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ORIGINAL REPORT

Risk of Myelodysplastic Syndromes in People Exposed to Ionizing Radiation: A Retrospective Cohort Study of Nagasaki Atomic Bomb Survivors

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose
The risk of myelodysplastic syndromes (MDS) has not been fully investigated among people exposed to ionizing radiation. We investigate MDS risk and radiation dose-response in Japanese atomic bomb survivors.

Patients and Methods
We conducted a retrospective cohort study by using two databases of Nagasaki atomic bomb survivors: 64,026 people with known exposure distance in the database of Nagasaki University Atomic-Bomb Disease Institute (ABDI) and 22,245 people with estimated radiation dose in the Radiation Effects Research Foundation Life Span Study (LSS). Patients with MDS diagnosed from 1985 to 2004 were identified by record linkage between the cohorts and the Nagasaki Prefecture Cancer Registry. Cox and Poisson regression models were used to estimate relationships between exposure distance or dose and MDS risk.

Results
There were 151 patients with MDS in the ABDI cohort and 47 patients with MDS in the LSS cohort. MDS rate increased inversely with exposure distance, with an excess relative risk (ERR) decay per km of 1.2 (95% CI, 0.4 to 3.0; $P < .001$) for ABDI. MDS risk also showed a significant linear response to exposure dose level ($P < .001$) with an ERR per Gy of 4.3 (95% CI, 1.6 to 9.5; $P < .001$). After adjustment for sex, attained age, and birth year, the MDS risk was significantly greater in those exposed when young.

Conclusion
A significant linear radiation dose-response for MDS exists in atomic bomb survivors 40 to 60 years after radiation exposure. Clinicians should perform careful long-term follow-up of irradiated people to detect MDS as early as possible.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by clonal and ineffective hematopoiesis, morphologic dysplasia, and an increased risk of developing acute myeloid leukemia (AML).[1] MDS can arise de novo or secondary after chemo- and/or radiotherapy (therapy-related MDS).

The pathogenesis and established causative factors remain elusive for most patients with MDS. A widely accepted multistep pathogenesis model involves initial damage to hematopoietic stem cells caused by genotoxic or environmental agents followed by additional genetic or cytogenetic changes, resulting in the expansion of the MDS clone and the subsequent leukemic transformation.[2,3] Ionizing radiation is a well-known environmental carcinogen that induces chromosomal and genetic abnormalities. When an individual's bone marrow is exposed to ionizing radiation, hematopoietic stem cells may be damaged randomly, and some of these changes could induce MDS.

In contrast to the well-documented radiation-induced leukemia,[4-6] there has been no conclusive evidence that radiation exposure plays a significant role in the development of MDS. So far, radiation exposure remains a probable causative factor for MDS.[2] Most review articles have described radiation exposure as a definite causative factor for MDS on the basis of clinical studies of therapy-related MDS/AML. However, the original sources seldom

evaluated the radiation dose-response relationship for MDS alone. Epidemiologic studies of people exposed to a variety of radiations reported only a small number of cases.[7-10] In a previous study of atomic bomb survivors,[11] a possible radiation dose-response relationship for MDS was suggested, but the analysis included only 12 patients. MDS research among the atomic bomb survivors has been hampered by the fact that case ascertainment was incomplete before publication of the 1982 French-American-British (FAB) classification[1] and that no regional cancer registry officially registered MDS until 2000.

A radiation dose-response relationship for MDS might be predictable from that for AML because of the clinical similarity between the two diseases. However, much data have been accumulated to support that MDS has features that are distinct from AML with regard to latency of onset, genetic and cytogenetic abnormalities, apoptotic activity, and so on.[12,13] These biologic differences between MDS and AML suggest that radiation-induced MDS and AML may have distinct features as a consequence of different damage caused by radiation exposure. Therefore, it is important to evaluate the radiation dose relationship for MDS risk in people exposed to radiation.

In response to the increasing concern about MDS risk in atomic bomb survivors,[14] we initiated a multi-institutional epidemiologic research project. The aim of this study was to assess MDS risk and the radiation dose-response relationship 40 to 60 years after exposure.

PATIENTS AND METHODS

Study Project

This project, begun in April 2004, was a collaboration between the Atomic Bomb Disease Institute (ABDI) of the Nagasaki University Graduate School of Biomedical Sciences, the Nagasaki Prefecture Cancer Registry (NPCR),[15] the hematology departments in five hospitals in Nagasaki City (see Acknowledgment), and the Radiation Effects Research Foundation (RERF). The Institutional Review Boards of Nagasaki University (Research Protocol 16031797) and RERF (Research Protocols 18-66 and 1-75) approved this study.

Patients

We collected clinical information on MDS patients diagnosed in the five hospitals from 1982 to 2004, without regard for exposure status. Skilled hematologists in the hospitals and two authors (M.I. and M.To.) re-evaluated the clinical information, including bone marrow specimens, by using FAB criteria[1] to classify patients as refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-t), or chronic myelomonocytic leukemia (CMML). We also classified the diagnostic certainty for each patient as either definite, possible, undetermined, or non-MDS by using the criteria listed in Table 1. All reviewed patients were reported to the NPCR to be checked for multiple enrollments, the earliest date of MDS diagnosis, and the presence of malignancies before the MDS diagnosis. MDS patients who received chemotherapy and/or radiation therapy for their earlier malignancy were treated as therapy-related MDS, but those who had only surgery for their earlier malignancy were treated as primary MDS. International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes[16] for MDS were assigned to all patients. We also added information on date of death, date of progression to overt leukemia, if present, and the last recorded follow-up date.

Population

We used two different cohorts of Nagasaki atomic bomb survivors: a cohort defined by the ABDI Data Center and RERF's Life Span Study (LSS) cohort. Although there is some overlap between the cohorts, they were established independently and each has its own strengths and limitations. The ABDI cohort is larger than the LSS cohort but lacks information on individual dose, whereas the LSS cohort has detailed individual dose estimates but fewer Nagasaki survivors. The main reason for using two cohorts in our study was to give more credibility to the LSS dose-response findings by confirming similar distance-response patterns in the two cohorts.

The ABDI database was established in 1977 and consists of data on approximately 120,000 Nagasaki atomic bomb survivors. Available data include information on exposure status, death and migration dates, and the results of medical checkups and cancer screenings conducted at the Nagasaki Atomic Bomb Casualty Council Health Management Center. Details about the ABDI database were given previously.[17]

The LSS database was established in 1950, consisting of approximately 94,000 Hiroshima and Nagasaki atomic bomb survivors and 26,000 nonexposed city residents. Available data include information on exposure status, death and cancer diagnosis dates, and individual organ dose estimates computed by using the Dosimetry System 2002 (DS02).[18] The LSS database includes approximately 32,000 Nagasaki survivors. Details about the LSS database were given previously.[19]

Identification of MDS in Atomic Bomb Survivors

Of the 796 patients with MDS registered in the NPCR, 44 were excluded because of misdiagnosis and 147 were excluded because of residence outside the catchment area. The remaining 605 eligible patients with MDS were linked to the ADBI and LSS databases to identify atomic bomb survivors with MDS (ABDI-MDS and LSS-MDS, respectively). Follow-up for this study began in January 1985 when the FAB classification of MDS had been widely used in Japan. Figure 1 summarizes the patient selection process and provides information on the final cohorts used for analyses.

Statistical Analysis

We performed risk analyses only for those with known exposure distances or dose. Patients were limited to those with a definite or possible level of diagnostic certainty for MDS. Patients of therapy-related MDS (ICD-O-3 code 9987/3) or with an undetermined level of certainty were censored at the date of diagnosis. Follow-up began on January 1, 1985, and continued to the earliest of the date of the primary MDS diagnosis, death, or December 31, 2004. The

Table 1. Criteria for the Level of Diagnostic Certainty for MDS in Case Review

Level	Objective Evidence
Definite	Reaffirmation of dysmegakaryopoiesis and/or dysgranulopoiesis on the bone marrow aspirate smear.
	Bone marrow aspirate smear was not available, but there was a clear description of dysmegakaryopoiesis and/or dysgranulopoiesis on the medical record.
	Bone marrow aspirate smear was not available and there was no clear description of dysmegakaryopoiesis and/or dysgranulopoiesis, but there was a description of the presence of dysplasia in blood cells, myeloblast $< 30\%$, and chromosome aberration on the medical record.
Possible	Morphologic evaluation was not available, but there was a clear clinical course from FAB-refractory anemia or refractory anemia with excess blasts to leukemia on the medical record.
Undetermined	Only the name of MDS was available on the medical record and the death certificate.

Abbreviations: MDS, myelodysplastic syndromes; FAB, French-American-British classification.

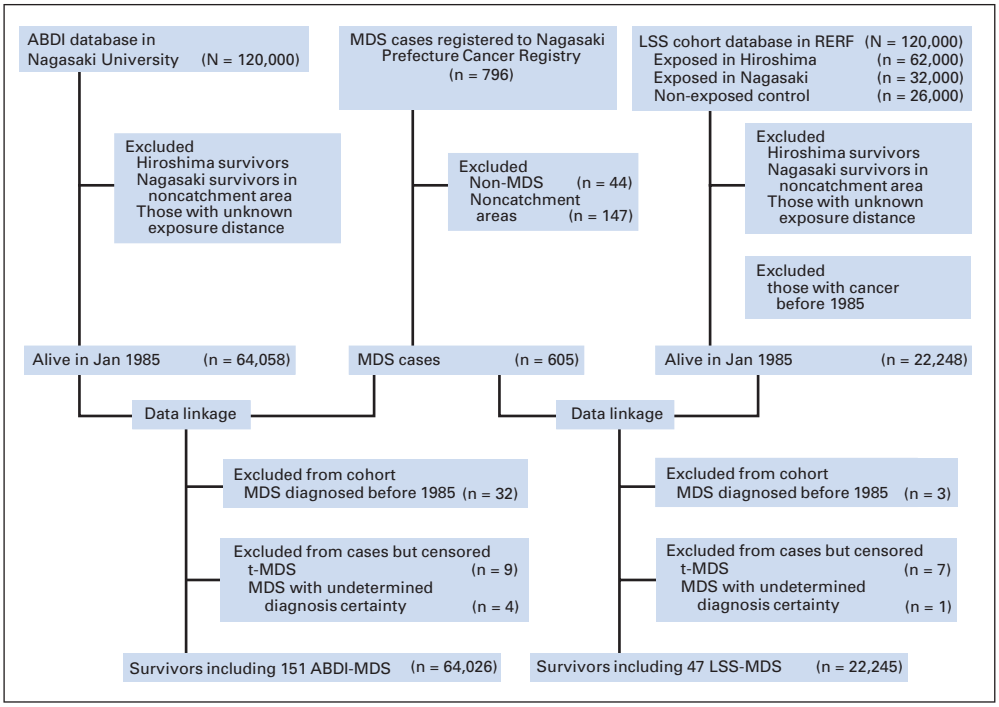

Fig 1. Study profile. ABDI, Atomic Bomb Disease Institute; MDS, myelodysplastic syndromes; LSS, Life Span Study; RERF, Radiation Effects Research Foundation; t-MDS, therapy-related MDS.

person-year calculations took into account date of migration in the ABDI data set, and a migration adjustment was made in the LSS data set. For the LSS data set, we also excluded those with cancer before 1985, and the follow-up was censored at the date of treatment with chemo- or radiotherapy for any cancer, if present, because all LSS cohort members are routinely linked to the NPCR. We treated patients with MDS either together, by FAB category, or by a dichotomized category of low-risk (RA and RARS) and high-risk (RAEB and RAEB-t).[20] We did not include CMML or "not otherwise specified" in the dichotomized category.

We used Cox regression models to estimate the effects of sex, age at exposure, exposure distance, and dose on MDS incidence rates. Relative risk (RR) estimates were computed by using SAS software (version 9.1; SAS Institute, Cary, NC). We used the asymptotic SEs as the basis for hypothesis tests and 95% CIs. Interactions between factors were also tested. We treated age at exposure as two (0 to19 and $\geq$ 20 years) or three groups (0 to 9, 10 to 19, and $\geq$ 20 years) or as continuous, as necessary, and exposure distance in km as three groups ($<$ 1.5, 1.5 to 2.99, and 3.0 to 10.0 km) or more detailed categories, and the weighted DS02 bone marrow dose in Gy as three groups ($<$ 0.005, 0.005 to 0.999, and $\geq$ 1 Gy) or as continuous. The cutoff values for exposure distance or dose were chosen on the basis of data from previous reports.[17,19,21] For categoric data, tests for independence or trend were carried out by using χ^2 or Fisher's exact tests, as appropriate. A two-tailed P value of $<$ 0.05 was judged significant.

We examined linear, linear-quadratic, and other dose-response functions for the LSS data adjusting for sex, age at exposure, and attained age or time since exposure, in a manner similar to earlier leukemia dose-response analyses,[6] and estimated the excess relative risk (ERR) per Gy by using weighted DS02 bone marrow dose. The basic ERR dose-response model can be written as BR $[1+\alpha d]$, where BR is the baseline rate described as a parametric function of sex and attained age. We also examined ERR distance-response functions in the ABDI and the LSS cohorts with exposure distance treated as a continuous variable truncated at 3km (r[inf]3k) or with exposure distance categories of $<$ 1.25, 1.25 to1.49, 1.5 to1.74, 1.75 to1.99, 2.0 to 2.49, 2.5 to 2.99, and $\geq$ 3.0 km. The continuous exposure-distance model can be written as BR $[1+\gamma \exp(-\beta r$[inf]3k)] where the BRs are modeled as for the dose-response model, β is a distance-decay parameter, and γ is a scaling parameter. The distance-decay parameter value (x) is transformed to the percentage decrease in the ERR per km, which is calculated from the formula, $[1-\exp(-x)] \times 100\%$. ERR models were fit and likelihood-based P values and CIs were computed by using EPICURE software (Hirosoft International, Seattle, WA).[22]

RESULTS

The ABDI data set consisted of 64,026 Nagasaki atomic bomb survivors with information on exposure distance, including 151 ABDI patients with MDS who were diagnosed from 1985 to 2004. Of those, 147 (97%) were definite MDS patients and 4 (3%) were possible patients. The LSS data set consisted of 22,245 Nagasaki atomic bomb survivors for whom dose estimates were available. The 47 LSS patients with MDS included 45 (96%) definite and two (4%) possible patients. Table 2 presents the frequencies of FAB subtypes in both data sets. The distribution of subtypes in the ABDI and LSS cohorts did not differ (P = .54). The distribution characteristics, particularly the high frequency of RA relative to RARS and CMML, were typical for Japanese patients with MDS.[23] Cytogenetics data were available for 107 (71%) of 151 ABDI-MDS patients (Appendix Table A1, online only). The median age at exposure and the median age at diagnosis were 18.5 years (range, 0.3 to 43.4 years) and 71.0 years (range, 42.0 to 96.6 years) for ABDI-MDS, respectively, and 16.5 years (range, 2.5 to 48.8 years) and 72.4 years (range, 48.5 to 94.3 years) for LSS-MDS, respectively. The median time to development of MDS from 1985 was 12.0 years (range, 0.3 to 19.9 years) for ABDI-MDS and 14.5 years (range, 0.9 to 19.5 years) for LSS-MDS.

The total numbers of person-years in the ABDI and LSS cohorts were 947,215 and 270,619, respectively. The crude MDS incidence rates in the ABDI and LSS cohorts were 15.9 and 17.4 patients per 100,000 person-years, respectively. Table 3 summarizes the crude incidence rate and crude RR estimates by exposure status. MDS rates were higher for men than for women and increased with age at exposure. MDS rates also increased with decreasing distance from the hypocenter and with increasing estimated dose.

Table 2. Distribution of MDS by Exposure Distance or Dose in Two Cohorts of Atomic Bomb Survivors

Variable	Exposure Distance (km) for Nagasaki Atomic Bomb Disease Institute Cohort				DS02 Bone Marrow Weighted Dose (Gy) for Life Span Study-Nagasaki Cohort			
	< 1.5	1.5-2.99	≥ 3.0	Total	≥ 1	0.005-0.999	< 0.005	Total
Sex								
Male	1,693	6,485	16,092	24,270	273	2,665	5,904	8,842
Female	2,258	10,663	26,835	39,756	351	4,201	8,851	13,403
Total	3,951	17,148	42,927	64,026	624	6,866	14,755	22,245
MDS FAB subtypes								
RA	15	28	57	100	5	9	20	34
RARS	0	1	3	4	0	1	0	1
RAEB	7	8	14	29	2	3	2	7
RAEB-t	2	2	2	6	1	2	0	3
CMML	1	3	4	8	0	0	0	0
Unclassified	0	2	2	4	0	0	2	2
Total	25	44	82	151	8	15	24	47

Abbreviations: MDS, myelodysplastic syndromes; DS02, Dosimetry System 2002; FAB, French-American-British classification; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RABEB-t, RAEB in transformation; CMML, chronic myelomonocytic leukemia.

In Cox analyses for the ABDI cohort with adjustment for sex and age at exposure, the MDS incidence rate was significantly and inversely related to the exposure distance. The RR estimates for those exposed at < 1.5 and 1.5 to 2.99 km from the hypocenter were 2.8 (95% CI, 1.8 to 4.5; $P < .001$) and 1.3 (95% CI, 0.9 to 1.9; $P = .13$), respectively. Analyses of the LSS cohort also revealed that dose was a strong risk factor for MDS. Effects of exposure distance and dose on MDS were observed in both high-risk and low-risk MDS in both cohorts (Figs 2A and 2B). In a joint analysis of the dose and distance effects on MDS rates, there was a suggestion ($P = .08$) of larger radiation effects in high-risk MDS than in low-risk MDS. A significant linear dose association was observed in each risk group ($P < .001$). Effects of exposure distance and dose on MDS were also observed for those exposed before and after age 20 in both cohorts (Figs 2C and 2D). When we adjusted for attained age in 1985 in the ABDI cohort, age-specific MDS risks increased with increasing year of birth, with risks for those born after 1925 being about 1.75 (95% CI, 1.05 to 2.90) times the risks for those born in earlier years. The adjusted MDS risk using exposure dose in the LSS data showed similar results (RR, 1.71; 95% CI, 0.95 to 3.10). After allowing for birth cohort effects on the MDS risk, there was no evidence of a statistically significant interaction between distance or dose and age at exposure in either cohort (ABDI $P = .06$; LSS $P = .36$).

MDS rates decreased significantly with increasing distance for both cohorts ($P < .001$ for both). The fitted ERR curves were similar for the two cohorts. The decay parameters for ABDI and LSS cohorts were 1.2 per km (95% CI, 0.4 to 3.0) and 2.1 per km (95% CI, 0.6 to 4.6), respectively. In other words, the ERR is estimated to decrease by 70% per km (95% CI, 33% to 95%) in the ABDI and 88% per km (95% CI, 43% to 99%) in the LSS cohort. Figure 2E shows the fitted distance-response curves and point estimates of the distance category–specific ERRs with 95% CIs. There was a statistically significant ($P < .001$) linear dose-response for MDS in the LSS cohort with an ERR per Gy estimate of 4.3 (95% CI, 1.6 to 9.5; Fig 2F). A linear-quadratic model that fit the AML[6] did not improve the fit ($P = .46$).

DISCUSSION

To the best of our knowledge, this is the largest study to date evaluating the association between MDS risk and radiation exposure, and the first to provide quantitative estimates of the effect of radiation on MDS risk. We observed a significant ($P < .001$) linear relation between radiation dose and MDS risk among atomic bomb survivors with an ERR per Gy of 4.3. We also observed that the effect of radiation on MDS risk was greater in advanced subtypes of MDS and in those exposed at younger ages.

Our finding of a significant linear dose-response pattern for MDS is in contrast to the significant linear-quadratic dose-response pattern for AML.[6] The fact that the radiation-associated increases of MDS risk still exist 40 or more years after exposure is also in contrast to the risk of radiation-induced leukemia in which the largest dose-related increases were seen in the first 10 to 15 years after the bombings and then decreased slowly with time.[5,6] The linear dose-response pattern and the appearance with a long latency for MDS in atomic bomb survivors seems similar to those seen for radiation-associated solid cancers.[19]

Differences in the dose-response patterns for MDS and AML suggest that the nature of the radiation-induced genetic damages in hematopoietic stem cells may differ for the two diseases. Mutations in the *AML1/RUNX1* gene[24,25] may be one of the genetic damages associated with MDS that occurred in hematopoietic stem cells of atomic bomb survivors because of radiation exposure. Accumulating data on the different characteristics of the molecular and clinical spectrum, including chromosome aberrations between MDS and AML,[12,13,26–29] could shed some light on differences in the role of radiation exposure on these diseases.

Why is radiation-induced MDS seen in atomic bomb survivors more than 40 years after exposure? A primary reason for the long latency of MDS risk could be that atomic bomb survivors, even those exposed early in life, are reaching ages at which MDS rates are increased. In fact, in recent years, hematologists in Nagasaki City have identified an increasing number of MDS occurrences among atomic bomb survivors. Moreover, on the basis of the multistep pathogenesis

Table 3. Crude Incidence and Crude Relative Risk of Myelodysplastic Syndromes by Exposure Status in Nagasaki Atomic Bomb Survivors

Variable	Nagasaki Atomic Bomb Disease Institute Cohort						Life Span Study-Nagasaki Cohort					
	Exposure Distance (km)				Crude RR	95% CI*	Weighted Bone Marrow Dose (Gy)				Crude RR	95% CI*
	< 1.5	1.5-2.99	≥ 3.0	Total			≥ 1	0.005-0.999	< 0.005	Total		
Sex												
Male												
Population at risk	1,693	6,485	16,092	24,270			273	2,665	5,904	8,842		
No. of patients	12	21	34	67			3	8	10	21		
Person-years	23,071	91,880	233,191	348,144			2,959	29,789	66,102	98,850		
Crude rate†	52.0	22.9	14.6	19.2	1.3	1.0 to 1.9	101.4	26.9	15.1	21.2	1.4	0.8 to 2.5
Female												
Population at risk	2,258	10,663	26,835	39,756			351	4,201	8,851	13,403		
No. of patients	13	23	48	84			5	7	14	26		
Person-years	34,946	158,144	405,980	599,071			4,480	52,926	114,363	171,769		
Crude rate†	37.2	14.5	11.8	14.0	Ref		111.6	13.2	12.2	15.1	Ref	
Age at exposure, years												
0-9												
Population at risk	615	4,770	13,730	19,115			161	2,464	5,064	7,689		
No. of patients	6	9	13	28			3	6	3	12		
Person-years	9,756	77,132	225,071	311,960			1,750	29,274	60,572	91,596		
Crude rate†	61.5	11.7	5.8	9.0	Ref		171.4	20.5	5.0	13.1	Ref	
10-19												
Population at risk	1,950	5,620	13,611	21,181			280	2,256	4,841	7,377		
No. of patients	13	16	29	58			2	5	8	15		
Person-years	31,325	91,011	225,009	347,346			3,532	29,182	63,714	96,428		
Crude rate†	41.5	17.6	12.9	16.7	1.9	1.2 to 3.0	56.6	17.1	12.6	15.6	1.2	0.6 to 2.5
≥ 20												
Population at risk	1,386	6,758	15,586	23,730			183	2,146	4,850	7,179		
No. of patients	6	19	40	65			1	11	8	20		
Person-years	16,937	81,882	189,091	287,909			2,157	24,259	56,179	82,595		
Crude rate†	35.4	23.2	21.2	22.6	2.9	1.9 to 4.5	46.4	45.3	10.7	21.8	1.8	0.9 to 3.8
Total												
Population at risk, n	3,951	17,148	42,927	64,026			624	6,866	14,755	22,245		
No. of patients	25	44	82	151			6	22	19	47		
Person-years	58,018	250,025	639,171	947,215			7,439	82,715	180,465	270,619		
Crude rate†	43.1	17.6	12.8	15.9			80.7	26.6	10.5	17.4		
Crude RR	3.2	1.4	Ref				8.1	1.4	Ref			
95% CI*	2.0 to 5.0	1.0 to 2.0					3.1 to 18.0	0.7 to 2.6				

Abbreviations: RR, relative risk; Ref, reference.
*Analyses were performed using the Cox regression.
†The crude incidence was calculated as the total number of patients divided by person-years accumulated in each row and is presented per 100,000 person-years.

model,[3] we may speculate that hematopoietic stem cells of people exposed to higher radiation doses had more genetic damage than those of people exposed to lower dose or than those of the elderly population in general. However, we feel that the multistep pathogenesis model does not fully explain the recent increased risk of MDS. Chromosomal and genetic instabilities as consequences of targeted and/or nontargeted effects of radiation exposure[30] may play a role in the late development of MDS as well as solid cancers in atomic bomb survivors. In fact, we observed higher frequencies of complex karyotypic abnormalities, including random aneuploidies, among proximally exposed MDS patients in this study (Appendix Table A1). Another possible paradigm is the cancer stem-cell theory, including leukemic stem cells.[31,32] Trosko[33] suggests the role of organ-specific adult stem cells as the target cells for radiation-induced carcinogenesis, and the age-related changes in quality of the injured stem cells could affect cancer risks later in life. This concept may explain the long latency of MDS risk in atomic bomb survivors, although little is known about MDS stem cells.

This study has several limitations. Follow-up is limited and there is no information on MDS risks until 40 years after exposure. It was not possible to determine whether or not the incidence rate of MDS were elevated in the decades immediately after the bombings, since MDS was not recognized as a distinct entity until the mid-1980s. The dose-response analyses were performed for a small number of patients. The distance analyses did not account for variations in shielding among survivors, which would modify their actual doses. Information on dates of prior cancers and other prior chemotherapy or radiotherapy was not available for the ABDI data set.

As of 2007, we confirmed that 42 patients among the 151 ABDI-MDS patients progressed to overt leukemia (data not shown). Further studies are needed to clarify the effect of radiation on leukemic transformation as well as the nature of the radiation-induced MDS and the dose-response pattern. Efforts to expand the study to include MDS occurring among Hiroshima survivors are underway.

In conclusion, this study showed that acute radiation exposure is associated with increased risk of developing MDS later in life. This

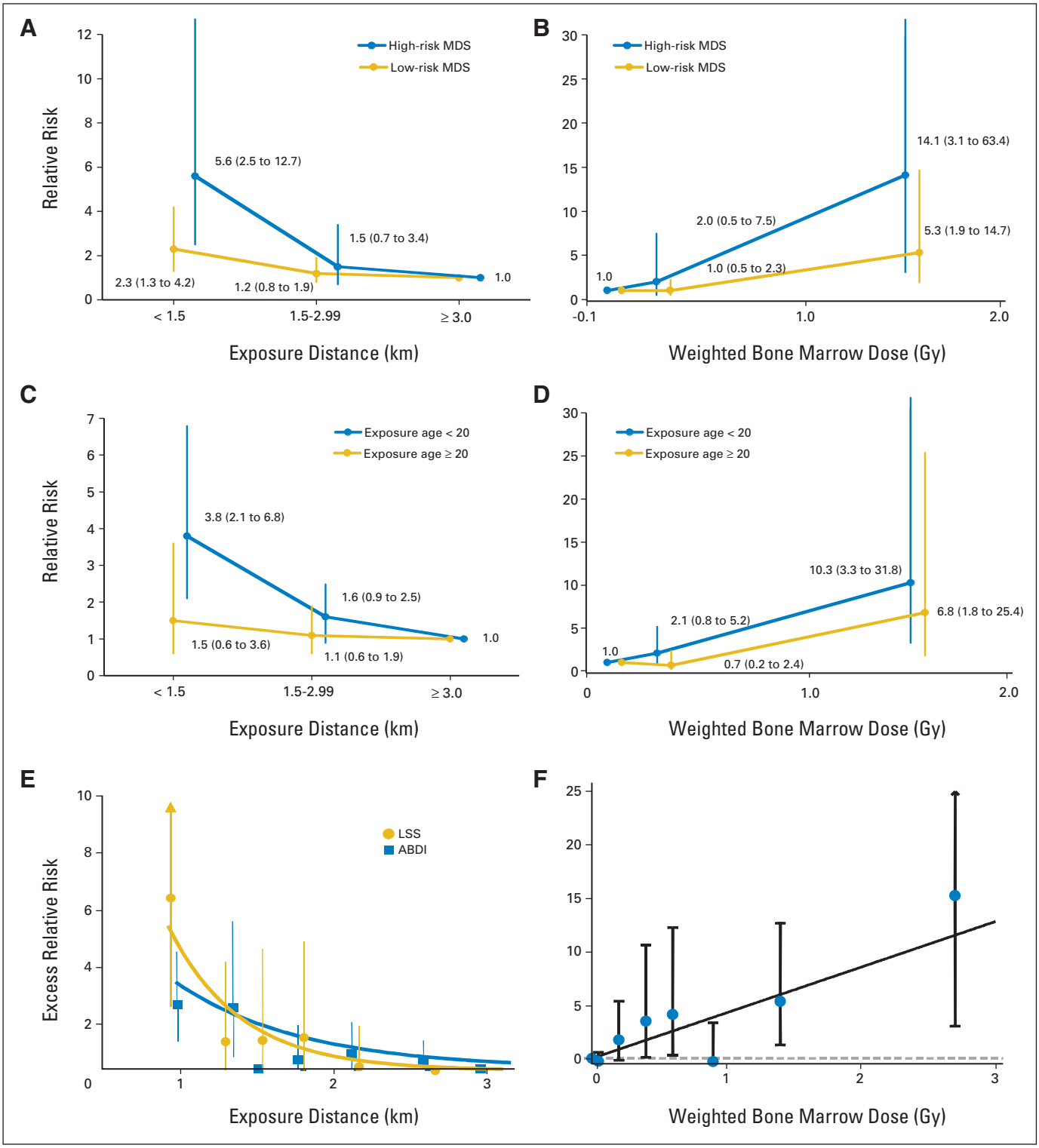

Fig 2. Risk of myelodysplastic syndromes (MDS) by exposure distance and dose. (A) Relative risks of MDS by French-American-British classification subtype in Atomic Bomb Disease Institute cohort, and (B) in Life Span Study-Nagasaki cohort. The high-risk MDS indicates French-American-British classification subtypes of refractive anemia with excess blasts and refractive anemia with excess blasts in transformation, and the low-risk MDS indicates the subtypes of refractive anemia and refractive anemia with ringed sideroblasts. (C) Relative risks of MDS by age at exposure in Atomic Bomb Disease Institute cohort, and (D) in Life Span Study-Nagasaki cohort. (E) Sex- and age-adjusted distance-response for MDS. The lines display the best-fitted excess relative risk curves based on distance category–specific relative risk. (F) Sex- and age-adjusted radiation dose-response for MDS. The line displays the best-fitted linear excess relative risk dose-response without risk modification based on dose category–specific relative risk. The dashed horizontal line represents excess relative risk = 0. Whiskers show the 95% CIs.

suggests that radiation-induced MDS might involve a different pathogenesis than radiation-induced leukemia. Clinicians should perform careful long-term follow-up of people who have been exposed to radiation to detect MDS as early as possible and reduce the risk of leukemic transformation by using new drugs such as DNA hypomethylating agents.[34]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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