放影研 RERF update
Radiation Effects Research Foundation News and Views
Hiroshima and Nagasaki, Japan
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*RERF conducts research and studies—for peaceful purposes—on the medical effects of radiation on humans with a view toward contributing to the maintenance of the health and welfare of atomic-bomb survivors and to the enhancement of the health of all mankind.*

**Editor-in-Chief:** *Seymour Abrahamson, Vice Chairman and Chief of Research*
**Managing Editor:** *Donald Pierce, Department of Statistics*

**Editorial Policy**

*Contributions to* Update *receive editorial review only and do not receive scientific peer review. The opinions expressed herein are those of the authors only and do not reflect RERF policies or positions.*

**Contact:** *Mailing address: RERF Editorial & Publications Section, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815 Japan*
*Telephone: 81-82-261-3131; Facsimile: 81-82-263-7279*
*Internet:* ***update@rerf.jp***

# The 34th Board of Directors Meeting Held in Washington, D.C.

The 34th meeting of the Board of Directors was held at the National Academy of Sciences (NAS) in Washington, D.C. on the 21 and 22 June 2000. The meeting was attended by 18 people including directors, supervisors, and observers. An animated discussion took place concerning RERF management and other issues.

Dr. Shigenobu Nagataki, Chairman, presented a status report on RERF. He also expressed the views of the Executive Committee on the five items that they had carried over from the previous Board meeting: US-Japan negotiation of funding, the number of directors, extending the retirement age of research staff and research staff increase, the reserve for retirement allowance and measures to cope with fluctuations in currency exchange rates, and the facilities and relocation.

Dr. Paul Seligman, Deputy Assistant Secretary for Health Studies, US Department of Energy (DOE), reported on the results of the US-Japan negotiation held prior to the Board meeting. He said that the US intends to secure 14 million US dollars for RERF annually for the next five years, and to observe the agreement made during the 1996 US-Japan negotiations that there would be only one permanent US director.

At this Board meeting, Dr. Warren R. Muir, Executive Director, Commission on Life Sciences, National Research Council, brought to light the following proposals from the National Academy of Sciences. He announced that the Clegg Committee would be organized to review the long-term institutional arrangements between the Academy, DOE and RERF. Discussion of the role of the US Permanent Director was emphasized.

The agenda of reports included the following: the present personnel status, the fiscal year 1999 salary revision, the Labor Union's fiscal year 2000 demands for the improvement of working conditions, international collaboration, and the health effects study for the children of A-bomb survivors ($F_1$). In the explanation of the Labor Union's demands, it was noted that the Union had acted as a mediator between RERF and $F_1$ groups concerning the $F_1$ health effects study issues.

It was reported that a full-scale survey would be initiated for the $F_1$ health effects study after the results of pilot study questionnaires were reviewed.

On the items for deliberation and action, Dr. Wolff presented the recommendations of the Multinational Peer Review of the Department of Genetics. He also presented a response to the recommendations of the 27th meeting of the Scientific Council. He highlighted the suggestion that the working scientific staff of RERF should engage in a process to define their own future. Dr. Shudo Yamazaki, Supervisor, presented the audit report of the fiscal year 1999 research activities.

Secretariat Chief Kazumasa Kunitoshi, delivered an explanation of the fiscal year 1999 settlement of accounts report. The working budget for fiscal year 2000 was approved.

## List of Participants

**Permanent Directors:**
Shigenobu Nagataki, Chairman
Sheldon Wolff, Vice Chairman and Chief of Research
Senjun Taira, Permanent Director

**Visiting Directors:**
Patricia A. Buffler, Dean and Professor of Epidemiology, Division of Public Health Biology and Epidemiology, School of Public Health, University of California, Berkeley
Toshiyuki Kumatori, Consultant, Radiation Effects Association
Jonathan M. Samet, Professor and Chairman, Department of Epidemiology, Johns Hopkins University School of Hygiene and Public Health
Richard B. Setlow, Senior Biophysicist, Biology Department, Brookhaven National Laboratory, Adjunct Professor of Biochemistry and Cell Biology Department, State University of New York at Stony Brook
Kazuaki Arichi, Councilor, Japan Institute of International Affairs (submitted a letter of attorney)
Masumi Oike, Chairman, Japan Anti-Tuberculosis Association (submitted a letter of attorney)

**Supervisors:**
Shudo Yamazaki, former Director-General, National Institute of Infectious Disease
David Williams, Senior Financial Advisor, US National Academy of Sciences

**Scientific Councilor**:
J. Martin Brown, Professor and Chairman, Division of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine

# The 27th Meeting of RERF Scientific Council

The Scientific Council met at RERF in Hiroshima on April 17–19, 2000. The meeting was co-chaired by Drs. J. Martin Brown, Professor, Stanford University, and H. Matsudaira, Chairman, Radiation Effects Association.

Dr. S. Nagataki, Chairman of RERF, opened the meeting. Dr. S. Wolff, Vice Chairman and Chief of Research, gave a brief review of RERF activities over the past 12 months and invited the Council's advice regarding future research directions.

The remainder of the first day was devoted to recent research and future plans in the Departments of Clinical Studies (Drs. G. Suzuki and M. Akahoshi), Radiobiology (Dr. D. MacPhee), Epidemiology (Drs. Y. Shimizu and A. Suyama), and Statistics (Dr. D. Preston). In the afternoon, there was a brief review of the recent US-Japan Joint Dosimetry Workshop (Drs. S. Fujita and H. Cullings) and discussion about current problems with the dosimetry system.

The morning of the second day was devoted to a review of database construction (Messrs. E. Grant and H. Katayama), and to a review of the use of stored serum samples (Drs. S. Fujiwara, M. Hakoda, G. Sharp, and J. Cologne). In the afternoon, Dr. N. Nakamura led a discussion concerning the responses to the November 1999 departmental peer review meeting recommendations for the genetics program.

On the third and final day, the Council co-chairmen, Drs. Brown and Matsudaira, presented a summary of the Council's report and its recommendations. The final report was presented to the RERF Board of Directors when they met in Washington, D.C. in June 2000.

## The Scientific Council's recommendations and RERF's responses [in italics]

*by Sheldon Wolff, Vice Chairman*

The Scientific Council made two general recommendations and several recommendations pertaining to specific individual departments.

Like many previous review groups that have indicated they would like to see RERF foster independent investigator originated research, this Council, too, has expressed such a desire, but have presented a variation on the theme by suggesting a procedure that might help to bring this about. They suggested that this should involve meetings of the scientific staff in groups of 5–10 for one or more hours every few weeks, or at one or more all-day retreats to discuss the questions "what could we be doing, or what would we like to be doing, at RERF in 10 years," and "what scientific environment would we like at RERF in 10 years?" The Council also presented a possible scheme for holding such meetings in which the members would sit in a circle and have flip charts on which to write their ideas. It was hoped that this somewhat informal approach would stimulate outspokenness and interaction between the scientists.

The second general recommendation of the Council was that instead of having a dinner attended only by the Council, the senior leadership of RERF, and the department chiefs, the initial social gathering and perhaps even some of the luncheons, should be an RERF wide reception. The purpose of this would be to increase the opportunity for more general and informal discussions with the working scientists, with opportunities for general mingling of the staff and councilors for one-on-one discussions.

*This constitutes a reprise of the way in which earlier Councils were run and which was very popular among the staff. RERF agrees wholeheartedly with this idea and intends to implement it at the next Council meeting.*

The Council then moved on to make specific recommendations for each department. It noted that in the Department of Clinical Studies there are a large number of active projects, some dating back to 1985. Some are closely related such as the various studies related to calcium metabolism and to cardiac disease. The Council recommended that the Department of Clinical Studies should review, consolidate, and further prioritize its studies to reduce the total number and to focus on those statistically most promising, where a relationship to radiation exposure can be shown.

*RERF believes that this recommendation is most timely and could even be implemented in other departments where Research Protocols have accumulated and could profit by consolidation.*

The long awaited $F_1$ study is about to get underway and the Council recommended that RERF

determine whether any increase in malignant tumors or non-neoplastic conditions occur in this group.

*The study as recommended by other advisory groups, however, is mainly a genetic study designed to determine if multifactorial diseases are increased in the offspring of the exposed survivors. The recommendation of the Council will be passed on to the Scientific Committee for the $F_1$ study to see if it fits with their assessment of what should be done in the study.*

Because RERF's statisticians might need tutelage in new techniques that are under development, it was recommended that scientists in the department be allowed to take short sabbatical leaves at other institutions where they can learn the new methods.

*RERF finds that this recommendation really applies to our ongoing programs in all departments including statistics, whereby we regularly send our people abroad to learn new techniques.*

RERF was also urged to investigate and solve some of the ethical issues confronting epidemiological studies and to investigate solutions to these issues agreed upon in the U.S. (e.g., at the Fred Hutchinson Research Center in Seattle) and elsewhere to see if some of these might be proposed for use here.

*RERF points out that individual institutions can no longer solve these issues independently since each country is promulgating separate national rules in this area. Currently Japan has a commission that is proposing a national law for Japan that will define what must be done legally in this country. This response also applies to a recommendation made to the Department of Radiobiology that the ethical issues that are currently hampering the collection of archival tumor material be resolved as soon as possible.*

## Scientific Councilors

J. Martin Brown, Professor and Chairman, Division of Radiation Biology, Department of Radiation Oncology, Stanford University School of Medicine (co-chairman)

Hiromichi Matsudaira, Chairman, Radiation Effects Association (co-chairman)

Maurice S. Fox, Lester Wolfe Professor of Molecular Biology, Massachusetts Institute of Technology

Joe W. Gray, Professor of Laboratory Medicine and Radiation Oncology, University of California, San Francisco (Absent)

Tomio Hirohata, Professor Emeritus, Kyushu University Faculty of Medicine, and Professor, Nakamura Gakuen University

Yusuke Nakamura, Director, Human Genome Center, Institute of Medical Science, University of Tokyo

Theodore L. Phillips, Wun-Kon Fu Distinguished Professor and Associate Director, University of California San Francisco Cancer Center

Susan Preston-Martin, Professor, Department of Preventive Medicine, University of Southern California

Masao Sasaki, Professor, Radiation Biology Center, Kyoto University

Shinichiro Ushigome, Professor, Department of Pathology, Jikei University School of Medicine

## ERRATA

In the Autumn 1999 *Update*, 10(2), on page seven in the article "Radiation and Noncancer Disease Mortality," the last sentence in the legend of Figure 2 (bottom line) should read: "ERR estimates and standard errors are given for six dose categories: <0.005, 0.005–, 0.2–, 0.5–, 1.0–, and ≥2.0 Sv."

In the Spring 2000 *Update*, 11(1), the following two errors were made:

- On page one in the article "U.S. Ambassador and Osaka Consul General Visit RERF," the bottom line in the photo caption should read: "Pictured at left is Ms. Fumiko Gregg, an interpreter for the ambassador."
- On page 11 in the article "Hiroshima and Nagasaki Open Houses," under the upper-left photo "Radiobiology and Genetics Above," the names of the left two persons were reversed. So, the first man on the left is Yoichiro Kusunoki and the next man is Tomonori Hayashi.

## Staff News

RERF Chairman Dr. Shigenobu Nagataki completes his four-year term in June 2001. Replacing him, as the first American Chairman of RERF, will be Dr. Burton Bennett, who recently completed 12 years service as UNSCEAR Secretary. The next issue of *Update* will carry more information about him. Dr. Senjun Taira, a Permanent (*i.e.* Resident) Director for the past four years, will become Vice Chairman. The first Permanent Director from Hiroshima will be Dr. Eiichi Tahara, who recently retired from the Hiroshima University Department of Pathology. In the fall, Dr. Charles Waldren of Colorado State University will join RERF as Chief Scientist, the new title for what has recently been Associate Chief of Research.

After extending his anticipated term for some time, Dr. Sheldon Wolff retired as Vice Chairman and Chief of Research in fall 2000, returning to California. As a temporary measure, at the request of RERF scientists and Board of Directors, Dr. Seymour Abrahamson returned to serve RERF in October 2000, for the fifth time, to fill the Vice Chairman and Chief of Research positions for a period that will end this June. Readers will appreciate that Dr. Abrahamson is responsible for the publication of this issue of *Update*, even though there is presently no managing editor.

Dr. Kei Nakachi has recently taken the post of Chief of Epidemiology, Hiroshima, coming from the Saitama Cancer Center. In addition to his other duties as department chief, he will be developing a program in molecular epidemiology.

Dr. James Cao joined Radiobiology as Research Scientist this May, having recently worked for Proctor and Gamble in Kobe following postdoctoral positions at Columbia and Stanford. Dr. Misa Imaizumi joined Clinical Studies, Nagasaki, as Research Scientist early this year, coming from Mount Sinai Medical College in the U.S. Dr. Shizue Izumi recently completed her Ph.D. in Biostatistics at Hiroshima University, and has been promoted from Research Assistant to Research Scientist in Statistics. Dr. Renju Maeda, former Director of Tarami Hospital, Nagasaki Prefectural Adult Disease Center, has joined RERF in Nagasaki as Senior Consulting Scientist.

Dr. Sadayuki Ban, Radiobiology, has left RERF after 21 years to take a position at the National Institute of Radiological Sciences. Dr. Ken Kuramoto, Clinical Studies, Hiroshima, has moved on after one year at RERF to take a Fellowship position at the National Heart, Lung, and Blood Institute in the U.S. National Institutes of Health.

## New Study of the Children of A-bomb Survivors

Following a recommendation from the Blue Ribbon Panel and consultations with various advisory committees, it was decided about three years ago that RERF should carry out a clinical study of the $F_1$ cohort. Although no radiation effects were found in studies of this cohort as children, nor in continued mortality and cancer incidence investigation, it might be that as these persons reach middle age there would be clinically ascertainable effects, particularly in adult-onset multi-factorial diseases such as hypertension, diabetes, and cardiovascular diseases.

A large number of survivors' children were examined shortly after birth, and again at 9 months, for clinical abnormalities. When they were teenagers, cytogenic and molecular protein analyses of blood samples were carried out for a large number of them. No radiation effects were seen in these studies, although it is known from experiments using animals and insects that the mutational effects of high-dose irradiation of male and female germ cells can be found in offspring. A cohort of 80,000 is followed up to study mortality and cancer incidence through Hiroshima and Nagasaki tumor registries. The new clinical study is thus an extension of those activities. The purpose is to estimate and obtain confidence limits for excess prevalence of diseases, which will be useful even if no apparent, or statistically significant, risks are seen.

After careful consideration, including consultations with experts on medical ethics and discussions with survivor groups, a pilot mail survey of about 300 of an identified cohort of 18,000 was done. The purposes were to determine the level of interest for participating in a clinical study, and to validate the questionnaire which will provide useful information on lifestyle and other matters, for purposes of the mortality and cancer incidence follow-up. About 77% of the 300 were reached and responded, and among respondents about 65% expressed such willingness to participate. It is estimated that 8,000–11,000 of the cohort will actually participate in the clinical study, which will be done over a four-year period. For each year the mail survey will be completed for one-fourth of the 18,000—the first having been mailed by now—and those willing to participate in the clinical study will be contacted. A pilot clinical study of 500 selected from the first group will begin in a few months. As usual at RERF, careful attention is being given to obtaining proper informed consent of the participants, and privacy of personal information. The informed consent will pertain distinctly to three different aspects of investigation: (1) the basic clinical study, (2) preservation of sera and plasma for future investigations not involving DNA, and (3) preservation of blood samples for genetic studies involving DNA.

## Current Status of Dosimetry Revision

Many readers will know that there have been major concerns in recent years regarding the adequacy of the DS86 radiation dose estimates. In particular, it was suggested—based on thermal neutron activation measurements in sampled materials—that the Hiroshima neutron estimates could be too low by factors of 10 at 1,600 m and 30 at 2,000 m. If this were true, correction could have substantial effect on both neutron and gamma-ray cancer risk estimates, partly involving reconsideration of the neutron relative biological effectiveness (RBE) used in cancer analyses if this became more critical than in the past. However, activation measurements also suggested that the current neutron estimates near the hypocenter are too high, leading to a dilemma in that re-evaluation of source term and transport calculations failed to provide results that would agree with both of these types of correction. That is, it was considered implausible that neutron doses could decrease as slowly with distance as suggested by the measurements.

Very good progress has now been made on resolving the uncertainties, through international activities organized by the Department of Energy and the Ministry of Health and Welfare, along with efforts of a National Academy of Sciences Dosimetry Committee. Several binational meeting were held, the uncertainties in activation measurements were evaluated, and further measurements on new samples were made—including important work done at the University of Munich.

It is now expected that the basic elements of a new dosimetry system will be in place before the end of 2001, and that the implementation might be complete by the middle of 2002. Preliminary indications are that the earlier activation measurements at substantial distance may have been misleading, and that changes in the distal Hiroshima neutron estimates will probably not exceed about 1/10 of those suggested above. There may be distance independent increases in Hiroshima gamma-ray estimates on the order of 10%.

# Multinational Peer Review: Department of Statistics

## Activities strongly supported and personnel increase advised

The fourth Multinational Peer Review was held on 7–9 November 2000 at the Hiroshima laboratory to evaluate RERF's statistics program. In accordance with the recommendations of the Blue Ribbon Panel, the RERF research departments have undergone multinational peer review on an annual rotating basis. The first department to undergo Multinational Peer Review was the Department of Radiobiology, second was the Department of Epidemiology, and next the Department of Genetics.

The gathering opened with greetings from Chairman Dr. Shigenobu Nagataki and an overview of RERF by Dr. Seymour Abrahamson, Vice Chairman and Chief of Research. Following an overview of the statistics program by Dr. Dale L. Preston, Chief of the Department of Statistics, the review proceeded with the following presentations and active discussions: Donald A. Pierce, *Age-time patterns of cancer risk to be anticipated in mutagenic exposure data*, and also *Joint effects on lung cancer of smoking and radiation*; Shizue Izumi, *Current analysis of $F_1$ mortality*, and also *Family pedigree study*; John Cologne, *Confounding and effect modification of radiation risk by other factors*, and also *Breast cancer molecular study design*; Fumiyoshi Kasagi, *The Adult Health Study population*, and also *Cardiovascular disease study*; Eiji Nakashima, *Radiation dose effect on height of atomic-bomb survivors—a longitudinal study of stature in adulthood*; Lennie Wong, *Longitudinal analyses of the Adult Health Study measurement data*; Shoichiro Fujita, *Atomic-bomb dosimetry*; Harry M. Cullings, *Analysis of physical measurements related to the A-bomb dosimetry*; Eric Grant, *RERF's research database*

The Department of Statistics provides statistical assistance to other departments (Epidemiology, Clinical Studies, Genetics, and Radiobiology) and is closely related to them scientifically. Thus, an additional session was held to allow the Panel to interact with chiefs of the other departments and laboratories in Hiroshima and Nagasaki and to listen to their requests concerning the Department of Statistics.

On the final day of the meeting, Dr. David W. Gaylor, panel chairman, provided general comments and some panel members spoke on certain aspects of the draft recommendations. The Panel strongly supported the activities of the Department of Statistics and requested an increase in number of statisticians to enable the department to collaborate fully with, and provide required statistical assistance to, the other RERF departments. Their final report, received later, included the recommendations paraphrased here:

- Additional statistics staff to ensure adequate support and collaboration with other departments
- That there should be a statistician on the Scientific Council
- Continuing support for the development of statistical techniques for the dose response analysis of health effects from low-dose radiation
- Continued support for description of age patterns of radiation-related cancer and the implications for mechanistic models of cancer induction
- Continued analyses of $F_1$ cancer incidence and untoward pregnancy outcomes in relation to parental radiation exposure
- Further development for case control studies of weighted sampling designs, generalizing on "matching on dose" and "counter matching" ideas, and study of their efficiency
- Continued work on analysis of the AHS taking care to distinguish between confounding and intermediate variables for radiation effects
- Continue longitudinal analysis of AHS measurements, including assessment of the sensitivity to different correlation structures
- Adjusted survivor doses allowing for imprecision in radiation dose estimates should be used in most RERF analyses, revisiting the methods for dealing with this when a revised dosimetry system becomes available
- RERF should consider the formation of a research data management committee to consider the design, access, and documentation of databases; this committee needs a member from the Department of Statistics
- Preliminary statistical power analyses for detecting familial sensitivity to radiation should be carried out before continuing a large scale family pedigree study
- Participation in outside professional activities related to radiation effects on health, and the improved analysis of such data, is encouraged
- Continue efforts for recruiting Japanese statisticians, including participation in professional meetings, links with university statistics programs including teaching, student internships, and collaborative research
- Consider the improved retention and recruitment of staff by investigating ways to compete for outside funding for projects related to the RERF mission

**Review Panel Members**

David W. Gaylor, Principal Scientist, Sciences International Incorporated, Virginia (chairman)

Tomio Hirohata, Professor Emeritus, Kyushu University Faculty of Medicine, and Professor, Nakamura Gakuen University (RERF Scientific Councilor)

Susan Preston-Martin, Professor, Department of Preventive Medicine, University of Southern California (RERF Scientific Councilor)

T. Shun Sato, Professor, Department of Epidemiology and Biostatistics, Kyoto University School of Public Health

Takao Shohoji, Professor, Section of Information and Behavioral Sciences, Hiroshima University Faculty of Integrated Arts and Sciences

Daniel O. Stram, Associate Professor, Department of Preventive Medicine, Division of Biostatistics, University of Southern California

Toshiro Tango, Director, Division of Theoretical Epidemiology, Department of Epidemiology, National Institute of Public Health

## New Datasets Available on RERF Home Page

Two datasets have recently been added to the scientific archives section of the RERF home page (www.rerf.jp/eigo/archives/archvtoc.htm). One is the LSS Report 12 noncancer mortality data for the period from 1950 through 1990.[1] Detailed descriptions of the models used in the paper, and examples illustrating how they were fitted, are included with the dataset. See www.rerf.jp/eigo/scidata/R12noncancer.pdf for more information.

The other dataset is a special version of the LSS Report 11 mortality data with additional information on the occurrence of acute radiation effects: epilation, flash burn, oropharyngeal lesions, and bleeding. These data have been used by Stewart and colleagues in recent efforts to investigate the potential impact of selection effects on LSS risk estimates.[2,3] See www.rerf.jp/eigo/scidata/R11acuteData.pdf for more information about these data.

Other datasets available from the RERF homepage include the LSS Report 12 cancer mortality data, detailed LSS solid cancer and leukemia incidence data, and data on stable chromosome aberrations.

### References

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2. Stewart A and Kneale G, A-bomb survivors: factors that may lead to a re-assessment of the radiation hazard. *International Journal of Epidemiology* 2000, 29:708-714.
3. Stewart A, A-bomb data: detection of bias in the Life Span Study cohort. Environmental Health Perspectives 1997, 105 Suppl 6:1519-21.

# Analysis of the Longitudinal Hematology Data in the Adult Health Study

F. Lennie Wong
Department of Statistics

Various laboratory measurements have been collected from the Adult Health Study (AHS) subjects since the program's inception in 1958. These include total serum cholesterol levels, blood pressure, hemoglobin and hematocrit, sedimentation rate, red and white blood cell counts, and lymphocyte and monocyte counts. Over the years, other laboratory data have been added. Anthropometric measurements such as of height, weight, and head circumference (in the *in utero* subjects) have been collected as well. Since the subjects are invited to participate in the clinical examination on a biennial basis, the AHS has amassed an inordinately large amount of data on nearly 20,000 individuals of all ages. The AHS is currently in its twenty-second examination cycle, so for subjects who have attended every examination since 1958, 22 measurements will be available by mid-2002. The serial data spanning over a 40-year period provide a unique opportunity for elucidating the temporal trends of these physiological determinations. They also enable examination of whether and how exposure to atomic-bomb radiation modified these trends.

Although appropriate statistical methodologies have been available for the analysis of longitudinal serial data, it was only within the last decade when, coupled with the ever-increasing computing speed and data storage space, efficient computer software became available that have made the analysis of the massive AHS measurement data feasible. Prior to that, data examination was relegated to cross sectional methods at each examination cycle, as was done in the AHS Report 6,[1] rather than taking full advantage of the longitudinal nature of the data that allowed one to examine and tease out birth cohort effects. The crude method also was not conducive for generalizing secular trends and radiation effects gleaned at each examination cycle.

Using the mixed-effects model for the analysis of serial measurement data,[2] which takes into account the correlation among measurements within a person, and the appropriate computing software,[3,4] longitudinal trends have been estimated for total serum cholesterol and systolic and diastolic blood pressures in the AHS.[5,6] Notable differences in cholesterol levels among birth cohorts were evident, which were attributed to changes in Japanese dietary habits and lifestyle over three decades. Significant radiation effects were also demonstrated for cholesterol, with higher levels shown for the irradiated subjects, and greater increase for irradiated women than for irradiated men.[7] Atomic-bomb radiation doses were also shown to significantly affect the long-term trends of blood pressures, although the direction of the effects depended on age at the time of bombing or birth cohort status.[6] More recently, we performed similar analysis of the hemoglobin and hematocrit data, for which radiation effects had been suggested in cross sectional analyses conducted before 1990.[1,8] The details of our preliminary analysis of hemoglobin data are described below.

Hemoglobin (Hb) levels of 12,323 subjects obtained from AHS examinations 1–20 (1958–2000) were used. The study population excluded those who were Not-In-City at the time of bombing (ATB) and those for whom Dosimetry System 1986 (DS86) doses were unavailable. Hb obtained at ages 80 years or more were excluded because of the low participating rate in the AHS of persons beyond that age, making the data non-representative. Hiroshima female represented the largest group in the data (45%), followed by Hiroshima male (26%), Nagasaki female (17%), and Nagasaki male (12%). Age ATB ranged from 0 to 66 years, and Hb data were available for ages 13 to 80 years. The median number of Hb determinations available was 10, with a range of 1 to 20.

As an initial step, the mean Hb was plotted against mean age at each examination cycle by city and sex according to birth cohort grouped into decades of age ATB (Figure 1). At first glance, a sizable difference appears to exist among the birth cohorts, with the levels of Hb being higher for younger than for older birth cohorts. Further examination reveals that mean Hb levels at some examination cycles are consistently high or low, and that there is a discernable pattern of peaks and valleys in mean Hb by examination cycles among the various birth cohorts in each city. In fact, a similar plot using examination cycle

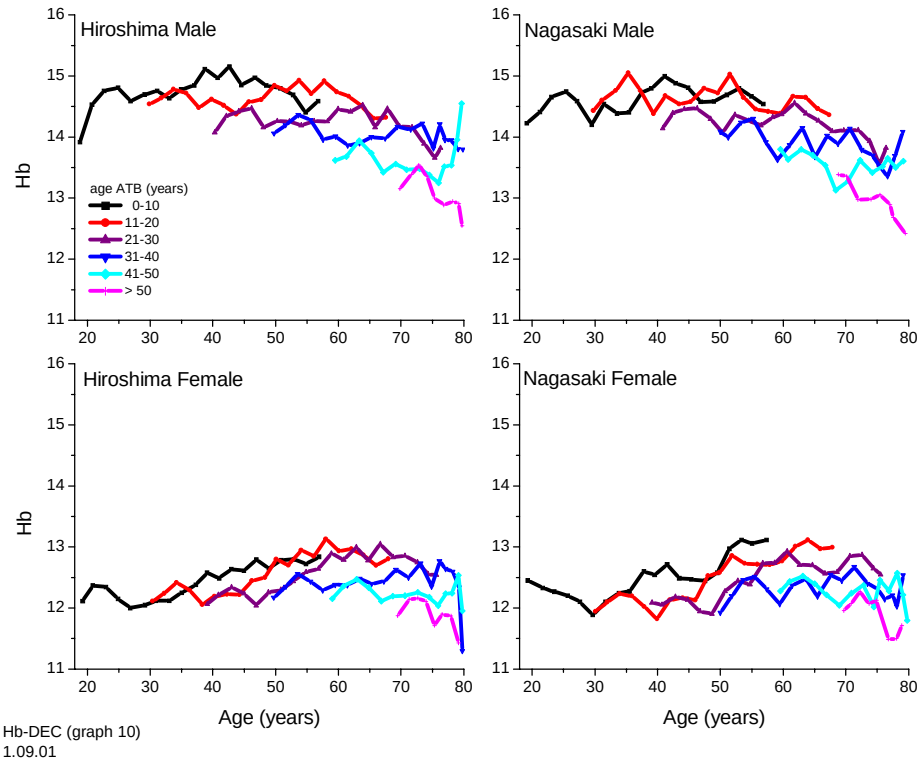
as the horizontal axis, instead of age, would reveal consistent patterns over examination cycles, suggesting that the observed cohort differences may be an artifact of the systematic variation associated with examination periods. The sources of systematic variation may include changes in equipment, personnel, study procedure, laboratory drift, and other unknown factors, all of which can occur in studies with long durations, such as the AHS. Thus, examination cycle variations must be taken into account to elucidate an accurate picture of the longitudinal trend of Hb.

To begin the analysis, we assumed that Hb level in each person is described by a linear-quadratic-cubic function of age at the time each Hb value was obtained. This function was allowed to vary by city and sex, and birth cohort differences were included through the use of indicator variables of age ATB grouped into decades (0–10, 11–20, 21–30, 31–40, 41–50, >50 years). Examination cycle variation was adjusted for by including a set of indicator variables for the 20 examination cycles for each city. The first examination cycle in each city served as the respective baseline. All variables except the indicators of examination cycle were allowed to interact with one another and only the statistically significant terms were retained in the final model estimate. The examination cycle indicators were kept in the model regardless of statistical significance.

The estimate of the longitudinal model of Hb, adjusted for examination cycle, is shown in Figure 2. For males in general, Hb levels rise from 18 years of age to about 30 years, then decline thereafter. For females, there is an initial tendency for Hb levels to decrease during the reproductive years, followed by an increase associated with menopausal period, and finally declining again with further aging. Even after adjusting for examination cycle variation, birth cohort differences appear to persist, with a tendency for Hb levels of the older cohort, particularly those who were 21–40 years ATB, to be lower than the younger, 0–20 years ATB, cohort. Those who were older than 40 years ATB appear to have the lowest Hb levels.

To determine if DS86 radiation doses significantly modify the longitudinal trend estimated for

**Figure 1**. Mean Hb level by mean age at AHS examination cycles 1–20, by birth cohort groups in males and females of Hiroshima and Nagasaki.



Hb, dose parameters were included in the model as a constant term of dose and as interactions with age, age,[2] and age.[3] The parameters in the resultant model were re-estimated and the significance of the dose terms tested. Dose effects were highly significant ($p < 0.1 \times 10^{-13}$). The predicted Hb levels of the irradiated AHS subjects were decreased compared to those of the minimally irradiated subjects (Figure 3). At 1 Gy exposure, the average reduction in Hb ranged from –0.3% to –1.8%, with the least reduction seen at the youngest age and the most at the oldest age considered. No difference in radiation effects was detected between Hiroshima and Nagasaki. The question of whether radiation effects are modified by sex and birth cohort status is currently under examination.

Using the mixed-effects model, we were able to estimate the longitudinal trend of the Hb levels in the AHS subjects. We also were able to show that Hb levels of the irradiated subjects were lower than those of the minimally exposed subjects, confirming statistically the impression obtained in earlier analyses based on cross-sectional methods. Thus it appears that exposure to atomic-bomb radiation is associated with mild anemia. Additional investigation underway includes re-analyses of the data by excluding subjects diagnosed with diseases that are associated with reduced levels of Hb, including cancer, chronic liver diseases, renal failure, collagen disease, and ulcer. This will be useful for determining whether primary anemia, not the secondary form that results as a symptom of these diseases, also occur as a result of exposure to atomic-bomb radiation.

**Figure 2.** Estimate of the longitudinal model of Hb levels.

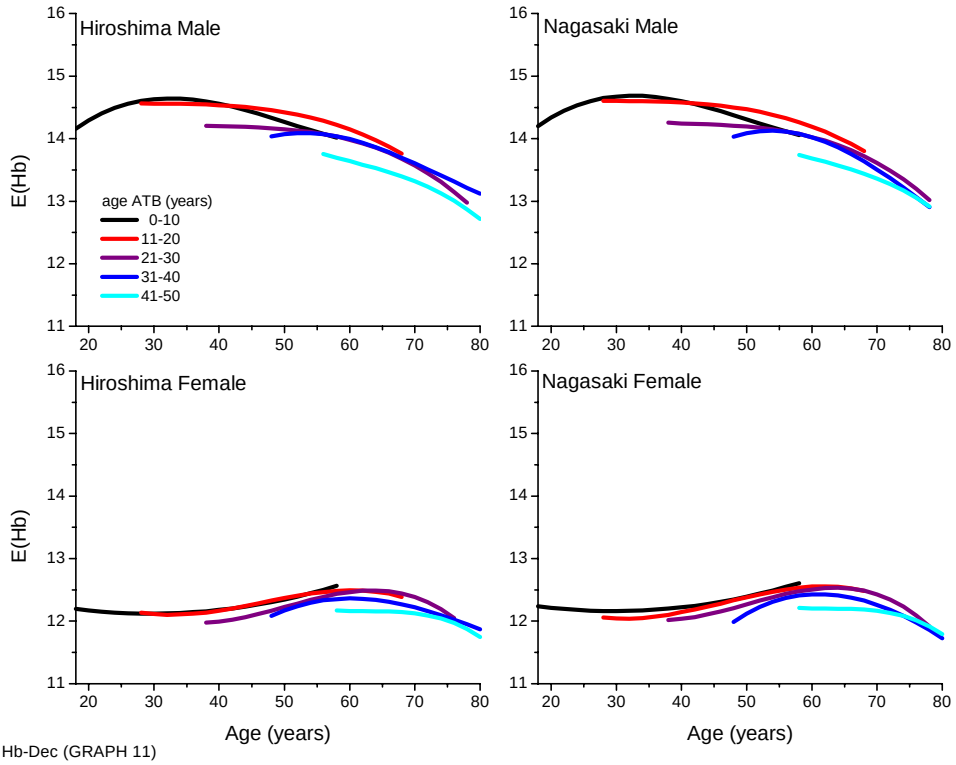
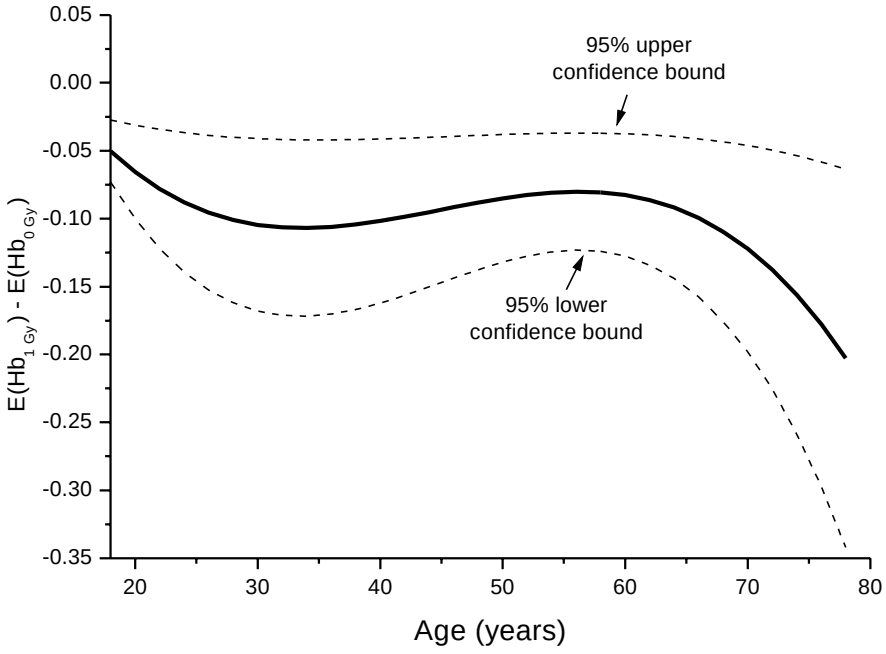


**Figure 3.** Percent reduction in the expected Hb level of the 1 Gy exposed subjects compared to 0 Gy exposed subjects.

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# Randomness of Radiation-induced Translocations Depends on Chromosome Length or Surface Area as Target

*Nori Nakamura, department chief; Kazuo Ohtaki, research scientist; Yoshiaki Kodama, chief, Cytogenetics Laboratory; Mimako Nakano, assistant senior scientist; Masahiro Itoh, research scientist; and Akio A. Awa, consultant, Department of Genetics, and John B. Cologne, senior scientist, Department of Statistics*

**Summary**

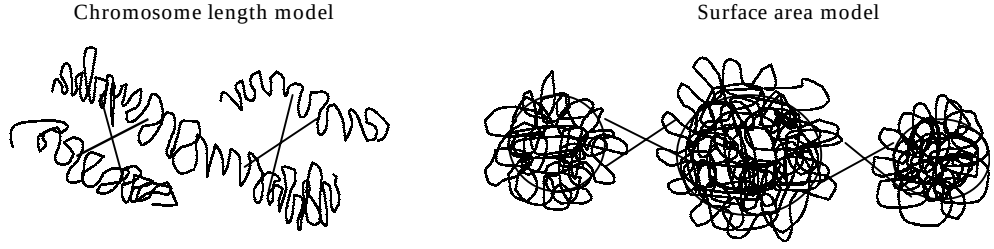
G-banded translocation data in blood lymphocytes from A-bomb survivors show an apparent linear relation between the number of translocations and chromosome length or DNA content. However, the observed-to-expected (O/E) ratio seems to be inversely related to DNA content. Do smaller chromosomes undergo exchanges preferentially? We think this is arguable because the inverse relation disappears when chromosome surface area rather than DNA content is considered the target for the expected aberration frequency. Under either hypothesis, our results indicate positive associations between satellite- and/or heterochromatin-bearing chromosomes in interphase nuclei, supporting earlier perceptions of such associations.

Repeatedly, it has been argued whether radiation-induced chromosome aberrations distribute randomly either within a chromosome or among chromosomes.[1,2] In the former case, aberration breakpoints may have appeared to cluster at certain bands of chromosomes, and in the latter case, aberrations may have occurred disproportionately in certain chromosomes according to DNA content. As ionization itself is a random physical process, if such a deviation from randomness exists, it is most likely biological. Constitutive associations among satellite- or heterochromatin-bearing chromosomes, which may undergo exchanges among themselves at higher-than-expected frequencies because of their spatial proximity, appear to be one factor influencing randomness.

However, in past cytogenetic studies, because only limited data were available, possible interchromosomal associations were not taken into account. We can now address this issue analyzing our latest G-band data, which comprise more than 11,000 radiation-induced reciprocal translocations in blood lymphocytes from A-bomb survivors among nearly 48,000 cells examined. The survivors were all proximally exposed and the mean kerma dose estimated by Dose System 1986 (DS86) is about 2 Gy. Identical aberrations from any one individual, i.e., clonal aberrations, and complex exchanges involving three or more breaks were excluded.

Two alternative models are considered to calculate expected translocation frequency (Figure 1). The classic chromosome length hypothesis assumes that radiation can induce chromosome breaks in proportion to DNA content and that all breaks participate in forming the exchanges with equal probability. The new surface area model assumes that though radiation can induce chromosome breaks in proportion to DNA content, only such damage near the surfaces of the two chromosome masses can interact because each chromosome occupies a discrete domain in interphase, and the interaction distance between the two lesions to generate dicentrics is suggested to be ex-

**Figure 1.** Two alternative models to describe radiation-induced interchromosomal exchanges in interphase nuclei. The figures indicate possible exchanges between one large and two small chromosomes.



tremely short (equal to or less than 7 nm).[3,4] In this model, we assume that each chromosome domain in interphase nuclei comprises a simple spherical structure whose volume is in proportion to DNA content. The model's general impact is that the smaller chromosomes have a larger surface-to-volume ratio than the larger chromosomes and thus bear more damage sites, which leads to the higher exchange rate per unit content of DNA.

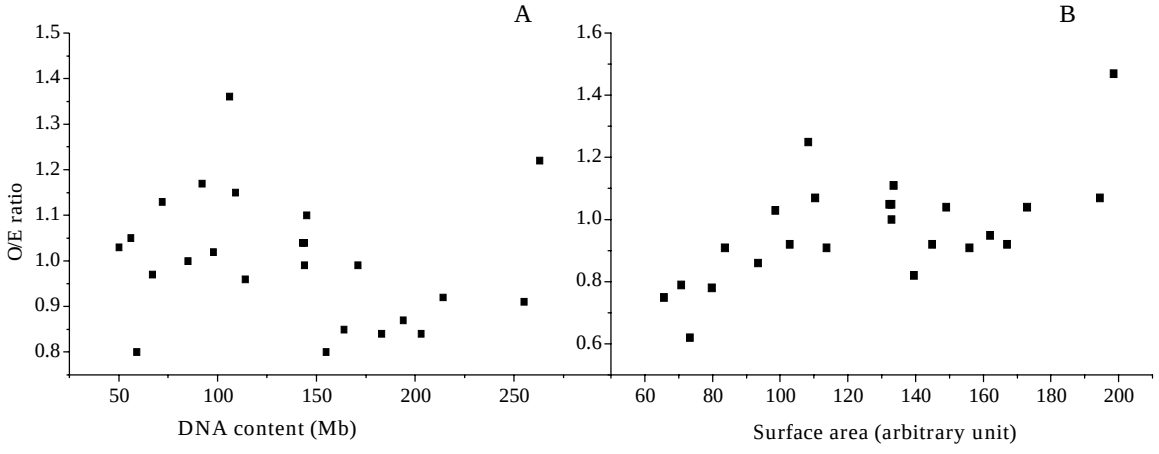
Results using the chromosome length model show that translocation frequency relates linearly to chromosome length while the O/E ratio of each chromosome varied from 0.80 to 1.36, mostly within 1 plus minus 0.2 (Figure 2A). Further, the ratio appears to be inversely related to the DNA content of the chromosomes. This inverse relation between O/E ratio and chromosomal DNA content is not a new finding; Cook reported the largest G-band data, comprising nearly 1,500 exchanges,[5] and Barquinero et al.[2] and Cigarran et al.[6] reported fluorescence *in situ* hybridization (FISH) results comprising about 3,600 and 1,000 exchanges, respectively.

Following the surface area model, we find that the negative trend observed in Figure 2A no longer holds and O/E ratios are more or less unified (Figure 2B). Cigarran et al.[6] reached a similar conclusion based on the same spherical model. Although the overall trend is now positive and statistically significant ($p = 0.0015$), the results largely depend on a few influential points. Exclusion of chromosome 1 and the smallest two chromosomes, Y and 21, for example, abolishes the significance of the relation ($p = 0.15$). Thus, the apparent positive relation should not be concluded generally. In fact, lower O/E ratios in small chromosomes are observed in neither the G-band[5] nor the FISH studies.[2] The FISH results reported by Barquinero et al.[2] show that, under the chromosome length hypothesis, the overall relation is highly significant ($p < 0.0001$), while the reanalyzed results following the surface area hypothesis are no longer ($p = 0.15$) (Figure 3A and B). Thus, it is clear that translocation distribution becomes closer to random according to the surface area model.

In addition to the surface area hypothesis, under the chromosome length hypothesis, two other explanations, not mutually exclusive, are possible for the apparent preferential occurrence of the aberrations in smaller chromosomes. Namely, exchanges of small segments may be detected more effectively by G-banding if they occur in smaller chromosomes, and/or smaller chromosomes may tend to position more centrally while larger chromosomes position nearer the periphery within nuclei.[7] The first explanation seems less likely because FISH data also showed a similar trend when regressed by chromosome length.[2] By contrast, the latter explanation suggests no obvious reason to be rejected and, indeed, seems reasonable provided that such chromosome-length-dependent, nonrandom positioning occurs constitutively. Here, the outermost or larger chromosomes have no interactive counterpart at their further outer space, which would limit their ability to undergo interchromosomal exchanges. Unfortunately, current data do not allow us to evaluate relative contributions among these possibilities.

Irrespective of the DNA content or surface area hypothesis, four observations stand out when we dissect the present translocation data into all possible combinations of two-chromosome pairs. First, translocations occur with significantly higher-than-expected frequencies (O/E ratio = 1.5–1.8) between chromosomes bearing heterochromatin (chromosomes 1, 9, 15, 16, and Y) and/or satellites (chromosomes 13 to 15) (results for chromosomes 21 and 22 vary according to the model) and between their homologues, supporting earlier ideas of such

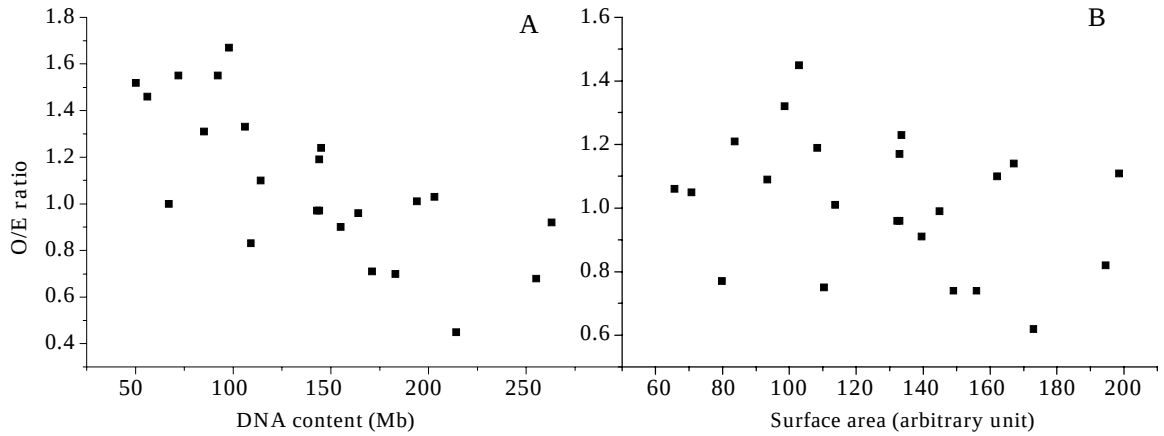
**Figure 2.** Observed-to-expected ratio of radiation-induced translocations observed in blood lymphocytes from A-bomb survivors in relation to A) DNA content (Mb) and B) surface area (arbitrary unit). Results for chromosomes X and Y in males are corrected because they are present as single copies whereas other chromosomes are present as pairs.



associations. Second, there are no clear remote associations of one inactive X chromosome from the remaining chromosomes in females. This is in line with *in vitro* FISH results in which aberration frequency of X chromosomes in female cells is similar to that for autosomes of similar lengths[2] and active and inactive X chromosomes contribute more or less equally to the pool of translocations induced by radiation exposures.[8] Third, no pairs of autosomal homologues underwent exchanges less frequently than expected, failing to support Nagele's suggestion of separate locations of autosomal homologues in interphase nuclei.[9] Finally, because O/E ratio varies among certain large chromosomes frequently used for FISH painting, for biodosimetric purposes, one should be cautious to use the same combination of chromosomes painted by FISH for both calibration and sample testing or to select combinations of chromosomes so that the results may represent a mean frequency of aberrations in the whole genome.

In conclusion, although the surface area model, which assumes a simple spherical structure, is far from the real organization of chromosome domains in interphase nuclei, the surface area hypothesis is more attractive than the physical length hypothesis not only on theoretical grounds, but because the O/E ratio is closer to unity irrespective of chromosome size, which is an indication for the randomness. And, in either hypothesis, it seems clear that certain chromosomes undergo positive associations in interphase nuclei, though the contribution of such associations to the aberrations in the whole genome is rather limited.

**Figure 3.** Observed-to-expected ratios of radiation-induced interchromosomal exchanges (dicentrics and translocations) observed in an *in vitro* FISH study using blood lymphocytes[2] in relation to A) chromosomal DNA content (Mb) and B) surface area (arbitrary unit).

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# Cancer Risks at Low Doses among A-bomb Survivors

Donald A. Pierce and Dale L. Preston
Department of Statistics

The RERF Life Span Study is often referred to as a "high-dose" study, requiring substantial extrapolation to estimate risks of interest for radiation protection. Further, many people think of the study as contrasting cancer rates of "A-bomb survivors" to those in a comparison population that might differ from the survivors in various respects not related to radiation exposure. Both of these would be serious limitations, but each characterization is only half true. Unfortunately most RERF analyses, including our previous ones, have done little to dispel such notions—much less to capitalize on the true strengths of the study in these respects. This article presents aspects of our recent *Radiation Research* paper (154:178–86, 2000), which was intended as a start in this direction. Part of the motivation was the increasing controversy about low-dose radiation risks for cancer, and in particular regarding the suitability of the "linear, no threshold" (LNT) interpretation.

What do we mean by the two characterizations being only "half true"? Regarding the first, while it is true that the usual linear risk estimates are largely determined from effects in the 0.5–2 Sv range, similar estimates result from restricting the dose range to below 0.5 Sv or even below 0.2 Sv. About 75% of the survivors in the significantly-exposed (>0.005 Sv) part of the population—about 35,000 persons presenting 5,000 cancer cases so far—had doses in the range 0.005–0.02 Sv of primary interest for radiation protection. The real limitation of the study is not lack of information about low doses, but that the exposures were only acute. As for the second characterization, it is important to realize that results from conventional analyses are virtually unchanged if the "comparison group" of those more than 2 or 3 km from the bombs, about half the study cohort, is simply omitted from the analysis. This is because of the large size of, and the wide variation in doses within, the proximal component.

Moreover, there is some interplay between the two issues of directly estimating low-dose cancer risks and whether this distal comparison group is employed. It appears that the largely rural population beyond 3 km has had about 5% higher cancer risks than the part of the urban population with doses of nearly zero. Such demographic variations in cancer rates are in general quite common. Such a bias would have negligible effect on inferences about risks at high doses; but eliminating it becomes a critical issue when estimating cancer risks at around 0.1 Sv, where the radiation risk may also be on the order of 5% of normal cancer rates. It greatly strains any epidemiological investigation to estimate risks of this level, since within the scope of the study cancer rates may vary to that extent due to other risk factors correlated with the exposure under investigation. But the special features of the RERF study, including its large size, adequate dosimetry, and especially the very sharp variation of dose with distance (decreasing by 1/3 each 100 m), may make this possible with reasonable confidence. This is extremely rare in any kind of observational study, particularly in epidemiology.

The following table is not intended for analysis, since adjustment for age and sex is crucial, but rather is given for perspective on the study.

**Table.** General summary of the 1958–1994 cancer incidence data

| Colon dose, Sv (distance) | Subjects | Solid cancers | Estimated excess |
|---|---|---|---|
| >3,000 m | 23,493 | 3,230 | 100 |
| <3,000 m and <0.005 Sv | 10,159 | 1,301 | 1 |
| 0.005–0.1 | 30,524 | 4,119 | 69 |
| 0.1–0.2 | 4,775 | 739 | 61 |
| 0.2–0.5 | 5,862 | 982 | 149 |
| 0.5–1 | 3,048 | 582 | 169 |
| 1–2 | 1,570 | 376 | 167 |
| >2 | 470 | 126 | 84 |

This tabulation shows that there are large numbers of survivors in the study with low doses, and also that there remains a large comparison group if those beyond 3 km are omitted. The estimated excess was computed from a linear regression on dose, but with an additional parameter for the group beyond 3 km.

Our primary analytical description is given by the following figure for which the underlying methods are documented in our paper. The aims of this plot are to "display the data" as clearly as possible, and to provide an unconstrained—or nonparametric—estimate of the dose response function. At the same time, we wish to avoid to the extent possible effects of utilizing arbitrary dose categories. We achieve that by computing rather imprecise risk estimates for a large number of categories and then smoothing the results as shown. The primary focus when looking at such plots should be the smooth curve, and we emphasize that the dashed curves are ±1 SE limits for the solid smooth curve, rather than for the plotted points.

We have no idea of the meaning of the "bump" at around 0.2 Sv, but note that it occurs in both Hiroshima and Nagasaki.Whether it is statistically significant is questionable, due to difficulties in testing effects suggested by the data. The main point of the plot is that there is no indication that low-dose risks are overestimated by linear regression on the full dose range. There is statistically significant risk in the dose range below 0.1 Sv ($P$ = 0.05, one-sided test). The upper 95% confidence limit for a threshold, beyond which the risk increases linearly from zero, is 0.06 Sv. It is visually clear, in view of the alternative baseline shown, that these inferences would change substantially if the restriction to <3 km were not made.

In our paper we also investigate whether results seen in this figure are likely to be markedly changed by possible revision of DS86 dosimetry system, currently under consideration. For several years there has been renewed interest and activities pertaining to discrepancies between physical measurements and DS86 estimates for neutrons in Hiroshima. Although other revisions are likely, the neutron issue is the most interesting since the suggestion is that required modifications would be distance-dependent, which might alter the apparent shape of the dose-response curve. Early suggestions were that to conform to measurements the DS86 Hiroshima neutron estimates would need to be increased by a factors of 1, 10, and 30 at distances 800, 1,600, and 2,000 m from the bomb.

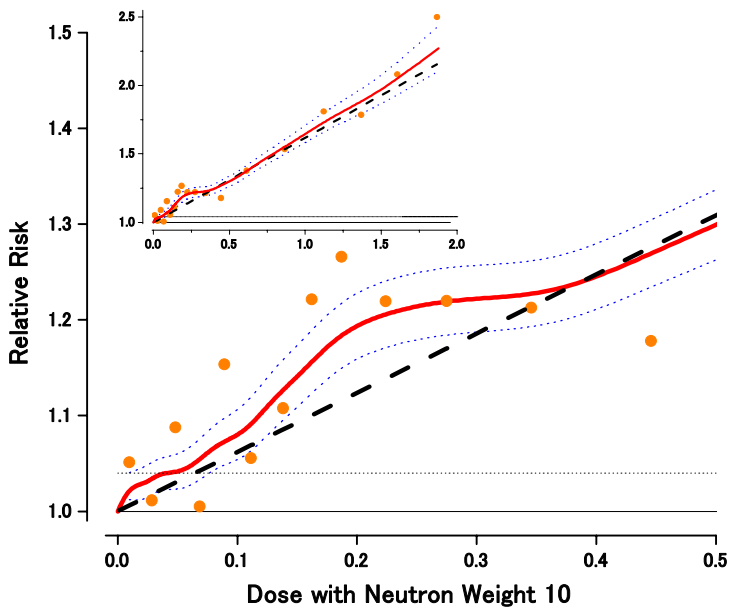


**Figure.** Estimated low-dose relative risks. Age-specific cancer rates over the 1958–1994 follow-up period relative to those for an unexposed person. Averaged over the follow-up and over sex, and for age at exposure 30. The dashed curves represent ±1 standard errors for the smoothed curve. The straight line is the linear risk estimate computed from the range 0–2 Sv. Because of an apparent distinction between distal and proximal zero-dose cancer rates, the unity baseline corresponds to zero-dose survivors within 3 km of the bombs. The dotted line represents the alternative baseline if the distal survivors were not omitted. The inset shows the same information on the fuller dose range.

We indicate in our paper why the physicists involved in radiation transport calculations find such a distance relationship for neutron doses physically impossible, bringing into question the interpretation of the measurements. These issues are currently under study by a bi-national group of physicists. In the paper we investigate consequences of a more modest—but perhaps still too large—modification that reduces the factors given above to 1, 5, and 15. We also employ for this a variable neutron relative biological effectiveness (RBE), taking values of about 10 at high survivor doses and about 40 at low survivor doses, since the likelihood of such a variable RBE is a reason that many expect neutron estimate modifications to be potentially important. Our tentative conclusion is that such a neutron dose estimate modification would not result in less apparent linearity of the dose response than seen in the figure here.

So to summarize, our paper clarifies that—contrary to widespread views—the RERF data provide substantial direct information about low-dose radiation risks for cancer. Further, the available information is by no means restricted to that from comparison of "A-bomb survivors" to some group not experiencing the disaster. For inference about low-dose risks it is necessary to take particular care in the choice of comparison population, which is equally true of any low-dose study of human radiation risks. The very rapid decrease of radiation dose with distance from the bombs means that useful comparisons are available between persons within a narrow distance range. Since substantial heat and blast effects reached further than radiation, those persons experienced similar effects of the bombings, e.g., severe disruption of their lives, aside from radiation dose.

Our results indicate that cancer risks for doses on the order of 0.05 Sv are not overestimated by the usual regression analysis on much wider dose ranges, such as 0–2 Sv. In our analysis there is direct statistically significant evidence of risk in the dose range of approximately 0–0.1 Sv, but we emphasize that this mode of reasoning, and certainly the precise limits of such a range, should not dominate interpretation of the data. In view of the highly linear dose response down to low doses, it is neither sound statistical interpretation nor prudent risk evaluation to take the view that the risk should be considered as zero in some low-dose range due to lack of statistical significance within that range. To do this would be to base risk protection on the smallest plausible risk at those low doses, since in statistical reasoning a non-significant result means precisely that the lower confidence limit is zero or less. There is every reason to conclude from the RERF data that the usual linear cancer risk estimation is appropriate for low doses.

## Research Protocols Approved 1998–2000

### RP 1-98 A prospective study of bladder cancer and diet

Nagano J, Kono S, Sharp GB, Fujita S, Moriwaki H, Mabuchi K

The number of epidemiologic studies that have investigated the role of dietary factors in bladder carcinogenesis is limited. We propose a prospective study to examine the relation between dietary factors and bladder cancer risk. Specific questions to be addressed are whether the consumption of green-yellow vegetables or fruits is related to a decreased risk and whether meat intake is related to an increased risk. Subjects are approximately 40,000 men and women in the Life Span Study (LSS) extended cohort who responded to a mail survey on lifestyle conducted in 1979 and 1980 and whose dose estimates of radiation exposure are available according to the Dosimetry System 1986 (DS86). Information on bladder radiation dose will be obtained from Radiation Effects Research Foundation (RERF) files, and consumption frequency is available for 22 dietary items. Bladder cancer incidence in the period from 1980 to the latest available year will be used. Statistical adjustment will be made for tobacco smoking, educational level, and radiation exposure. Possible interactions between the dietary factors and radiation exposure as well as tobacco smoking will be examined.

### RP 1-99 Primary liver cancer incidence study among atomic-bomb survivors, 1958–87 (Addendum to RP 5-90)

Sharp GB, Mizuno T, Fujiwara S, Cologne JB, Mabuchi K, Kodama K

RP 5-90 describes a case-control approach to assessing hepatitis B virus (HBV) infection and testing the joint effects of radiation and HBV on primary liver cancer (PLC) in the Life Span Study (LSS). Originally, HBV was the only hepatitis virus under study with infections to be measured by staining methods (orcein and immunohistochemical stain) and by polymerase chain reaction (PCR). The hepatitis C virus (HCV) was discovered shortly before RP 5-90 was written and is recognized as a possible PLC risk factor in the protocol. One specific stated objective of RP 5-90 is " . . . to lay the groundwork for a continuing study of the role . . . of hepatitis C virus in the future incidence of hepatocellular carcinoma in the LSS sample." Although there were serum-based tests for HCV at the time the protocol was written, there was at that time no method for detecting HCV—an RNA virus—in liver tissue. Subsequent to the writing of protocol 5-90, it became possible to assess HCV in liver tissue using reverse transcriptase-polymerase chain reaction (RT-PCR), and an investigator on this protocol in the Department of Radiobiology (T.M.) began testing cases and controls for HCV in addition to HBV. To date, 364 cases and 596 matched controls have been tested for HBV using PCR and for HCV using RT-PCR, although in some instances, lack of tissue or poor tissue quality resulted in unsuccessful tests. These tissue-based tests are still required on approximately 250 controls.

Although the use of PCR on archival liver tissue samples is an innovative procedure that has allowed RP 5-90 to make the most of RERF resources and greatly increased the value and power of the study, one problem with this technique is that it has not been used previously and lacks validation. We, therefore, propose to utilize serum samples stored in the Adult Health Study to validate PCR and RT-PCR of liver tissue as a means of detecting HBV and HCV. We also want to compare the pathology staining tests for HBV against standard serum measures. In total, we expect to test about 45 serum samples from subjects for whom both tissue and serum samples are available.

### RP 2-99 Thyroid diseases in Hiroshima and Nagasaki atomic-bomb survivors

Tominaga T, Akahoshi M, Soda M, Neriishi K, Fujiwara S, Yamada M, Ezaki H, Kodama K, Nakashima E, Shibata Y, Okubo M, Ashizawa K, Sera N, Yokoyama N, Eguchi K

The effect of atomic-bomb radiation on thyroid diseases will be analyzed in 5,489 Adult Health Study (AHS) participants in Hiroshima and Nagasaki to elucidate thyroid disease incidence. All subjects will undergo thyroid gland palpation, function testing, autoantibodies testing, and ultrasound examination. The previous thyroid study conducted in Nagasaki from 1984 to 1987 demonstrated increased thyroid tumor prevalence and a radiation-dose-response relationship in autoimmune hypothyroidism among atomic-bomb survivors. This study will assess whether there is a closer relationship between these diseases and radiation dose after more than ten years. This is the first thyroid disease prevalence study of the Hiroshima AHS since 1971. Previously detected solitary thyroid nodules will be investigated by precise ultrasound nodule-volume measurement.

### RP 1-00 Molecular mechanisms of radiation-induced hyperparathyroidism

Fujiwara S, Arnold A, Mallya S, Ezaki H

Primary hyperparathyroidism (HPT) is a common endocrine disorder and most often is due to a solitary adenoma in one of the parathyroid glands. Irradiation of the head and neck is an established risk factor for the development of primary HPT.

Dr. Arnold's laboratory has recently developed a transgenic mouse model to study the pathogenesis of parathyroid neoplasia in a setting that simulates the

human disease. Targeted overexpression of cyclin D1 in the parathyroid glands of these mice (PTH-D1) causes the animals to develop HPT. To exploit the advantage offered by this mouse model, we have initiated studies that will ultimately localize and/or identify genes that contribute to development of radiation-induced murine parathyroid tumors.

This research protocol will apply to future all cases of hyperparathyroidism detected in the Adult Health Study (AHS) cohort that require surgical removal of the parathyroids. The studies proposed here will analyze radiation-induced human parathyroid tumors for chromosomal alterations using molecular genetic and cytogenetic approaches in a way that is intimately complemented by and intertwined with Dr. Arnold's ongoing murine studies. Thus, our studies are designed to localize and/or identify novel tumor suppressor genes/oncogenes that play a role in radiation-induced human parathyroid neoplasia.

### RP 2-00 Studies on microbial infection and cell-mediated immunity in the Adult Health Study population

Hakoda M, Kusunoki Y, Yamada M, Kasagi F, Hayashi T, Shimizu M, Kodama K, Kyoizumi S, Katayama H, MacPhee DG, Fujiwara S, Suzuki G, Akahoshi M

Increased mortality from and incidence of atherosclerotic diseases, such as ischemic heart disease and cerebrovascular diseases, with radiation dose have been demonstrated among atomic-bomb survivors. However, biological mechanisms relating radiation exposure to atherosclerotic diseases among atomic-bomb survivors remain unclear. Recently, the inflammatory process has been suggested as playing important roles in atherosclerosis initiation and progression, with microbial infection regarded as a plausible trigger. A number of reports investigating the relationship between infection with *Chlamydia pneumoniae*, *Helicobacter pylori*, or cytomegalovirus and atherosclerotic diseases have been published. Of note, cell-mediated immunity, which is important for antimicrobial defense, has been reported as impaired in atomic-bomb survivors, and the decreased cell-mediated immunity is associated with myocardial infarction. Furthermore, laboratory tests have shown that inflammatory responses in the survivors increase according to radiation dose, which may suggest the presence of some chronic infection. Accordingly, it seems important to analyze the interrelationships among radiation dose, microbial infection, and cell-mediated immunity among the survivors to explain the mechanism for atherosclerotic disease development in the survivors. To evaluate infection with *Chlamydia pneumoniae*, *Helicobacter pylori*, and cytomegalovirus, specific antibodies to these pathogens will be measured in the sera of Adult Health Study (AHS) participants in this study. Cell-mediated immunity will be evaluated on several subsets of T cells, especially on T-helper subsets. Among T-helper subsets, the T-helper 1 (Th1) subset has been regarded as an important T-cell population for the antimicrobial defense mechanism. Analysis of study results will clarify whether atherosclerotic diseases are related to infections among the survivors and if cell-mediated immunity impairment is the basis for infections or infection-related diseases.

### RP 3-00 Ophthalmologic study of atomic bomb survivors

Minamoto A, Taniguchi H, Mishima HK, Amemiya T, Nakashima E, Neriishi K, Hida A, Fujiwara S, Suzuki G, Akahoshi M

Almost two decades have passed since the previous ophthalmologic study. Since then, substantial new information concerning radiation and senile cataracts has become available, suggesting the need for re-evaluation of cataracts in atomic-bomb survivors. Recent findings include biological evidence of radiation influence on the lens, new evaluation methods for ocular damage, new epidemiological confounders to assess ocular damage, and a better understanding of risk factors. Because a simple resection operation has become available for treatment, this may be a last opportunity for epidemiological evaluation of cataracts in A-bomb survivors.

Study subjects will be (1) those who participated in the previous study and (2) those who were age 13 or less at the time of the bombs. In the first group, we will investigate the natural history of radiation cataracts over a period of several decades. In the second, we will estimate the risk of radiation on the lens. Regression analysis will be conducted for possible late-onset subcapsular axial opacities and polychromal changes and early-onset peripheral opacities using the Lens Opacity Classification System II for grading and incorporating a variety of confounding factors. This study will enable us to make new estimates of the risk of lens changes with enhanced quantitation and precision and could lead to a more accurate description of the shape (threshold) of the dose response for radiation cataracts. Lens photographs will be stored permanently as digital computer images.

### RP 4-00 Pilot mail survey of the children of atomic bomb survivors

Koyama K, Nagano J, Suyama A, Watanabe T, Fujiwara S, Takahashi N, Preston DL, Mabuchi K, Taira S

A mail survey is being planned in the RERF $F_1$ cohort to obtain epidemiological information that will be used for ongoing mortality and cancer incidence studies and the establishment of a sub-cohort for a clinical health examination program that is being

planned. A pilot survey has been designed to test the forms and to identify administrative and other problems that might arise during the full survey. The pilot survey will be conducted among 300 (200 in Hiroshima and 100 in Nagasaki) $F_1$ cohort members randomly selected from the subset of the $F_1$ population that is to be included in the full survey, i.e., those $F_1$ subjects who are residing in or around Hiroshima and Nagasaki and whose parents received doses of less than 0.005 Gy. A self-administered questionnaire that asks about smoking, alcohol consumption, diet, exercise, occupation, and past and present health status will be sent to the pilot study subjects. In addition, the subjects will be asked to provide comments on difficulties they had in answering the questions and on their reaction to some of the questions that are considered "sensitive." Their responses will be evaluated and considered in developing the final study plan for the full mail survey.

**RP 5-00 The prevalence, incidence, and prognosis of the Brugada type electrocardiogram: A population-based study of four decades**

Matsuo K, Akahoshi M, Nakashima E, Suyama A, Seto S, Hayano M, Yano K

Brugada syndrome, a new clinical entity causing sudden death due to ventricular fibrillation, was established in 1992. This syndrome has no structural abnormality in the heart but has characteristic electrocardiogram (ECG) manifestation; right bundle branch block and ST-segment elevation in leads $V_1$ to $V_2$/$V_3$. Because of a new clinical entity, the prevalence and incidence of such ECG manifestation, i.e., the Brugada-type ECG, and rate of sudden death among those who have the Brugada-type ECG have not been determined in general population. Using the data of Adult Health Study cohort, we would like to examine the prevalence, incidence, and prognosis of the Brugada-type ECG. Because cardiac sodium channel gene (autosomal dominant inheritance) is involved in development of the Brugada syndrome, we also examine the relationship between the Brugada-type ECG and radiation dose.

**RP 6-00 Molecular alterations in early-onset breast and ovarian cancers among atomic bomb survivors**

Hirai Y, Ban S, MacPhee DG, Mabuchi K, Tokuoka S, Koyama K, Suyama A, Soda M, Tokunaga M, Cologne JB, Nakamura N, Katayama H, Dohi K, Fukuhara T, Matsuura H, Hayashi Y, Fujihara M, Takahashi R, Yoshikawa K, Land CE, Tucker MA, Buetow KH, Iwamoto KS

Breast cancer is one of the most obviously radiogenic tumors so far identified among the atomic bomb (A-bomb) survivor population. Excess relative risk (ERR) per sievert is especially high for early-onset cases (i.e., cases where the patient is less than 35 years of age at diagnosis). This study is proposed to test the hypothesis that the high incidence of early-onset breast cancers in the A-bomb survivor population may be due to the damaging effect of A-bomb radiation on the normal allele of a breast cancer susceptibility gene in women who are heterozygous carriers of germline mutations of the gene. The first step in initiating these investigations will be to collect 700 samples of breast cancer tissue from survivors and suitable unexposed women with breast cancer for comparison. The second step will be to search for damage to, or deletion of, the normal allele of the breast cancer susceptibility genes (*BRCA1* and *BRCA2*) using available methods for detection of alterations in gene expression and protein localization. When abnormalities are detected in a screening of all cases, DNA will be sequenced to characterize the aberrations. With regard to the Ataxia-telangiectasia mutated (*ATM*) gene, an immunohistochemical staining technique will be used to screen for abnormalities and the relationship between early-onset breast cancer and mutations in the *ATM* gene will be investigated. Each specimen will be coded and hence rendered anonymous before being subjected to molecular analysis. Information linking individual identification to biological samples will be maintained by the data linkage coordinator.

## Recent Publications

*(Japanese): the original article is in Japanese; (JTr): a Japanese translation is available.*


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## Publications Using RERF Data

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