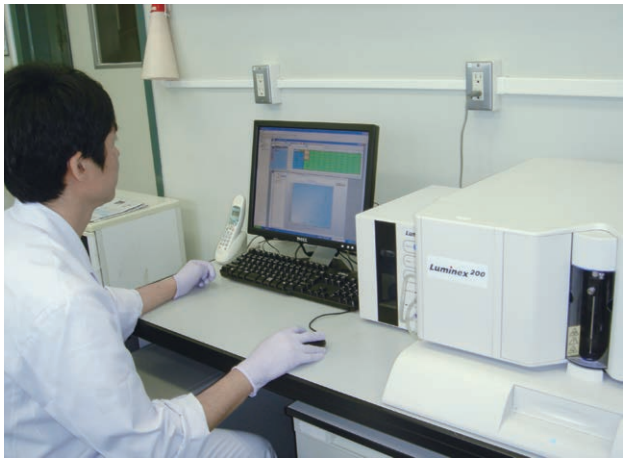
Research Departments

Departments of Clinical Studies, Hiroshima and Nagasaki

The Adult Health Study (AHS) is an indispensable program for determining radiation risk for diseases that cannot be documented adequately through the mortality study. For instance, we are studying how much radiation affects the risk of nonfatal heart disease or stroke, high blood pressure, cataracts, various benign tumors, etc. This is accomplished by giving a group of up to 20,000 A-bomb survivors detailed clinical examinations every two years. An increased risk for a number of these diseases or conditions has been observed in the AHS cohort.

However, it is well known that both lifestyle factors and genetic factors, in addition to radiation exposure, contribute to the development of disease. To determine whether or not the increased risk observed for nontumor diseases in the Life Span Study and the AHS cohorts is actually attributable to radiation exposure, it is necessary to further analyze the lifestyle-related factors, including smoking and dietary habits, biological characteristics, psychological factors, and genetic background. Studies using stored biological samples collected from the AHS population help clarify the joint effects of radiation and other environmental and genetic factors. AHS subjects have provided biological samples for such investigations at every examination, repeated samples that are rarely available elsewhere in the world and that allow us to observe changes over time in important biological risk factors and indications of subclinical disease.

Previous RERF studies demonstrated that younger survivors showed higher radiation risk for cancer and certain noncancer diseases compared with those exposed in adulthood or when elderly. The subjects exposed at younger ages are an extremely important group in terms of risk assessment. Therefore, we have added >1,900 survivors who were exposed before the age of 10 years to the AHS population to investigate their radiation risk of noncancer diseases, which will substantially improve our knowledge about radiation risk for this younger age group.



Luminex Complete System 200 (fluorescent microbead array system). This system made it possible to measure multiple cytokines simultaneously using limited sample volume (serum, plasma, etc.) by the multiplex bead array assay.

In a 4-year F_1 clinical study, approximately 12,000 offspring of atomic-bomb survivors, children born after 1 May 1946, have participated in a health examination to evaluate the possible association between parental radiation exposure dose and the prevalence of various common diseases in the offspring (such as, heart disease, stroke, hypertension, and diabetes). This group is still young—their average age is only about 55 years—and thus relatively little disease has developed yet. The highest incidence and mortality from noncancer diseases is still a number of years in the future. We have begun a continued clinical follow-up to older ages of this group of offspring of the A-bomb survivors.

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Department of Genetics

The Department of Genetics consists of two groups: One is working on chromosome aberrations in white blood cells, and the other on DNA alterations in the offspring of A-bomb survivors to detect heritable genetic mutations. The chromosome study aims to estimate radiation doses received by individuals using the frequency of a certain type of chromosome aberration (translocation) as an indicator of radiation dose. A translocation occurs when a piece of a chromosome gets broken off, damage that radiation tends to do, and re-attaches to a different chromosome. We also use the electron spin resonance (ESR) method to detect a trace material in tooth enamel that is caused by radiation exposure; the amount of this material gives a measure of radiation dose. The results can provide information to confirm or improve our current estimates of individual doses, which are used to evaluate both cancer and noncancer risks of A-bomb radiation exposures. Genetic studies of breast cancer, skin cancer, and high blood pressure are also being conducted.

The molecular studies of heritable radiation effects include several approaches. (1) We estimated how frequently radiation causes mutations in about 1,000 genes in the reproductive cells of male mice. That was done because past estimates that were based on the analyses of very few genes have been regarded as inaccurate, so a better estimate is needed. (2) Using a microarray system containing about 2,500 probes (where each probe contains cloned DNA fragments derived from various parts of the human genome [the "genome" is the complete set of genetic information in a person's DNA]), it was possible to detect a few large deletions or duplications in the genomes of 225 offspring of the A-bomb survivors. Because of the low frequency of such mutations and the availability of new, more powerful technology, we are planning a study using >2 million probes. (3) We investigated whether radiation may have caused what is called "genomic instability" in the germ cells of the survivors. If "genomic instability" were related to radiation exposure, it would be a way by which radiation disease risk could be transmitted to offspring. However, we found no evidence for radiation-associated genetic defects related to transmission of genomic instability.

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Department of Radiobiology/Molecular Epidemiology

For accurate risk estimation and effective prevention of radiation-associated diseases, it is essential to understand the mechanisms causing harmful effects of radiation exposure on humans as well as to identify individuals sensitive to such radiation-related harm. This will help clarify the biological basis for the findings among A-bomb survivors of increased risks for selected cancers, cardiovascular disease, and possibly diabetes. There is a potential for effective prevention and treatment if we understand the mechanisms behind radiation-associated diseases. We have therefore conducted several types of studies in order to improve mankind's knowledge.

First, since RERF scientists in the department's Immunology Laboratory have observed alterations in the immune system that are associated with A-bomb radiation dose as well as with aging of the survivors, we are exploring in *Immunology Studies* whether radiation-accelerated aging in the immune system may be related to the increased risk of several aging-associated diseases among A-bomb survivors including cardiovascular disease and selected cancers. Immune system aging is detected by changes in the relative numbers of various types of immune cells and how well they function. We are also studying how radiation may damage the cells and tissues that produce the mature immune cells.

To study the biological implications of radiation damage to the immune system, a study is being undertaken to see the degree to which the dose of A-bomb radiation received decreased people's ability to develop an immune response to influenza vaccination.

The human genome (the complete set of genetic information in people's DNA) differs among individuals, and such variation is in part responsible for how individuals differ in their biological susceptibility to environmental chemicals or radiation exposure and in their development of lifestyle-associated diseases. *Immunogenome Studies* are investigating genetic factors responsible for differences among individuals in susceptibility to radiation effects and to the development of lifestyle-associated diseases, to help

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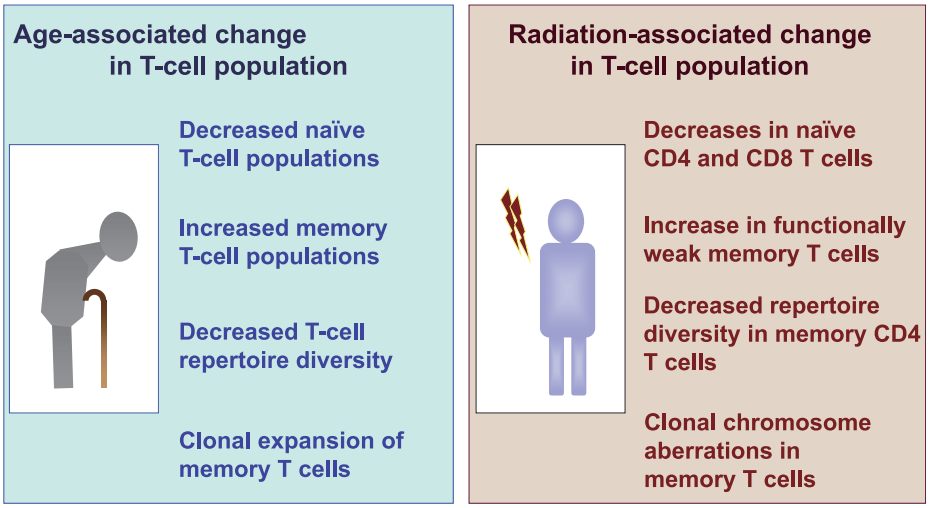
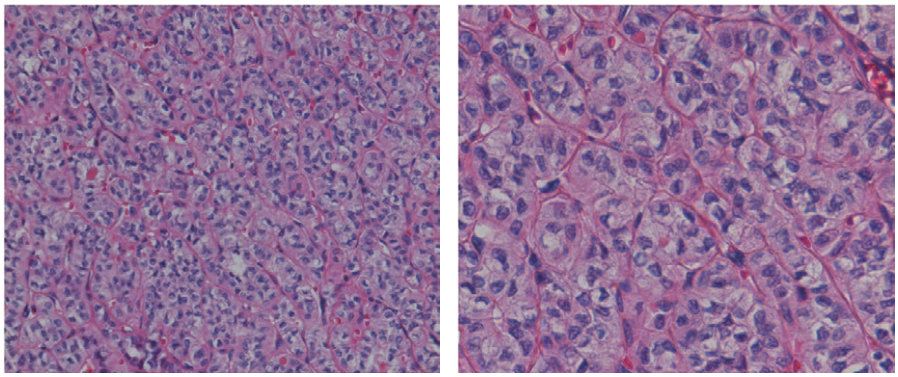
characterize individual risks for principal radiation-associated diseases.

The department's *Cell Biology Studies* principally aim at examining genetic and epigenetic (i.e., modification of genetic functions without a change in the DNA sequence) characteristics of thyroid, colorectal, and lung cancers among A-bomb survivors, in order to understand molecular mechanisms behind radiation-related cancer. We are seeking to clarify which carcinogenic pathways/molecular events are preferentially associated with radiation exposure. In radiation-associated adult-onset papillary thyroid cancers (PTC), for example, we found that the frequency of two types of genetic change (rearrangements in the *RET/PTC* and *ALK* genes) significantly increased with increasing radiation dose.



Age- and radiation-associated alterations in the T-cell system in humans (modified from Kusunoki et al., *Radiat Res* 2010; 174:870–6). Left panel shows an outline of aging of the T-cell system. Right panel indicates that similar alterations in the T-cell systems have been observed in association with radiation exposure among A-bomb survivors.

Trabecular/solid-like architectures observed in PTC cases with *ALK* rearrangement



Trabecular/solid-like architectures as shown in these pictures are frequently observed in PTC cases with *ALK* rearrangements that we have found for the first time in PTC cases among A-bomb survivors. Similar structures have also been observed in Chernobyl PTC cases.

Departments of Epidemiology, Hiroshima and Nagasaki

The primary task of the Department of Epidemiology is to study the atomic-bomb populations to document the health risks associated with human radiation exposure. For over 60 years, follow-up studies of about 120,000 A-bomb survivors (the Life Span Study [LSS]), 3,600 with prenatal exposures and 77,000 children of survivors have been conducted. These observations have been clarifying many aspects of radiation risk estimates for various cancers and noncancer diseases such as cardiovascular diseases, and have been examining other factors that may modify radiation risk.

Since more than 80% of survivors exposed when young are still alive, there is currently appreciable uncertainty as to lifetime cancer and noncancer risks from radiation exposure. Therefore, it is essential to continue the follow-up for an additional 20 years or more to document the full impact of the radiation exposure. Radiation-related cancer and noncancer diseases are continuing to increase among A-bomb survivors throughout their life, including among those who were young at the time of the bombing.

The risks of stroke and heart diseases also increase at moderate-to-high doses, though the degree of risk at low doses is uncertain. Although the radiation risk for the adult incidence and mortality of solid cancers appears to be somewhat lower in the *in utero* cohort than for those exposed in early childhood, the risk of noncancer diseases was suggestively higher in the *in utero* cohort. It is expected that further follow-up will provide more definitive evidence on cancer and noncancer disease risks from *in utero* exposure since they are approaching the ages at which most disease is expressed. To date, in the children of A-bomb survivors (F_1 generation) there has been no increase in cancer incidence or noncancer mortality associated with parental radiation exposure. However, since the average age of the F_1 cohort at the recent follow-up was less than 50 years, most of their pathology lies in the future, so that studies of this cohort will become increasingly important in the future.

The Department of Epidemiology is also responsible for the operation of the tumor registries in Hiroshima and Nagasaki prefectures and for analyzing data from those registries. Those data are of high quality and are extremely important for determining accurate cancer incidence rates among the A-bomb survivors.

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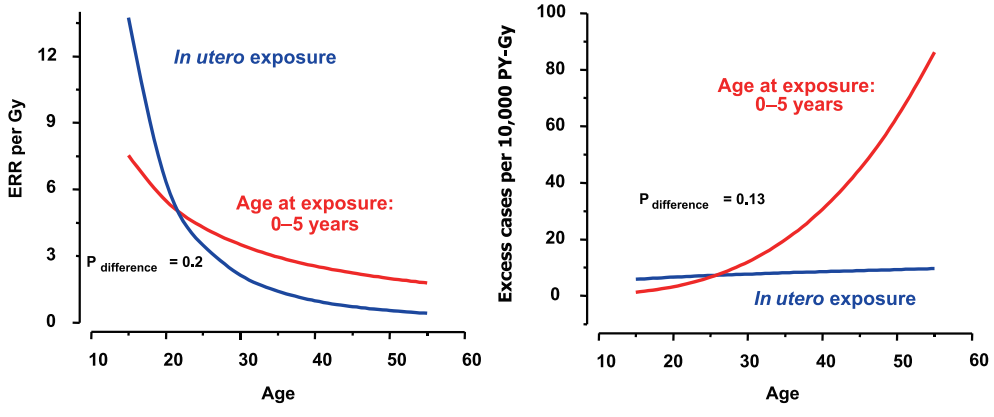


***In utero* ERR/Gy = 1.0 (95% CI: 0.2, 2.3)**

Figure. Solid cancer risk patterns for *in utero* and childhood exposure in A-bomb survivors (Preston et al., *J Natl Cancer Inst* 2008; 100:428–36)

Department of Statistics

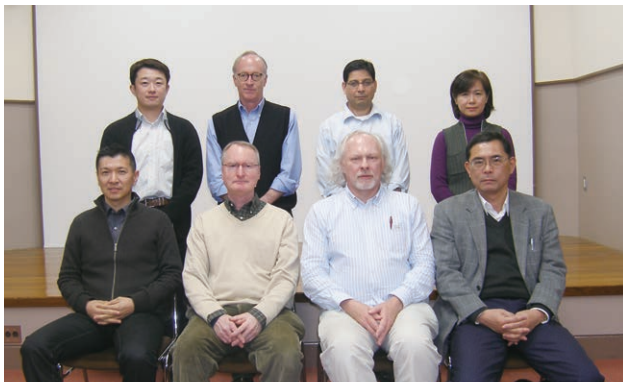
Radiation risk assessment and dosimetry

The Department of Statistics has historically led in the development of analytical methods for major aspects of the RERF research program such as risk estimation and actively supports the application of those methods in major studies by having a statistician serve as part of the team performing a study. This includes not only the development of tools such as Poisson regression but methods to handle various problem areas in follow-up data of major RERF cohorts, such as dose uncertainty and undocumented out-migration from cancer tumor registry catchment areas, among many others.

The department also implements RERF dosimetry systems and maintains a database of survivor dose estimates, presently using the DS02 system provided by a combined external and internal scientific working group, and provides key statistical and dosimetric support to RERF projects in biodosimetry.

Statistical methodology for other RERF studies

The department also develops methods for analysis of longitudinal data from the Adult Health Study. Members of the department evaluate and develop special methods of sub-cohort sampling for various special clinical studies, such as nested case-control studies of cancer radiation effect modification using serum biomarkers, or molecular epidemiology studies of the immunogenome and cancer susceptibility in response to radiation. They also develop many special methods to meet the requirements of RERF's basic science research in genetics, immunology, radiation biology, and molecular epidemiology, including methods for the increasing number of research projects that generate high-dimensional data (hundreds or thousands of measurements per sample).



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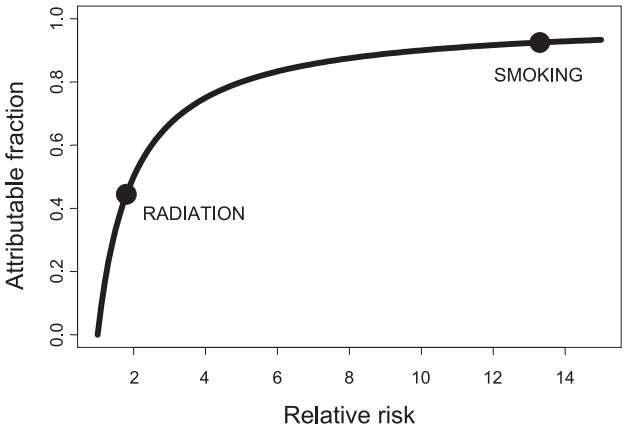

Figure. Probability of causation is most simply estimated by using the attributable fraction. Attributable fraction (AF) is related to relative risk (RR) by the formula AF = (RR–1)/RR. Because this relationship is non-linear, risk factors with relatively smaller relative risks have proportionately larger attributable fractions. This is illustrated by the figure, which shows the attributable fractions for lung cancer at age 70 with radiation (1 Gy lung dose; relative risk 1.9) and heavy smoking (more than 25 cigarettes/day; relative risk 13.3) from the analysis by Pierce *et al.* (Pierce DA, Sharp GB, Mabuchi K: Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat Res* 2003; 159:511–20). Corresponding estimated probabilities of causation are 47% for 1 Gy radiation and 92% for heavy smoking. Thus, comparing relative risks alone does not give an accurate assessment of the probability of causation. A risk factor with a relative risk of 2.0 produces an attributable fraction of 50%, implying that half of the cases of disease might be related to the risk factor. However, this interpretation implies that the risk is independent of other risk factors; in other words, that the joint risk is multiplicative. An additive joint risk would lead to smaller attributable fraction for radiation in the presence of smoking (Figure reproduced from Cologne J, Cullings H, Furukawa K, Ross P: Attributable risk for radiation in the presence of other risk factors. *Health Phys* 2010; 99:603–12).

Department of Information Technology

Hiroaki Katayama, Research Scientist and Department Chief, ITD

The Department of Information Technology (ITD) consists of the Systems Technology Section and the Library and Archives Section, both of which engage in activities to support RERF research efforts. The Systems Technology Section is in charge of maintenance of the computer/network environment as well as maintenance and management of large-scale and complex research databases. The Library and Archives Section manages scientific reports and historical documents, and provides literature retrieval systems.

For both ABCC and RERF, the department has continued to engage in data processing and provide the necessary computer environments, but many issues that must be considered have emerged because of personnel reduction, increase in average age of staff members due to the drastic decrease in number of new employees, and increased complexity of requested systems. It was therefore decided this fiscal year to establish a committee to review future information processing systems at RERF (committee chairman: RERF Chairman Toshiteru Okubo). Prior to that, we delegated the task of analyzing the present status and clarifying relevant issues to an outside expert organization (NTT Data, Inc.), and on June 6, received the organization's final report on its investigation and assessment. The report recommended that work methods be documented to prevent risks in the information processing systems that can be predicted at the present stage and that may surface in the future due to shortage of personnel. We need to take measures through the streamlining of other areas of work to secure staff members who can engage in such documentation work. For that purpose, we will establish a committee including representatives of all users of our systems (from the research departments and the Secretariat, which initiate job requests to ITD) in order to discuss future directions and measures for improvement.