Acute and Late Effects of A-Bomb Radiation Studied in a Group of Young Girls with a Defined Condition at the Time of Bombing

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Ninety girl students have been identified, who were 14-15 years old when exposed to the atomic bomb while at the Central Telephone Office in Hiroshima located at a distance of 550 meters from the hypocenter. The mortality rate of the students exposed on the second floor of the building was estimated to be 50.9\% and those exposed on the first floor (ground level) 33.3\%. Doses to the students exposed on the second floor were estimated from cytogenetic evidence to be around 6 Gy in the T65 Dose system or appear to be 4 Gy in the DS86 system. These data indicate that LD\textsubscript{50} is around 4 Gy in these young females. Among 28 students who were confirmed to be alive in 1965 and followed to the end of 1988, six students had breast cancer, mostly of invasive ductal type carcinoma. The incidence of breast cancer in the adolescent group was very high, the relative risk being 23.1 with 95\% confidence limits of 12.9 to 42.2.

INTRODUCTION

Study of the atomic bomb survivors involves large populations that are heterogenous in age and vary widely in the level of individual radiation exposure. We have identified a small group consisting of 90 girls who were students at the Shintoku Girl’s High School in Hiroshima. These girls were all working at the Central Telephone Office in Hiroshima at the time of the bombing. The telephone office was 550 meters from the hypocenter.
This group is of particular interest because of the homogeneity of the sample with regard to sex and age. The radiation doses, although not yet known precisely, were sufficiently high to kill a high proportion of the group. The long term survivors constitute a small but interesting cohort. At the time of exposure the girls were 14—15 years of age, and therefore, at a greater risk for cancer in general, particularly breast cancer, compared to the general population exposed at Hiroshima. The follow up of this cohort was thorough, and six survivors developed breast cancers which have been histologically identified and confirmed. The incidence of breast cancer in this cohort can be compared with the larger sample in the Life Span Study of the Radiation Effects Research Foundation (RERF) and an estimate can be made of the doses that must have been involved in the induction of the cancers in the small cohort.

When doses based on DS86 are assigned to each of the 90 girls it may be possible to provide information relevant to the LD50 for humans. The information about the documented acute effects, such as epilation and the rate of induced cancer, will help to estimate boundaries on the doses that are lethal.

**MATERIALS AND METHODS**

**Enumeration of study sample:**

Ninety girls were selected from a larger number of students exposed in the Telephone Center. The basis of selection was the records of the Shintoku Girls High School and the telephone company. These records described the places where all the girls of the school were at the time of the bombing, their injuries including death, and their post-exposure clinical condition until their death. There were a total of 111 students in these records but there was consistent information for only 102 students. This sample was reduced because it turned out that twelve of the girls were not in the Central Telephone Office at the time of bombing. Thus, a total of 90 students, of whom 60 died and 30 survived, were included in the study. Thirty survivors were alive in 1946. In the Survey of the Actual State of A-bomb Survivors performed in 1965, 28 of the women were confirmed to be alive and were interviewed about their health.

These 28 women constituted the denominator for the incidence of breast cancer. One of the original 30 survivors died of colon cancer in 1956. To die of colon cancer at an age of less than 30 years is remarkable.

Further follow-up made use of the data kept at the Research Institute for Nuclear Medicine and Biology, Hiroshima University, which had been derived from the Survey of the Actual State of A-bomb Survivors, 1965. These computerized records include place of exposure, current address, date of birth, the A-bomb survivors Health Handbook number and other data for 172,851 survivors. The information about the students obtained previously was confirmed and those survivors identified were contacted by telephone.

The next step in establishing the fate of the cohort was to inspect the medical charts at the Hiroshima City Funairi Hospital and the Hiroshima A-bomb Survivors Health Clinic where most of the survivors were examined twice a year. In some cases further telephone calls were made to ascertain their health status. This step in the investigation revealed that seven women had
undergone mastectomy. The hospital at which the operations were carried out and the Hiroshima Prefectural Tissue Registry Committee supplied tissue sections. The histological diagnoses were confirmed by Dr. Yuzo Hayashi, Assistant Professor, Second Department of Pathology, Hiroshima University School of Medicine.

Cytogenetic analysis:

To estimate the exposure doses, chromosome abnormalities of the peripheral lymphocytes were studied by conventional Giemsa staining and also Giemsa banding methods. Most of survivors were examined between 1976 and 1985, 30 to 40 years after the exposure. All metaphases were photographed and chromosomes counted\textsuperscript{3}). Numerically and structurally abnormal cells were confirmed by karyotypes. Translocation were divided into two types; balanced and unbalanced\textsuperscript{(+der)}. The calculation of the exposed radiation dose was made from cytogenetic data using the formula: \( Y = 0.91 + 1.3 \times 10^3 X \), where \( X \) is the radiation dose in cGy and \( Y \) is the frequency of breaks per cell. The dose-response relationship was obtained from a separate group of 18 survivors whose estimated T65D dose and cytogenetic data were available\textsuperscript{3}).

Calculation of incidence of breast cancer:

The incidence of breast cancer was calculated for the students who were exposed at the telephone office and were still alive after 1965. The incidence was compared with those for exposed and non-exposed groups in the fixed population established by RERF.

RESULTS

Mortality:

Of a total of 90 students who were exposed in the Central Telephone Office, 31 died on the day of the explosion and 29 died within two months; of the latter 27 were exposed on the second floor and the remaining two on the first floor (ground level). Thus, a total of 60 students died by the beginning of October, 1945 (Table 1). Thirty surviving students were alive in 1946, of whom 26 were exposed on the second floor and the remaining four on the first floor. Assuming that the deaths on the day of the explosion were caused by blast and/or fire and those on later days were due to radiation injuries, the mortality from radiation damage was calculated for the students on the two floors of the building, the mortality was estimated to be 50.9\% (27 of 53

<table>
<thead>
<tr>
<th>Date of deaths</th>
<th>August</th>
<th>September</th>
<th>October</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6</td>
<td>8</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>No. of deaths</td>
<td>31</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

* One of the two was exposed on the first floor.
students) for those on the second floor and 33.7% (two of six students) for those on the first floor.

Cytogenetic analysis:

Peripheral lymphocytes from nine students including two (Case 8 and 9 in Table 2) exposed on the first floor were analysed cytogenetically. Table 2 shows the results of chromosome analysis and cytogenetically estimated radiation doses as well as calculated T65D doses. Most of chromosome abnormalities found in those students were stable types, such as deletions, inversions and translocations. There were very few unstable type abnormalities. The students exposed on the second floor (Case 1−7) showed higher percentages of abnormal cells (B/A) and chromosome aberrations/cell (F) than those exposed on the first floor. Cytogenetic analysis revealed that students exposed on the second floor seemed to have exposed to around 6 Gy, probably in a range between 2 Gy and 7.3 Gy. The dose estimated for students exposed on the first floor was around 1.5 Gy.

Health status after exposure

Of the 30 surviving students alive in 1946, one was not identified her residence and another was confirmed to have died of colon cancer in 1956, at 26 years of age. Of the remaining 28 students who were confirmed to be alive in 1985, the following immediate post-bomb acute radiation symptoms had been; epilation (27/28), bleeding tendency (26/28), diarrhea (26/28), burn (4/28) and injuries (25/28) as acute radiation symptoms. By 1983 six students had developed breast cancer and one had mastopathy; there were eight with myoma uteri including three who had proceeding or subsequent operation for breast cancer; other disorders include one student
Table 3. Date of Operation and Histological Type of Breast Cancer

<table>
<thead>
<tr>
<th>Case</th>
<th>Date</th>
<th>Age</th>
<th>Hospital</th>
<th>Histological type</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>W.S.</td>
<td>Sept. 1971</td>
<td>41</td>
<td>Hiroshima Red Cross Hosp.</td>
<td>Invasive ductal carcinoma</td>
<td>Alive estimated dose of 385 rad*</td>
</tr>
<tr>
<td>I.A.</td>
<td>May 1979</td>
<td>43</td>
<td>Okamoto Hosp.</td>
<td>Invasive ductal carcinoma</td>
<td>Alive</td>
</tr>
<tr>
<td>T.N.</td>
<td>Aug. 1974</td>
<td>44</td>
<td>Hiroshima Red Cross Hosp.</td>
<td>Medullary carcinoma</td>
<td>Alive Case 1 in Table 2</td>
</tr>
</tbody>
</table>

* T65D dose

with radiation cataracta who had both breast cancer and myoma uteri, one each of hypo- and hyperthyroidism, two with polyp of the stomach and one student with benign mediastinal tumor, all presumably as late effect of radiation. Three students died during the follow-up period from 1965 to 1988; Two of breast cancer in 1980 and 1983, and the third of heart attack in 1988.

Table 3 shows the date of operation for breast cancer, age at the time of operation, name of hospital, and histological type of breast cancer. The age of onset was distributed from 41 to 53, some 26-38 years after exposure to the A-bomb. The histological type of breast cancer was invasive ductal carcinoma (WHO histological classification criteria for breast tumor) in five of the six cases, the remaining being medullary carcinoma.

Incidence of breast cancer:

Of the 28 survivors who were confirmed to be alive in 1965, seven underwent mastectomy: six were histologically confirmed as breast cancer and one as mastopathy.

A person year of observation was calculated for all the 28 survivors calculated from the time when they received Health Handbook (first physical examination) to date of termination of observation, i.e. date of onset for breast cancer cases, date of death, and date of final physical examination for living students, whichever is earliest. The average incidence as expressed by the rate per year per 1,000 was 11.9 (6 breast cancers in 504 person years) (Table 4).

In contrast, during 1967-1980, there were 37 breast cancers in 71,726 women-years among Hiroshima Life Span Study Sample members, both “Not in City” and “0 dose”, and 10—19
Table 4. Incidence of Breast Cancer among Survivors Exposed at Central Telephone Office

<table>
<thead>
<tr>
<th>Cases of breast cancer</th>
<th>Sample (person-years)</th>
<th>Incidence per 1,000 person-years</th>
<th>Test of significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Students exposed at Central Telephone Office</td>
<td>6</td>
<td>504*</td>
<td>11.90</td>
</tr>
<tr>
<td>Controls**</td>
<td>37</td>
<td>71,726</td>
<td>0.52</td>
</tr>
</tbody>
</table>

* Calculated from the time when they received Health Handbook to the time of final physical examination.

** Results of observations made from 1967 to 1980 of women belonging to the RERF Life Span Study sample who were either exposed to 0 rad or were out of Hiroshima City aged 10-19 at the time of the bombing (See text for details).

years old at the time of the bombing. This gives a rate of 0.52 per 1,000 per year which is considered to be an appropriate control for the incidence rate of this study group. Thus, the relative risk is 23.1 with 95% confidence limits of 12.9 to 42.2.

**DISCUSSION**

By counting the number of deaths in a group at the time of bombing, it is possible to find the mortality rate at that point. In the present study, of the 90 students aged 14—15 years old who were exposed at the Central Telephone Office located 550 meters from the hypocenter, 31 died within 24 hours. The causes of the death were direct injuries due to the explosion.

Of the 27 students who were exposed on the 2nd floor and died within the succeeding nine weeks, 74.1% of them died between the 3rd and 6th week after exposure (Table 1). The cause of the death in this group was probably bone marrow failure caused by A-bomb radiation5,6. Since another 26 were still alive in May 1946, the mortality rate mainly arising from radiation damage was estimated as 50.9% (27 of the 53 students) in this population. Also, the mortality rate of those exposed on the first floor (ground level) of the building was calculated as 33.3% (two of six students). No population has ever been found that could provide an estimate of LD50 for humans. The population presented in this study seems to be the most reliable one for such an estimation.

It seems to be difficult to evaluate the chromosome abnormalities found in the peripheral blood from survivors 30 to 40 year after exposure. However it has been well documented that stable type of chromosome abnormalities remain with almost the same in frequency from the time of exposure to 20 years7 or 30 years8 after exposure, though unstable type of abnormalities decrease with elapsed time. In a different group including 56 survivors who were exposed within
500 meters to the Hiroshima bombing, we have found almost the same frequency of chromosome abnormalities as among the students presented here.

Cytogenetic analysis of the second floor exposed group yields a radiation dose of around 6 Gy. The formula used for the estimation of the exposure doses by means of cytogenetic analysis was based on "tentative 1965 radiation dose estimation". Recently a new dosimetry system called "Dosimetry System 1986 (DS86)" was developed by working groups of a US-Japan Joint Reassessment Committee. According to the new dosimetry system, 6 Gy of T65 Dose appears to be equivalent to around 4 Gy. Previous estimates of LD50/60 in man vary among studies; some reported 2.5 to 4 Gy, others 4 to 6 Gy. The value estimated by the present study seems to be higher than some other studies. This may arise from the unique situation of the young female.

Studies on A-bomb survivors of the same age group exposed at the same place would provide significant data on the incidence of tumors in that age group. Age is an important factor in breast and thyroid cancers. In our small group, six breast cancers were found in the observation period from 1965 to 1983.

Wanebo et al. in 1968 reported for the first time a relationship between A-bomb exposure and female breast cancer. Later studies showed that the incidence of breast cancer thought to be attributable to the effects of A-bomb radiation in women exposed to a high dose of radiation began to rise in the middle part of the 1950s. It could be estimated from the data of Tokunaga et al. that the relative risk of breast cancer in females 10—19 of age at the time of the bombing exposed to 4 Gy or more of radiation was 17.5 with 90% confidence limits of 10.7 to 28.8 between 1967 to 1980 as compared to a control group, i.e., "Not in city" or "0 dose group". Our results showed a relative risk of 23.1 with 95% confidence limits of 12.9 to 42.2 using the same control groups. As the majority of our study group could have been exposed to 4 Gy or more radiation, our data is consistent with Tokunaga's data. Tokunaga et al. further suggested that the risk of breast cancer is also higher for those under 10 years of age at the time of the bombing as they enter the so-called "cancer-prone age" of the 40's and 50's and the magnitude of risk seems to be even higher than for those age 10—19 years at the time of bombing. Boice et al. observed that the incidence of breast cancer was high in females less than 20 years of age with tuberculosis who underwent repeated fluoroscopic chest examinations following pneumoconiosis or pneumoperitoneum therapy for tuberculosis, and that breast cancer began to appear 15 years after radiation exposure, sometimes not appearing until 40 years after the exposure. For the subjects of our study, 40 years have passed since exposure to the A-bomb radiation, and breast cancer generally develops in the 50's and 60's. Health management of this group is therefore of particular importance.

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REFERENCES

6. The committee for the compilation of materials on damage caused by the atomic bombs in Hiroshima and Nagasaki (1979) HIROSHIMA AND NAGASAKI. The Physical, Medical, and Social Effects of the Atomic Bombings. pp130-185, Iwanami Shoten Publishers, Tokyo.