

# Myelodysplastic Syndromes in Atomic Bomb Survivors in Nagasaki: A Preliminary Analysis

Masako IWANAGA,<sup>1</sup> Midori SODA,<sup>2</sup> Takashi KOBAYASHI,<sup>3</sup> Masaomi YAMAMURA,<sup>4</sup> Sunao ATOGAMI,<sup>5</sup> Saburo MOMITA,<sup>6</sup> Tatsuro JOH,<sup>6</sup> Yoshiharu YOSHIDA,<sup>7</sup> Masao TOMONAGA<sup>1</sup>

<sup>1</sup>Department of Hematology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Science, Nagasaki, Japan

<sup>2</sup>Department of Epidemiology, Radiation Effects Research Foundation, Nagasaki, Japan

<sup>3</sup>Department of Internal Medicine, Nagasaki Atomic Bomb Casualty Council Health Management Center, Nagasaki, Japan

<sup>4</sup>Department of Hematology, Nagasaki Municipal Hospital, Nagasaki, Japan

<sup>5</sup>Department of Hematology, Nagasaki Municipal Medical Center, Nagasaki, Japan

<sup>6</sup>Department of Hematology, Japanese Red-Cross Nagasaki Atomic Bomb Hospital, Nagasaki, Japan

<sup>7</sup>Department of Internal Medicine, St. Francis Hospital, Nagasaki, Japan

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Myelodysplastic syndromes (MDS) are a heterogeneous hematological group characterized by an ineffective hematopoiesis resulting in a variety of cytopenias, morphological abnormalities of blood cells, chromosomal aberrations, and an increased risk of transformation into acute myeloid leukemia. Despite its nature of close relation to leukemia, MDS has been not well investigated in atomic bomb (A-bomb) survivors. We conducted a retrospective cohort study with over 80,000 A-bomb survivors in Nagasaki to assess the incidence of MDS and its relation with A-bomb exposure status. In a preliminary analysis, we confirmed 162 MDS cases during 1980 to 2004. The median age at diagnosis was 71 years old. The incidence rate was higher in men than women, and an inverse relationship was observed between incidence of MDS and the distance from the hypocenter. We suggest that A-bomb radiation may affect the occurrence of MDS in A-bomb survivors even more than 50 years passed after the explosion. Further detail analyses are necessary to confirm these results.

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## Introduction

Myelodysplastic syndromes (MDS) are characterized by an ineffective hematopoiesis resulting in a variety of cytopenias, morphological abnormalities of blood cells, chromosomal aberrations, and an increased risk of transformation into acute myeloid leukemia (AML).<sup>1</sup> Prevalence of MDS is high in elderly people and more common in developed countries.<sup>2</sup> The etiology of MDS has been still unclear. Chemotherapeutic agents, benzene, herbicides, pesticides, and ionizing radiation have been reported as possible etiological factors for MDS, but the actual causal-relationship between such factors and MDS has been not established.<sup>3</sup>

A wealth of information has been reported concerning an association between the atomic bomb (A-bomb) radiation and the leukemia risk since physicians in Nagasaki and Hiroshima began to no-

tice an increased number of leukemia in the late 1940s.<sup>4-7</sup> Because of a close relationship between MDS and AML, the occurrence of MDS is supposed to be affected by A-bomb radiation in a similar fashion with radiation-induced leukemia. However, MDS has been not well investigated in A-bomb survivors so far. Only a few studies with small sample size reported with respect to the relationship between A-bomb irradiation and the incidence of MDS.<sup>8,9</sup> Therefore, a comprehensive large-scaled study has been needed for a long time.<sup>10,11</sup>

There has been some challenges to conduct a study for MDS: (1) MDS is a relatively new concept of disease that was first defined by French-American-British (FAB) Cooperative group in 1982,<sup>12</sup> (2) MDS has been not registered actively into any tumor-registries even in Nagasaki or Hiroshima because of non-malignant nature, and (3) a heterogeneous and vaguely condition of MDS makes its diagno-

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**Address correspondence:** Masako Iwanaga, M.D., M.P.H., Department of Hematology, Atomic Bomb Disease Institute, Nagasaki University Graduate School of Biomedical Science, 1-12-4 Sakamoto, Nagasaki 852-8523 JAPAN

TEL: +81-(0)95-849-7111, FAX: +81-(0)95-849-7113, E-mail: masako iw@net.nagasaki-u.ac.jp

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sis difficult. To overcome these difficulties of research situation, we established the Nagasaki-City MDS Project, in January 2004, consisting of the Nagasaki University Hospital, 5 affiliated hospitals in Nagasaki city, and the Nagasaki cancer registry. Our aim was to assess the incidence of MDS in A-bomb survivors during 1980 to 2004 and the effects of age, sex, and the exposure status including age at the time of the bombing (ATB) and exposure distance from the hypocenter on the risk of MDS. Here we report a preliminary analysis of this study.

**Methods**

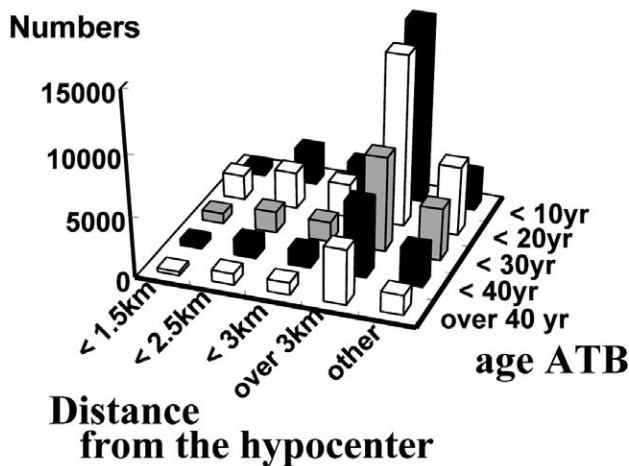
A study population was 87,506 Nagasaki A-bomb survivors (35,529 men and 51,967 women) who were alive as of January 1, 1980 and were registered in the database of the Scientific Data Center at the Atomic Bomb Disease Institute of the Nagasaki University Graduate School of Biomedical Science. Since the operation of the database started in 1977, it has kept the data of approximately 120,000 A-bomb survivors in Nagasaki.<sup>13</sup> The median of attained age as of 1980 was 54 years with the range of 34 to 100 years. The distribution of survivors as of January 1980 by distance of exposure and age at the time of the bombing is shown in Figure 1.

After we obtained approvals by the institutional ethical committees of all institutes, MDS cases diagnosed from January 1980 to December 2004 were retrospectively accumulated into the study list irrespective of whether they were atomic bomb survivors or not. During the study period, 647 MDS cases were collected and we identified A-bomb survivors among them using the database of the Scientific Data Center at the Atomic Bomb Disease Institute of the Nagasaki University Graduate School of Biomedical Sciences. Diagnosis of MDS was made according to FAB criteria<sup>12</sup> by conducting hematological review of bone marrow specimen and clinical information. Cases diagnosed before 1980, secondary MDS, and cases not confirmed as MDS were excluded from the analysis.

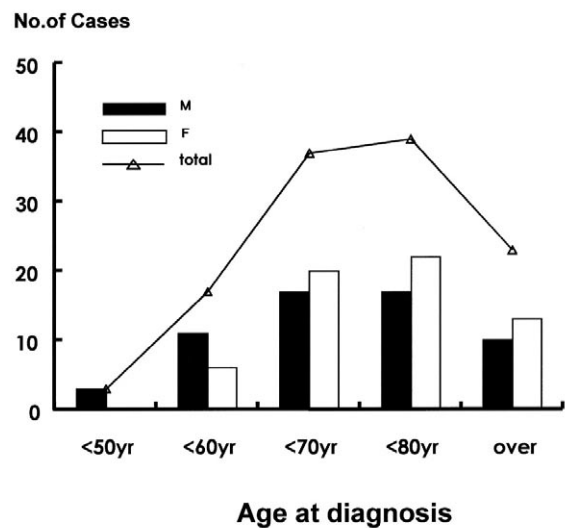
The A-bomb survivors were followed up from the latest of January 1, 1980 and the time of the first registration to the database through the earliest of the following: time of death, time of migration out of Nagasaki city, time of diagnosis of MDS and the end of December 2004. We calculated the cumulative incidence per 100,000 persons during 24 years and the incidence rates per 100,000 person-years with stratification by sex, age ATB in years (0-9, 10-19, 20-29, 30-39,  $\geq 40$ ) and the distance from the hypocenter in km (0-1.49, 1.5-2.49, 2.5-2.99,  $\geq 3.0$ ). We used the distance from the hypocenter as a substitute for the radiation dose. A comparison of incidence among groups was performed by the rate ratio (RR), the chi-square statistic, nonparametric statistic, and when necessary, the Cochran-Armitage test for trend. All statistical analyses were performed with SAS 8.2 software (SAS Japan Institute, Tokyo, Japan). All tests were two tailed, and a statistically significance level was set at 0.05.

**Results**

A total of 162 MDS cases were confirmed in A-bomb survivors by the end of 2004. Among them, 119 were directly exposed to the A-bombing and the rest were early entrants to the city who were engaged in rescue service and fetuses. One hundred twenty-four cases were classified into FAB subtypes so far. In a preliminary analysis, the cumulative incidence of MDS during 24 years was 185 (the crude incidence rate, 10.7) per 100,000 A-bomb survivors in total. Almost all patients were diagnosed at the age over 60 years, and the median age at diagnosis was 70.7 with the range of 42.0 to 97.4 years (Figure 2). There was no significant difference in age at diagnosis between men and women ( $p = 0.12$ ). The incidence of MDS was higher in men than women (RR = 1.7). An inverse relationship was observed between the incidence of MDS and the distance from the hypocenter; the more proximally exposed A-bomb survivors, the higher incidence of MDS ( $p < 0.0001$ ).



**Figure 1.** Distribution of study population by distance from the A-bombing hypocenter (km) and age at the time of the bombing (age ATB) (years).



**Figure 2.** Distribution of MDS patients by sex and age at diagnosis (years).

## Discussion

Several European studies reported that the crude annual incidence of MDS in general population was between 2 to 8 cases per 100,000 people and that the rate increased by age.<sup>14,17</sup> One study on the skewed elderly population in the United Kingdom reported 12.6 cases per 100,000 people of the crude annual incidence.<sup>18</sup> In our preliminary analysis, the crude incidence rate of MDS in A-bomb survivors in Nagasaki showed 10.7 cases per 100,000 person-years, which is slightly higher than that of general European population. Such a relatively high incidence in A-bomb survivors may be due to that they are more aged than the general European population or even the general Japanese population; the youngest A-bomb survivors were aged 34 years in 1980. To ascertain whether the incidence rate of MDS in A-bomb survivors is truly higher or not compared to the general population, further age-adjustment analyses will be required. The incidence rate of MDS was significantly higher in men than women in A-bomb survivors, which is consistent with all of the previous reports of general population.<sup>14-18</sup> The median age at diagnosis was 70.7 years in A-bomb survivors, which was almost same as the general German patients, 72 years old.<sup>19</sup>

One of the important concerns in A-bomb survivors is whether the incidence of MDS is increasing yearly or not. Although our preliminary analysis showed a slightly upward trend of the incidence (data not shown), it remains unclear whether the trend is actually true or not. Even in general population, the trend of the incidence of MDS is controversial. Several investigators have reported increasing trends of MDS,<sup>20-22</sup> while others found no evidence for an increase in the incidence of MDS in general population over time based on their well-defined epidemiological studies.<sup>14,17,23</sup> Studies including cases diagnosed early 1980s tend to report a significant increase in the incidence of MDS, which might be affected by physicians' awareness of MDS and the improvement of case ascertainment through the publication of the FAB criteria for classifying MDS in 1982. Our results also might be affected by the misclassification bias due to the improvement of case ascertainment and a selection bias because of a retrospective study. To ascertain whether the incidence rate of MDS in the atomic bomb survivors is actually increasing yearly or not, further well-designed epidemiological analyses will be required.

There were some reports supporting that high-dose radiation exposure may induce MDS.<sup>24-26</sup> The link between radiation therapy and secondary MDS with abnormalities of chromosome no.5 and 7 were also well known.<sup>27</sup> However, MDS risk in occupational and environmental exposure to radiation was argued.<sup>28,29</sup> In the population of the atomic bomb survivors, 12 MDS cases were reported out of the LSS cohort of Radiation Effects Research Foundation (RERF) during 1950 to 1990,<sup>8</sup> and 26 cases were detected at Hiroshima University Hospital from 1985 to 1999.<sup>9</sup> Both studies showed a dose-dependent increase in the risk of MDS, but they were too small in the number of cases for the statistical evaluation to show a precise relationship between radiation and MDS. Too few cases of MDS were also reported in the Chernobyl accident cleanup workers.<sup>30,31</sup> Such previous studies might have failed to detect MDS in

view of the fact that MDS is actually as common as AML. In our preliminary analysis based on a large-scaled study of A-bomb survivors in Nagasaki, we found the incidence of MDS was higher in A-bomb survivors who were proximally exposed than in those distally exposed. This result suggests that high-dose atomic bomb irradiation affected the occurrence of MDS in a long latency, around 40 to 60 years passed after the bombing. Further detailed analyses are necessary to confirm this result. Also, a systematic case detection of A-bomb survivors from both Hiroshima and Nagasaki cities is left for further challenges.

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