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Solid Cancer Incidence among Atomic Bomb Survivors: Preliminary Data from a Second Follow-Up

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More than half a century after the atomic bombings in Hiroshima and Nagasaki, an increased risk of cancer incidence is still apparent among the Life Span Study (LSS) cohort of survivors. Although a great deal has been learned from the long follow-up of the LSS cohort, questions regarding radiation-related cancer risks still remain. We are conducting a second comprehensive cancer incidence follow-up to help answer some of these questions. Since the 1987 follow-up, there was a 24% increase in person-years and 56% increase in cancer cases. With the additional 11 years of follow-up, i.e. now including the years from 1958 to 1998, almost 17,500 first primary solid cancers were identified among over 105,000 LSS members with estimated DS02 organ doses.

The LSS cohort includes 120,321 people including about 50,000 survivors who were within 2.5 km of the bombings, about 45,000 who were within 2.5-10 km, and also about 25,000 who were not in either Hiroshima or Nagasaki at the time of the bombings, the so-called Not-In-City (NIC) group. In the past, the NIC group was not included in most of the overall comprehensive studies, but they are included in the second follow-up because they can improve inference about baseline risk patterns.

There are several important strengths of the LSS cohort. It is a large, healthy non-selected population that includes all ages and both sexes (though there are more females due to the fact that many male soldiers were not in the cities of Hiroshima and Nagasaki); members were exposed to a wide range of doses and they have well characterized dose estimates; mortality follow-up is virtually complete since 1950; cancer incidence ascertainment is complete in Hiroshima and Nagasaki tumor registry catchment areas since the establishment of the registries in 1958, and there is more than 50 years of follow-up.

When studying cancer incidence or mortality, certain differences in methods should be noted. For evaluating cancer incidence, we must exclude people who either died or had cancer diagnosed before the cancer registries were established in 1958. Therefore, there are about 8,000 fewer people in incidence analyses than in mortality analyses. Also, the mean age at the time of the bombing is a little younger in the survivors included in the incidence (26.8 years) compared with mortality (29.0 years) analyses because people who developed cancer before 1958 tended to be old and, as already mentioned, they are excluded from the incidence analyses.

Cancer incidence ascertainment is based on the LSS Tumor Registry. This registry includes all cancer cases diagnosed among LSS members registered in either the Hiroshima or Nagasaki Tumor Registries. The Hiroshima and Nagasaki Tumor Registries are of high quality because they employ active case identification in all large hospitals in their catchment areas. Data from tissue registries, death certificates, and medical associations (for the small hospitals) are also collected. Earlier analyses demonstrated that there is no dose bias in case ascertainment. Mortality data are obtained from the family registry (called Koseki) and they are nationwide.

The LSS cancer incidence studies add a valuable component to radiation risk assessment of the atomic bomb survivors because they include data on non-fatal cancers, some of which are quite radiation sensitive. Cancers of the breast, thyroid and skin, for example, are radiation sensitive but since they have very good survival a large number of them would be missed if only mortality data were evaluated. The incidence data are characterized by a high level cancer ascertainment, accurate diagnoses, information on histology, and long follow-up. For some organs, information on benign tumors also is collected.

The LSS cancer incidence studies do have some limitations. In particular, solid cancer data from 1945 to 1958 and leukemia data from 1945 to 1950 are incomplete, cancer ascertainment is limited to Hiroshima and Nagasaki area residents, and treatment data are limited. This means that some early cancer cases have been missed, especially leukemia and thyroid cancers which have a short latency period.

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The second comprehensive cancer incidence report includes follow-up from 1958 to 1998, with data on 105,427 people; 50% of whom were still alive in 1998 (currently about 45% are alive). Of note is that about 85% of individuals less than 20 years of age at the time of bombing were still alive in 1998 (about 80% today). In this report, we are studying only first primary tumors to prevent confounding from radiation treatment for the first cancer and possible detection bias in persons who already have cancers. All analyses in this report are based on the new DS02 dosimetry system which has incorporated several important improvements over DS86. Improvements in DS02 include refinements in the shielding calculations, transport calculations, and source term adjustment. In DS02, gamma doses increased and neutron doses decreased slightly. We used weighted colon dose in Gy to evaluate solid cancer and weighted organ doses for most site-specific analyses.

Table 1 shows the study population by dose categories. Excluding the non-exposed NIC group, 35,545 (slightly over 44% of the 80,180 exposed LSS members) A-bomb survivors were exposed to less than 0.005 Gy and 63,334, or 79% of the exposed cohort, were exposed to less than 0.1 Gy. Thus, the LSS is not such a high dose study as some may think, and it can provide substantial information on low dose radiation.

We used Poisson regression analysis to estimate the excess relative and absolute risks of all solid cancers combined and of individual cancer sites. The excess relative risk (ERR) quantifies the percentage change in risk for a unit of dose, in this case in Gy, i.e. it shows the relative change in cancer rates. The excess absolute rate (EAR) quantifies the absolute change in rates for a unit of dose, i.e. it shows the difference in cancer rates. The ERR and EAR can vary with age at exposure, gender, attained age, and other factors. They are both important and provide complementary information. In the analyses, we adjusted the person years of follow-up for the estimated migration of persons out of the Hiroshima and Nagasaki areas. We used a linear dose-response model as our standard, and considered the modifying effects of gender, attained age, age at exposure, and time since exposure.

In the second follow-up, 17,448 cancers were identified among the LSS cohort members (Table 2). The largest group of tumors (n=10,052) is of the digestive system, and stomach cancer which is a very common cancer in Japan was the most frequent cancer of the digestive tract. There were over 1000 cancer cases of the respiratory system, female genital organs, and breast cancer.

For all solid cancers combined, the dose response was linear and we saw no evidence of non-linearity. A statistically significant dose response trend was seen in the 0 - 0.15 Gy range, and this trend was consistent with that observed for the full dose range. The ERR per weighted colon dose in gray (ERR/Gy) for solid cancer was higher for women than men and decreased with increasing age at exposure and attained age. The EAR per 10,000 person years per weighted colon dose in Gy (EAR/10^4 PY Gy) was also higher among women and decreased with increasing age at exposure, but increased with increasing attained age. When gender-specific cancers were excluded from the analyses, the ERR/Gy remained significantly higher for females than males, but the gender difference disappeared when an absolute risk model was used. Lifetime solid cancer risk estimates appear to be about 20 times higher than those observed for leukemia.

Table 1. Dose distribution in the LSS incidence cohort

Dose (Gy)	Number of Subjects	Percentage (%)
Not in city	25,247	23.9
< 0.005	35,545	33.7
0.005 - 0.1	27,789	26.4
0.1 - 0.2	5,527	5.2
0.2 - 0.5	5,935	5.6
0.5 - 1	3,173	3.0
1 - 2	1,647	1.6
2+	564	0.5
Total	105,427	100

Table 2. Distribution of solid cancers identified among the LSS cohort members during the period of 1958-1998

Site	Number of subjects
Digestive system	10,052
Respiratory system	2,001
Female genital	1,457
Breast	1,082
Urinary system	741
Thyroid	471
Skin	347
Male genital	420
Oral cavity	277
Nervous system	281
Other solid cancers	319
Total	17,448

As a result of the second follow-up, there is now a suggestion of an excess relative risk for endometrial cancer among women exposed before age 20. We also have identified radiation effects for male breast cancer, and found strong evidence that some time patterns differ when using the ERR and the EAR models. Using an EAR model, risk increased with increasing age, whereas the risk decreased with an ERR model.

Patterns of organ (or site) specific risks generally were similar to those seen in the previous follow-up, but the risk patterns have become clearer for some cancers. High ERRs were found for cancers of the bladder, breast and lung, while high EARs were seen for cancers of the stomach, breast, colon and lung. Assessing site-specific cancer risks is important, but because there are considerably fewer cases, it is difficult to identify significant differences in risk estimates or patterns. Biologically it is almost certain that variation in site-

specific risks exists, while current analyses suggest some differences much of the observed variability is consistent with random variation because formal statistical tests generally lack the power to detect real differences.

In summary, the updated solid cancer incidence data indicate that the shape of the dose response is well described by a linear model. Solid cancer excess rates increased throughout life for all ages, while excess relative risks decreased with increasing age. Excess risks for all solid cancers were higher for women than men, and lifetime risk estimates were considerably larger than for leukemia. The relatively small number of cancers for most individual sites made it difficult to identify statistically significant differences in age-time patterns. While overall patterns were similar to those seen in previous analyses, we continue to find new results with each new follow-up.

A large proportion of the radiation-associated excess solid cancers are likely to occur over the next 15 to 20 years. We therefore expect that the accumulating data will continue to offer important new insights into radiation effects on cancer risks. Continued follow-up is necessary to understand risk patterns for persons less than age 20 years at the time of the bombings. Additional site-specific incidence studies incorporating pathological reviews will provide needed information on the radiation-sensitivity of specific histologies. With close collaboration among statisticians, epidemiologists, biologists and pathologists; we should be able to improve our understanding of these data and their implications for radiation protection.