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Analysis of Cancer Mortality among Atomic Bomb Survivors in Hiroshima Prefecture, 1968–1997

Tamara ZHUNUSSOVA[1)], Masaaki MATSUURA[2)] and Norihiko HAYAKAWA[1)]

1) Department of Epidemiology, Research Institute for Radiation Biology and Medicine, Hiroshima University, 1–2–3, Kasumi, Minami-ku, Hiroshima, 734–8553, Japan

2) Japanese Foundation for Cancer Research, Cancer Institute, 1–37–1, Kami-Ikebukuro, Toshima-ku, Tokyo, 170–8455, Japan

ABSTRACT

The Research Institute for Radiation Biology and Medicine has a cohort of atomic bomb survivors, residents of Hiroshima Prefecture, followed up since 1968. An epidemiological project on cancer mortality has been extended by the 5 years from 1992 to 1997. In this paper we aim to evaluate the relative risk pattern of specific cancers by radiation dose over time and during this recent 5 years. We obtained the late effects and temporary changes from cancer sites on mortality such as leukemia, all cancers except leukemia, and cancers of the lung, esophagus, liver, stomach, colon, pancreas, breast and uterus. Although results for the additional 5 years were not statistically significant due to the relatively small sample size, we observed decreasing trends for many cancer sites including all cancers except leukemia, esophagus, colon, stomach, liver and breast cancers. In particular the sharply increased excess relative risk for female breast cancer shown in 1988–1992 dramatically declined during the period 1993–1997.

Key words: *Hiroshima prefecture, Atomic bomb survivors, Cancer mortality, Excess relative risk*

Evidence from studies of atomic bomb survivors reveals that the late mortality effects of large, single doses of ionizing radiation are focal and largely confined to cancer[2)]. Radiation effects do not appear immediately after exposure but occur some years later[41)] with different latent periods, defined as the time between exposure and the clinical appearance of the cancer[20)]. We also have to admit that survivors who were exposed in the first or second decade of life have just entered the cancer-prone age[43)] and excess cancer rates have generally continued to increase with certain ages[31)]. Most of the information on radiation-related cancer risk comes from the Life Span Study (LSS), on Japanese atomic bomb survivors conducted by the Radiation Effects Research Foundation (RERF)[5,28,31,32,34,36–39,41–43)], the cohorts stored at the Atomic Bomb Disease Institute, Nagasaki University[27,30)], and the Research Institute for Radiation Biology and Medicine (RIRBM)[11,12,19,24,25)], Hiroshima University. Current protection standards for environmental and occupational exposure to ionizing radiation are mainly based on estimates of radiation-induced cancer risk derived from the RERF studies[16)]. Studies on nuclear industry workers[3,15)] and the population exposed therapeutically to high-dose fractions[13,14)] are also helpful sources in understanding the late effects of ionizing radiation. Accumulating information derived from previous investigations on those exposed as children is important for the additional years of follow-up[32)]. The possibility of very late effects of atomic-bomb exposure is suggested by recent reports of increased frequencies of certain types of cancers[26)]. An updated database of surveillance for the survivors registered at RIRBM covers 30 years of follow-up study, from 1968 to 1997, and includes survivors in Hiroshima Prefecture with Health Handbooks issued by the Hiroshima local government.

The objective of our study was to investigate the radiation risk during the study period and the temporary effects of the exposure for an additional 5 years among atomic bomb survivors in Hiroshima Prefecture registered at the RIRBM, Hiroshima University.

MATERIALS AND METHODS

The cohort of atomic bomb survivors used in this study consists of a total of 51,532 subjects followed up from January 1, 1968 till December 31, 1997. All the subjects are atomic bomb survivors, with radiation doses estimated by the Dosimetry System, the Atomic Bomb Survivors 1993 (ABS93D)[12)]. We used the ABS93D as an individual exposure radiation dose, based on the method of interpolation of doses represented in the final report of Dosimetry System 1986 (DS86)[37)], which provides the shielded *kerma* and the organ-absorbed dose based on individual exposure status, including ground distance, shielding conditions and age at the bombing. In this analy-

sis gamma ray and neutron doses were added and the relative biological effectiveness of neutron was assumed to be equal to one. Risk estimates are given in sieverts. As for the application of organ-absorbed doses, the active bone marrow dose was used for leukemia and the large intestinal doses for lung, esophagus, stomach, pancreas, liver, colon cancer and all cancers except leukemia. The breast dose was used for breast cancer and the uterus dose for uterus cancer.

The follow-up period 1968–1997 was divided into six intervals: 1968–1972, 1973–1977, 1978–1982, 1983–1987, 1988–1992 and 1993–1997. Age at the time of the bombing (age ATB) categories were also divided into six intervals: 0–9, 10–19, 20–29, 30–39, 40–49 and 50+. By exposure category, the data are defined for 10 exposure groups (0–0.004, 0.005–0.05, 0.06–0.09, 0.10–0.19, 0.20–0.49, 0.50–0.99, 1.00–1.99, 2.00–2.99, 3.00–3.99, 4.00+Sv), where the 0–0.004 Sv group is the control (0 Sv) group.

As a statistical method, we used Poisson regression analysis where i is the index stratum defined by the combination of sex, age ATB groups and follow-up intervals, and j=0, ... , J-1 indicates J exposure groups. In this analysis, we used J= 10 according to the exposure categories. We calculated the number of deaths (denoted by Y_{ij}), person-years (PY_{ij}), mean dose (D_{ij}) and mortality rate (M_{ij}) for the ij group. Parameters are estimated using the maximum likelihood method, assuming that the number of deaths Y_{ij} in ij cells is an independent Poisson random variable with expected values $E\ (Y_{ij}) = PY_{ij} \cdot M_{ij}$, where PY_{ij} is considered constant and M_{ij} is defined as $M_{ij} = M_{i0} \cdot RR_{ij}$, where M_{i0} represents the background or spontaneous mortality rate of stratum i, i.e., the rate that pertains in the absence of exposure to atomic bomb radiation. We used $RR_{ij}=1+bD_{ij}$, where b is an unknown parameter and excess relative risk (ERR) is expressed by b. To estimate the relative risk by sex, the model was applied separately for each sex group. Similarly, in the analysis by age ATB and temporal change of relative risk, the model was applied separately for each age ATB group and each follow-up interval, respectively. In the analysis by exposure group we used the model with the relative risk $RR_{ij}=exp(b_j)$ instead of $RR_{ij}=1+bD_{ij}$. Calculation of person-years in any interval is based on each subject's person-months, representing time at risk in Hiroshima Prefecture, for each month in every year from 1968 to 1997, and added for each interval as person-years. The subjects who emigrated from Hiroshima Prefecture were considered as lost to follow-up at the time of emigration. In the case of returning as residents to Hiroshima Prefecture during the study period we count the person-years repeatedly. To fit the various models for our variables we used the AMFIT program in Epicure software[35]. Mortality information was obtained from Vital Statistics Death Schedules which are based on death certificates[19]. Ten types of cancer mortality among A-bomb survivors were considered and classified according to the International Classification of Diseases (ICD; World Health Organization 1965[47], 1975[48], 1989[49]) including: leukemia (204–207, 204–208, C91–C95), all cancers except leukemia (140–207, 140–208, C00–C97), lung (162, 162, C33–C34), esophagus (150, 150,C15), liver (155, 155, C22), stomach (151, 151, C16), colon (153, 153, C16), pancreas (157, 157, C25), breast (174, 175, C50) and uterus (181–182, 172, C53–C55), respectively.

RESULTS

Table 1 summarizes the number of subjects and deaths that occurred among atomic bomb survivors during 1968–1997 by defined cancer sites separately for males and females. The estimated ERR-s at 1 Sv with 95% confidence intervals by type of cancer and sex are presented in Table 2. The results for ERR at 1 Sv were obtained on the basis of the assumption that relative risk was expressed by linear form of dose. For both sexes a statistically higher excess relative risk was observed for leukemia, all cancers except leukemia, liver, pancreas, lung and breast cancers. For leukemia, the ERR at 1 Sv for both sexes was 1.61 [95% confidence interval (CI): 0.65, 2.58]. For all cancers except leukemia the ERR at 1 Sv for both sexes were 0.25 [95% CI: 0.18, 0.32]. The ERR at 1 Sv for liver cancer was 0.34 [95% CI: 0.17, 0.52]. A high ERR at 1 Sv was observed for breast cancer at 2.35 [95% CI: 1.19, 3.51]. For pan-

Table 1. Number of subjects and death 1968-1997

	Total	Control	Exposed
Number of subjects	21,227 (30,305)	9,948 (13,619)	11,279 (16,686)
Number of deaths			
Leukemia	69 (59)	20 (22)	49 (37)
All cancers except leukemia	2,458 (2,340)	910 (832)	1,548 (1,508)
Stomach	666 (523)	260 (190)	406 (333)
Colon	123 (154)	46 (71)	77 (83)
Lung	421 (298)	158 (104)	263 (194)
Liver	478 (252)	169 (86)	309 (166)
Pancreas	113 (116)	34 (42)	79 (74)
Esophagus	121 (38)	45 (8)	76 (30)
Breast	(159)	(48)	(111)
Uterus	(165)	(64)	(101)

Numbers of females are shown in parentheses

Table 2. Excess Relative Risk at 1Sv of mortality between 1968-1997 by selected cancers and sexes

Site of cancer	All	Male	Female
Leukemia	1.61 (0.65 2.58)	1.64 (0.38 2.90)	1.59 (0.08 3.10)
All cancers except leukemia	0.25 (0.18 0.32)	0.12 (0.05 0.20)	0.50 (0.35 0.64)
Esophagus	0.16 (–0.15 0.46)	–0.02 (–0.26 0.20)	2.01 (–0.16 4.17)
Stomach	0.02 (–0.06 0.12)	–0.21 (–0.12 0.07)	0.20 (–0.01 0.41)
Colon	0.22 (–0.06 0.51)	0.44 (–0.03 0.91)	–0.02 (–0.35 0.31)
Liver	0.34 (0.17 0.52)	0.23 (0.05 0.41)	0.66 (0.22 1.10)
Pancreas	0.42 (0.03 0.80)	0.39 (–0.08 0.86)	0.48 (–0.17 1.12)
Lung	0.19 (0.03 0.34)	0.10 (–0.05 0.26)	0.47 (0.10 0.84)
Breast	—	—	2.35 (1.19 3.51)
Uterus	—	—	0.15 (–0.23 0.54)

Numbers in parentheses indicate the 95% confidence interval.

Table 3. Estimated relative risk of mortality during 1968-1997 compared with control group

	Dose categories								
Site of cancer	0.005–0.05	0.06–0.09	0.10–0.19	0.20–0.49	0.50–0.99	1.0–1.99	2.0–2.99	3.0–3.99	4.0+
Leukemia	0.27	0.37	–0.42	–0.14	0.71	2.62	4.51	5.77	5.27
	(–0.66;0.55)	(–0.24;1.52)	(–0.7;0.27)	(–0.54;0.59)	(–0.08;2.21)	(1.02;5.49)	(1.45;11.3)	(1.42;18.04)	(1.23;16.68)
All cancers except leukemia	–0.04	0	0.07	0.18	0.25	0.39	0.92	1.13	0.29
	(–0.13;0.06)	(–0.09;0.11)	(–0.02;0.18)	(0.08;0.29)	(0.11;0.40)	(0.22;0.59)	(0.56;1.37)	(0.56;1.91)	(–0.08;0.83)
Esophagus	–0.08	–0.13	0.43	0.55	0.58	0.98	–0.49	—	0.77
	(–0.52;0.75)	(–0.55;0.65)	(–0.12;1.35)	(–0.01;1.44)	(–0.10;1.77)	(0.04;2.72)	(0.07;2.63)	(—)	(–0.56;6.32)
Stomach	–0.11	–0.06	–0.11	0.14	–0.08	–0.08	0.4	0.22	0.11
	(–0.28;0.10)	(–0.18;0.22)	(–0.27;0.07)	(–0.03;0.34)	(–0.27;0.15)	(–0.31;0.24)	(–0.05;1.11)	(–0.36;1.37)	(–0.56;0.77)
Colon	–0.36	–0.08	–0.18	–0.15	–0.29	0.7	0.95	—	0.38
	(–0.60;0.00)	(–0.38;0.38)	(–0.45;0.23)	(–0.41;0.21)	(–0.59;0.23)	(0.11;1.85)	(–0.14;3.45)	(—)	(–0.65;4.61)
Liver	0	0.46	0.08	0.29	0.63	0.43	1.46	1.72	0.7
	(–0.25;0.34)	(0.14;0.86)	(–0.16;0.40)	(0.02;0.61)	(0.25;1.13)	(0.02;1.02)	(0.58;2.81)	(0.44;4.13)	(–0.16;2.44)
Pancreas	0.14	0.23	0.29	0.54	0.71	0.47	1.24	2.93	0.03
	(–0.48;0.43)	(–0.21;0.94)	(–0.21;1.00)	(0.05;1.25)	(0.04;1.81)	(–0.20;1.72)	(–0.18;5.14)	(0.23;11.51)	(–0.85;6.44)
Lung	0.03	–0.16	0	0.09	0.04	0.47	0.79	1.05	–0.01
	(–0.20;0.34)	(–0.37;0.12)	(–0.21;0.28)	(–0.12;0.36)	(–0.22;0.39)	(0.07;1.02)	(0.10;1.89)	(0.05;3.00)	(–0.59;1.40)
Breast	–0.28	–0.18	0.42	0.57	1.71	3.12	3.92	7.25	12.93
	(–0.69;0.66)	(–0.61;0.72)	(–0.16;1.43)	(–0.03;1.56)	(0.63;3.51)	(1.26;6.50)	(1.10;10.55)	(1.96;21.35)	(5.27;29.92)
Uterus	–0.01	–0.1	0.08	–0.13	0.03	–0.26	2.2	—	1.21
	(–0.42;0.68)	(–0.48;0.54)	(–0.32;0.75)	(–0.46;0.38)	(–0.49;0.82)	(–0.73;1.03)	(0.28;6.96)	(—)	(–0.69;14.98)

Numbers in parentheses indicate the 95% confidence interval.
Dashes indicate no convergence.

creas and lung cancers the ERR-s at 1 Sv were 0.42 and 0.19, respectively. However the ERR-s for esophagus, stomach and colon cancer were not statistically significant. Considering the sex difference, the excess relative risk was higher for females compared to males in all types of cancer except colon. Almost no difference between the sexes was observed for leukemia where the ERR was 1.64 [95%CI: 0.38, 2.90] for males and 1.59 [95%CI: 0.08, 3.10] for females. But for all cancers except leukemia, lung and liver cancers the ERR-s were higher for females compared to the male group. The ERR at 1 Sv for all cancers except leukemia for males was 0.12 [95% CI: 0.05, 0.20] and females 0.50 [95%CI: 0.35, 0.64]. The ERR at 1 Sv for liver cancer was 0.23 [95%CI: 0.05, 0.41] and 0.66 [95%CI: 0.22, 1.10] for males and females respectively. For lung cancer the ERR at 1 Sv was higher for females at 0.47 [95%CI: 0.10, 0.84] compared with 0.10 [95%CI: –0.05, 0.26] for males. There was an increased risk for pancreas cancer mortality where the ERR at 1 Sv was 0.42 [95%CI: 0.03, 0.80]. However, this was not statistically significant by sex difference. Furthermore, we did not observe a statistically significant increased excess relative risk for uterus cancer mortality.

Table 3 shows the dose-response relationship based on the model $RRij$=exp (bj). For all cancers except leukemia, lung and breast cancers, the excess relative risks were statistically significant for almost all dose groups > 0.50 Sv. For leukemia esophagus and colon cancers the ERR was significant in the dose group 1.0–1.99 Sv. A clear relationship with dose was not found for stomach cancer. As for liver cancer, the excess relative risk was significant for >1.0 Sv. The ERR was significant for pancreas cancer in the ranges 0.20–0.99 Sv and 3.0–3.99 Sv. For uterus cancer the excess

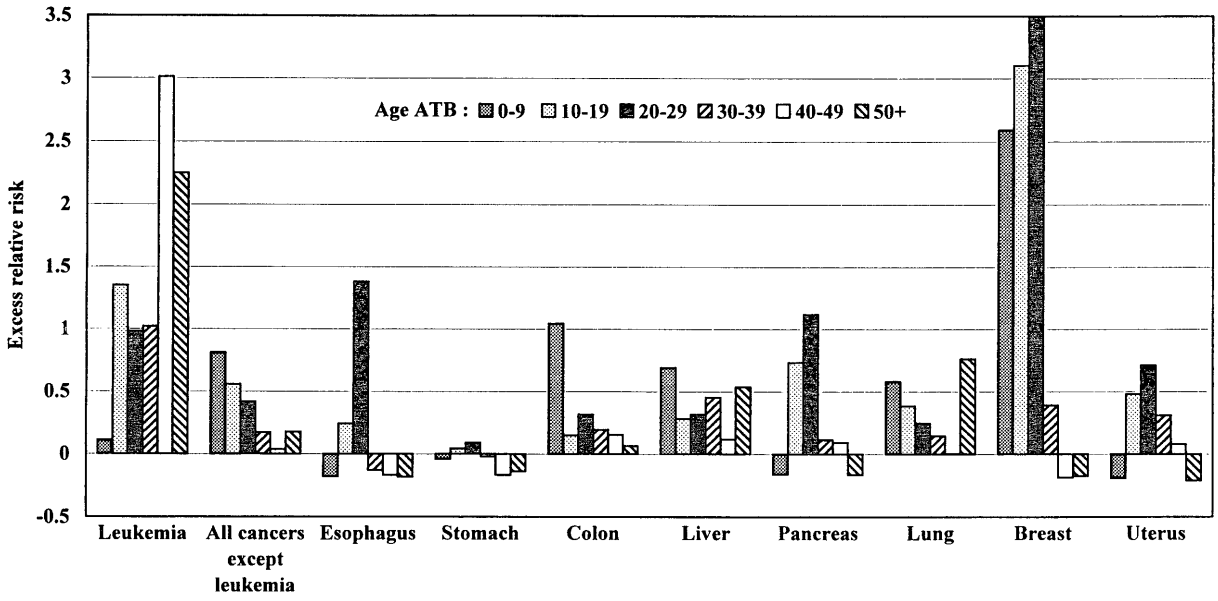

Fig. 1. Excess Relative Risk by age, Age at the time of bombing

relative risk was significant in the group 2.0–2.99 Sv.

The ERR at 1 Sv by age ATB is shown in Fig. 1. A high ERR was observed in the age ATB <10 years old for all cancers except leukemia, and for cancers of the lung, liver and colon. For leukemia the ERR was high in the age ATB 40–49. For esophagus, pancreas, stomach and uterus cancers the ERR was higher in the age group 20–29 than in other age groups. For breast cancer statistically high ERR-s were observed in ages ATB less than 30.

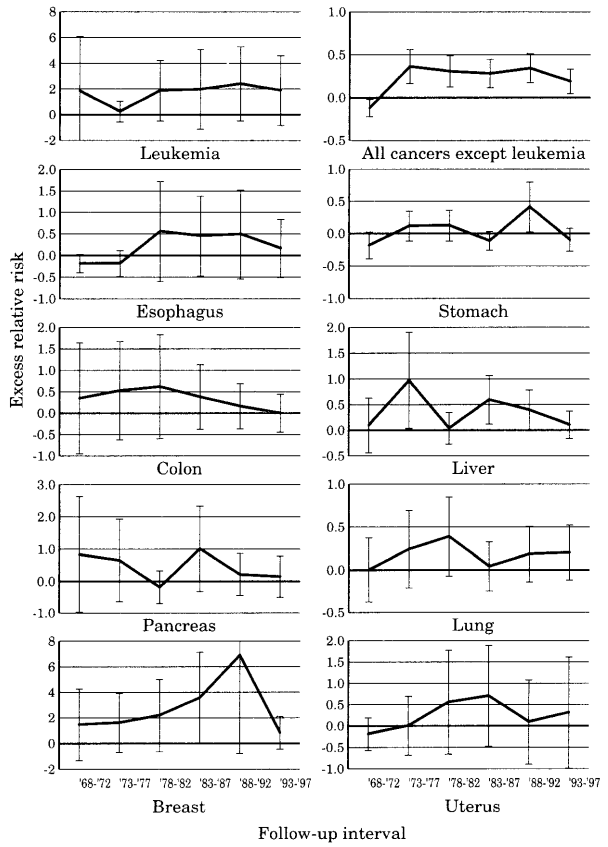

Fig. 2. Excess relative risks for cancer sites by follow-up interval

The ERR at 1 Sv by follow-up intervals are shown in Fig. 2. The ERR increased for leukemia, all cancers except leukemia, breast cancer, liver, stomach, and lung cancers in the intervals before 1992, but there was no apparent additional increase in ERR in 1992–1997 except lung and uterus cancers. The follow-up study for all cancers except leukemia also showed high ERR-s during 1973–1997. Significantly increased excess relative risks during the 1988–1992 period for lung and breast cancers were not statistically significant during 1993–1997. A slightly elevated ERR for esophagus cancer in the interval 1988–1992 was not statistically significant and in the following interval 1993–1997 there was no increase in excess relative risk. The ERR for stomach cancer was high during 1988–1992 compared to previous and following years but was not statistically significant. There was no increase in the ERR for colon cancer during the follow-up period. A remarkable finding was observed for female breast cancer. Starting in 1983–1987 the ERR increased sharply with a peak in 1988–1992, but during the following interval 1993–1997 the ERR declined.

DISCUSSION

Many organ sites are involved at various levels of radiation effect. The sensitivity to the induction of cancer following exposure to ionizing radiation is considered to be different by site[42]. Previous radiotherapy treatment[6,9,17,40] for benign and malignant diseases[23] needs to be considered as well as the interaction of the carcinogenic effect of radiation with other risk factors such as smoking

habits[33] or HCV infection for liver cancer[7]. Moreover, the interaction of radiation-associated cancer risk with cancer-prone disorders and geographical difference must be taken into consideration because some cancers tend to occur in particular areas. Many reports on the cancer mortality of atomic bomb survivors have been published during past decades and a relation to radiation exposure has been demonstrated for leukemia, thyroid, breast and lung cancers and also a presumed relation of exposure to stomach and esophagus cancers has been noted[2,19,41–43,46].

The main purpose of the present analysis in this follow-up study was to examine late effects, especially for the latest five years, using data for atomic bomb survivors registered at RIRBM, Hiroshima University. We assumed that the confounding factors noted above were homogeneous between exposed and control groups because all the subjects are directly exposed survivors in Hiroshima City. Furthermore, all are Health Handbook holders. Thus, both groups have the same opportunity to receive the benefit of the many health and medical programs for survivors. In our results the ERR-s for cancers such as leukemia, all cancers except leukemia, breast and liver cancer were significantly related to radiation dose among survivors residing in Hiroshima Prefecture between 1968 and 1997. Important findings were observed in liver and breast cancers between 1993 and 1997.

The ERR at 1 Sv for liver cancer was high for both sexes. As liver cancer is frequent in Japan and the incidence and mortality rates have risen over the last decade[18] atomic bomb survivors are at high risk and estimation of the risk from liver cancer is important for the purpose of radiation protection and possibly for risk reduction. A dose-response for liver cancer has been reported in the prevalence of hepatitis B surface antigen in the sera of atomic bomb survivors[1], and the previous studies on the incidence of primary liver cancer indicate that low-linear-energy transfer (LET) radiation is capable of causing liver cancer[4,8,44]. In addition a prevalence study of primary billiary cirrhosis among atomic bomb survivors in Nagasaki has indicated a possible influence of radiation[29].

The most remarkable finding in this analysis for an additional five years has been shown for breast cancer. A generally low level of population risk in the absence of radiation exposure for breast cancer and the strength of radiation dose response has led to a clear description of excess risk and its variation by age at exposure and over time following exposure[22]. The sharply elevated excess relative risk for breast cancer in 1988–1992 declined during the period 1993–1997, possibly because the high mortality risk due to radiation among the exposed group became smaller after 1993 and the mortality risk of the control group elevated and approached that of the exposed group. Although the ERR decreased between 1993 and 1997 the number of deaths due to breast cancer increased in both groups. ERR for breast cancer mortality was high for those exposed to radiation at ages ATB less than 30. The possible modifying effects of age ATB from ionizing radiation is important in understanding biological mechanisms in the development of breast cancer. Due to earlier investigations on breast cancer mortality among atomic bomb survivors, it is a reasonable assumption that an already-initiated, but untransformed cell is equally likely, at age 70, to have developed into a detectable cancer whether initiation occurred at age 10 or age 40[45]. Even though the ERR for breast cancer declined during the additional period of study further careful follow-up with an adjustment to other possible risk factors is suggested, because according to the Canadian fluoroscopy study there was a strong linear trend of increasing risk with increasing dose for breast cancer mortality and a suggestion that excess relative risk may start to decrease 40 or more years after exposure[14]. The observed pattern, like that for breast cancer in the present study, could reflect the existence of a susceptible subgroup or a relatively rare type of radiation effect in the general population[45]. Other studies on breast cancer have revealed the fact that reproductive factors and hormone use may act independently of radiation exposure[10] and that age at menarche or age at menopause has no association with dose[21]. The results of an analysis of the late effects of age or time on radiation-related cancer mortality showed the importance of continued investigation of atomic bomb survivors in follow-up study and adjustment to various factors. A family history of breast cancer, which is among the factors most strongly associated with risk in Western populations, might be applied to Japanese families with a history of breast cancer. We are now in preparing a familial study of breast cancer.

To obtain a complete picture of excess relative risks of mortality from the above mentioned cancer sites we need to conduct further research in the low dose group and a more careful investigation of the nature of site-specificity.

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