.03)	1.30 (1.10–1.55)	1.18 (1.00–1.39)	1.17 (1.00–1.36)	1.11 (0.95–1.29)

( ): 95% confidence interval
†: Risk relative to that for early entry after 3 days from the bombing.

Table 5. Relative risk† of malignant neoplasms by exposure level

Beginning of follow-up	Directly exposed				Early entry within 3 days
	Within 1 km	1–1.5 km	1.5–2 km	Beyond 2 km	
Male					
1968	1.64 (1.34–2.00)	1.65 (1.40–1.95)	1.42 (1.21–1.67)	1.39 (1.19–1.63)	1.14 (0.98–1.32)
1971	1.64 (1.32–2.04)	1.65 (1.38–1.98)	1.47 (1.24–1.75)	1.39 (1.17–1.65)	1.23 (1.05–1.44)
1974	1.46 (1.15–1.86)	1.46 (1.20–1.77)	1.28 (1.06–1.54)	1.23 (1.02–1.47)	1.15 (0.98–1.36)
1977	1.48 (1.13–1.93)	1.41 (1.14–1.75)	1.22 (0.99–1.49)	1.15 (0.94–1.40)	1.10 (0.92–1.31)
1980	1.37 (0.93–2.02)	1.28 (0.95–1.74)	1.27 (0.97–1.68)	1.20 (0.92–1.57)	1.19 (0.93–1.51)
Female					
1968	2.87 (2.21–3.73)	1.80 (1.45–2.23)	1.51 (1.22–1.86)	1.32 (1.07–1.63)	1.24 (1.01–1.52)
1971	2.78 (2.11–3.65)	1.64 (1.31–2.04)	1.39 (1.12–1.73)	1.25 (1.01–1.54)	1.23 (1.00–1.50)
1974	2.34 (1.74–3.14)	1.38 (1.10–1.74)	1.19 (0.95–1.49)	1.06 (0.85–1.32)	1.10 (0.90–1.36)
1977	2.53 (1.79–3.59)	1.45 (1.11–1.89)	1.26 (0.98–1.63)	1.18 (0.93–1.51)	1.14 (0.90–1.45)
1980	3.11 (1.97–4.91)	1.58 (1.10–2.27)	1.40 (0.99–1.98)	1.30 (0.93–1.81)	1.17 (0.85–1.61)

( ): 95% confidence interval
†: Risk relative to that for early entry after 3 days from the bombing.

up beginning in 1968, and 3.11 (95%CI= 1.97–4.91) in that followed up beginning in 1980. There was no significant difference between the directly exposed beyond 2 km and early entry within 3 days in the risk of mortality from malignant neoplasm during the later half of the study period for either sex.

Results concerning each confounding factor can be summarized as follows. For family destruction, the risk for the severe level was higher than that for the slight level, but the statistical significance was not observed. Survivors living in Hiroshima City had a higher risk than those living in places other than Hiroshima City. As for the time of

Table 6. Relative risks by date of first entry compared to that for early entrants after 3 days from the bombing (All causes of death and malignant neoplasm)

Beginning of follow-up	Date of first entry			
	August 6	August 7	August 8	August 9
All causes of death				
1968	1.05 (0.97–1.14)	1.02 (0.95–1.10)	1.03 (0.95–1.11)	0.94 (0.86–1.04)
1971	1.07 (0.99–1.16)	1.04 (0.96–1.12)	1.04 (0.96–1.12)	1.01 (0.92–1.11)
1974	1.04 (0.95–1.14)	1.04 (0.96–1.12)	1.02 (0.94–1.11)	1.03 (0.93–1.14)
1977	1.10 (0.99–1.22)	1.07 (0.97–1.17)	1.04 (0.94–1.15)	1.05 (0.93–1.18)
1980	1.13 (0.98–1.30)	1.03 (0.91–1.17)	1.00 (0.87–1.14)	1.06 (0.90–1.24)
Malignant neoplasm				
1968	1.22 (1.02–1.47)	1.08 (0.91–1.27)	1.07 (0.90–1.28)	1.05 (0.84–1.30)
1971	1.33 (1.10–1.60)	1.12 (0.94–1.33)	1.12 (0.93–1.35)	1.13 (0.90–1.40)
1974	1.26 (1.04–1.54)	1.02 (0.85–1.23)	1.07 (0.88–1.30)	1.09 (0.87–1.38)
1977	1.22 (0.98–1.52)	0.98 (0.80–1.19)	1.06 (0.85–1.31)	1.03 (0.79–1.34)
1980	1.29 (0.95–1.74)	1.03 (0.78–1.35)	1.11 (0.83–1.48)	1.24 (0.88–1.75)

( ): 95% confidence interval

Table 7. Relative risk† of mortality from malignant neoplasm as a result of staying within the city limits of Hiroshima

Beginning of follow-up	Date of staying in city			
	August 6	August 7	August 8	August 9
1968	1.15 (1.03–1.28)	1.02 (0.93–1.11)	0.99 (0.90–1.09)	1.01 (0.92–1.12)
1971	1.20 (1.07–1.34)	1.03 (0.94–1.13)	1.00 (0.90–1.11)	1.04 (0.94–1.14)
1974	1.22 (1.08–1.39)	0.98 (0.89–1.09)	0.98 (0.88–1.09)	1.05 (0.94–1.16)
1977	1.22 (1.05–1.42)	0.94 (0.84–1.06)	1.02 (0.90–1.16)	0.96 (0.85–1.10)
1980	1.22 (0.99–1.51)	0.93 (0.79–1.10)	0.97 (0.81–1.16)	1.05 (0.88–1.26)

( ): 95% confidence interval
† : Risk relative to that in those who left the city limits of Hiroshima on the corresponding day.

issuance of Health Handbook, survivors receiving the Handbook more recently had a slightly higher risk, but no significant difference was observed. The risk for age at the time of the bombing increased as the age increased. These confounding factors were included continually in the model, and the marked lack-of-fits of the model were not observed.

Analyses of early entrants

Table 6 shows the relative risk of death due to all causes and due to malignant neoplasm by date of first entry for subjects who entered within 3 days compared to that for entrants after 3 days. The relative risk by date of first entry was not adjusted for the length of stay. While the mortality risk due to all causes for any group of first entrants was slightly higher than that for the control group, this difference was not significant in any year in the study period. However, of the early entrants, only those who entered the region on August 6, the date of the bombing, had a significantly higher risk of mortality from malignant neoplasm than that in the control group.

The risk of mortality from malignant neoplasm as a result of staying within the city limit of Hiroshima was examined, taking into account not only the date of first entry but also the length of stay of each subject. The relative risk was estimated with adjustment for the length of stay between August 6 to 9 (Table 7). There was a significant difference between the subjects who entered the region on August 6 and those who did not enter on that day but had the same duration of stay excluding August 6. The relative risk of staying on August 6 was 1.15 (95%CI=1.03–1.28) in the sub-population followed up beginning in 1968. However, no such one day effect was observed in subjects staying from August 7 to 9. No temporal change of relative risk was found.

DISCUSSION

On the entire population of atomic bomb survivors

In a previous study[6], the SMR due to all causes of death in the entire group of atomic bomb survivors in Hiroshima Prefecture was found to be 8% lower than that in the non-exposed residents. A similar pattern was also observed among survivors in Nagasaki City[11]. These results may be interpreted as indicating that medical aid, which includes examination, treatment, and living guidance, particularly for circulatory diseases, has substantially contributed to the health of the survivors. Okajima et al noted that the most effective medical aid was considered to be the health screening program for A-bomb survivors[14]. To make the study population homogeneous for the health screening, non-exposed residents who had not been able to take part in the health screening program were excluded in this study, although the previous studys[6] included these subjects.

Before conducting this research, we considered the possibility that a relationship between mortality risk and exposure status would not be recognized after adjustment for various confounding factors such as place of residence, level of family destruction, time of issuance of Health Handbook, and age at the time of bombing, because high mortality might be strongly correlated with some of these confounding factors, for example, level of family destruction. However, even after adjustment for these confounding factors, the results indicated that the relative risk of death due to all causes and due to malignant neoplasm decreased as the distance from the hypocenter increased. Because the magnitude of radiation exposure dose is strongly related to the distance from the hypocenter, our result supports the thesis that the late effects of radiation have affected A-bomb survivors. Analyses in which many confounding factors are taken into consideration have not previously been conducted by RIRBM or RERF; this study is the first such attempt.

A recent RERF report[18] based on DS86[16] indicates that the relative risk of all cancers other than leukemia has not changed over time during the period 1950–1985, except in the youngest group. The same pattern was observed in both sexes in our subjects. These results support the use of the proportional hazards model because the estimated relative risks were almost stable over time and, thus, the proportionality assumption is valid throughout the study period. The relative risks for females were found to be higher than those for males in our study, as was observed in the LSS sample. While the results we obtained are in essential agreement with those of the LSS study[19], the amount of overlap between A-bomb survivors' files in the RERF and RIRBM is not confirmed at present. To investigate this point, joint study with RERF is now in progress. A precise report concerning this overlapping will be published elsewhere.

One of the applications of our findings is in the improvement of the medical care offered to survivors in accordance with the known late effects due to radiation. In this regard, one of our important findings is that proximally exposed survivors, even those still alive during the later part of the study period, invariably showed higher mortality risks.

The cause of death was not examined in detail in this study. Such analyses may require a longer observation period. We are conducting distance-confirmation and radiation dose estimation research which takes into account the shielding condition for each survivor. Furthermore, we are trying to devise a statistical method to analyze the dynamic population with interval dropout, without transforming it into sub-fixed-populations, in the framework of survival analysis. Further studies will be conducted on the basis of the information noted above in the near future.

On the early entrants

Kato et al investigated the mortality ratio of early entrants in the RERF LSS sample during the period from 1950 to 1978[8]. The early entrants in their study were defined as individuals who entered the cities (Hiroshima and Nagasaki) within 1 month after the bombing; these 4,512 subjects were divided into three groups based on their dates and places of entry. They found no significant differences among the three groups in death from all causes or from all cancers except leukemia. However, their definition of early entrants differed from the one used herein, their analysis did not take into account the length of stay in the cities, and the early entrant sample size was smaller than that in our study.

Hirose suggested that the incidence of leukemia is increased in early entrants[7]. The mortality rate due to leukemia and other cancers during 1968–1972 in early entrants was higher than that in non-exposed residents[10]. However, Shimizu et al noted that the results of these two studies were affected by some uncertainties due to a possible bias, i.e., the chance of finding out leukemia and other cancer cases of the survivors received the Health Handbook was more than that of the non-exposed residents[19]. The results reported herein are not affected by such a bias because the study subjects were only survivors and were thus homogeneous with respect to the bias factors pointed out by Shimizu et al.

We found a significant difference between the early entrants within 2 km of the hypocenter on the day of the bombing and those who entered after 3 days in the risk of mortality due to malignant neoplasm throughout the study period. Furthermore, those who entered the region on the day of the bombing had a significantly higher risk of malignant neoplasm than those who did not enter on that day, even after adjustment for the length of stay. While there are other interpretations, we consider that this finding strongly suggest an immediate radiation effect. There was marked attenuation of neutron-induced gamma dose with time after the bombing[16], and the date with the highest residual radioactivity is therefore considered to be August 6. Thus, the implications of association between the mortality risk among early entrants and radiation dose should be discussed.

In the analyses of early entrants, individuals who were exposed directly at a distance of over 2km from the hypocenter were excluded. Therefore, the source of radiation considered here is the residual radioactivity produced by neutron activation of materials near the hypocenter and radioactive fallout of activation and fission products from the cloud formed by the explosion. It is estimated that the level of residual radioactivity after the atomic bombing in Hiroshima was low[1,5,16]. However, as noted in the final DS86 report, it is not possible to evaluate potential exposure to the short-lived fission products[16]. Thus, in previous major assessments of the survivor dose, radiation from short-lived fission products was not considered. Furthermore, there has been little research regarding internal exposure due to intake of food and water contaminated by radiation because this issue is considered difficult to evaluate. We consider that internal exposure is an issue which should not be ignored and that many uncertainties obscure the radioactivity exposure of early entrants. Although precise estimation of the dose of residual radioactivity for each entrant is difficult, it is important to determine conclusively whether the differences among entrants in mortality risk are due to residual radiation.

To address these issues, in our next study, we plan to analyze data acquired during a longer study period using more detailed classification of the early entrants, including their place of entry.

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