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Multiple Primary Cancers in Nagasaki Atomic Bomb Survivors

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This year is the 60th anniversary since two atomic bombs were exploded in Japan; the average age of survivors is now approximately 73 years, in whom substantial numbers of cancers will arise. The increased risk of cancers has continued for decades, and the incidences of some types of cancers are still higher than in general population.

The occurrence of multiple primary cancers (MPC) is considered to be a reflection of severe exposure to carcinogens or of a predisposition to cancer. The relation of radiation exposure from the A-bomb with the development of MPC has not been fully studied, but is of interest in terms of learning more about radiation effects on carcinogenesis.

To elucidate the late effects of radiation on the incidence of MPC among the survivors, the present study studies the correlation between incidence of MPC in A-bomb survivors and exposure distance. This study may provide a better insight into the etiology of cancer among survivors and may also provide information for a more effective medical care of the survivors.

Atomic Bomb Casualty Commission ABCC, the predecessor of Radiation Effects Research Foundation (RERF), was established in 1946 and started an epidemiological study with the Life span study (LSS) cohort in 1950. In 1957 the Japanese government passed the Atomic Bomb Survivors' Medical Treatment Law. In the same year Nagasaki City Tumor Statistics Committee was established in Nagasaki city and tumor registration was started in cooperation with RERF (Figure 1).

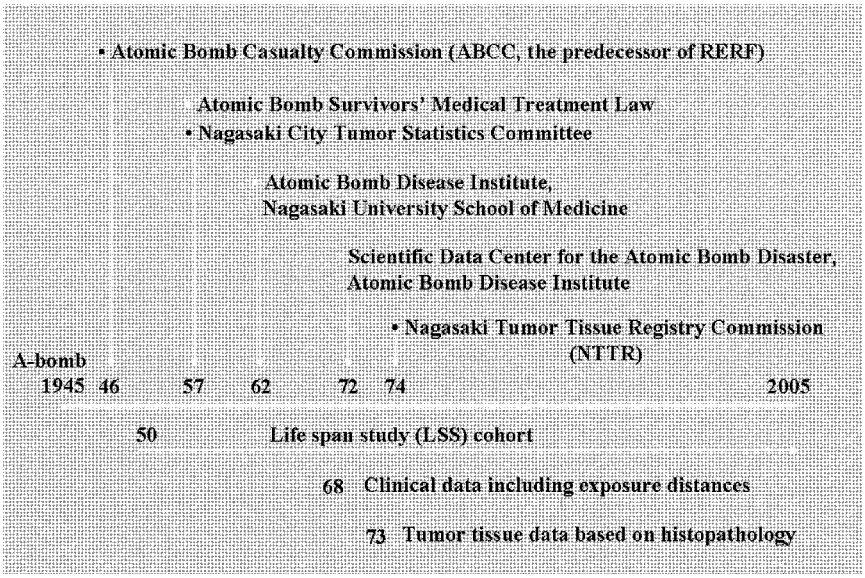

Figure 1. The historic events related to data collection of Nagasaki A-bomb survivors.

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The Atomic Bomb Disease Institute, Nagasaki University School of Medicine was established in 1962, 17 years after the bombing. The Scientific Data Center for the Atomic Bomb Disaster, Atomic Bomb Disease Institute, was established in 1972, and started the registry of clinical data on survivors since 1968. In 1974 the Nagasaki Tumor Tissue Registry (NTTR) Commission was established with a research grant from the US National Cancer Institute and is carrying out tissue registry based on the histopathological data since 1973.

The number of Nagasaki survivors by the exposure distance in Division of Scientific Data Registry is about 100,000. The number of tumor cases in NTTR is annually increasing. Totally 235,631 cases were registered since 1973 till 1999, which includes both benign and malignant tumors.

As for subjects of our study, data of 28,117 Nagasaki survivors of the LSS cohort is not available in our institute, so subjects of our study are completely different from that cohort. We used the NTTR database which included 235,631 since 1973 to 1999 and 66,042 cases since 1961 through 1972. Taken together, they constitute 301,673 tumor cases from 1961 to 1999. Unfortunately the pathological data before 1960 were not available in the study because they were in completely documented. A linkage was made between these data and the survivors' data since 1968 in our institute to identify Nagasaki survivors' cases. Finally we identified 11,802 Nagasaki survivors bearing malignancy.

Multiple primary cancer (MPC) is defined as any of the following conditions:

1- Multiple (two or more) primaries occurring in different organs
2- Multiple primaries occurring in stomach or colorectum but apparently different sites (e.g. antrum and fundus, ascending and sigmoid colon)
3- Multiple lesions of different histological types occurring in paired organs but apparently different sites (e.g. adenocarcinoma in left lung and small cell carcinoma in right lung, ductal carcinoma of left breast and lobular carcinoma of right breast)

It must be noted that multiple lesions of the same histological type occurring in paired organs are not counted as a MPC but a single primary. Also it must be differentiated from metastatic tumors.

NTTR has already classified each tumor by its biological behavior to the following types: 0 for benign tumors, 1 for unknown malignant potency, 2 for carcinoma in situ, 3 for malignancy, and 6 for metastatic tumor. Tumors with a 1 or 2 behavior were selected as primary malignancy to identify MPC. At the next step, we checked both the pathological diagnosis and site of the tumor and made a decision as to consider it MPC or not: 0 is not MPC, 1 is an undetermined case (121 cases), and 2 is definitely MPC (480 cases). Furthermore, to confirm whether each malignancy is primary or metastasis, we reviewed it with original pathological reports, specimens, and a series of immunohistochemistry tests. Recently, we can use immunohistochemical profiles in primary carcinoma by each organ to realize whether it is a primary tumor or not. We study the expression patterns of the following markers: cytokeratins 7 and 20, thyroid transcription factor-1, pulmonary surfactant, CA125 as a tumor marker of ovarian cancer, estrogen receptor, progesterone receptor, etc. Through this process, we found 31 cases of MPC among 121 undetermined cases. So the total number of MPC cases in our database increased from the original 480 cases to 511 cases (female/male = 242/269).

To evaluate the correlation of MPC and A-bomb radiation, first the incidence rate per 100,000 person-years was calculated (Table 1) with stratification by the exposure distance and the age at the time of the bombing (ATB), respectively. Then the time trend in the incidence rate of MPC per 100,000 person-years was analyzed in two different distant groups separated for 1.5 km from the hypocenter. In general, survivors who were less than 1.5 km from the hypocenter were exposed to a significant dose of radiation. Although the actual dose may have been influenced on the shielding condition, the estimated doses for Nagasaki survivors who were not shielded at the time of explosion were 9.2 Gy at 1 km, 1.2 Gy at 1.5 km, 0.8 Gy at 2 km, and 0.3 Gy at 2.5 km. For the statistical analysis, we used the Cox proportional hazard model to evaluate the effects of change in exposure distance and age ATB on the incidence rate of MPC. The incidence rate of MPC by each period between two different distant groups separated at 1.5 km from the hypocenter was compared with the use of the chi-square statistic. The PHREG procedure in the SAS 8.2 software (SAS Institute, Cary, NC, USA) was used for calculation.

When the exposure distance is divided into two different distance

Table 1. The number of MPC cases, person-years (PY) and incidence rate (IR) in survivors by exposure distance

Distance (km)	Female			Male			Total		
	PY	Cases	IR	PY	Cases	IR	PY	Cases	IR
≤1.0	24,481	18	73.5	17,208	6	34.9	41,689	24	77.6
1.1-1.5	54,655	22	40.3	42,950	35	81.5	97,605	57	58.4
1.6-2.0	98,597	18	18.3	62,764	24	38.2	161,361	42	26.0
2.1-2.5	121,383	28	23.1	73,478	18	24.5	194,861	46	23.6
2.6-3.0	148,841	36	24.2	87,053	30	34.5	235,894	66	28.0
3.0<	701,579	120	17.1	419,841	156	37.2	1,121,420	276	24.6

Table 2. The incidence rates of PMC in the proximal and the distal groups

Distance (km)	Person-years	Cases	Incidence rate[a]
≤1.5	139,294	81	58.2
1.5<	1,713,536	430	25.1
Total	1,852,830	511	27.6

[a]Per 100,000 person-years.

groups separated at 1.5 km, the incidence rate of PMC in the proximal group was 2.3 times higher than the distal group (Table 2).

We defined the "attained age" as the age at the time of diagnosis of the 2nd cancer, meaning the onset of MPC. The incidence rate of MPC seems to be decreasing with increasing age ATB at the respective attained age group.

Radiotherapy and chemotherapy for the first primary might be associated with an increased risk of developing a second primary. However, the effect of treatment on a subsequent primary would be negligible in both synchronous and short-term metachronous MPC because treatment-associated risk for second primaries typically had at least a 10-15 year interval between the two tumors.

Only approximately 1% of the long-term follow-up patients developed a second malignancy after treatment for the first primaries, with an interval of 82-136 months. Therefore, putative mechanisms other than therapy-related should be postulated for the development of the second primary in synchronous and short-term metachronous MPC.

Of the 511 MPC cases, 467 (91.4%) were double, 35 (6.8%) were triple, 8 (1.6%) were quadruple, and 1 (0.2%) was quintuple. The incidence of colon and gastric cancers was highest among double cancers, with 72 cases (15.4%). Among the quadruple cases, the possibility of a genetic syndrome of cancer susceptibility such as familial adenomatous polyposis (FAP) and Li-Fraumeni syndrome was suggested. However, we could not find any well known familial cancer syndromes among them. Moreover, familial cancer syndromes usually show a lower age of onset of tumors but the average attained age of our MPC cases was 62 years, which is the usual cancer prone age.

There were 511 confirmed cases of MPC in the 29,647 tumor-bearing survivors (the crude incidence rate was 27.6 per 100,000 person-years). Relative risks of MPC in the survivors significantly increased when they were exposed at a closer distance from ground zero and with younger age at the time of the bombing, suggesting the radiation effects on MPC in survivors.

Furthermore, the incidence of MPC in those exposed closer to ground zero began to increase since 39 years after the explosion of the atomic-bomb, and has continued to increase into the 1990s. It is likely that the survivors who have been exposed at a younger age still have a higher risk for a wide range of cancers after reaching a cancer-prone age, even 60 years after the bombing. Most importantly, 48% of the survivors are still alive, who were mostly children at the time of the bombing.

The summary of our results indicate that since 1968 through 1999, 511 MPC cases were identified in 99,853 Nagasaki Survivors who suffered direct exposure (the crude incidence rate was 27.6 per 100,000 person-years). A careful histopathological review was done to identify MPC cases in a series of archival tumor registry data. The incidence of MPC significantly increased with closer exposure distance and younger ATB. The incidence rate of MPC continued to increase annually and was significantly higher in the population exposed at proximal distance than distal distance since 1984.

These results, on the incidence of MPC in the tumor-bearing survivors and its correlations with the atomic bombing of 60 years ago, are described for the first time in this report. They also strongly support the necessity of a long-term health care follow-up for the aged survivors of the atomic bomb, and also emphasize the need for special attention on other victims of radiation-associated accidents around the world.

It is worth noting that most survivors who were children at the time of the A-bombing are still alive, and have already reached a cancer-prone age, indicating the necessity of a long-term health care follow-up for the aged survivors.

We have made the conclusion that there is a correlation between the incidence of MPC and the atomic bombing of 60 years ago. Further information is thereby provided which shows another perspective of the late radiation effects on human carcinogenesis.