Scientific Category

Clinical trials and observations

Relationship between Monoclonal Gammopathy of Undetermined Significance and Radiation Exposure in Nagasaki Atomic Bomb Survivors

Short title

MGUS and Radiation exposure

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Abstract

Radiation exposure is a possible predisposing factor for monoclonal gammopathy of undetermined significance (MGUS), but the association has been uncertain. We investigated the relationship between radiation exposure and MGUS prevalence by using data from the M-protein screening for Nagasaki atomic bomb survivors during 1988-2004. Radiation exposure was assessed by exposure distance from the hypocenter and exposure radiation dose. We computed prevalence ratios (PRs) and the 95% confidence intervals (CIs) adjusting for exposure age and sex. A total of 1082 MGUS were identified from 52525 participants. MGUS prevalence was significantly higher in people exposed at distance within 1.5 km than beyond 3.0 km (PR, 1.4; 95%CI, 1.1-1.9) among those exposed at ages 20 years or younger, but it was not found among those exposed at ages 20 years or older. MGUS prevalence was also significantly higher in people exposed to more than 0.1Gy than those exposed to less than 0.01Gy (PR, 1.7; 95%CI, 1.0-2.8) among those exposed at ages 20 years or younger. Thus, people exposed at younger age exhibited significantly high risk of MGUS when exposed to high radiation dose. There was no clear association between radiation exposure and the malignant progression of MGUS. Further detailed analysis is needed.

Key words

Monoclonal gammopathy of undetermined significance, Multiple myeloma, Cancer epidemiology, Radiation exposure, Atomic Bomb Survivors

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder, which is defined by a serum monoclonal-protein (M-protein) concentration of 3 g/dL or less, 10% or fewer plasma cells in bone marrow, and the absence of anemia, osteolytic lesions, hypercalcemia, and renal dysfunction.[1] Although the majority of MGUS remain stable for prolonged periods, malignant transformation to multiple myeloma occurs at a constant rate of 1% per year.[2] Given that myeloma is an incurable hematological malignancy, it is important to elucidate etiology and predisposing factor of MGUS.

Etiologic factors for MGUS have not been investigated fully.[3-5] There are currently no consistent risk predictors, beyond age, sex, and race, for developing MGUS. Although radiation exposure is well known to initiate leukemogenesis, there have been conflicting reports about the association between radiation exposure and plasma cell disorders.[6-11] An Italian case-reference study reported an increased risk of MGUS among people suffered by occupational radiation exposure.[12] However, a small survey for atomic bomb survivors showed no association between radiation dose and the relative risk of MGUS.[13] Sample sizes of these previous studies were too small to obtain reliable results for association between radiation exposure and incidence of the disease.

We have recently reported that the age-specific MGUS prevalence in Japanese population, indicating 2.4% in those older than 50 years.[14] The report used a M-protein screening data from approximately 52000 atomic bomb survivors but did not yet report the relationship between radiation exposure and MGUS risk. The large number of study participants from the radiation-exposed population could provide a great opportunity to investigate the relationship between radiation exposure and the risk of MGUS. Our preliminary analysis observed that MGUS risk was higher in those exposed to higher radiation among young age.[15] However, the preliminary observation lacked detailed analyses for the relationship and did not include clinical characteristics. In the present study, we performed comprehensive analyses for the screening data by considering distance from the hypocenter of the nuclear explosion, radiation dose, age at exposure, age at diagnosis, and monoclonal protein level to elucidate whether radiation exposure is related with the development of MGUS and the progression.

Materials and Methods

Data source

Screening for M-protein was initiated in October 1988 for atomic bomb survivors at the Health Management Center of Nagasaki Atomic Bomb Casualty Council where a comprehensive medical check-up has been offered twice a year since 1968, and several cancer screenings have been offered once a year since 1988. All examinations are free of charge and supported by the Nagasaki City Government based on the Law Concerning the Relief for Atomic Bomb Survivors. Data of all medical check-ups and cancer screenings were stored by online into the computer database at the Data Center in the Atomic Bomb Disease Institute at Nagasaki University Graduate School of Biomedical Sciences since 1977. The ongoing database keeps data from approximately 120000 atomic bomb survivors who have Atomic Bomb Victim's Handbook, including fundamental information, age at exposure, city at the time of the bombings, exposure categories, exposure distance from the hypocenter in km, date of the certificate handbook acquisition, date of examination, date of death, and date of moving-in or -away from Nagasaki City, and all laboratory results.[16] Data of participants underwent the M-protein screening were extracted as anonymous data from the computer database in the Data Center of Atomic Bomb Disease Institute. Use of the database for this study was approved by the Atomic Bomb Disease Institute on June 2004 (No.224).

Screening procedure

Screening procedures were described in detail previously.[14] Briefly, routine laboratory tests including the first-step M-protein screening were offered every year for atomic bomb survivors who visited the Health Management Center. Results of the first-step M-protein screening were evaluated on the sheet in the double-checking system by hematologists of Nagasaki University Medical Hospital regardless of exposure condition. Subjects with the presence of possible M-protein or low gammaglobulinemia were informed by mail or telephone to take the second-step screening. The second-step screening procedure consisted of physical examination by hematologists, immunoelecrophoresis of serum and urine, a qualitative test for Bence-Jones (BJ) protein, and a

quantitative determination of serum concentration of immunoglobulins using nephelometry. Subjects with a high level of M-protein or with other abnormal laboratory data were referred to the tertiary hospitals to undergo further examination with bone marrow aspiration, bone surveys, and other investigations. Skilled hematologists made a final diagnosis comprehensively based on screening data, routine laboratory data, physical examinations, and feedback letters from the reference hospitals. The diagnostic criteria used for MGUS were based on an M-protein level less than 3.0 g/dl in serum Igs, no symptom of multiple myeloma or Waldenström's macroglobulinemia (WM), no anemia, no hypercalcemia, no osteolytic lesion, and less than 10% marrow plasma cells if done.[1] Cases with high M-protein level more than 3.0 g/dl at the first-time detection day but showing the "reconfirmed" M-protein levels of less than 3.0 g/dL were also treated as MGUS.

Radiation exposure

Radiation exposure was assessed by exposure distance and exposure dose. In the database, exposure categories were divided into 4 categories; "directly exposed" indicates those who were exposed to atomic bomb radiation within 10 km from the hypocenter at the time of the bombing, "early entrants" indicates those who entered the city within approximately 2 km from the hypocenter within two weeks of the explosion, "relief" indicates those who were engaged in disposal of the dead or relief works for atomic bomb victims, and "exposed In-utero" indicates children who were exposed prenatally at the time of the bombing. Although information of exposure distance was available for "directly exposed" and "exposed In-utero", we used only "directly exposed" people for the analysis to investigated relationship between radiation exposure and MGUS risk. Information of whole-body radiation dose estimate by the Atomic Bomb Survivors 1993 Dose (ABS93D) were available for a limited number of Nagasaki atomic bomb survivors.[17] The ABS93D was calculated according to three parameters, free-in-air kerma, shielded kerma, and organ kerma, same as Dosimetry System (DS) 86,[18] which was used for the Life Span Study (LSS) cohort of the Radiation Effects Research Foundation (RERF).[11] As a strong correlation between DS86 and ABS93D was fully documented,[19] we used ABS93D as a substitute of DS series to estimate radiation-dose response.

Participants

The target population for the M-protein screening was 74411 atomic bomb survivors exposed in Nagasaki City, consisting of 71675 people who were alive at the time of the start of the M-protein screening in October 1988 and 2736 people who were included in the database after 1988 to 2004 because some obtained newly Atomic Bomb Victim's Handbook and others moved in Nagasaki City from elsewhere. Those exposed in Hiroshima City moving-in Nagasaki City were excluded. Among 74411 people, ABS93D dose information was available for 6837 (9.2%). **Table 1** presents the breakdown of participants and non-participants by demographic characteristics. The participant rates were around 70% in all categorized groups except in those 30 years or older age at exposure (36%). Finally, a total of 52525 Nagasaki atomic bomb survivors were underwent the M-protein screening during 1988-2004 (the overall participation rate, 70.6%) and were used for analyses to examine the relationship between MGUS risk and exposure distance from the hypocenter. Among those having radiation dose, 4758 (the participation rate, 69.6%) underwent the screening and were used for the dose-response analyses.

Follow-up procedure

Subjects who were once diagnosed as having MGUS also underwent annually the M-protein screening in the same way as described in the screening procedure. They were followed to check the change of size of M-protein on individual M-protein chart, which was reviewed by skilled hematologists in the Health Management Center. Subjects with a high level of M-protein or with other abnormal laboratory data were referred to the tertiary hospitals to undergo further examination. Diagnoses of multiple myeloma or other related diseases were obtained from the tertiary hospitals.

Statistical analysis

Statistical analyses for prevalence were performed using all the screening data accumulated during the period from October 1, 1988, to March 31, 2004. Patients who were diagnosed as having multiple myeloma or WM at the first-time screening were excluded from the analyses. MGUS patients diagnosed during the period above were also analyzed the risk of the malignant progression during the period from the date of diagnosis to July 31, 2008. All statistical analyses were performed using SAS 8.2 software (SAS Japan Institute, Tokyo, Japan). All tests were 2-tailed, and the level of statistical significance was .05.

Age at exposure was treated as a continuous data or stratified into four categories (0-9, 10-19, 20-29, 30 yr or older). Exposure distance from the hypocenter in km was treated as a continuous data or stratified into three categories (within 1.5, 1.5-3.0, and 3.0 up to 10.0 km). The cut-off values for exposure distance were chosen based on previous reports.[20,21] Among those in the exposure category of "directly exposed", subjects with no information of distance position were treated as those exposed at unknown distance. The ABS93D dose estimate in Gy was treated as continuous data or stratified into three categories (lower than 0.01, 0.01-0.1, and 0.1 or higher). Age at diagnosis of MGUS was stratified into five categories (< 50, 50-60, 60-70, 70-80, ≥80 yr). Basic demographic analyses were assessed using Chi-square test or trend test for categorical variables and nonparametric test for continuous variables, if necessary. Simple prevalence (%) of MGUS and the 95% confidence intervals (CI) were calculated using the exact binomial method in each category. Exposure-response analyses were performed for two data sets, one for people with assured exposure distance from the hypocenter to examine the relationship between MGUS risk and the exposure distance, and another for people with assured ABS93D dose to examine the relationship between MGUS risk and exposure dose. To evaluate the relationship between MGUS risk and exposure distance or exposure dose, we calculated prevalence ratios (PR) and the 95% CI by using the log-binomial regression model using PROC GENMOD in SAS.[22,23] Univariate and multivariate analyses were performed including relevant factors and/or interaction terms to test effect-modification. To obtain the best-fit model for dose-response effect, we ran additional analyses including sex, continuous age at exposure per year, continuous radiation dose (linear or quadratic term), and interaction terms between covariates. The most appropriate model was selected on the basis of Akaike's Information Criterion (AIC).[24] The cumulative probability of developing multiple myeloma or other lymphoid malignancy among MGUS was calculated using the Kaplan-Meier method and compared using the log-rank test. Patients who died or were lost to follow-up were censored in the analysis.

Results

Of 52525 participants, 1103 were confirmed as having monoclonal immunoglobulin, in which 1082 were diagnosed as having MGUS, 19 were multiple myeloma, and 2 were WM. The 21

patients with multiple myeloma or WM were excluded from analyses. Therefore, a total of 52504 participants were used for analyses by exposure distance. Of the 21 patients excluded, 3 had ABS93D dose information. Therefore, a total of 4755 participants with ABS93D dose were used for dose-response analyses.

Clinical characteristics of MGUS at diagnosis

Table 2 shows the clinical characteristics of 1082 MGUS patients. The median age at diagnosis was 68.5 years (ranges, 45.0 to 100.9). Age at diagnosis was significantly older than in female (median; 68.3 yr) than male (median; 66.3 yr) (*P*=.003). The distribution of age at diagnosis by exposure categories was presented in **Table 3**. Although patients exposed at younger age tended to be younger age at diagnosis **(Figure 1C),** there was no difference in age at diagnosis across exposure distance groups (*P*=.65) but was some tendency for age at diagnosis to be younger in those exposed to the higher dose (>0.1Gy) than those exposed to the lower dose in each exposure age group, though the differences were not statistically significant (*P*=.46 among three dose categories and *P*=.23 between dose group of 0-0.01 and >0.1Gy) **(Figure 1A,1B).** Median serum M-protein level at diagnosis was 1.5 g/dL (range 0.1 to 3.4 g/dL). The distribution of serum M-protein level by demographic characteristics was summarized in **Table 4 (and *see* a supplemental Table).** MGUS with M-protein level greater than 1.5 g/dL were highly frequent those exposed at 20 yr or older. However, the level was not different among age at diagnosis, exposure distance, or exposure dose.

Prevalence of MGUS by exposure distance from the hypocenter

MGUS prevalence in 52504 participants by sex and exposure status was shown in **Table 5**. The over all prevalence of MGUS in participants was 2.1% (95%CI, 1.9 to 2.2), 2.8% (95%CI, 2.6 to 3.0) in male, and 1.6% (95%CI, 1.5 to 1.7) in female. MGUS prevalence was 2.7% (95%CI 2.1 to 3.4) in those directly exposed at within 1.5km from the hypocenter, 1.9% (95%CI 1.7 to 2.2) at 1.5-3.0km, 2.0% (95%CI 1.8 to 2.1) at over 3.0km, and 2.3% (95%CI 2.0 to 2.6) in other exposure categories. **Table 6** summarizes results of univariate and multivariate regression analyses. The unadjusted PR was significantly higher in male, in those of older age at exposure, and in those exposed at within 1.5 km compared to those exposed at over 3.0km. A multivariate analysis

including interaction terms among all variables showed a significant interaction (P<.03) between age at exposure and the exposure distance, but no significant interaction between sex and age at exposure (P<.7) or exposure distance (P<.9), suggesting that the effect of exposure distance on MGUS prevalence might be different by age at exposure. Therefore, we analyzed data by dividing into two age categories; those exposed in age younger than 20 years and 20 years or older. Because age function is a strong risk factor for MGUS, we included age at exposure as a continuous variable into both stratified multivariate analyses. In the multivariate analysis for those of age at exposure younger than 20 years, the adjusted PR of MGUS showed 40% increase per every 5-year increase of age at exposure (adjusted PR, 1.4; 95%CI, 1.3-1.5) and the probability of MGUS among subjects who were exposed at within 1.5 km was overall 40 % higher than among those exposed at far from 1.5km (adjusted PR, 1.4; 95%CI, 1.1-1.9). The adjusted PR of MGUS showed no difference among exposure distance categories in those of age at exposure older than 20 years.

Prevalence of MGUS by radiation dose

Table 7 presents the breakdown of MGUS prevalence in people with information of ABS93D dose. Among dose categories, the prevalence was 2.5% (95%CI, 1.7-3.5) in those exposed at 0.1Gy or more, 2.0% (95%CI; 1.4-2.8) in those at 0.01-0.1Gy, and 1.6% (95%CI, 1.1-2.3) in those at 0.01Gy or lower. Before applying dose as continuous data, doses are truncated to correspond to the 4 Gy level according to previous RERF studies.[11,25] **Table 8** summarizes results of univariate and multivariate regression analyses for PRs. For those exposed when younger than 20 years, univariate analyses showed significantly higher PR in those exposed to 0.1Gy or more compared to those exposed to lower dose category. However, no significant dose-effect was observed when dose was treated as continuous variables. After adjusting sex and age at exposure, the PR of MGUS in those exposed to 0.1Gy or more was estimated 1.66, suggesting that radiation exposure over 0.1Gy had 1.66 times higher risk of MGUS compared to the dose of lower than 0.1Gy. However, the linear-dose model failed to find a clear dose-response effect even after controlling sex and age at exposure (multivariate analysis-1 in **Table 8**). We performed additional models, including dose as treated quadratic transformation. The AIC value in each multivariate analysis was 587.7646 for a model using a linear term (the parameter estimate [beta] for dose; 0.2179, standard error [SE]; 0.1651, P=.2), 588.0652 for a simple quadratic term (dose squared) (beta; 0.0569, SE; 0.0469, P=.2), and 589.7468 for a quadratic term (beta; 0.2794, SE; 0.4867, P=.5). For those exposed when

older than 20 years, both univariate and multivariate analyses showed no effect of radiation dose on MGUS prevalence even after controlling other covariates. **Figure 2A** shows PR of MGUS by exposure dose squared adjusting for sex and age at exposure. Prevalence ratio at 1 Gy was 1.06 (95%CI, 0.97 to 1.16, *P*=.2) among those of age at exposure younger than 20 yr. **Figure 2B** shows PR of MGUS by age at exposure adjusting for sex and exposure dose square. Advanced age was significantly associated with increased prevalence of MGUS among those of age at exposure younger than 20 yr (PR, 2.24 for 10-year increase; 95% CI, 1.39-3.62; *P*=.001) and those older than 20 yr (PR, 1.77 for 10-year increase; 95% CI, 1.03-3.03; *P* =.04).

Risk of progression

MGUS patients were followed for a total of 8822.5 person-years (median, 7.4 years; range, 0 to 19.6 years). There were 365 patients (33.7%) who were followed until death. During this period of observation, 44 (4.1%) patients experienced the progression to multiple myeloma (41 cases) and WM (3 cases). All of myeloma cases were developed from IgG or IgA MGUS. Among 3 WM, two were developed from IgM MGUS and one was developed from IgG MGUS.[26] The median latent period between the diagnosis of MGUS and the development of multiple myeloma or WM was 5.3 years (range, 0.1 to 15.9 years). The overall cumulative probability of the progression was 6.9% (95%CI, 4.9% to 9.6%) at 10 years and 8.0% (95%CI, 5.4 to 11.9) at the latest follow-up (**Figure 3A**). Among the 44 patients, 36 had information of exposure distance, and only 2 had information of exposure dose. Therefore, risk analyses were performed by only exposure distance. The frequency of malignant progression by factors was summarized in **Table 9**. The cumulative probability of the progression was greater in those exposed at within 1.5 km distance than those exposed at 1.5-3.0 km and 3.0 km or more distance, but the difference was not statistically significant (13.9% vs. 6.7% vs. 7.7%, log-rank test *P*=.34) **(Figure 3B**). The probability was significantly higher in age at exposure 20 years or older than younger than 20 years (18.1% vs. 5.4%, *P*=.04) (**Figure 3C**). Among those age at exposure 20 years or older, there was no difference in the progression between those exposed within 3km and over 3km distance from the hypocenter (*P*=.90), but among those age at exposure younger than 20 years, the probability was a tendency to be high in those exposed at within 3 km than those exposed distantly (7.4% vs. 4.2%, *P*=.17) (**Figure 3D**). Among those age at exposure 20 years or older, those diagnosed in younger than the median age 68.5 yr was significantly progressed to myeloma than those in older than 68.5 yr

(35.4% vs. 7.6%, *P*=.02) (**Figure 3E**). The cumulative probability was significantly higher in those of the higher M-protein level at diagnosis (≥1.5g/dL) than the lower level (<1.5g/dL) (12.5% vs. 2.0%, *P*=.0002) (**Figure 3F**). The older age at exposure showed the greater risk of progression among those with the higher M-protein level at diagnosis (*P*=.06) but there was no different risk in age categories among those with the lower M-protein level (*P*=.80) (**Figure 3G**). There was no risk difference between the exposure distance categories among those with the higher M-protein level at diagnosis (*P*=.60) but there was a tendency to be greater risk in those exposed at within 3 km among those with the lower M-protein level (*P*=.0007) (**Figure 3H**).

Discussion

The present study is the first comprehensive evaluation of the effects of radiation exposure on MGUS prevalence using a large number of atomic bomb survivors. We observed that, among those exposed at younger than 20 years, the probability of MGUS was 1.4 times greater in those exposed at near hypocenter than those exposed at far from the hypocenter and 1.7 times greater in those exposed to radiation dose of 0.1Gy or more than less than the level. We also observed that the strongest factor on the progression of MGUS was the high level of M-protein at diagnosis beyond the effect of the higher radiation exposure.

Only a few epidemiological studies reported an effect of radiation exposure on MGUS. *Pasqualetti et al.* observed that occupational exposure to radiation was significantly associated with an increasing risk of MGUS.[12] However, the result was based on only 13 cases and no dose-response analysis was performed. *Neriishi* et al. reported no association between radiation dose (DS86) and the incidence of 112 MGUS (1.7%) among 6737 atomic bomb survivors who were members of the Adult Health Study (AHS) of RERF.[13] The study found that the MGUS risk was not different between those exposed more than 0.01Gy and those exposed less than 0.01Gy (relative risk [RR]=1.35, 95%CI 0.9-2.0). There were several differences between the AHS study and the present study in terms of analytic method and observed results. The overall prevalence was lower in the AHS study than our result (1.7% vs. 2.1%) in spite of same study periods. The cut-off value to compare MGUS risk by dichotomized dose category was also different as the present study used 0.1Gy but the AHS study used 0.01Gy. This difference might affect the different interpretation of

the results. In addition, the AHS study did not observe the significant interaction between age at exposure and dose, and neither demonstrated dose-response analysis by age at exposure. Nevertheless, they realized marginally significant increase of MGUS risk in those less than 80 years old of onset age, which might support our result that a significantly higher prevalence risk of MGUS was observed in only participants who were exposed in younger age. Even though there were some differences between the AHS study and our present study, the estimated MGUS risk was similar as the RR was 1.603 (*P*=.05) in less than 80 years old age at diagnosis in the AHS study, and the PR was 1.66 (*P*=.05) in less than 20 years age at exposure in our study. This suggests that it is consistent that there exists a significant weak association between radiation exposure and MGUS risk among those exposed when young.

Although we found that only younger age at exposure had a significant association between the higher dose radiation exposure and the higher MGUS risk, the result does not necessarily deny the association in those of older exposure age. As shown in **Table 1**, the participation rate was lower in older ages, which suggests less representative of the actual MGUS prevalence among the older target population. As known well, older atomic bomb survivors, especially exposed at the higher radiation dose, had the higher mortality due to both cancers and non-cancer diseases.[21,27] Therefore, results among those exposed in 20 years or older in our study might be strongly affected by detection loss.

For the association between radiation and myeloma, a number of epidemiological studies analyzed people exposed to environmental, occupational, and medical radiation.[5,28,29] A series of reports from Hanford nuclear workers in the US and Sellafield workers of British Nuclear Fuels indicated a significant dose-response trend between myeloma death and cumulative external radiation dose.[30-35] A recent international report of the 15-Country collaborative study of nuclear workers also found a borderline significant association with radiation dose and 87 myeloma deaths (RR 1.61 at 100 mSv).[36] The age effect in most of nuclear worker studies reported that a significant dose-response was observed in those of older ages at exposure, which differs from findings in the experiences of atomic bomb survivors including our study that significant dose-response were observed more likely in those younger ages at exposure. For this discrepancy, *Wing et al*. discussed that selection bias and basic differences in the characteristics of the study populations may be considered.[7] Another difference might be due to the differences in way of exposure to radiation that

nuclear workers received chronic exposures to cumulative lower doses over lifetime in contrast with atomic bomb survivors who received acute exposure to high doses radiation.

Unlike nuclear workers, there is no epidemiological evidence supporting an increased risk of myeloma among atmospheric nuclear test participants.[8,9,37-40] All of these studies had less power to evaluate dose-response association because the observed number of myeloma cases was too small, less than 8. A mixed association has been observed between risk of myeloma and diagnostic or therapeutic radiation.[41-43] In a large international study of radiation treatment for cervical cancer, there was no difference in risk of myeloma between those who were received less than 2Gy and 2Gy or greater, however, increased risks were observed among patients followed long-term and those irradiated at relatively younger ages.[44] The observation supports our result that the higher MGUS risk was observed in those exposed to the higher radiation in younger age.

Among atomic bomb survivors, the relationship between exposed radiation dose and myeloma has been also inconsistent. *Ichimaru et al.* analyzed 29 cases of myeloma accumulated between 1950 and 1976, and found a statistically significant increase in the incidence among the higher dose group (over 0.5 Gy) since 1965, suggesting a prolonged latency period for radiation-induced myeloma.[10] The study also indicated a different dose effect by exposed age that the positive effect was seen only in those exposed age 20-59 years old, which was very similar to our present study. *Shimizu et al.* also reported a statistically significant excess risk for myeloma during from 1950-1985.[45] However, the latest report did not observe a significant dose response (P=.12) when analyses were limited to first-primary myeloma cases, though a statistically significant increase was observed when excluded cases were included the analysis (P=.02).[11] In the latest report, only 59 among 94 cases were used for the analysis because many cases were excluded due to a variety of reasons. The report explained the discrepancy within the same cohort might be affected by differences in the inclusion criteria of case and dosimetry system.

The majority of MGUS patients will never develop MM. So far, the size of serum M protein, the IgA isotype, an abnormal serum free light chain ratio, detectable BJ protein excretion, and more than 5% of plasma cells in BM have been identified as predictors of MM progression.[46-48] Nevertheless, precise predictors to define high-risk MGUS cases should be identified. In the present study, we confirmed that the strongest factor on the progression of MGUS was the high level of

M-protein at diagnosis beyond the effect of radiation exposure. Exposure age and age at diagnosis showed complicated effects on the prognosis. Those exposed at 20 years or older progressed greater than the younger (Figure 3C), but those diagnosed younger than 68.5yr more likely progressed to myeloma in both exposure age categories (Figure 3E). These results might be affected by the competing cause of death, thus the older patients would die before the progression of MGUS, which could introduce the underestimate of the progression risk among older patients. Although the present study did not find confident evidence that radiation exposure was related with the malignant progression of MGUS, there was a tendency to be a greater risk of progression among patients exposed proximally. *Neriishi et al.* also reported that MM mortality rate was higher among the exposed group (>0.01Gy, 10 cases) than the non-exposed group (0-0.01Gy, 4 cases), though the difference was not significant.[13] Both studies suggested a potential adverse effect of radiation exposure on the progression from MGUS to MM.

The present study has several limitations. Dose analyses were performed for a limited number of subjects. A healthy screenee bias[49] might affect the results especially in older age group. Indeed, the participation rate decreased by age (Table 1). Over-diagnosis bias surly exists because of the long-term prognosis of MGUS in nature. Potential factors including in analyses were also insufficient. These limitations would have introduced over or under estimate of the association. Further researches including other potential factors as covariate together are needed to confirm the effect of radiation on MGUS.

The mechanism how radiation exposure affects the increasing risk of MGUS has been still unknown. As known well, radiation exposure induces chromosomal and genomic instabilities by direct and indirect ways.[50] Meanwhile, a variety of chromosome abnormalities have been reported even though MGUS is a benign hematological disorder.[51,52] These facts might explain that MGUS risk increase when exposed to the higher level of radiation dose through radiation-induced chromosomal and genomic instabilities. Beyond the effect of radiation on MGUS risk, recent epidemiological studies provided clear evidences of a significant racial disparity in MGUS prevalence[3,4,14] and familial aggregation for MM/MGUS,[53] both of which suggest a role for genetic susceptibility as MGUS etiology. More recently, *Brown et al.* reported a possible role for immune-related and inflammatory conditions in the causation of MGUS.[54] This report may also suggest another perspective on radiation-induced MGUS because recent molecular studies have

revealed that radiation-induced inflammatory reaction and radiation-induced genomic instability may be interrelated with a predisposition to radiation carcinogenesis.[50,55]

We previously reported that, even allowing for atomic bomb survivors, our Japanese population had a lower prevalence of MGUS compared to whites.[14] Although the conclusion is solid evidence, the present findings suggest that the prevalence data of atomic bomb survivors may not be generalizable to other Japanese population, but rather suggest that MGUS prevalence in a general Japanese population might be lower than our population because the present study showed that those who were exposed to lower radiation had a significantly low prevalence. Further population-based epidemiological studies using general population are needed to estimate more reliable MGUS prevalence in Japanese and other Asians.

In conclusion, the present study suggests that atomic bomb survivors exposed at high level of radiation at young ages are at high risk of the evolution of MGUS even many years after radiation exposure. During the screening period from 1988 to 2004, the population of atomic bomb survivors becomes older. The youngest atomic bomb survivors reach around 60 years old. Unlike leukemia, the risk of solid cancers following exposure to ionizing radiation becomes manifest after a relatively long latency period,[27] after which the excess risk persist for decades. MGUS and myeloma is also one of such diseases with a long latency. Further investigations of MGUS and myeloma are needed for this large- and long-followed population, especially people exposed at younger ages.

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Authorship and Conflict of Interest Statements

M. Iwanaga was involved in the screening procedure, analyzed data, and wrote the manuscript. M. Tagawa established and managed the screening procedure. T. Matsuo managed the screening procedure. K. Yokota administrated and extracted data from the Data Center in the Atomic Bomb Disease Institute. Y. Miyazaki, T. Fukushima, T. Hata, Y. Imaizumi, D. Imainishi, J. Taguchi were responsible for the first screening procedure. S. Kamihira, S. Momita, and K. Tsukasaki were responsible for the final diagnosis of the screening procedures. M. Tomonaga established the screening procedure and managed the database of the Atomic bomb survivors. All authors revised the article critically and approved the final version.

There was no conflict of interest for this study. All medical examinations for A-bomb survivors are charge-free based on support of the medical aid by the Nagasaki City Government.

References

1. Kyle RA. Monoclonal gammopathy of undetermined significance: natural history in 241 cases. *Am J Med* 1978; 64:814-826.
2. Kyle RA, Therneau TM, Rajkumar SV, et al. A long-term study of prognosis of monoclonal gammopathy of undetermined significance. ***N** Engl J Med.* 2002; 346: 564-569
3. Munshi NC. Monoclonal gammopathy of undetermined significance: genetic vs environmental etiologies. *Mayo Clin Proc.* 2007;82:1457-1459.
4. Landgren O, Gridley G, Turesson I, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood.* 2006;107:904-906.
5. Alexander DD, Mink PJ, Adami HO, et al. Multiple myeloma: a review of the epidemiologic literature. *Int J Cancer.* 2007;120:40-61.
6. Cardis E, Gilbert ES, Carpenter L, et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res.* 1995;142:117-132
7. Wing S, Richardson D, Wolf S, et al. A case control study of multiple myeloma at four nuclear facilities. *Ann Epidemiol.* 2000;10:144-153.
8. Muirhead CR, Bingham D, Haylock RG, et al. Follow up of mortality and incidence of cancer 1952-98 in men from the UK who participated in the UK's atmospheric nuclear weapon tests and experimental programmes. *Occup Environ Med.* 2003;60:165-172.
9. Pearce N, Prior I, Methven D, et al. Follow up of New Zealand participants in British atmospheric nuclear weapons tests in the Pacific. *BMJ.* 1990; 300:1161-1166.
10. Ichimaru M, Ishimaru T, Mikami M, Matsunaga M. Multiple myeloma among atomic bomb survivors in Hiroshima and Nagasaki, 1950-76: relationship to radiation dose absorbed by marrow. *J Natl Cancer Inst.* 1982;69:323-328.
11. Preston DL, Kusumi S, Tomonaga M, et.al. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. *Radiat Res.* 1994; 137:S68-97
12. Pasqualetti P, Collacciani A, Casale R. Risk of monoclonal gammopathy of undetermined significance: a case-referent study. Am J Hematol. 1996, 52:217-20.
13. Neriishi K, Nakashima E, Suzuki G. Monoclonal gammopathy of undetermined significance in atomic bomb survivors: incidence and transformation to multiple myeloma. *Brit J Haematol*.

2003; 121: 405-410

14. Iwanaga M, Tagawa M, Tsukasaki K, Kamihira S, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance: study of 52,802 persons in Nagasaki City, Japan. *Mayo Clin Proc.* 2007;82:1474-1479.
15. Tsukasaki K, Iwanaga M, Tomonaga M. Late hematological effects in the atomic bomb survivors. In: Shibata S, Yamashita S, Tomonaga M. eds. Radiation Risk Perspectives. Elsevier: Tokyo, Japan; 2007:67-72. International Congress Series 1299.
16. Mori H, Mine M, Kondo H, Okumura Y. Medical database for the atomic bomb survivors at Nagasaki University. *Acta Med Nagasaki*. 1992; 37:52-65.
17. Hoshi M, Matsuura M, Hayakawa N, Ito C, Kamada N. Estimation of radiation dose for atomic-bomb survivors in the Hiroshima University Registry. *Health Phys* 1996; 70: 735-740.
18. Roesch WC, Editor, US-Japan Joint Reassessment of Atomic bomb Radiation Dosimetry in Hiroshima and Nagasaki, Final Report Vols 1 and 2, Radiation Effects Research Foundation, Hiroshima, Japan, 1987.
19. Hayakawa N, Hoshi M, Matsuura M, et al. Comparison between DS86 and ABS93D. Studies on radiation effects for atomic bomb survivors. Proceedings of the Cooperative Committee of Atomic Bomb Casualties. Shigematsu group, *Radiation Effects Research Foundation*: 1994; pp. 119- 123.
20. Preston DL, Cullings H, Suyama A, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. *J Natl Cancer Inst*. 2008;100:428-36.
21. Preston DL, Shimizu Y, Pierce DA, et al. Studies of Mortality of Atomic Bomb Survivors. Report 13: Solid Cancer and Noncancer Disease Mortality: 1950–1997. *Radiat Res*. 2003; 160:381-407.
22. Spiegelman D, Hertzmark, E. Easy SAS calculations for risk or prevalence ratios and differences. *American Journal of Epidemiology*, 2005; 162: 199-200.
23. Petersen MR, Deddens JA. A comparison of two methods for estimating prevalence ratios. *BMC Med Res Methodol*, 2008;8:9.
24. Akaike H. A new look at the statistical model identification. *IEEE Trend*, 1974; AC-19:716–723
25. Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res*. 1990;123:275-284.
26. Iwanaga M, Yoshida Y, Tagawa M, et al. Waldenström's macroglobulinemia in a 10-year stable

IgG monoclonal gammopathy of undetermined significance. *Leuk Res*. 2008 May 1, [Epub ahead of print].

27. Nakashima M, Kondo H, Miura S, et al. Incidence of multiple primary cancers in Nagasaki atomic bomb survivors: association with radiation exposure. *Cancer Sci*. 2008;99:87-92.
28. Dainiak N. Hematologic consequences of exposure to ionizing radiation. *Exp Hematol* 2002; 30: 513-528
29. Morgan GJ, Davies FE, Linet M. Myeloma aetiology and epidemiology. *Biomed Pharmacother.* 2002;56:223-234.
30. Tolley HD, Marks S, Buchanan JA, Gilbert ES. A further update of the analysis of mortality of workers in a nuclear facility. *Radiat Res.* 1983;95:211-213.
31. Gilbert ES, Petersen GR, Buchanan JA. Mortality of workers at the Hanford site: 1945-1981. *Health Phys.* 1989;56:11-25.
32. Gilbert ES, Omohundro E, Buchanan JA, Holter NA. Mortality of workers at the Hanford site: 1945-1986. *Health Phys.* 1993;64:577-590.
33. Smith PG, Douglas AJ. Mortality of workers at the Sellafield plant of British Nuclear Fuels. *Br Med J (Clin Res Ed).* 1986;293:845-854.
34. Douglas AJ, Omar RZ, Smith PG. Cancer mortality and morbidity among workers at the Sellafield plant of British Nuclear Fuels. *Br J Cancer.* 1994;70:1232-1243.
35. Omar RZ, Barber JA, Smith PG. Cancer mortality and morbidity among plutonium workers at the Sellafield plant of British Nuclear Fuels. *Br J Cancer.* 1999;79:1288-1301.
36. Cardis E, Vrijheid M, Blettner M, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. *Radiat Res.* 2007;167:396-416.
37. Darby SC, Kendall GM, Fell TP, et al. A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes. *BMJ* 1988;296:332–338.
38. Darby SC, Kendall GM, Fell TP, et al. Further follow-up of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapon tests and experimental programmes. *BMJ* 1993;307:1530–1535.
39. Pearce N, Winkelmann R, Kennedy J, et al. Further follow-up of New Zealand participants in United Kingdom atmospheric nuclear weapons tests in the Pacific. *Cancer Causes Control.* 1997; 8: 139-145.

40. Watanabe KK, Kang HK, Dalager NA. Cancer mortality risk among military participants of a 1958 atmospheric nuclear weapons test. *Am J Public Health.* 1995;85:523-527.
41. Boice JD Jr, Morin MM, Glass AG, et al. Diagnostic X-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. *JAMA.* 1991;265:1290-1294.
42. Weiss HA, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. *Int J Cancer.* 1994;59:327-38.
43. Darby SC, Reeves G, Key T, Doll R, Stovall M. Mortality in a cohort of women given X-ray therapy for metropathia haemorrhagica. *Int J Cancer.* 1994;56:793-801.
44. Boice JD Jr, Engholm G, Kleinerman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res.* 1988;116:3-55.
45. Shimizu Y, Schull WJ, Kato H. Cancer risk among atomic bomb survivors. The RERF Life Span Study. Radiation Effects Research Foundation. *JAMA.* 1990;264(5):601-604.
46. Cesana C, Klersy C, Barbarano L, et al. Prognostic factors for malignant transformation in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *J Clin Oncol*. 2002;20:1625-1634.
47. Rajkumar SV, Kyle RA, Therneau TM, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood.* 2005;106:812-817.
48. Rosiñol L, Cibeira MT, Montoto S, et al. Monoclonal gammopathy of undetermined significance: predictors of malignant transformation and recognition of an evolving type characterized by a progressive increase in M protein size. *Mayo Clin Proc*. 2007;82:428-34.
49. Weiss NS, Rossing MA. Healthy screenee bias in epidemiologic studies of cancer incidence. *Epidemiology* 1996;7:319–322.
50. Lorimore SA, Coates PJ, Wright EG. Radiation-induced genomic instability and bystander effects: inter-related nontargeted effects of exposure to ionizing radiation. *Oncogene.* 2003;22:7058-69.
51. Kuehl WM, Bergsagel PL. Multiple myeloma: evolving genetic events and host interactions. *Nat Rev Cancer*. 2002;2:175-87.
52. Seidl S, Kaufmann H, Drach J. New insights into the pathophysiology of multiple myeloma. *Lancet Oncol*. 2003;4:557-64.
53. Lynch HT, Ferrara K, Barlogie B, et al. Familial myeloma. *N Engl J Med*. 2008 ;359:152-7.
54. Brown LM, Gridley G, Check D, Landgren O. Risk of multiple myeloma and monoclonal

gammopathy of undetermined significance among white and black male United States veterans with prior autoimmune, infectious, inflammatory, and allergic disorders. *Blood*. 2008;111:3388-94.

55. Wright EG, Coates PJ. Untargeted effects of ionizing radiation: implications for radiation pathology. *Mutat Res*. 2006;597:119-32.

Figure legends

Figure 1. Distribution of age at diagnosis. (A) By exposure dose categories. The horizontal bar indicates the median age at diagnosis: 68.1 yr in those exposed at 0-0.01Gy, 68.0 yr in those exposed at 0.01-0.1Gy, and 65.5 yr in those exposed at >0.1Gy. (B) By exposure dose categories and exposure age categories. The points indicate the mean values and the whiskers indicate the standard errors. (C) By age at exposure. Each red circle indicates each case exposed to dose of more than 0.1 Gy. Each diamond indicates each case exposed to dose 0.01 to 0.1 Gy. Each triangle indicated each case exposed to dose less than 0.01 Gy.

Figure 2. Prevalence ratio (PR) of MGUS. (A) By exposure dose in Gy adjusting for sex and age at exposure among each exposure category. PR at 1 Gy was 1.06 (95%CI, 0.97 to 1.16, *P*=.2) among those of age at exposure younger than 20 yr and was 1.01 (95%CI, 0.88 to 1.16, *P*=.9) among those of age at exposure older than 20 yr. (B) By age at exposure (yr) adjusting for sex and exposure dose among each exposure category. PR for 10-year increase of age was 2.24 (95% CI, 1.39-3.62; *P*=.001) among those of age at exposure younger than 20 yr and 1.77 (95% CI, 1.03-3.03; *P*=.04) among those older than 20 yr. The dashed line shows 95% CI in each dose.

Figure 3. Risk of progression of MGUS to myeloma or related disorders. (A) The overall cumulative probability of the progression was 6.9% (95%CI, 4.9% to 9.6%) at 10 years and 8.0% (95%CI, 5.4 to 11.9) at the latest follow-up. (B) By exposure distance, (C) By exposure age, (D) By exposure distance and exposure age, (E) By exposure age and age at diagnosis, (F) By the dichotomized serum M-protein level, (G) By exposure age and the serum M-protein level, and (H) By exposure distance and serum M-protein level. The *P*-values were calculated using the Log-rank test. MP indicates M-protein.

Table 1. Demographic characteristics of participants and non-participant among Nagasaki atomic bomb survivors during 1988-2004

	Whole population (n=74411)			Population with ABS93D (n=6837)		
	Participants No. (%)	Non-participants No. (%)	Rates of participation (%)¶	Participants No. (%)	Non-participants No. (%)	Rates of participation (%)¶
Total	**52525**	**21886**	**70.6**	**4758**	**2079**	**69.6**
Sex						
Male	20450	9021	69.4	1652	794	67.5
Female	32075	12865	71.4	3106	1285	70.7
Age at exposure (yr)						
< 10	16993	5522	75.5	1636	515	76.1
10 to < 20	20569	4967	80.5	1735	473	78.6
20 to <30	10554	3768	73.7	961	348	73.4
30 or older	4409	7629	36.6	426	743	36.4
Exposure status *						
Directly exposed (km), all	40814	16808	70.8	4674	2079	69.2
< 1.5	2496	1035	70.7	614	277	68.9
1.5 to < 3.0	10457	4771	68.7	4055	1797	69.3
3.0 to 10	27857	11000	71.7	5	5	50.0
Unkown distance	4	2	66.7	0	0	
Early entrants	9399	3713	71.7	5	0	100.0
Relief	714	940	43.2	0	0	
Exposed In-Utero	885	392	69.3	79	0	100.0
Unkown	713	33	95.6	0	0	
Exposed dose of ABS93D (Gy) †						
Available for directly exposed, all	4674	2079	69.2	4674	2079	69.2
0 to < 0.01	1673	767	68.6	1673	767	68.6
0.01 to < 0.1	1720	734	70.1	1720	734	70.1
$\geq$ 0.1	1281	578	68.9	1281	578	68.9
Available for early entrants ‡	5	0	100.0	5	0	100.0
Available for exposed In-utero ‡	79	0	100.0	79	0	100.0
Not available	47767	19807	70.7			

* “Directly exposed” indicates those who were directly exposed to atomic radiation within 10 km from the hypocenter. "Early entrants" indicates those who entered the city within approximately 2 km from the hypocenter within two weeks of the explosion. “ Relief” indicates those who were engaged in disposal of the dead or relief works for atomic bomb victims. “Exposed In-Utero” indicate children who were exposed prenatally at the time of the bombing.

† ABS93D indicates the Atomic Bomb Survivors 1993 Dose which is calculated for a limited number of Nagasaki atomic bomb survivors

‡ Some people exposed in-utero and early entrants have also ABS93D dose information, but the information was not presented in this study.

¶ Rates were calculated as the number of participants divided by the number of target population in each stratum.

Table 2. Clinical characteristics of MGUS patients

	MGUS among all participants (n=1082)	MGUS among participants with dose (n=93)
Sex, no. (%)		
Male	569 (53)	48 (52)
Female	513 (47)	45 (48)
Age at diagnosis, yr, no. (%)		
< 50	25 (2)	3 (3)
50-59	166 (15)	16 (17)
60-69	407 (38)	38 (41)
70-79	349 (32)	26 (28)
≥80	135 (13)	10 (11)
Median (range), yr	68.5 (45.0-100.9)	67.5 (48.2-100.9)
M-component heavy chain, no. (%)		
IgG	796 (74)	75 (81)
IgA	191 (18)	16 (17)
IgM	82 (7)	1 (1)
IgD	1 (0.1)	0
Biclonal	12 (1)	1 (1)
M-component light chain, no. (%)		
κ	609 (56)	52 (56)
λ	440 (41)	40 (43)
Biclonal	12 (1)	0
Not determined	21 (2)	1 (1)
Serum Monoclonal protein level, g/dL, no. (%)*		
< 1.5	496 (48)	31 (34)
1.5 to < 3.0	525 (50)	60 (65)
3.0 to < 3.5 †	22 (2)	1 (1)
Median (range), g/dL	1.5 (0.1-3.4)	1.6 (0.4-3.1)
Median Serum albmin level, g/dL, (range)	4.5 (3.0-5.8)	4.5 (3.8-5.8)
Median Serum calcium level, mg/dL, (range)	9.4 (8.1-12.1)	9.3 (8.4-10.9)
Median Serum creatinin level, mg/dL, (range)	1.0 (0.5-7.5)	1.0 (0.5-2.0)
Median Hemoglobin level, g/dL, (range)	13.5 (6.7-18.2)	13.5 (8.3-17.8)

* Data from 12 cases of biclonal gammopathy were not included and 27 cases were not available for M-protein level at the first-time diagnosis but were available for data at the next follow year.

† These cases were diagnosed with MGUS in the referral hospitals based on the "recurrent" examination of immunoglobulin and the plasma cell percentage in the bone marrow.

Table 3. Age at diagnosis of MGUS by exposure distance, exposure dose, and age at exposure

Overall population		Distance from the hypocenter (km)			Total
		< 1.5	1.5 - 3.0	> 3.0	
Age at exposure (yr)	0-9	57.0 (50.3-67.1)	56.4 (47.4-67.5)	57.5 (45.0-68.0)	57.2 (45.0-68.0)
	10-19	68.5 (56.0-77.5)	65.8 (56.4-75.7)	65.1 (54.8-77.8)	65.9 (54.8-77.9)
	20-29	74.6 (68.3-78.5)	74.2 (64.5-86.4)	74.2 (64.5-87.4)	73.6 (63.7-87.4)
	≥ 30	86.4 (79.5-88.4)	81.3 (74.9-100.9)	81.4 (73.3-93.7)	82.1 (73.3-100.9)
	All ages	69.7 (50.3-88.4)	67.5 (47.4-100.9)	67.5 (45.0-93.7)	68.5 (45.0-100.9)
Subpopulation with radiation dose		**Radiation dose of ABS93D (Gy)**			**Total**
		> 0.1	0.01 - 0.1	0 - 0.01	
Age at exposure (yr)	0-9	55.2 (49.7-67.1)	58.1 (48.2-64.0)	59.5 (49.3-67.5)	58.1 (48.2-67.5)
	10-19	64.5 (56.0-70.7)	65.2 (58.2-73.7)	67.7 (57.4-70.5)	65.5 (56.0-73.7)
	20-29	72.6 (71.1-77.1)	72.9 (67.7-79.5)	74.8 (67.4-86.4)	73.0 (67.4-86.4)
	≥ 30	83.0 (77.3-87.5)	86.1 (74.9-91.9)	87.2 (79.9-100.9)	86.4 (74.9-100.9)
	All ages	65.5 (49.7-87.5)	68.0 (48.2-91.9)	68.1 (49.3-100.9)	67.5 (48.2-100.9)

Data in each column indicates median (range) age at diagnosis in years.

ATB=at the time of the bombing; NIC=not in city at the time of the bombing.

Table 4. Comparison of M-protein level by sex, age at diagnosis, and exposure status*

	MP < 1.5 g/dL	MP ≥ 1.5g/dL	*P*-value†
Total	378 (48.4)	403 (51.6)	
Sex			
Male	195 (50.7)	190 (49.4)	.21
Female	183 (46.2)	110 (27.8)	
Age at exposure (yr)			
0-9	83 (51.2)	79 (48.8)	.004
10-19	183 (53.2)	161 (46.8)	
20-29	78 (42.9)	104 (57.1)	
≥ 30	34 (36.6)	59 (63.4)	
Age at diagnosis (yr)			
< 50	7 (35.0)	13 (65.0)	.93
50 - 59	68 (50.8)	66 (49.2)	
60 - 69	141 (47.8)	154 (52.2)	
70 - 79	125 (50.8)	121 (49.2)	
≥ 80	37 (43.0)	49 (57.0)	
Exposure distance (km)			
< 1.5	34 (52.3)	31 (47.7)	.25
1.5 - 3.0	79 (40.5)	116 (59.5)	
≥ 3.0	265 (50.9)	256 (49.1)	
Exposure dose (Gy)			
> 0.1	9 (34.6)	17 (65.4)	.92
0.01 - 0.1	10 (29.4)	24 (70.6)	
0 - 0.01	11 (35.5)	20 (64.5)	

*Data were used for only MGUS patients with heavy chain class of A, G, and M and available for imformation of exposure distance and exposure dose.

† P-values were calculated using Chi-square test or Fisher exact test.

MP=monoclonal protein concentration

Table 5. Prevalence of MGUS by sex, age at exposure, and distance from the hypocenter.

Exposure status		Sex	Male					Female					Total				
		Age at exposure (yr)	0-9	10-19	20-29	≥ 30	All ages	0-9	10-19	20-29	≥ 30	All ages	0-9	10-19	20-29	≥ 30	All ages
Directly exposed																	
Distance from the hypocenter (km)	< 1.5																
		No. participants	195	522	164	97	978	225	861	363	68	1517	420	1383	527	165	2495
		No. cases	7	22	4	3	36	2	21	5	2	30	9	43	9	5	66
		Prevalence (%)	3.6	4.2	2.4	3.1	3.7	0.9	2.4	1.4	2.9	2.0	2.1	3.1	1.7	3.0	2.7
	1.5 to < 3.0																
		No. participants	1452	1726	367	272	3817	1825	2411	1753	650	6639	3277	4137	2120	922	10456
		No. cases	25	46	14	12	97	21	40	33	10	104	46	86	47	22	201
		Prevalence (%)	1.7	2.7	3.8	4.4	2.5	1.2	1.7	1.9	1.5	1.6	1.4	2.1	2.2	2.4	1.9
	≥ 3.0																
		No. participants	4639	4207	782	575	10203	5603	6231	4240	1569	17643	10242	10438	5022	2144	27846
		No. cases	70	133	30	34	267	46	95	98	42	281	116	228	128	76	548
		Prevalence (%)	1.5	3.2	3.8	5.9	2.6	0.8	1.5	2.3	2.7	1.6	1.1	2.2	2.6	3.5	2.0
Others *																	
		No. participants	1419	2483	1043	497	5442	1633	2121	1835	676	6265	3052	4604	2878	1173	11707
		No. cases	16	81	38	34	169	10	33	37	18	98	26	114	75	52	267
		Prevalence (%)	1.1	3.3	3.6	6.8	3.1	0.6	1.6	2.0	2.7	1.6	0.9	2.5	2.6	4.4	2.3
Total																	
		No. participants	7705	8938	2356	1441	20440	9286	11624	8191	2963	32064	16991	20562	10547	4404	52504
		No. cases	118	282	86	83	569	79	189	173	72	512	197	471	259	155	1082
		Prevalence (%)	1.5	3.2	3.7	5.8	2.8	0.9	1.6	2.1	2.4	1.6	1.2	2.3	2.5	3.5	2.1

*Others included survivors with unkown exposure distance, those early entered in the city, those who were engaged in disposal of the dead or in relief works for atomic bomb victims, those exposed in utero, and those with unkown exposure status.

Table 6 Prevalence Ratios (PRs) for MGUS in relation to sex, age at exposure, and distance from the hypocenter in Participants with information of exposure distance

	All		Age at exposure < 20 yr		Age at exposure ≥ 20 yr	
	PR (95% CI)	***P*-value**	**PR (95% CI)**	***P*-value**	**PR (95% CI)**	***P*-value**
Univariate analysis						
Sex						
Male	1.7 (1.5-1.9)	<.0001	1.8 (1.5-2.1)	<.0001	2.0 (1.5 - 2.5)	<.0001
Female	referent		referent		referent	
Age at exposure						
per yr	1.4 (1.3 - 1.5)	<.0001	1.1 (1.1 - 1.1)	<.0001	1.0 (1.0 - 1.1)	0.0013
per 5yr	1.2 (1.1 - 1.2)	<.0001	1.4 (1.3 -1.5)	<.0001	1.2 (1.1 - 1.3)	0.001
Age at exposure group (yr)						
30 or older	2.6 (2.0-3.3)	<.0001			1.3 (1.0 - 1.7)	0.02
20 to <30	2.0 (1.6-2.4)	<.0001			referent	
10 to < 20	1.8 (1.5-2.2)	<.0001	1.8 (1.5-2.2)	<.0001		
< 10	referent		referent			
Exposure distance group (km)						
< 1.5	1.3 (1.0-1.7)	0.02	1.7 (1.3 - 2.3)	0.0002	0.7 (0.4 - 1.2)	0.2
1.5 to < 3.0	1.0 (0.8-1.1)	0.7	1.1 (0.9 - 1.3)	0.5	0.8 (0.6 - 1.0)	0.1
3.0 to 10.0	referent		referent			
Multivariate analysis *						
Male sex			1.9 (1.6 - 2.3)	<.0001	1.9 (1.5 - 2.4)	<.0001
Age at exposure per 5 yr			1.4 (1.3 - 1.5)	<.0001	1.1 (1.0 - 1.2)	0.03
Exposure distance group (km)						
< 1.5			1.4 (1.1 - 1.9)	0.02	0.6 (0.4 - 1.1)	0.1
1.5 to < 3.0			1.0 (0.8 - 1.2)	0.9	0.8 (0.6 - 1.0)	0.1
3.0 to 10.0			referent		referent	

PR = prevalence ratio; CI = confidence interval.

Table 7. Prevalence of MGUS by sex, age at exposure, and exposure dose by ABS93D

Sex	Male					Female					Total				
Age at exposure (yr)	0-9	10-19	20-29	≥ 30	All ages	0-9	10-19	20-29	≥ 30	All ages	0-9	10-19	20-29	≥ 30	All ages
ABS93D dose (Gy)															
0 to < 0.01															
No. participants	238	207	57	35	537	336	382	306	111	1135	574	589	363	146	1672
No. cases	3	7	3	0	13	3	3	5	3	14	6	10	8	3	27
Prevalence (%)	1.3	3.4	5.3	0	3.7	0.9	0.8	1.6	2.7	1.2	1.1	1.7	2.2	2.1	1.6
0.01 to < 0.1															
No. participants	288	245	34	40	607	336	357	292	127	1094	624	602	326	167	1719
No. cases	5	4	3	4	16	4	6	6	2	18	9	10	9	6	34
Prevalence (%)	1.7	1.6	8.8	10	2.7	1.2	1.7	2.1	1.6	1.6	1.4	1.7	2.8	3.6	2.0
≥ 0.1															
No. participants	164	225	51	29	469	195	315	219	82	811	359	540	270	111	1280
No. cases	3	14	0	2	19	1	7	3	2	13	4	21	3	4	32
Prevalence (%)	1.8	6.2	0	6.9	4.1	0.5	2.2	1.4	2.4	1.6	1.1	3.9	1.1	3.6	2.5
Total															
No. participants	690	677	142	104	1613	867	1054	817	320	3058	1557	1731	959	424	4671
No. cases	11	25	6	6	48	8	16	14	7	45	19	41	20	13	93
Prevalence (%)	1.6	3.7	4.2	5.8	3.0	0.9	1.5	1.7	2.2	1.6	1.2	2.4	2.1	3.1	2.0

Table 8. Prevalence Ratios (PRs) for MGUS in relation to sex, age at exposure, and radiation dose in participants with ABS93D dose

	Age at exposure < 20 yr		Age at exposure ≥ 20 yr	
	PR (95% CI)	***P*-value**	**PR (95% CI)**	***P*-value**
Univariate analysis				
Sex				
Male	2.11 (1.26 - 3.52)	0.0043	2.64 (1.31 -5.30)	0.0062
Female	referent		referent	
Age at exposure				
per 1 yr	1.08 (1.03 - 1.13)	0.002	1.07 (1.02 - 1.13)	0.01
per 5yr	1.44 (1.14 - 1.82)	0.002	1.40 (1.08 - 1.83)	0.01
ABS93D Dose				
per 0.1 Gy	1.02 (0.99- 1.06)	0.1	0.99 (0.63 - 1.57)	0.9
per Gy	1.25 (0.93- 1.71)	0.1	0.99 (0.63 - 1.57)	0.9
ABS93D Dose group (Gy)				
> 0.1	2.02 (1.09 - 3.76)	0.03	0.85 (0.33 - 2.17)	0.7
0.01 to < 0.1	1.13 (0.58- 2.18)	0.7	1.41 (0.65 - 3.04)	0.4
0 to < 0.01	referent		referent	
Multivariate analysis-1				
Male sex	2.30 (1.38 - 3.84)	0.002	2.30 (1.13 - 4.68)	0.02
Age at exposure per 1 yr	1.49 (1.17 -1.89)	0.001	1.06 (1.00 - 1.12)	0.04
ABS93D Dose per 1 Gy	1.24 (0.90 - 1.71)	0.2	0.96 (0.59 - 1.62)	0.9
Multivariate analysis-2				
Male sex	2.24 (1.34 - 3.74)	0.002	2.34 (1.15 - 4.77)	0.02
Age at exposure per 1 yr	1.08 (1.03 -1.13)	0.003	1.06 (1.00 - 1.12)	0.04
ABS93D Dose > 0.1 Gy (vs. < 0.1 Gy)	1.66 (0.99 -2.77)	0.05	0.69 (0.30 - 1.58)	0.4

PR = prevalence ratio; CI = confidence interval.

Table 9. Frequency of malignant progression among MGUS with information of exposure distance.

	No. MGUS with Distance Information	No. Progression (%)	P-value*
Total	815	36 (4.4)	
Sex			
Male	400	14 (3.5)	**.21**
Female	415	22 (5.3)	
Age at exposure, yr			
< 10	171	6 (3.5)	**.43**
10 to < 20	357	14 (3.9)	
20 to <30	184	12 (6.5)	
30 or older	103	4 (3.9)	
Exposure distance, km			
< 1.5	66	5 (7.6)	**.16**
1.5 - 3.0	201	10 (5.0)	
3.0 - 10	548	21 (3.8)	
Age at diagnosis, yr			
< 59	165	7 (4.2)	**.11**
60-69	304	21 (6.9)	
≥70	346	8 (2.3)	
M-component heavy chain			
IgG	148	29 (4.8)	**.77**
IgA	599	5 (3.4)	
IgM	61	2 (3.3)	
Biclonal	7	0	
Serum M-protein level, g/dL,			
< 1.5	385	5 (1.3)	**<.0.0001**
≥ 1.5 to less than 3.0	387	24 (6.2)	
≥ 3.0 to less than 3.5 †	16	4 (25.0)	

* P-values were calculated using Chi-square test or Fisher exact test for sex and M-compornent and using Mantel-Haenszel trend test for age at exposure, exposure distance, age at diagnosis, and aerum M-protein level.

Figure 1

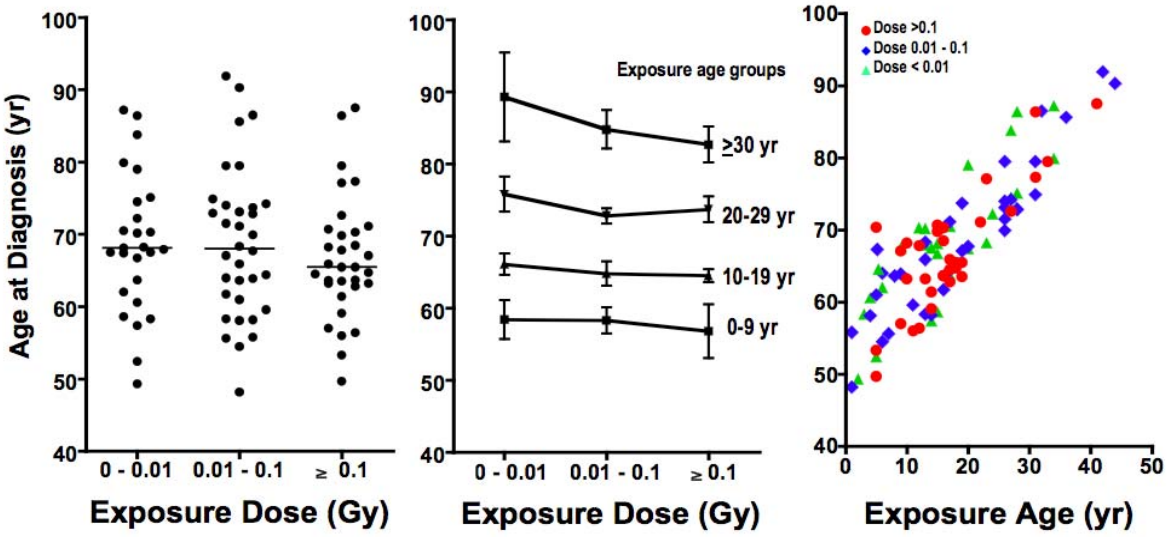

Age at Diagnosis (yr)
100
90
80
70
60
50
40
0 - 0.01
0.01 - 0.1
≥ 0.1
Exposure Dose (Gy)
Exposure age groups
≥30 yr
20-29 yr
10-19 yr
0-9 yr
Dose >0.1
Dose 0.01 - 0.1
Dose < 0.01
0
10
20
30
40
50
Exposure Age (yr)

Figure 2

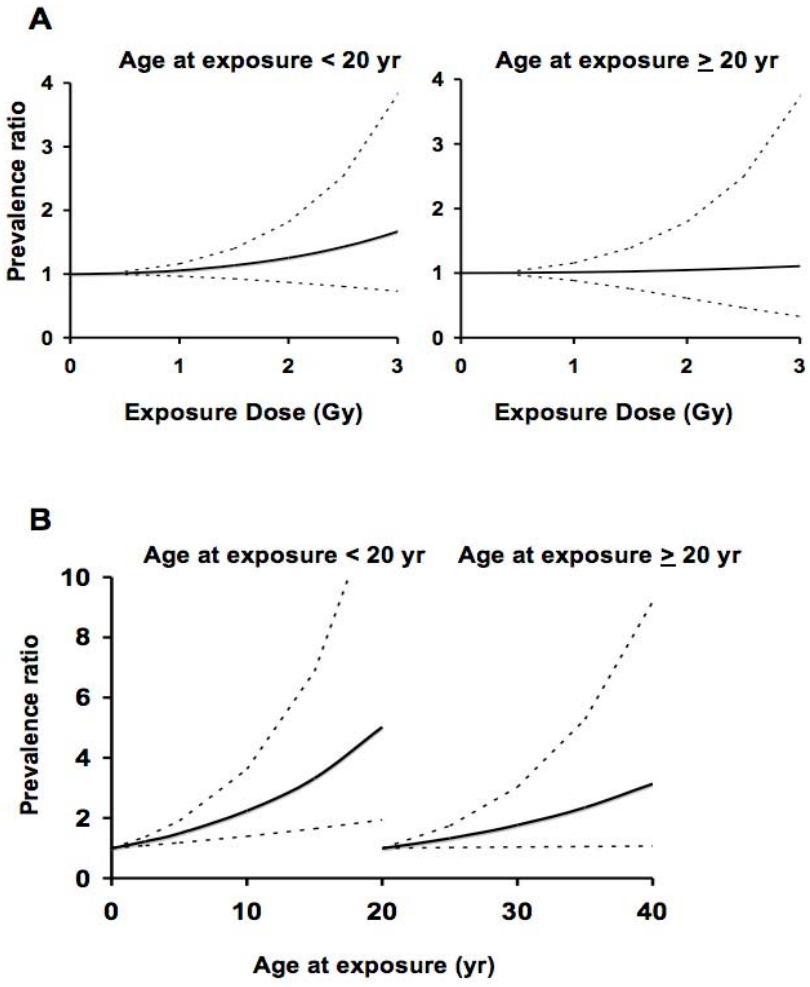
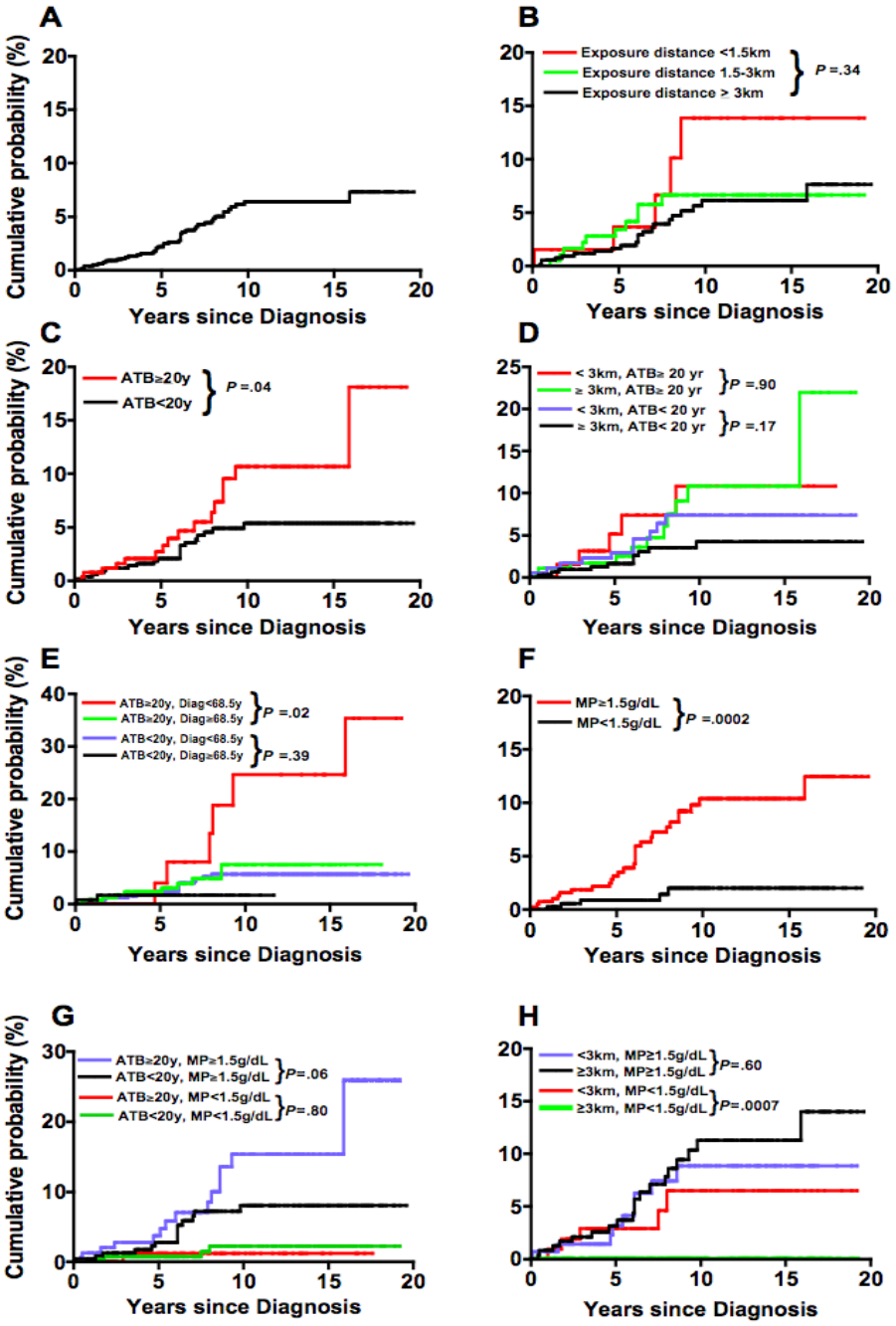

A
Age at exposure < 20 yr
Age at exposure ≥ 20 yr
Prevalence ratio
0
1
2
3
4
Exposure Dose (Gy)
B
Age at exposure < 20 yr
Age at exposure ≥ 20 yr
Prevalence ratio
0
2
4
6
8
10
0
10
20
30
40
Age at exposure (yr)

Figure 3


A
Cumulative probability (%)
Years since Diagnosis
B
Exposure distance <1.5km
Exposure distance 1.5-3km
Exposure distance > 3km
P =.34
Years since Diagnosis
C
ATB≥20y
ATB<20y
P =.04
Years since Diagnosis
D
< 3km, ATB≥ 20 yr
≥ 3km, ATB≥ 20 yr
P =.90
< 3km, ATB< 20 yr
≥ 3km, ATB< 20 yr
P =.17
Years since Diagnosis
E
ATB≥20y, Diag<68.5y
ATB≥20y, Diag≥68.5y
P =.02
ATB<20y, Diag<68.5y
ATB<20y, Diag≥68.5y
P =.39
Years since Diagnosis
F
MP≥1.5g/dL
MP<1.5g/dL
P =.0002
Years since Diagnosis
G
ATB≥20y, MP≥1.5g/dL
ATB<20y, MP≥1.5g/dL
P=.06
ATB≥20y, MP<1.5g/dL
ATB<20y, MP<1.5g/dL
P=.80
Years since Diagnosis
H
<3km, MP≥1.5g/dL
≥3km, MP≥1.5g/dL
P=.60
<3km, MP<1.5g/dL
≥3km, MP<1.5g/dL
P=.0007
Years since Diagnosis