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# Autoantibodies and Immunoglobulins among Atomic Bomb Survivors

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**The purpose of this study was to determine if exposure to atomic bomb radiation affects immune responsiveness, such as the occurrence of autoantibodies and levels of immunoglobulins. Rheumatoid factor, antinuclear antibody, antithyroglobulin antibody, anti-thyroid-microsomal antibody and immunoglobulin levels (IgG, IgM, IgA and IgE) were measured among 2,061 individuals exposed to atomic bomb radiation in Hiroshima and Nagasaki whose estimated doses ranged from 0 to 5.6 Gy. The prevalence and titers of rheumatoid factor were found to be increased in the individuals exposed to higher radiation doses. The IgA level in females and the IgM level in both sexes increased as radiation dose increased, although the effects of radiation exposure were not large. No effect of radiation was found on the prevalence of antinuclear antibody, antithyroglobulin antibody and anti-thyroid-microsomal antibody or on the levels of IgG and IgE.**

## INTRODUCTION

The immune system is a prime target for radiation injury. It has been demonstrated that transitory disorders occur in the number of immunologically competent cells as acute effects of radiation exposure. Experimental studies (*1*) using mice have shown dose-dependent decreases in antibody production to sheep erythrocytes and in the induction of killer T cells immediately after whole-body irradiation, but these returned to control levels after more than 3 months. However, there have been reports (*2–5*) on the significant effects of exposure to atomic bomb radiation on immunological function more than 35 years after the exposure. More recently, certain genetic changes (*6, 7*) were found to be long-lasting in the cells of the immune system of atomic bomb survivors.

There has been no systematic study to investigate the prevalence of autoantibodies among atomic bomb survivors. In this study, the levels of autoantibodies [rheumatoid factor (RF), antinuclear antibody (ANA), antithyroglobulin antibody and anti-thyroid-microsomal antibody] and immunoglobulins (IgG, IgM, IgA and IgE) were measured among a sample of 2,061 Adult Health Study (AHS) participants in Hiroshima and Nagasaki, consisting of atomic bomb survivors, to determine the effect of radiation on these measurements.

## MATERIALS AND METHODS

### *Selection of Study Subjects*

The study subjects were selected as described below from approximately 6,000 AHS participants in Hiroshima and Nagasaki, consisting of atomic bomb survivors. Their estimated radiation doses ranged from essentially 0 Gy for individuals exposed at locations far from the hypocenter of the atomic bomb to a maximum of 5.6 Gy for individuals close to the hypocenter. To obtain an appropriate balance with respect to age, sex and radiation dose, individuals were selected randomly within these three categories. When there was a shortage of subjects in a category group, for example, persons who were exposed at younger ages or in Nagasaki, all subjects were selected; when there were too many subjects in a category group, about 50 subjects were selected at random.

A total of 2,069 persons were examined from December 1987 to November 1989. Eight individuals who were under treatment for active autoimmune diseases (one case of systemic lupus erythematosus, two of progressive systemic sclerosis and five of rheumatoid arthritis) were excluded from all analyses.

### *Dosimetry*

Dose estimates were based on the Dosimetry System 1986 (DS86) (*8*). The estimates of radiation dose in air at the survivor's location, corrected for shielding by buildings or terrain, were used in this report, because radiation dose in air was thought to reflect organ doses of the thymus and lymphoid organs as well as the bone marrow, in which cells of the immune system and their function are modulated.

### *Methods*

For each participant, 4.5 ml of peripheral blood was drawn and serum was separated to measure levels of ANA, antithyroglobulin antibody, anti-thyroid-microsomal antibody, RF and immunoglobulins (IgG, IgA, IgM and IgE).

The ANA, antithyroglobulin antibody, anti-thyroid-microsomal antibody and RF were measured using kits available commercially. An indirect agglutination test was used to detect antithyroglobulin antibody and anti-thyroid-microsomal antibody. A kit for detecting these two autoan-



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**TABLE I**
**Composition of the Study Population**

| City, sex | Age ATE[a] (years) | Radiation dose (Gy) 0 | 0.01–0.99 | ≥1 | Total |
|---|---|---|---|---|---|
| Total | | 777 | 683 | 601 | 2061 |
| Hiroshima | | | | | |
| Total | | 409 | 396 | 374 | 1179 |
| Males | 40–49 | 38 | 35 | 40 | 113 |
| | 50–59 | 47 | 41 | 42 | 130 |
| | 60–69 | 63 | 63 | 54 | 180 |
| | ≥70 | 47 | 40 | 40 | 127 |
| Females | 40–49 | 34 | 37 | 37 | 108 |
| | 50–59 | 53 | 54 | 53 | 160 |
| | 60–69 | 51 | 48 | 46 | 145 |
| | ≥70 | 76 | 78 | 62 | 216 |
| Nagasaki | | | | | |
| Total | | 368 | 287 | 227 | 882 |
| Males | 40–49 | 34 | 24 | 21 | 79 |
| | 50–59 | 47 | 35 | 29 | 111 |
| | 60–69 | 40 | 23 | 16 | 79 |
| | ≥70 | 52 | 9 | 6 | 67 |
| Females | 40–49 | 35 | 29 | 22 | 86 |
| | 50–59 | 50 | 54 | 39 | 143 |
| | 60–69 | 58 | 57 | 58 | 173 |
| | ≥70 | 52 | 56 | 36 | 144 |

[a]ATE = at the time of examination.

tibodies (Fuji-Rebio Inc., Tokyo, Japan) was prepared using particle carriers made of article gelatin sensitized with thyroglobulin or thyroid-microsomal antigen, which were extracted and purified from human thyroid tissue. The RF was measured by a direct agglutination test using particle carriers made out of article gelatin sensitized with denatured rabbit IgG (Fuji-Rebio Inc.). Individuals were judged to have positive responses when agglutination was found in a serum diluted 40-fold for RF and a serum diluted 100-fold for anti-thyroid-microsomal antibody and antithyroglobulin antibody. Antinuclear antibody was determined by indirect immunofluorescence using HEp-2 cells derived from human laryngeal cancer cells (obtained from MBL, Nagoya, Japan). Individuals were diagnosed as having ANA when immunofluorescence-positive cells were found in a serum diluted 20-fold.

For individuals having a positive response to any one of these four autoantibodies, the magnitude of response was measured using either the twofold (ANA, RF) or fourfold (anti-thyroid-microsomal antibody, antithyroglobulin antibody) dilution methods. The maximum dilution in which a positive reaction was found was judged as the titer of each antibody.

The IgG, IgM and IgA were measured quantitatively with an autoanalyzer (Hitachi 7050, Tokyo, Japan). An enzyme immunoassay reagent kit (Fuji-Rebio Inc.) was used for measurement of IgE. This kit was designed for quantification of IgE using the one-step-sandwich enzyme immunoassay method.

*Statistical Methods*

*1. Positive Response Rates*

Stepwise logistic regressions (*9*) were used to relate positive reaction rates to the four autoantibodies to city, sex, age at examination, radiation dose and all possible interactions. A forward-selection procedure was used with a significance level of 0.10 for entry into and 0.05 for exit from the model. Radiation dose and age at examination were treated as continuous variables in this analysis.

The number of subjects for autoantibody analyses is shown in Table I.

*2. Autoantibody Titers*

Analyses of autoantibody titers were performed only on the items for which a significant radiation effect was found. The autoantibody titers resulted in a ratio scale but categorical data. Therefore, the methods of Grizzle *et al.* (*10*) for categorical data analyses were used to estimate mean titers.

In the context considered here, these methods can be described as follows. Let $y$ denote the vector of potential antibody titer responses and $\pi_i$ the vector of probabilities of observing these responses in the $i$th city-by-sex-by-age-by-radiation dose population. Then the mean titer for the $i$th population is $M_i = y\pi_i$. We assume these means result from linear combinations of effects of city, sex, age and radiation dose. That is, that $M_i = X_i\beta$, where $X_i$ is a row vector of these covariate values defining the $i$th population and $\beta$ is a parameter vector of the effects to be estimated. Now, let $P_i$ be the vector of sample proportion estimates of $\pi_i$. Then

$$y'P_i = C_i\beta + e_i,$$

where $\mathrm{Var}(e_i)$ is $y'V_iy$ and $V_i$ is the variance–covariance matrix of multinomial proportions, $P_i$. The method of Grizzle *et al.* for estimating $\beta$ amounts to a weighted least-squares fit of this model using the sample estimate $V_i$ in place of $V_i$ in the calculation of weights.

For computational convenience, dose and age were divided into two groups, radiation dose <0.01 Gy or ≥0.01 Gy and age <62 or age ≥62. The mean radiation dose levels in the low- and high-exposure groups were 0.00 and 1.178 Gy, respectively. The mean ages in the young and old age groups were 53 and 73 years. Initially, models including all main effects and interactions between city, sex, exposure category and age category were fitted. Then effects were dropped from the model in a stepwise fashion using a 0.05 level of significance for removal. The strategy described above was then applied to the resulting models.

*3. Immunoglobulins*

Stepwise regression analyses with the simplifying modifications described above were performed to obtain prediction equations for the logarithm of immunoglobulin level. A forward-selection routine with a 0.10 level of significance for entry and 0.05 for exit, the model was used for model-building (*11*). Radiation dose and age at the time of examination were treated as continuous variables in these analyses.

Analysis of immunoglobulins was undertaken on 1,961 subjects, after excluding 100 individuals who had disorders that affected their immunoglobulin levels, such as chronic liver diseases, benign monoclonal gammopathy and multiple myeloma.

*Computations*

All computations except those required to analyze positive reaction rates were carried out using the Statistical Analysis System (SAS) package of programs for personal computers (*12*). The stepwise logistic regression analyses for positive reaction rates were performed using the mainframe version of the BMDP Statistical Software package (*13*).

## RESULTS

A summary of the results from the model-building procedure described above are presented in Table II. The final equations derived for each variable are given in Appendices 1 and 2.

### *Autoantibodies*

Exposure to atomic bomb radiation had a positive effect on the prevalence and titers of RF ($P = 0.008$). The preva-

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**TABLE II**
**Summary of Results: Direction of Relationships and *P* Value**

| Outcome measures | City | Sex | Age | Radiation dose | Sex × age | Sex × radiation dose | Percentage variance[a] |
|---|---|---|---|---|---|---|---|
| Positive response rates | | | | | | | |
| RF[b] | H > N<br>0.003 | | | ↑<br>0.008 | | | NA |
| ANA | | M < F<br><0.001 | NS<br>0.823 | | M = ↑, F = NS<br>0.001 | | NA |
| Micro. | | M < F<br><0.001 | | | | | NA |
| Thyro. | | M < F<br><0.001 | ↑<br>0.024 | | | | NA |
| Antibody titers | | | | | | | |
| RF | H > N<br>0.005 | | | ↑<br>0.011 | | | NA |
| Immunoglobulins | | | | | | | |
| IgA | H > N<br>0.001 | M > F<br><0.001 | ↑<br><0.001 | ↑<br><0.001 | | M = NS, F = ↑<br>0.002 | 3.7 |
| IgG | H > N<br>0.002 | M < F<br><0.001 | NS<br>0.195 | | M = ↑, F = NS<br><0.001 | | 4.5 |
| IgM | H > N<br>0.002 | M < F<br><0.001 | ↓<br><0.001 | ↑<br><0.001 | M = NS, F = ↓<br><0.001 | | 8.9 |
| IgE | H > N<br>0.048 | M > F<br><0.001 | ↓<br>0.042 | | | | 6.1 |

*Note:* No significant interaction between age and radiation dose was found.
[a]The percentage of variance explained by the final model.
[b]RF = rheumatoid factor; ANA = antinuclear antibody; Micro. = anti-thyroid-microsomal antibody; Thyro. = antithyroglobulin antibody; H = Hiroshima; N = Nagasaki; M = male; F = female; ↑ = increase; ↓ = decrease; NS = not significant; and NA = not applicable.

lence rate of RF by city and radiation dose is shown in Fig. 1. The effect of radiation on the prevalence of RF still remained after excluding 100 subjects who were diagnosed as having liver disease at the medical examination. Radiation exposure had no significant effect on the prevalence of ANA, antithyroglobulin antibody or anti-thyroid-microsomal antibody.

Prevalence rates by age group are shown in Table III. Prevalence rates of antithyroglobulin antibody and ANA in males increased significantly with age ($P = 0.024$ and $P = 0.001$, respectively), whereas no such significant tendency was observed for RF, anti-thyroid-microsomal antibody and ANA in females. We did not find a significant nonlinear relationship between age and logit of prevalence of autoantibodies. There was no significant interaction between age and radiation dose for each autoantibody.

Concerning the effect of sex, the prevalences of ANA, anti-thyroid-microsomal antibody and antithyroglobulin antibody were higher in females than in males ($P < 0.001$). No sex difference was found for the prevalence of RF. Except for RF, no city difference was observed in autoantibody prevalence.

*Immunoglobulins*

Levels of IgA in females and IgM in both sexes increased with increasing radiation dose ($P < 0.001$). In Fig. 2, the levels of IgA and IgM at the mean age of population (age = 62) were estimated from the model. There was still a significant effect of radiation on the levels of IgA in females and IgM after excluding 100 subjects with liver disease and 48 subjects with benign monoclonal gammopathy or multiple myeloma. Levels of IgG and IgE were not affected by radiation exposure.

The levels of IgA increased with increasing age in both sexes ($P < 0.001$); however, this age effect was not accelerated by radiation exposure. The level of IgG in males increased with increasing age ($P < 0.001$), while the levels of IgM in females and IgE in both sexes decreased with age.

Mean levels of IgA and IgE were higher in males than in females ($P < 0.001$), and mean levels of IgG and IgM were lower in males than in females ($P < 0.001$). We found that all immunoglobulin levels were higher in Hiroshima than in Nagasaki. However, these effects of sex, city, age and radiation dose were not great, and less than 10% of the variance was explained by these models.

## DISCUSSION

Our study has shown that the prevalence and titers of RF increased with increasing exposure to atomic bomb radiation,

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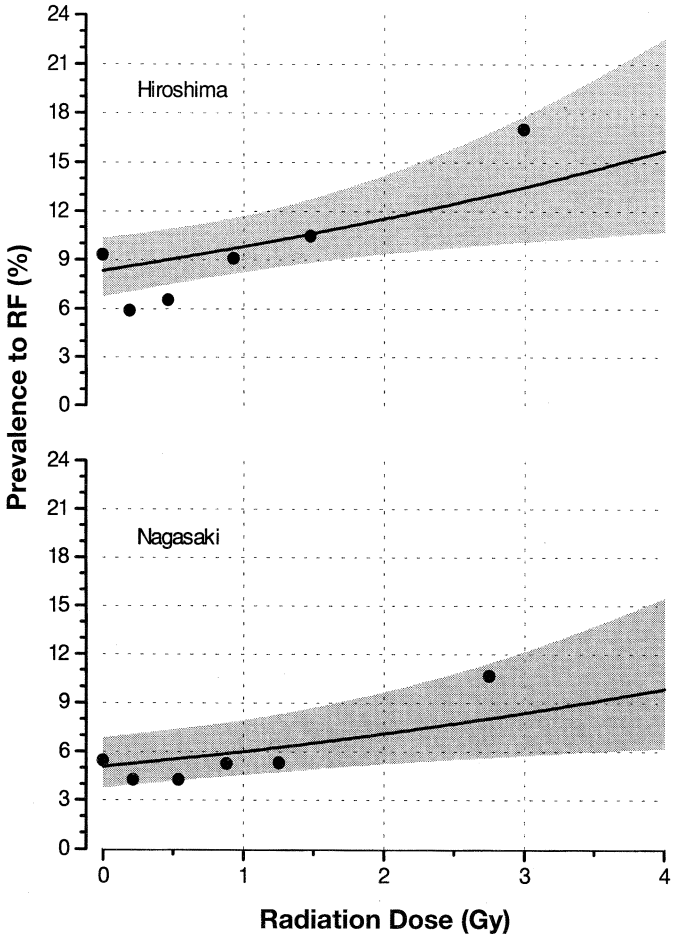


FIG. 1. Prevalence of rheumatoid factor by city and radiation dose. Each line and shaded region give the estimated prevalence and its 95% confidence interval as predicted by the logistic regression model in Appendix 1. The points are the average prevalence observed in six dose groups, a control group and five exposed groups formed such that they have equal sample sizes.

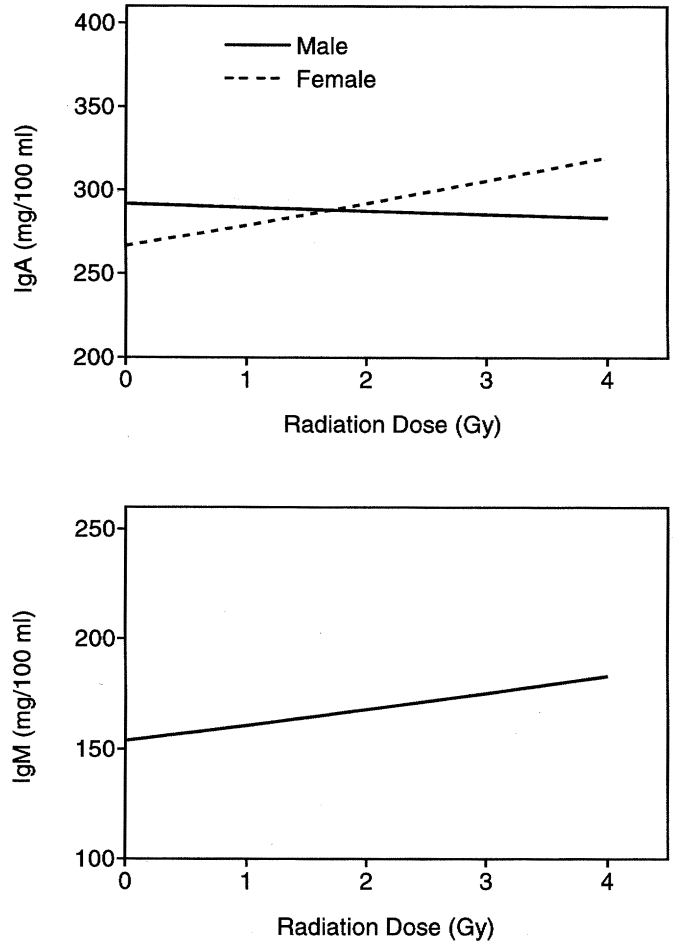


FIG. 2. Levels of IgA and IgM by radiation dose at age 62. The lines are the levels predicted by the models in Appendix 2.

**TABLE III**
**Prevalence Rates of Autoantibodies Categorized by Age Group**

| | | Age (years) | | | |
|---|---|---|---|---|---|
| Autoantibody | Sex | 40–49 | 50–59 | 60–69 | ≥70 |
| RF[a] (%) | Males | 6.8 | 8.7 | 11.6 | 7.2 |
| | Females | 6.7 | 8.9 | 6.0 | 7.5 |
| ANA (%) | Males | 2.1 | 3.3 | 3.9 | 9.3 |
| | Females | 9.3 | 16.8 | 11.3 | 12.8 |
| Micro. (%) | Males | 2.1 | 2.5 | 4.2 | 5.2 |
| | Females | 5.7 | 7.3 | 8.8 | 8.1 |
| Thyro. (%) | Males | 2.6 | 9.1 | 5.8 | 7.7 |
| | Females | 8.2 | 13.5 | 14.5 | 10.8 |

[a]RF = rheumatoid factor, ANA = antinuclear antibody, Micro. = anti-thyroid-microsomal antibody, Thyro. = antithyroglobulin antibody.

whereas radiation exposure had no significant effect on the prevalence of ANA, anti-thyroid-microsomal antibodies and antithyroglobulin antibodies. The IgA level in females and IgM levels in both sexes increased with radiation dose. However, the actual radiation effects detected are very minor in comparison to the overall variability within the population.

Lymphocyte subpopulations and immunological function have been studied previously among the atomic bomb survivors. Akiyama *et al.* reported that the responsiveness of T lymphocytes to phytohemagglutinin (*2*) and to alloantigenes (*4*) in heavily exposed persons, especially those of older ages, was moderately depressed, and that the reactivation of Epstein–Barr virus in the latent stage occurs more frequently in the survivors (*5*). The other report has also shown the effects of radiation on the number of $CD5^+$ mature T lymphocytes in peripheral blood (*3*). However, radiation exposure did not significantly affect circulating immune complex levels (*14*), which increase in autoimmune diseases. With regard to the prevalence or incidence of autoimmune disease among atomic bomb survivors, radiation exposure did not

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significantly affect the prevalence rates of rheumatoid arthritis (*15, 16*) and Hashimoto's disease (*17*) or the incidence rates of systemic lupus erythematosus and progressive systemic sclerosis.[1] Irradiation is one of the most effective ways to cause immunosuppression. It was reported that sublethal whole-body irradiation could result in prolonged survival in mice which have potential autoimmune diseases (*18*). Exposure to atomic bomb radiation may suppress or delay the development of autoimmunity, preventing the increase in autoimmune diseases.

The formation of RF is the result of an immune reaction by the host to one or more specific antigenic determinants present in his or her denatured immunoglobulins. Rheumatoid factor is one of the diagnostic features of rheumatoid arthritis. However, RF is also found in patients with chronic liver diseases and other kinds of arthritis. It is possible that RF represents antibodies to antigen–antibody complexes formed during the course of the disease. In this study, of the four autoantibodies, only RF seemed to be affected by radiation exposure. This may indicate that radiation exposure may affect general immunoglobulin production but not the production of specific ones. A recent study showed a significant increase in the proportion of B lymphocytes in peripheral blood of heavily exposed survivors (Akiyama *et al.*, manuscript in preparation). The increased tendency was also observed in a B-lymphocyte subset, $CD5^+$ B lymphocytes, which produce polyreactive IgM to various antigens (*19*). Thus atomic bomb radiation might affect the development of such B lymphocytes, leading to hyperproduction of RF and IgM in heavily exposed survivors.

The immunoglobulins are thought to represent the sum of all antibodies in response to various antigens. If the prevalence of infections increased among the atomic bomb survivors, then the levels of immunoglobulins may have increased with radiation dose. A few reports have suggested that the prevalence of chronic inflammations increased with exposure to atomic bomb radiation (*20, 21*). In our study, the serum level of IgA but not IgG in female survivors showed an increasing trend with radiation dose, indicating that local infections in female-specific organs may be more prevalent in the survivors exposed to higher doses.

There have been reports that low doses of ionizing radiation were associated with enhanced immune function in mice (*22*). However, little effect of low doses on the immune functions was detected in the study of atomic bomb survivors (*3, 14, 23*). This study also suggested no hormetic effect of radiation specific to the low-dose range.

[1]S. Fujiwara, H. Sasaki, S. Akiba, K. Kodama, M. Akahoshi, and M. Akiyama, Autoimmunity and autoimmune disease in atomic bomb survivors. FY-1989 Report of Atomic Bomb Disease Research Teams; Hiroshima and Nagasaki. 1990. [in Japanese]

In the population-based study of adults ranging in age from about 20 to about 90 years, Couchman *et al.* (*24*) reported that the prevalence of RF, anti-thyroid-microsomal antibody and antithyroglobulin antibody in females rose steadily with age. Other reports have indicated that the prevalence of autoantibodies increased with age (*25–27*). The reason why we did not find age effects on RF, ANA in females and antithyroid-microsomal antibody may be the different age distribution of our population, which was restricted to relatively older people.

Most reports (*28, 29*) have shown that serum IgG and IgA increased with age whereas serum IgM decreased with age, which almost agrees with our results.

In 1970, measurements of IgA, IgG and IgM were undertaken among 2,043 AHS subjects (*32*). No significant effects of radiation were observed in that study. The analyses performed, however, used categorization of immunoglobulins and did not adjust for age effects. Such categorization of response variables results in a loss of statistical power. In our study, the levels of IgA in females and IgM in both sexes increased with increasing dose. The magnitude of these effects, however, was small relative to the variation in these data ($R^2 < 0.10$). The effect of age at examination on IgG, IgM and IgA reported here is consistent with that in the previous study.

The IgE is closely related to allergic reaction, and the measurement of IgE is useful for the diagnosis and evaluation of therapeutic effects in such conditions as atopic diseases and parasitic infections. It has been reported that the serum IgE concentration tended to be higher in males than in females and to decrease with advancing age (*30, 31*). We observed the same effect in our data.

In this study, all samples except that for IgE were measured separately in Hiroshima and Nagasaki. The fact that the assessments of positive response of autoantibodies were based on the judgments of technicians also could have introduced a source of variation. The handling of blood samples, assay techniques and analytical machines was arranged so as to maintain consistency of the results over time and in both cities. The technicians checked each other's judgments to lessen possible inter- or intraobserver variability. Assuming the dosimetry is correct, especially the estimate of the neutron component at Hiroshima, the city differences in the prevalence of RF and immunoglobulin levels are not likely due to a true city difference but are more likely due to a difference in the judgment of the observers. The technicians were not informed of the subject's atomic bomb radiation dose, sex and age. This should have precluded the introduction of any biases in the analyses of the relationship between radiation exposure and the prevalence of autoantibodies and levels of immunoglobulins among the subjects from each city.

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## APPENDIX 1

### Statistical Models for Autoantibody Measurements

1. Prevalence of autoantibodies
   *C*: 1 if the city of exposure was Hiroshima, 0 if Nagasaki;
   *A*: age at the time of examination (ATE) in 1987–1988;
   *S*: 1 if male, 0 if female; and
   *D*: radiation dose (Gy).

The values within parentheses are standard deviations.

Rheumatoid factor: $\log(P/1-P) = -2.93 + 0.533C + 0.18D.$
(0.16) (0.18) (0.07)

Antinuclear antibody:
$\log(P/1-P) = -1.937 - 4.717S + 0.0017A + 0.0552SA.$
(0.482) (1.09) (0.007) (0.016)

Anti-thyroid-microsomal antibody:
$\log(P/1-P) = -1.954 - 0.700S.$
(0.09) (0.16)

Antithyroglobulin antibody:
$\log(P/1-P) = -3.631 - 0.772S + 0.0180A.$
(0.54) (0.22) (0.008)

2. Titer of rheumatoid factor
   *C*: 1 if the city of exposure was Hiroshima, 0 if Nagasaki;
   *S*: 1 if male, 0 if female;
   *A*: 1 if age ATE in 1987–1989 ≥ 62 years, 0 if age < 62 years; and
   *D*: 1 if radiation dose (Gy) ≥ 0.01, 0 if 0 ≤ radiation dose < 0.01.

The values within parentheses are estimated standard errors.

Log of RF titer: $y = 4.238 + 0.426C + 0.384D.$
(0.139) (0.113) (0.113)

## APPENDIX 2

### Statistical Models for Immunoglobulin Measurements

*C*: 1 if the city of exposure was Hiroshima, 0 if Nagasaki;
*A*: age at the time of examination (ATE) in 1987–1989;
*S*: 1 if male, 0 if female; and
*D*: radiation dose (Gy).

The values within parentheses are standard deviations.

IgA: log(IgA) =
$5.265 + 0.058C + 0.091S + 0.005A + 0.046D - 0.053SD,$
(0.051) (0.018) (0.022) (0.001) (0.012) (0.017)
where $R^2 = 0.036$;

IgG: log(IgG) =
$7.293 + 0.032C - 0.303S + 0.001A + 0.004SA,$
(0.037) (0.010) (0.056) (0.0006) (0.001)
where $R^2 = 0.045$;

IgM: log(IgM) =
$5.748 + 0.070C - 0.724S - 0.010A + 0.044D + 0.008SA,$
(0.078) (0.022) (0.119) (0.0010) (0.010) (0.002)
where $R^2 = 0.089$; and

IgE: log(IgE) =
$4.297 + 0.127C + 0.673S - 0.006A,$
(0.175) (0.063) (0.063) (0.003)
where $R^2 = 0.061$.

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