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業績報告書シリーズ

原爆被爆者の自己抗体および免疫グロブリン§

Autoantibodies and Immunoglobulins among Atomic-bomb Survivors

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要 約

この研究の目的は，原爆放射線被曝が，自己抗体出現や免疫グロブリン値のような免疫反応性に影響するかどうかを調べることであった。リウマチ因子，抗核抗体，抗サイログロブリン抗体，抗甲状腺マイクロゾーマル抗体，および免疫グロブリン値（IgG，IgM，IgA，およびIgE）を，1987年12月から1989年11月までの広島，長崎の成人健康調査受診者2,061人について測定した。

リウマチ因子の陽性率および値は，放射線量が増加するにしたがって統計的に有意に高くなった。抗核抗体，抗サイログロブリン抗体，抗甲状腺マイクロゾーマル抗体の陽性率には，放射線の影響は認められなかった。

女性のIgA値と男女のIgM値は，放射線線量の増加に従って高くなり，統計的に有意な関係が見られた。しかし，これらの放射線の影響は大きくなく，その影響の程度は各々の測定値の全体の変動の10％以下であった。IgG値とIgE値は，放射線の影響を受けていなかった。

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Summary

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 2061 Adult Health Study participants in Hiroshima and Nagasaki from December 1987 to November 1989.

The prevalence and titers of rheumatoid factor increased in a statistically significant manner with increasing radiation dose. No radiation effect was found on the prevalence of antinuclear antibody, antithyroglobulin antibody, and anti-thyroid-microsomal antibody.

A statistically significant relationship was also found between radiation exposure and the IgA level in females and the IgM levels in both sexes—both levels increased as radiation dose increased. However, the effects of radiation exposure were not large and accounted for less than 10% of the total variation in each measurement. Levels of IgG and IgE were not affected by radiation exposure.

Introduction

The immune system is a prime target for radiation injury. It has been demonstrated that transitory disorders occur in the immunological functions as acute effects of radiation exposure. More recently, certain genetic changes[1,2] were

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found to persist in the immunological cells of atomic-bomb (A-bomb) survivors. To our knowledge, there has been only one report[3] on the effects of A-bomb radiation exposure on immunologic function. This report showed that phytohemagglutinin (PHA) responsiveness decreased with age in both a nonexposed group and a group exposed to 0.2 Gy (200 rad) or more, with the greatest decrease occurring in the older group exposed to high-dose radiation.

There has been no systematic study to investigate the prevalence of autoantibodies among A-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 2061 Adult Health Study (AHS) participants in Hiroshima and Nagasaki to determine the effect of radiation on these measurements.

Material and Methods

Selection of study subjects

The study subjects were randomly selected, using the following method, from approximately 6000 AHS participants in Hiroshima and Nagasaki consisting of A-bomb survivors and their nonexposed controls. To obtain an appropriate balance with respect to age, sex, and radiation dose, individuals were randomly selected within categories. When there was a shortage of subjects in a category, for example, persons who were exposed when younger or in Nagasaki, all subjects were selected; when there were too many subjects in a category, about 50 subjects were selected at random. A total of 2069 persons was 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.

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).

ANA, antithyroglobulin antibody, anti-thyroid-microsomal antibody, and RF were measured using commercially available kits. An indirect agglutination test was used to detect antithyroglobulin antibody and anti-thyroid-microsomal antibody. A kit (Fuji-Rebio, Tokyo) for detecting these two autoantibodies was prepared using particle carriers made of article gelatine sensitized with thyroglobulin or thyroid-microsomal antigen, which were extracted and purified from human thyroid tissue. RF was measured by a direct agglutination test using particle carriers made of article gelatin sensitized with denatured rabbit IgG (Fuji-Rebio). Individuals were judged to have positive responses when agglutination was found in a 40-fold-diluted serum for RF and 100-fold-diluted serum for anti-thyroid-microsomal antibody and antithyroglobulin antibody. ANA was determined by indirect immunofluorescence using HEp-2 cells derived from human laryngeal cancer cells (MBL, Nagoya). Individuals were diagnosed as having ANA when immunofluorescence-positive cells were found in a 20-fold-diluted serum.

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.

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

Dosimetry

Dose estimates were based on the Dosimetry System 1986 (DS86).[4] The estimates of free-in-air kerma at the survivor's location, corrected for shielding by buildings or terrain, were used in this report, because kerma was thought to reflect organ doses of the thymus and lymphoid organs as well as the bone marrow, in which immunological cells and their function are modulated.

Statistical methods

Positive response rates. Stepwise logistic regressions[5] were used to relate positive reaction rates to the four autoantibodies to city, sex, age at examination, kerma, and all possible interactions. A forward-selection procedure was used with a significance level of .10 for entry and .05 for exit from the model. In our regression analyses, those individuals with doses of 0 Gy served as the control group. When the resulting model contained interactions without a corresponding main effect, the main effects were added. When the addition of a main effect reduced an interaction to nonsignificance, the interaction was replaced by the main effect. This strategy led to simpler models and hence simpler interpretations and presentation with only a slight degradation of the fit to these data.

The number of subjects for autoantibody analyses is shown in Table 1.

Autoantibody titers. The 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[6] for categorical data analyses were used to estimate mean titers.

In the context considered here, these methods can be described as follows. Let $\mathbf{y}$ denote the vector of potential antibody titer responses and π_i the vector of probabilities of observing these responses in the ith city-by-sex-by-age-by-kerma population. Then, the mean titer for the ith population is $M_i = \mathbf{y}'\pi_i$. We assume these means result from linear combinations of city, sex, age, and kerma effects. That is, that $M_i = \mathbf{X}_i\beta$, where $\mathbf{X}_i$ is a row vector of these covariate values defining the ith population and β is a parameter vector of the effects to be estimated. Now, let $\mathbf{P}_i$ be the vector of sample proportion estimates of π_i. Then

$$\mathbf{y}'\mathbf{P}_i = \mathbf{X}_i\beta + e_i ,$$

where $\mathrm{Var}(e_i)$ is $\mathbf{y}'\mathbf{V}_i\mathbf{y}$ and $\mathbf{V}_i$ is the variance covariance matrix of multinomial proportions, $\mathbf{P}_i$. The method of Grizzle et al of estimating β amounts to a weighted-least-squares fit of this model using the sample estimate $\mathbf{V}_i$ in place of $\mathbf{V}_i$ in the calculation of weights.

Table 1. Composition of the study population

City, sex	Age ATE (yr)	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

Note: ATE = at the time of examination.

Dose and age were divided into two groups, kerma < 0.01 Gy or ≥ 0.01, and age < 62 yr or ≥ 62 yr. The mean kerma levels in the low- and high-exposure groups were 0 and 1.178 Gy, respectively. The mean ages in the young and old groups were 53 yr and 73 yr. Initially, models including all main effects and interactions between city, sex, exposure category, and age category were fitted. Then effects were dropped stepwise from the model using a .05 level of significance for removal. The modifying strategy described above was then applied to the resulting models.

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 .10 level of significance for entry to the model, and .05 for exit from the model, was used for model building.[7]

Analysis of immunoglobulins was undertaken on 1961 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.[8] The stepwise logistic regression analyses were performed using the mainframe version of the BMDP Statistical Software package.[9]

Results

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

Autoantibodies

A-bomb radiation exposure had a positive effect on the prevalence and titers of RF ($p = .008$). The prevalence rate of RF predicted by the model is shown in Figure 1. Radiation exposure had no significant effect on the prevalence of ANA, antithyroglobulin antibody, or anti-thyroid-microsomal antibody.

Prevalence rates by category are shown in Table 3. Prevalence rates of antithyroglobulin antibody in both sexes and ANA in males increased significantly with age ($p < .001$ and $p = .001$, respectively), whereas no such significant tendency was observed for RF, anti-thyroid-microsomal antibody, or 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 ($p < .001$). No sex difference was found for the prevalence of RF. Except for RF, no city difference was observed in autoantibody prevalence.

Immunoglobulins

Levels of IgM and IgA in females increased with increasing radiation dose ($p < .001$; Figure 2). Levels of IgG and IgE were not affected by radiation exposure.

IgA levels increased with increasing age in both sexes ($p < .001$); however, this age effect was not accelerated by radiation exposure. IgG level in males increased with increasing age ($p < .001$), but IgM level in females and IgE levels in both sexes decreased with age.

Mean levels of IgA and IgE were higher in males than in females ($p < .001$); mean levels of IgG and IgM were lower in males than in females ($p < .001$). We found that all immunoglobulin levels were higher in Hiroshima than in Nagasaki.

Table 2. Summary of results from model-building procedures: direction of relationships and *p* value

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

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

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 A-bomb radiation exposure, 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.

Lymphocyte subpopulations and immunological function have been studied previously among the A-bomb survivors. Akiyama et al[3] reported that the PHA responsiveness of T lymphocytes in heavily exposed persons, especially those of advanced ages, is moderately depressed. However, the other reports have not shown any radiation effect on the number of lymphocyte subpopulations, such as cells positive for CD 4 (helper/inducer T cells), CD 8 (suppressor/cytotoxic T cells), and CD 19 (B cells),[10] or on the differentiation of immunoglobulin-producing cells.[11] Akiyama et al[12] reported that radiation exposure did not significantly affect circulating immune complex levels, which increase in autoimmune diseases. Regarding the prevalence or incidence of autoimmune disease among A-bomb survivors, radiation exposure did not significantly affect the prevalence rates of rheumatoid arthritis (RA)[13,14] or Hashimoto's disease[15,16] or the incidence rates of systemic lupus erythematosus and progressive systemic sclerosis.[17]

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. RF is one of the diagnostic features of RA. However, RF is also found in patients with the other kinds of arthritis and with chronic liver diseases. It is possible that RF represents antibodies to antigen-antibody complexes formed during the course of the disease. In this study, of the three autoantibodies, only RF seemed to be affected by radiation exposure. This may be because radiation exposure may affect a part of the immunoglobulin-producing system and induce

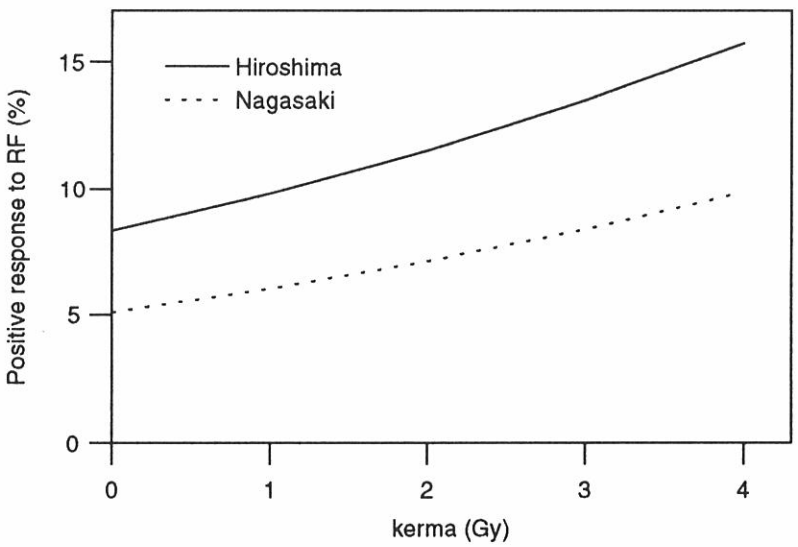

Figure 1. Prevalence of rheumatoid factor (RF) by radiation dose. The lines are the rates predicted by the model in Appendix A.

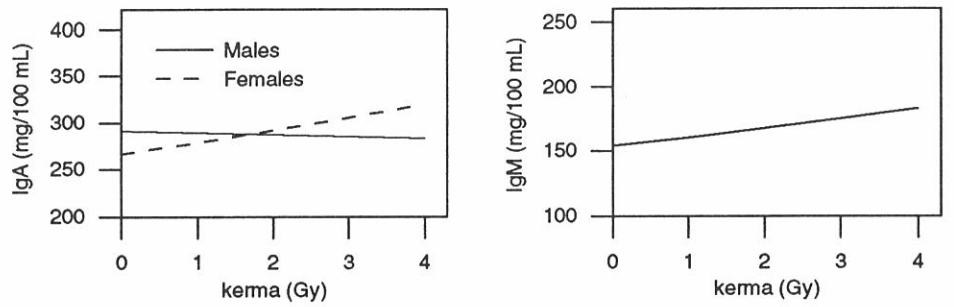

Figure 2. Levels of IgA and IgM by radiation dose at age 62 yr. The lines are the levels predicted by the models in Appendix B.

susceptibility to producing autoantibodies to antigen-antibody complexes.

In a population-based study among adults ranging in age from about 20 yr to about 90 yr, Couchman et al[18] 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.[19–23] Our failure to find age effects on RF, ANA in females, and anti-thyroid-microsomal antibody may be due to the different (compared to the earlier studies) age distribution of our population, which was restricted to relatively older people.

Immunoglobulins are thought to represent the sum of all antibodies produced in response to various antigens. Therefore, if the prevalence of infections increased among the A-bomb survivors with dose, then the levels of immunoglobulins may also have increased as radiation dose increased. A few reports have suggested that the prevalence of chronic inflammations increased after A-bomb radiation exposure.[24–26] Our findings of increased levels of IgA and IgM with increasing radiation dose may support the idea that A-bomb survivors experience stimulation by nonspecific antigens more frequently than nonexposed persons.

Cassidy et al[27] reported on a large community-based study in which IgG and IgA levels increased, but IgM level did not change, with age. However, many reports[28–32] have shown that serum IgG and IgA increase with age, whereas serum IgM decreases with age, which almost agrees with our results. These age effects were not accelerated by increasing radiation dose.

In 1970, measurements of IgA, IgG, and IgM were made on 2043 AHS subjects.[33] Significant radiation effects were not observed in that study. The analyses performed, however, used categorization of immunogloblins 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 and IgM increased as radiation dose increased. The magnitude of these effects, however, was small relative to the variation in these data ($R^2 < .10$). The effect of age at examination on IgG, IgM, and IgA reported here is consistent with that in the previous study.[33] However, these data could not be combined to examine the effect of aging, because the measurement methods used in 1970 were different from those used in 1987–89.

IgE is closely related to allergic reactions, and the measurement of IgE is useful for the diagnosis and evaluation of therapeutic effects in such conditions as atopic diseases and parasitic infections, among others. It has been reported that serum IgE concentration tends to be higher in males than in females and decreases with advancing age.[34,35] We observed the same effect in our data.

In this study, all analyses of autoantibodies and levels of immunogloblins among the subjects from each city, except for the analyses for IgE, were done separately in Hiroshima and Nagasaki. However, blood-sample handling procedures, assay techniques, and analytical-machine operations were standardized to foster consistency of results over time and between cities. Variation in technician judgement was another possible source of variation in the results, although the technicians checked each other's results to lessen possible inter- or intraobserver variability. Nevertheless, the differences by city found in this study in the prevalence of RF and immunoglobulin levels are not likely due to a true city difference but are more likely due to a technical problems. However, the technicians were not informed of the subjects' sex, age, or A-bomb radiation dose,

Table 3. Prevalence rates of autoantibodies by group

Auto-antibody	Age (yr)	Males			Females		
		No. exam	No. of cases	Prev rate (%)	No. exam	No. of cases	Prev rate (%)
RF	40–49	192	13	6.8	194	13	6.7
	50–59	241	21	8.7	303	27	8.9
	60–69	259	30	11.6	318	19	6.0
	≥70	194	14	7.2	360	27	7.5
ANA	40–49	192	4	2.1	194	18	9.3
	50–59	241	8	3.3	303	51	16.8
	60–69	259	10	3.9	318	36	11.3
	≥70	194	18	9.3	360	46	12.8
Micro	40–49	192	4	2.1	194	11	5.7
	50–59	241	6	2.5	303	22	7.3
	60–69	259	11	4.2	318	28	8.8
	≥70	194	10	5.2	360	29	8.1
Thyro	40–49	192	5	2.6	194	16	8.2
	50–59	241	22	9.1	303	41	13.5
	60–69	259	15	5.8	318	46	14.5
	≥70	194	15	7.7	360	39	10.8

Note: ANA = antinuclear antibody; exam = examined; Micro = anti-thyroid-microsomal antibody; Prev = prevalence; RF = rheumatoid factor; and Thyro = antithyroglobulin antibody.

which should have precluded the introduction of bias into the effects of sex, age, and radiation dose.

In conclusion, radiation effects were observed on the prevalence of RF and on levels of IgA in females and IgM in both sexes, though these effects were not large.

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References

1. Awa AA: Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors. II. Biological effects. G. Chromosome aberrations in somatic cells. J Radiat Res 16 (Suppl):122–31, 1975
2. Hakoda M, Akiyama M, Kyoizumi S, Awa AA, Yamakido M, Otake M: Increased somatic cell mutant frequency in atomic bomb survivors. Mutant Res 201:39–48, 1988 (RERF TR 18-87)
3. Akiyama M, Yamakido M, Kobuke K, Donald SD, Hamilton HB, Awa AA, Kato H: Peripheral lymphocyte response to PHA and T cell population among atomic bomb survivors. Radiat Res 93:573–80, 1983
4. Roesch WC (ed): *US–Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki, Final Report* (2 vol). Hiroshima, Radiation Effects Research Foundation, 1987
5. Afifi AA, Clark V: *Computer-aided Multivariate Analysis*. Belmont, Calif, Lifetime Learning Publications, 1984. pp 287–308
6. Grizzle GE, Starmer CF, Koch GG: Analysis of categorical data by linear models. Biometrics 25:489–504, 1969
7. Draper NR, Smith H: *Applied Regression Analysis* (2nd ed). New York, John Wiley and Sons, 1981. pp 307–11.
8. SAS Institute Inc. *SAS/STAT User's Guide, Release 6.03 Edition.* Cary, NC, SAS Institute Inc, 1988. pp 1028
9. Dixon WJ (ed): *BMDP Statistical Software 1983*. Berkeley, University of California Press, 1983
10. Kusunoki Y, Akiyama M, Kyoizumi S, Bloom ET, Makinodan T: Age-related alteration in the composition of immunocompetent blood cells in atomic bomb survivors. Int J Radiat Biol 53:189–98, 1988
11. Yamada Y, Ishimaru T, Neriishi S, Hamilton HB, Ichimaru M: Effect of atomic bomb radiation on the differentiation of human peripheral blood B lymphocytes and the function of concanavalin A induced suppressor T lymphocytes. RERF TR 1-84
12. Akiyama M, Kusunoki Y, Bloom ET, Korn EL, Makinodan T: Immunological responses of A-bomb survivors. RERF TR 12-88

13. Wood WJ, Kato H, Johnson KG, Uda Y, Russell WJ, Duff IF: Remitted arthritis in Hiroshima and Nagasaki, Japan. Prevalence, incidence, and clinical characteristics. Arthritis Rheum 10:21–31, 1967 (ABCC TR 3-66)

14. Kato H, Duff IF, Russell WJ, Uda Y, Hamilton HB, Kawamoto S, Johnson KG: Rheumatoid arthritis and gout in Hiroshima and Nagasaki, Japan. A prevalence and incidence study. J Chronic Dis 23:659–79, 1971 (ABCC TR 20-68)

15. Morimoto I, Yoshimato Y, Sato K, Hamilton HB, Kawamoto S, Izumi M, Nagataki S: Serum TSH, thyroglobulin, and thyroid disorders in atomic bomb survivors exposed in youth: A study 30 years after exposure. RERF TR 20-85

16. Asano M, Norman JE, Kato H, Yagawa K: Autopsy studies of Hashimoto's thyroiditis in Hiroshima and Nagasaki, 1954–74; relation to atomic bomb radiation. RERF TR 15-78

17. Fujiwara S, Sasaski H, Akiba S, Kodama K, Akahoshi M, Akiyama M: Autoimmunity and autoimmune disease in atomic bomb survivors. Hiroshima and Nagasaki: FY-1989 Report of Atomic Bomb Disease Research Teams, Portion by Joint Field Research Team (the Shigematsu Team). Tokyo, Nippon Koshueisei Kyokai–Jpn Public Health Assoc, 1990, pp 132–3 (in Japanese)

18. Couchman KG, Wigley RD, Prior IAM: Autoantibodies in the Carterton population survey. The prevalence of thyroid and gastric antibodies, antinuclear and rheumatoid factors, in a probability based population sample. J Chron Dis 23:45–53, 1970

19. Hooper B, Whittingham S, Mathews JD, Mackay IR, Curnow DH: Autoimmunity in a rural community. Clin Exp Immunol 12:79–87, 1972

20. Shu S, Nisengard RJ, Hale WL, Beutner EH: Incidence and titers of antinuclear, antismooth muscle, and other autoantibodies in blood donors. J Lab Clin Med 86:259–65, 1975

21. Rowley MJ, Buchanan H, Mackay IR: Reciprocal change with age in antibody to extrinsic and intrinsic antigens. Lancet 2:24–6, 1968

22. Hallgren HM, Buckley CE, Gilbertsen VA, Yunis EJ: Lymphocyte phytohemagglutinin responsiveness, immunoglobulins and autoantibodies in aging humans. J Immunol 111:1101–7, 1973

23. Mathews JD, Rodger BM, Stenhouse NS: The significance of the association of tissue autoantibodies and rheumatoid factor with angina in the Busselton population. J Chron Dis 29:345–53, 1976

24. Freedman LR, Phair JP, Seki M, Hamilton HB, Nefzger MD: The epidemiology of urinary tract infections in Hiroshima. Yale J Biol Med 37:262–82, 1965 (ABCC TR 21-64)

25. Sawada H, Otake M, Omori Y, Freedman LR: Long-term follow-up of urinary tract infection in women, Hiroshima. ABCC TR 31-72

26. Yamada M, Neriishi K, Fujiwara S, Sasaki H, Sawada H, Ochi Y: Erythrocyte sedimentation rate in Adult Health Study participants, Hiroshima Igaku–J Hiroshima Med Assoc 39:446–51, 1986

27. Cassidy JT, Nordby GL, Dodge HJ: Biologic variation of human serum immunoglobulin concentrations: Sex-age specific effects. J Chron Dis 27:507–16, 1974

28. Riesen W, Keller H, Skvaril F, Morell A, Barandun S: Restriction of immunoglobulin heterogeneity, autoimmunity and serum protein levels in aged people. Clin Exp Immunol 26:280–5, 1976

29. Weeke B, Krasilnikoff PA: The concentration of 21 serum proteins in normal children and adults. Acta Med Scand 192:149–55, 1972

30. Radl J, Sepers JM, Skvaril F, Morell A, Hijmans W: Immunoglobulin patterns in humans over 95 years of age. Clin Exp Immunol 22:84–90, 1975

31. Buckley CE, Buckley EG, Dorsey FC: Longitudinal changes in serum immunoglobulin levels in older humans. Fed Proc 33:2036–9, 1974

32. Takaishi M: Studies on changes of immune function in aged humans and its regulation mechanism. Hiroshima Daigaku Igaku Zasshi–Med J Hiroshima Univ 29:671–719, 1981

33. King RA, Milton RC, Hamilton HB: Serum immunoglobulin levels in the ABCC–JNIH Adult Health Study, Hiroshima and Nagasaki. RERF TR 14-73

34. Orren A, Dowdle EB: The effects of sex and age on serum IgE concentrations in three ethnic groups. Int Arch Allergy Appl Immunol 48:824–35, 1975

35. Grundbacher FJ: Causes of variation in serum IgE levels in normal populations. J Allergy Clin Immunol 56:104–11, 1975

Appendix A. Statistical Models for Autoantibody Measurements

Prevalence of autoantibodies

C(City): 1 if the city of exposure was Hiroshima, 0 if Nagasaki

A(Age): age at the time of examination (ATE) in 1987–88

S(Sex): 1 if male, 0 if female

D(Dose): in gray

The values within parentheses are standard deviations.

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

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

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

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

Titer of rheumatoid factor

C(City): 1 if the city of exposure was Hiroshima, –1 if Nagasaki

S(Sex): –1 if female, 1 if male

A(Age): –1 if age ATE in 1987–89 < 62 yr, 1, if age ≥ 62 yr

D(Dose): –1 if 0 ≤ radiation dose < 0.01 Gy, 1 if radiation dose ≥ 0.01 Gy

The values within parentheses are estimated standard errors.

Log of RF titer: $y = 4.643 + 0.213C + 0.192D.$
$(0.08) \quad (0.08) \quad (0.08)$

Appendix B. Statistical Models for Immunoglobulin Measurements

C(City): 1 if the city of exposure was Hiroshima, 0 if Nagasaki

A(Age): age at the time of examination (ATE) in 1987–89

S(Sex): 1 if male, 0 if female

D(Dose): in gray

The values within parentheses are standard deviations.

$$\text{IgA: } \log(\text{IgA}) = \underset{(0.051)}{5.265} + \underset{(0.018)}{0.058}C + \underset{(0.022)}{0.091}S + \underset{(0.001)}{0.005}A + \underset{(0.012)}{0.046}D - \underset{(0.017)}{0.053}SD,$$

where $R^2 = 0.036$;

$$\text{IgG: } \log(\text{IgG}) = \underset{(0.037)}{7.293} + \underset{(0.010)}{0.032}C - \underset{(0.056)}{0.303}S + \underset{(0.0006)}{0.001}A + \underset{(0.001)}{0.004}SA,$$

where $R^2 = 0.045$;

$$\text{IgM: } \log(\text{IgM}) = \underset{(0.078)}{5.748} + \underset{(0.022)}{0.070}C - \underset{(0.119)}{0.724}S - \underset{(0.0010)}{0.010}A + \underset{(0.010)}{0.044}D + \underset{(0.002)}{0.008}SA,$$

where $R^2 = 0.089$; and

$$\text{IgE: } \log(\text{IgE}) = \underset{(0.175)}{4.297} + \underset{(0.063)}{0.127}C + \underset{(0.063)}{0.673}S - \underset{(0.003)}{0.006}A,$$

where $R^2 = 0.061$.