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Late Health Effects in the Atomic Bomb Survivors

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Introduction

To determine the possible late health effects of atomic-bomb radiation, Radiation Effects Research Foundation (RERF) has been conducting mortality surveillance on a fixed cohort (Life Span Study, or LSS, of 93,000 atomic bomb survivors and 27,000 non- exposed residents of Hiroshima and Nagasaki) since 1950.

Deaths are routinely identified through the family registry system and ascertainment is virtually complete. Through record linkage with local cancer registries in Hiroshima and Nagasaki, RERF also embarked on cancer incidence studies in 1957. Data analyses have been conducted on a periodic basis, with release of a report on mortality analyses that took place between 1950 and 1997. Meanwhile, a report was published on 1958-1987 cancer incidence analyses, with an up-to-date report now being prepared.

The present report mainly describes the results of the analyses of cancer and non-cancer mortality in the LSS.

Outline of the Life Span Study

As of 2002, approximately 55% of the cohort members had died. About 22% of the deaths are attributed to cancer, 73% to other diseases and 5% to external causes. A comprehensive analysis on site-specific cancer mortality in the LSS for the period through 2002 is currently underway.

We have the outcome data one of which is causes of death based on death certificates and we have information on cancer incidence which is based on local tumor and tissue registry programs. We have another set of data which is based on routine health examinations that have been gathered on morbidity (Table 1).

As for mortality follow-up based on death certification, we have been publishing a series of reports starting from report No. 1 to No. 13 which is the most recent publication, published in 2003, and now we are working on report No. 14 which covers the period from 1950 to 2002 (Table 2).

Table 1. Epidemiological studies of A-bomb survivors (outcome information)

1. Death certificate
   - Causes of death
2. Tumor/Tissue registries
   - Cancer incidence
   - Pathological findings
3. Health examination
   - Morbidity
   - Biological materials
     (Serum, lymphocyte etc.)
4. Mail survey
   - Confounders, risk modifiers

Table 2. The Report series of Life Span Study data publications

Report	Observation period	Year of publication
1	1950-1955	1962
2	1950-1959	1964
3	1950-1960	1965
4	1950-1959	(1964)
5	1950-1966	1971
6	1950-1970	1972
7	1950-1972	(1973)
8	1950-1974	1978
9	1950-1978	1982, 1983
10	1950-1982	1987
11	1950-1985	1989, 1990, 1992
12	1950-1990	1996, 1999
13	1950-1997	2003
14	1950-2002	Under preparation

There are 35 tumor registry programs going on in Japan as of this year and among them 6 are said to be the best (Figure 1).

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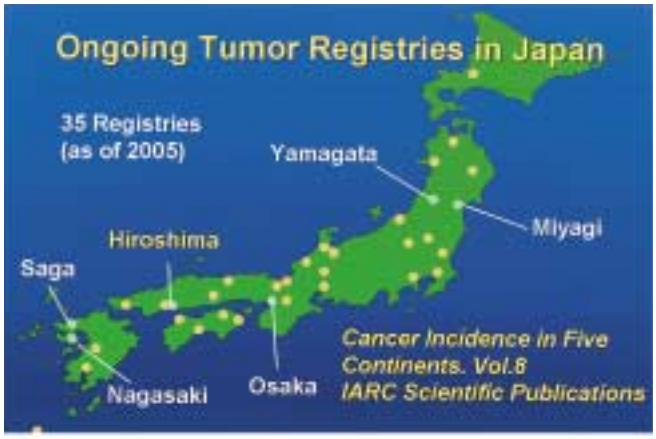

Figure 1. Tumor registries in Japan as of 2005.

Summary of the results

Among the group of people known to have dose estimation by the DS02 system who are about 86,000, a little bit more than 10,000 solid cancer deaths have occurred and about 300 leukemia deaths have happened.

As for risk estimation, both excess relative risk (ERR) and excess absolute rate (EAR) provide complimentary information.

For leukemia, the excess relative risk per 1 Sv exposure is 4.9, meaning they have 5.9 times higher risk of death due to leukemia. For solid cancers, ERR is 0.50 meaning that a 50% increase is observed in cancer death for 1 Sv exposed people (Figure 2). Among 10,127 solid cancer deaths observed, 479 are estimated to be caused by radiation (Table 3), and among 296 leukemia deaths, 93 are estimated to be caused by atomic bomb radiation (Table 4).

There has been some change in risk estimation for cancer after the introduction of the DS02 system which is 7% lower than the estimation by DS86 (Figure 3); for leukemia it is 10% less (Figure 4).

As for difference in mortality rates for specific cancer sites (Figure 5), the possible explanation is that there is indeed a difference in radiation sensitivity by tissue organ or it may also be caused by a difference in the power of detection.

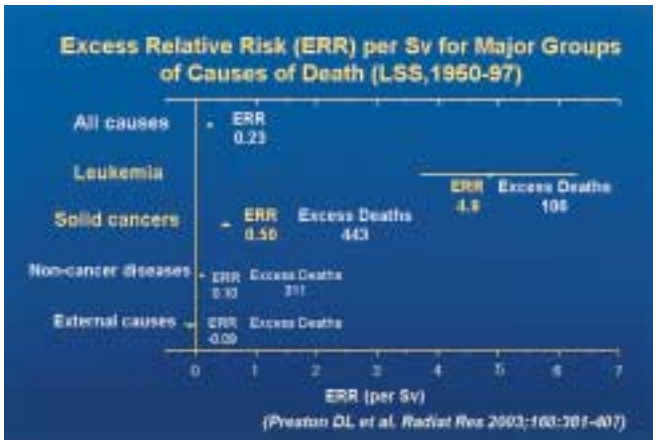

Figure 2. Excess relative risk (ERR) per Sv for major groups of causes of death (LSS, 1950-1997).

As for dose response, for leukemia it appears to be linear quadratic, and for solid cancers it appears to be linear (Figure 6) and still supports the so called linear non-threshold LNT hypothesis.

As for risk modification, there are obviously the effects of sex (male or female), or age at exposure, for example among those exposed at age 10 the excess relative risk appears to be higher than those exposed at age 50. So it appears that the younger the age of exposure, the larger the risk of developing cancers. However, this needs to be confirmed by further studies.

Also in those who do not smoke or smoke a small amount, adding of a 1 Sv of radiation increases the risk of lung cancer by 60% to 100% but in those who smoke excessively, the risk does not appear to be increased. Such issues are important when we think of transferring our risk estimates to a different population.

The central finding of the LSS is an increase in cancer risk. Besides the increase in leukemia, increases in solid cancer such as cancers of the lung and stomach have also been demonstrated. Radiation-induced leukemia occurred 2 to 3 years after exposure, reached its peak within 6 to 8 years after the bombing, and has since declined steadily. However, this has not been the case for solid cancers.

Radiation-related solid cancer began to appear at later years when

Table 3. Solid cancer mortality in the LSS cohort: 1950-2002

DS02 Dose (Sv)	People	Person-years	Total	Excess
<0.005	38,507	1,415,830	4,270	2
-0.1	29,960	1,105,215	3,387	44
-0.2	5,949	218,670	732	41
-0.5	6,380	232,407	815	99
-1	3,426	125,243	483	116
-2	1,764	64,689	326	113
2+	625	22,302	114	64
Total	86,611	3,184,356	10,127	479

Source: Preston DL et al. *Radiat Res* 162: 377-389, 2004.

Table 4. Leukemia mortality in the LSS cohort: 1950-2002

DS02 Dose (Sv)	People	Person-years	Total	Excess
<0.005	37,407	1,376,521	92	0
-0.1	30,387	1,125,891	69	4
-0.2	5,841	208,445	14	5
-0.5	6,304	231,149	27	10
-1	3,963	144,276	30	19
-2	1,972	71,485	39	28
2+	737	26,589	25	28
Total	86,955	3,184,256	296	93

Source: Preston DL et al. *Radiat Res* 162: 377-389, 2004.

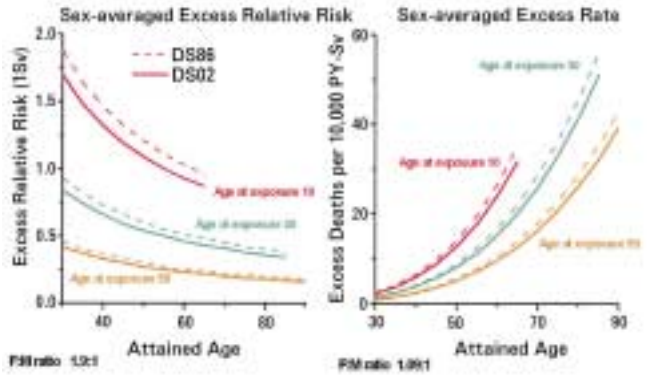

Figure 3. Effect of changes in atomic bomb survivor dosimetry on solid cancer mortality risk estimates (Preston DL et al. Radiat Res 162: 377-389, 2004).

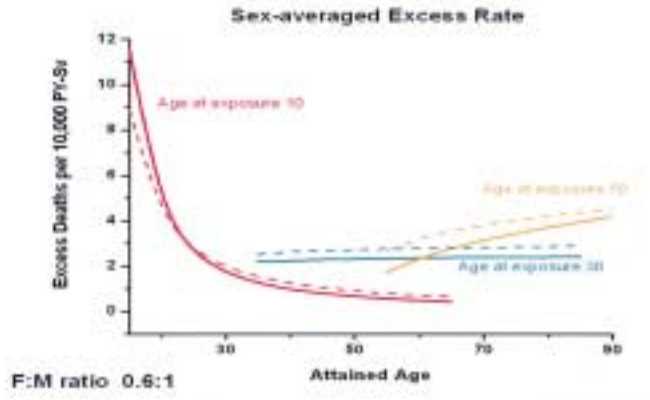

Figure 4. Effect of changes in atomic bomb survivor dosimetry on leukemia mortality risk estimates (Preston DL et al. Radiat Res 162: 377-389, 2004).

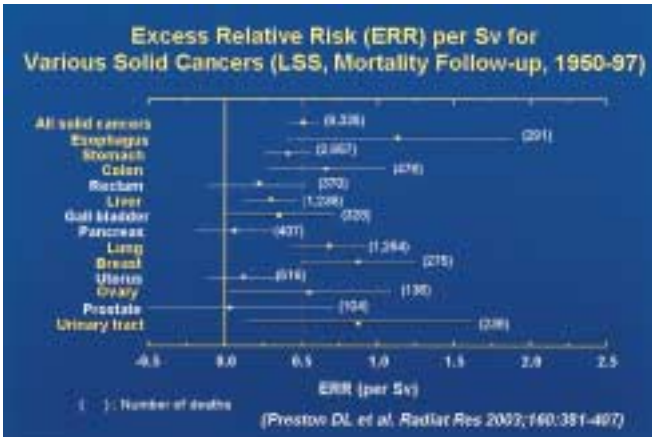

Figure 5. Excess relative risk (ERR) per Sv for various cancers (LSS, Mortality, 1950-1997).

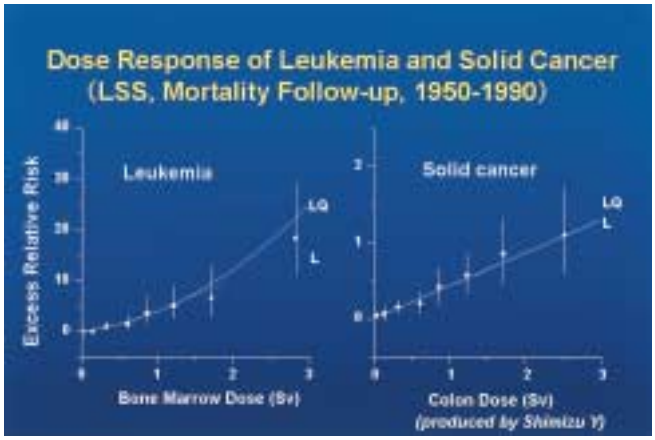

Figure 6. Dose response of leukemia and solid cancer (LSS, mortality, DS86, 1950-1990).

survivors reached an age when cancer is normally prone to develop. Relative to background rates, an increase in solid cancer is larger for those exposed as children than those exposed as adults. Since a majority of those exposed as children are still alive and risk estimates for them are uncertain at this stage, it is essential to continue their follow-up. Other issues include the shape of dose response and evidence for heterogeneity in site-specific excess solid cancer risk.

There are new findings on chronic inflammation among survivors that apparently suggest inflammatory cytokines such as IL 6 or Interferon gamma or TNF have somehow increased. But these results are based on cross-sectional studies and the number of subjects is quite small. So it is really difficult to draw any definitive conclusions at this point of time and further studies are needed.

Recently, the LSS also demonstrates an excess risk of death from non-cancer diseases, largely from cardiovascular, digestive and respiratory diseases. We have seen a 10% increase in excess relative risk among non-cancer diseases.

However, it is not yet known whether these apparent increases in the risk of non-cancer diseases are caused by atomic bomb radiation. Therefore further investigation is of absolute necessity in order to determine whether the excess risk is caused by the atomic bomb radiation or not.

Issues that need further investigation

There are issues that need further investigation (Table 5) such as site-specific cancers, lifetime risk of cancer, non-cancer diseases, confounding factors, risk modifying factors low-dose exposure, immune function, psychological effects and acceleration of aging among survivors of atomic bombing, cancer and non-cancer disease among those exposed in uterus and DNA abnormalities, cancer and non-cancer disease in the offspring of survivors.

Table 5. Issues that need further investigation

Survivor	In-utero exposed	Offspring
1. Cancer (site-specific)	1. Cancer	1. DNA abnormality
2. Cancer (life-time risk)	2. Non-cancer disease	2. Cancer
3. Confounding factors, Risk modifying factors		3. Non-cancer disease
4. Low-dose exposure	・Continuation of ongoing studies	
5. Non-cancer diseases	・Nested case-control study (stored sera)	
6. Immunology	・Molecular biology (high risk group)	
7. Psychological effects	・Molecular biology (radiation fingerprint?)	
8. Acceleration of aging	・24 color FISH ?	

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