

FY2022 Report of Activities

Radiation Effects Research Foundation

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I. Report of Major Activities

Epidemiologic data on mortality and cancer incidence from the A-bomb survivors (the Life Span Study [LSS], the in utero study) and their children (the F1 generation studies) have long been a primary basis for national and international estimates of the risks of cancer and other diseases from exposure to ionizing radiation. The unique importance of the LSS study stems from the combination of its large size, wide range of exposure levels, inclusion of all ages at exposure, and long, high-quality follow-up of mortality and cancer incidence. However, the LSS is only one facet of RERF's research activities. Clinical examinations and the collection of biosamples in the Adult Health Study (AHS, a subsample of the LSS) and the clinical, epidemiological and genetic studies of the children of A-bomb survivors provide more detailed information on health conditions of interest, including radiation-related non-cancer conditions, and the pathogenesis of those conditions in relation to radiation exposure, as well as the study of heritable mutations. Our basic science groups, in collaboration with the clinical studies and epidemiology departments, utilize the biosamples to further address the nature and extent of genetic (both heritable and somatic) effects, and molecular changes associated with health risks. These three components within the RERF research program provide an integrative approach into epidemiological, clinical, biological, and mechanistic aspects of human radiation risk. Such integrated opportunities are unique to RERF and demand the best possible science be conducted for the benefit of the survivors and the radiation research community. As we move forward, the primary focus of RERF studies will be on such integrated research programs through their development within the cancer, genetic and non-cancer research clusters. An additional and essential component of our research program development is the expansion of collaborations with institutions outside of RERF both in Japan and internationally. We have recently developed in partnership with our Board of Councilors a strategic plan emphasizing integrative approaches in our future studies.

1. Research Projects Examining A-bomb Survivors Health

1) Radiation and Cancer:

- To investigate the genomic alteration of subjects who developed MDS, the whole exome sequencing (WXS) of stored blood samples obtained from AHS subjects who developed MDS during follow-up has been conducted for serially collected blood samples of those subjects before the onset of MDS. The somatic mutations were identified, and the data will be analyzed with their clinical measurements collected through the AHS examinations. The number of subjects is 16, and the sequence data is only for subjects who developed MDS. Therefore, several challenges for the statistical analysis are expected in this project including the statistical power to detect associations among variables. However, these data will provide important information for the clonal hematopoiesis program project, and longitudinal hematopoietic measurements recently investigated in AHS such as RDW (Yoshida, Misumi, Kusunoki, et al. *British Journal of Hematology*, 2020) and monocytes (Yoshida, French, Yoshida, et al. *British Journal of Hematology* 2017) will be combined with this genomic data. Along with the statistical analysis of this project, a methodological study will be conducted for the investigation of causal relationship among longitudinal measurements of genomic and clinical measurements.

- [Chronic myeloid leukemia (CML) study (RP-P2-19 and RP-P1-23, Yoshida N)]
Leukemia is the only malignancy that developed shortly after the A-bomb, and it is widely recognized that radiation exposure can induce leukemia. A study of leukemia morphological classification (French-American British classification) among A-bomb survivors in 1950-1980 revealed that chronic myeloid leukemia (CML) most frequently developed during the period. CML is currently diagnosed based on the presence of the fusion gene BCR-ABL1. We have conducted a preliminary study to assess whether formalin-fixed paraffin-embedded (FFPE) samples of 3 CML autopsy cases are available for molecular analysis. We performed pathological analysis and extracted DNA and RNA from the unstained slides. Using the extracted DNA and RNA, we evaluated the existence of BCR-ABL1 and several genomic mutations with a diagnostic value for hematological malignancies.
- *Updated LSS mortality report (RP 1-75)*: Analysis of mortality risk due to atomic bomb radiation among survivors is the most important in evaluation of late health effects due to exposure to atomic bomb radiation. It is because vital status and cause of death of cancer and noncancer diseases are the most essential for evaluation of health outcomes in epidemiology. Also information of vital status and cause of death is collected for LSS subjects living over the whole Japan whereas information on cancer incidence is collected from those living in Hiroshima and Nagasaki prefectures. International risk assessment groups use the results of mortality risk as the primary basis for radiation-risk estimation. Since the first LSS report was published in 1962, the results have been published periodically and the latest 14th report was published in 2012 for the follow-up data during 1950-2003. Analysis for a new LSS mortality report (15th) has started using the data through 2017, updated dose estimates, and newly available information on lifestyle and residential factors in collaboration with the Dept. of Statistics. These analyses include investigation of dose-response shape and radiation risk at low dose levels considering potential confounding by geospatial factors, lifestyle factors (smoking, alcohol drinking, body mass index), some indicators representing socioeconomic status, and so on, and also variation in baseline rates. Analysis of the same models that were used in the LSS 14 Report has been conducted for the data extended to 2017, and the results were substantially similar to the previous report. An integrated lifestyle dataset including information obtained from the Mail Survey 2008 has been prepared. Currently, analysis is continued using the parametric background model used in our cancer incidence studies (Sakata R, et al.).
- *Hiroshima and Nagasaki tumor/tissue registries (RPs 18-61, 29-60)*: Precise information of cancer incidence and histological diagnosis of cancers is essential for radiation risk analyses of cancer. The Dept. of Epidemiology has a long history of taking care of the local systems of national and local cancer registries and tissue registries in Hiroshima and Nagasaki, including communication with local community, publishing annual reports, and contribution to the related committee to establish the basic plan for cancer control in each municipality. Also, the Department is collecting the information regarding the members of all cohorts from those registries. Since the legal system of national cancer registry is active for cancer cases diagnosed in 2016 or later, the department staff has made huge efforts to utilize the information for studies in RERF. Although there are practical problems due to the legal restrictions such as strict safety control standards of facilities, unlinkable anonymization in analytical datasets, and discarding the datasets after completion of the study, the safety control organizationally, physically, technically, and educationally has been completed for the cancer information users in RERF. The infrastructure for the users in RERF has been arranged (e.g., construction of office door locks, restriction of PC for analysis, internal web

page for providing information on how to use the cancer incidence data for research, data dictionary, and application to make the dataset linked with cancer incidence data). The webinar introduced the related-law and regulations that users must follow and the new infrastructure in RERF. However, no transfer of the data linked with the National Cancer Registry data to foreign countries is not allowed. We must overcome this problem together with epidemiologists and outside RERF researchers to share RERF cancer incidence data for collaborative studies. Tissue registry in Hiroshima was ceased in 2021, so we are planning alternative methods to collect the information of histological materials of LSS subjects with local pathologists in Hiroshima. Tissue registry in Nagasaki is continued and the information is continuously available for us. Cancer incidence information of LSS through 2019 in both Hiroshima and Nagasaki will be obtained by March 2023, from the National Cancer Registry (Sugiyama H). Population-based information has been analyzed for specific purposes to underpin radiation risk analyses and has been submitted to the worldwide summary program, the Cancer Incidence in Five Continents, XII, by the International Agency for Research on Cancer (IARC)/International Association of Cancer Registries (IACR). In addition, the cancer information is planned to contribute on CONCORD-4 study by the London School of Hygiene & Tropical Medicine (RP-S2-17, Sugiyama H).

- Since the blood specimens of approximately 25,000 A-bomb survivors who were all subjects of the Adult Health Study, including those who developed cancer early after the A-bombings, have been stored since the health examinations in 1958, genome analysis using these specimens, initially for GWAS studies, will enable us to elucidate the mechanisms of radiation-related cancer development in detail and to identify individual differences in susceptibilities to these cancers. There are complete blood samples from all AHS subjects, and a large amount of smear samples from blood tests performed during every 2-year examination are stored. To determine the feasibility of this approach, it is necessary to investigate the availability of smears prepared from trace amounts of blood specimens. In this study, we compared the ability of the Axiom Japonica Array NEO (AJAN) and the Infinium Japanese Screening Array (IJSA) to accurately identify SNPs in DNA extracted from smears prepared from blood specimens of six in-house volunteers. The call rates and concordances of the SNPs in these two SNP arrays were examined and compared using DNAs obtained from fresh-blood specimens (W-DNA) and DNAs extracted from smears prepared from the blood specimens and amplified with the QIAGEN REPLI-g DNA amplification kit (amplified DNA). As a result, the average call rates of W-DNA and amplified DNA for two SNP arrays were more than 99% and 96%, respectively, and concordances were more than 93%, but IJSA showed more reliable results with an average concordance of 99.7%. Subsequently, a new preliminary study is being conducted using DNA extracted from fresh and previously stored blood specimens. DNAs were extracted from smears stored 10, 30, and 50 years ago, paper discs stored 20 years ago, and Giemsa-stained specimens stored 30 years ago. (Hayashi, Yoshida K, Ohishi, Yoshida N, Kato, Sposto, Tokunaga, Ueki, and Ozasa, RP-P1-19, terminated by September 2022, and Hayashi, Ohishi, Brenner, Kato, Cologne, Yoshida N, Hamasaki, Kodama, Tokunaga, Ueki, Matsuura, Yoshida K, Tanabe, and Noda, RP-P2-22). PI: Hayashi.
- The purpose of this study is to investigate whether the radiation risk of colon cancer differs between anatomical sites taking the carcinogenesis pathway of colon cancer into account. Likelihood-based inference is conducted based on mathematical models that assume two-path-multi-stage carcinogenesis with some parameters related to radiation exposure. This is a collaboration between Dr. Misumi of RERF and Dr. Kaiser, formerly of Helmholtz

Zentrum München, Institute of Radiation Protection (HMGU). This project has recently been on hold due to a variety of reasons – Dr. Casteletti and Dr. Simonetti, who played leading roles in this project, left Dr. Kaiser’s group, and due to funding considerations Dr. Kaiser has decided to move from HMGU to another institute in January 2023 in order to continue conducting radiation research. Dr. Kaiser has agreed to continue conducting mechanistic modeling of the LSS data after his move. Mechanistic models developed for colon cancer are ready for use in a simplified setting such as two-paths two-stage. Also, the R script for mechanistic model has been completed and an R package msce was developed. At the Zoom meeting in 2022, the milestones have been updated. Dr. Misumi will start investigating the R package Dr. Kaiser’s group developed and will also start analyzing the LSS data. Also, Drs. Kaiser and Misumi will both analyze the adenoma data of Bavaria and LSS, respectively, and will continue discussions in 2023.

2) Radiation and Non-Cancer Effects:

- Ophthalmologic examinations for our cataract study using these devices were initiated in Hiroshima and Nagasaki in collaboration with ophthalmologists in Hiroshima and Nagasaki Universities in April 2016. Supervision for this study is made by a cataract specialist in Kanazawa Medical University. Ophthalmologic examinations among 1048 AHS subjects who were ≤ 15 years of age at the time of bombings (including 115 *in utero* exposed subjects) were finished in March 2020 in Hiroshima and Nagasaki. Scoring of cataract severity using photographed images was completed by an ophthalmologist and a statistical analysis was completed in collaboration with the Statistics Department.
The presence or absence of cataracts was analyzed by inverse probability weighting logistic regression model (IPWLR) to account for possible missing data due to cataract surgery. The results of analysis suggested that cataract prevalence was significantly associated with age, sex, city, smoking, ultraviolet, and axial length. A significant association between radiation and posterior subcapsular cataracts was also shown. However, radiation effect on cortical cataracts was not observed. 86% of the participants of the present study did not participate in the past cataract study conducted in 2000-2002. This may be one of the reasons for the difference between the results of the previous and current studies.
- It has been recognized since the 1960s that the heart may be damaged by substantial doses of radiation (> 30 Gy), such as doses used during mantle radiotherapy for Hodgkin lymphoma. With regard to lower dose radiation, epidemiological data are insufficient and biologically plausible mechanisms are lacking, although there are several theories which may be applied to lower dose exposure, including microvasculature effects, oxidation, inflammation, and mutation theories. Previous results from the LSS and AHS indicated the association between radiation exposure and CVD mortality or incidence, but the diversity of disease subtypes and confounding risk factors related to CVD risk complicate the estimates of radiation effects. We have conducted studies the objectives of which are to examine in detail the association between radiation exposure and atherosclerosis, heart disease, chronic kidney disease (CKD), stroke, and myocardial infarction.
- [*Atherosclerosis study, Part 1 (RP7-09, Nakamizo T)*]
Past studies have reported an association between radiation exposure and cardiovascular disease mortality/morbidity. Although the mechanism is unclear, a plausible one is radiation-induced atherosclerosis. To examine the association between radiation and atherosclerosis, we measured a comprehensive set of indicators of atherosclerosis including ankle-brachial

index, carotid intima-media thickness, augmentation index, central systolic blood pressure, brachial-ankle pulse wave velocity, upstroke time, and aortic calcification evaluated from chest and lumbar X-rays among 3,775 AHS participants in 2010-2014. Data were analyzed by structural equation modeling with latent variables representing main atherosclerotic pathologies: 1) arterial stiffness, 2) aortic calcification, and 3) plaque.

Aortic calcification and plaque were linearly associated with radiation, but arterial stiffness was not related to radiation. The association was not so strong—comparable to about 2 years of aging per Gray of radiation exposure. The results of this cross-sectional study suggest a possible causative role of radiation on atherosclerosis, which should be confirmed by future longitudinal studies. A paper on the results has been published (*Eur J Epidemiol*, 2021; 36).

- *[Atherosclerosis study, Part 2 (RP2-11, Nakamizo T)]*
A recent study (RP 7-09) suggested a relationship with subclinical atherosclerosis. The mechanism is, however, unclear. In addition to potential involvement of inflammation to be investigated in the Clonal Hematopoiesis Program Project, we will investigate disturbance in vascular repair driven by the proliferation and differentiation of vascular (mesenchymal) stem/progenitor cells. This is a cross-sectional study among about 2,000 AHS subjects in Hiroshima. We have measured several multi-functional cytokines involved in the injury-repair system such as osteopontin, osteoprotegerin, and vascular endothelial growth factor (VEGF)-A. We have assessed reliability and pre-analytical properties of the measurements, in terms of intra- and inter-assay reproducibility (coefficient of variation: CV), storage stability, and intra-individual variation (intraclass correlation coefficient: ICC).
- *[Program project: Clonal hematopoiesis and inflammatory phenotypes potentially related to atherosclerosis risk in atomic-bomb survivors (Yoshida K, PI), project 2 (Nakamizo T)]*
Previous studies in A-bomb survivors suggest a relationship between radiation exposure and atherosclerotic diseases and inflammation. Recent evidence in studies in not involving radiation exposure suggests that clonal hematopoiesis (CH) can cause chronic inflammation leading to atherosclerotic diseases. To evaluate the hypothesis that CH caused by irradiation to hematopoietic stem cells is a cause of chronic inflammation and subsequent atherosclerosis in A-bomb survivors, we are initiating a study that analyzes stored AHS datasets relating hematological profiles with inflammatory and atherosclerotic indicators. The relevant data has been extracted from the RERF database.
- Clonal hematopoiesis (CH), potentially associated with radiation exposure and increased risks of inflammatory diseases, is of substantial interest to the scientific community. To develop strategies for assessments of CH linking to radiation-associated noncancer diseases, specifically arteriosclerosis as a part of CH program project, we conducted preliminary experiments to establish one or more mouse models that can test the hypothesis that CH in irradiated mice is involved in pro-inflammatory phenotypes and can promote atherosclerosis formation. Preliminary mouse experiments ensured an extremely high prevalence of CH in 3-Gy whole-body irradiated mice, and CH in each of the irradiated mice contained multiple clones that expanded to collectively comprise 60-80% of a whole population of bone marrow nuclear cells, suggesting that high-dose radiation can induce massive hematopoietic cell generation and proliferation from a tiny number of stem/progenitor cells. We also examined longitudinal trajectories of CH mutations in irradiated mice by using longitudinally-collected blood cells. The blood of irradiated mice exhibited elevated levels of both pro-inflammatory myeloid cells and red blood cell distribution width (RDW), which is often observed in human populations having CH. These preliminary study results have been published in Scientific

Reports (2022). To assess a feasibility study to examine CH and atherosclerosis formation in LDLR-knockout mouse model, we have initiated a preliminary experiment assessing clonal hematopoietic cell populations in the bone marrow, the peripheral blood, and the aorta of LDLR-knockout mice irradiated with 3 Gy and fed with a high-fat diet (Yoshida, Kusunoki et al., CR155). PI; Yoshida. *Scientific Reports* 12: 17276 (2022) doi: 10.1038/s41598-022-21621-6

- In this study of the reliability and stability over long-term storage and inter-individual variation of assays for cytokines, Dr. Cologne employed linear random effects models to assess reliability via coefficients of variation (CV), intra-class correlations (ICC), and rate of decay over time. This work has resulted in the draft manuscript: *Nakamizo T, Cologne JB, Kishi T, Takahashi T, Inoue M, Ryukaku H, Hayashi T, Kusunoki Y, Fujiwara S, Ohishi W. Reliability, stability during long-term storage, and intra-individual fluctuation of the serum levels of osteopontin, osteoprotegerin, vascular endothelial growth factor-A, and interleukin-17A. [Target Journal - TBD]. 2022; In Development. [RP 2-11] [Ahs]*

3) Genetic Effects of Radiation:

- The most important research initiative in the MBS genetics program and for RERF in general is the whole genome sequencing (WGS) study focusing on human trios consisting of atomic bomb survivors and their offspring. This is a major part of the institutional-wide F₁ umbrella program. In FY2022, we held meetings with external collaborators, developed the scientific research protocol that has been approved following external review. These studies will be conducted in collaboration with Dr Stephen Chanock (US NCI) and Dr Nakagawa at RIKEN. Mutation analysis will be performed on an external cloud server and an on-premise server, and our external collaborators will be able to perform analysis on the cloud server, but will not be able to download the data, assuring the protection of subjects' genome information. In addition, the correlation analysis between genome data, epidemiological data, and clinical data of the subjects will be performed only within RERF so that personal information will be thoroughly managed. One of the most important challenges in this WGS research has been obtaining social consensus and addressing ethical issues. On this point, we hosted an ELSI International Workshop last year, and this year, we have held an external advisory committee on the trio-WGS research in Hiroshima and Nagasaki which included survivors and F₁s. The ethical procedural part of the research plan reflecting their comment has been included in our protocol which is currently under review by the IRB. When approved, we plan to obtain informed consent from the subjects as soon as possible and conduct the research. Uchimura, Satoh, Noda (MB) and Sposto (S) A part of CR162, PI; Uchimura.
- In 2022, Dr. Misumi conducted statistical analysis of longitudinal trajectories of mutations identified in the WXS. We observed different characteristics in the variant allele frequency (VAF) of mutations between subjects with higher radiation dose exposure and those with lower radiation exposure. Relatively higher VAF existed a long time before the diagnosis of MDS in higher dose subjects compared to lower dose subjects and the VAF increased near the time at MDS diagnosis. Dr. Misumi applied multi-level linear mixed effects models to describe the longitudinal difference of mutational clones between dose groups. Also, Dr. Miyazaki and other collaborators are conducting whole genome sequencing (WGS) for selected subjects to investigate the mutational signature of atomic bomb survivors who developed MDS. The WGS will be completed during 2023. A manuscript will be written based on the WXS and WGS results.

2. Research Projects on the Health of A-bomb Survivors Children (F₁)

- We have developed the analysis plan with Statistics Department's FOCS Analysis Working Group through monthly meeting to examine associations between parental radiation dose and the development of multifactorial diseases in the F₁ offspring of A-bomb survivors. The datasets are being prepared in collaboration with Departments of Statistics and Epidemiology.

- [*Pathogenesis of Myelodysplastic Syndrome (MDS) (RP1-17, Miyazaki Y and Imaizumi M)*] This project has been developed in collaboration with the Nagasaki University and the Kyoto University. Radiation is one of the causes of the development of hematological malignancies. A-bomb survivors have a high risk of hematological malignancies, even 50 years after exposure, such as acute myeloid leukemia (AML) and MDS. Recent genome analyses of these diseases have demonstrated that most of samples contain several gene mutations, and that these mutations might be found before clinical diagnosis. We hypothesize that a hematopoietic progenitor or stem cell with a small number of gene mutation acquires additional gene mutations over time (more than several years) and causes hematological malignancies and that ionizing radiation increases the chance of such gene mutations occurring. We are conducting a study to detect mutations in serially stored blood samples of AHS participants who developed MDS using next-generation genome analysis technology. Objectives are to determine dynamics of mutated clones before clinical diagnosis of MDS and to explore how it differs by exposed radiation dose. This study will answer the very important question about how radiation-induced myeloid malignancies develop, which has never been tested.

Whole exome sequencing of blood samples serially collected before and after MDS diagnosis in 17 subjects were successfully conducted with average depth of 200-fold. MDS clones were detected 4-22 years before diagnosis and expanded during the development of MDS. There are two patterns in clonal evolution; 1) sustained expansion of MDS clones which had clonal-hematopoiesis related alterations (ex. *DNMT3A*, *TET2*) and 2) remarkable clonal shift and/or rapid expansion of MDS clones which had complex karyotypes and del11q including *ATM*. The former pattern was mostly observed in the less-exposed survivors (<1Gy) and the latter one was mostly observed in the high-exposed survivors (≥1Gy). There was a difference in the trajectory of variant allele frequencies of mutations between less-exposed and highly-exposed survivors.

Whole genome sequencing of blood samples serially collected before and after MDS diagnosis in 9 subjects were successfully conducted with average depth of more than 100-fold and the analysis is ongoing.

- [*Chronic myeloid leukemia (CML) study (RP-P2-19 and RP-P1-23, Yoshida N)*] Leukemia is the only malignancy that developed shortly after the A-bomb, and it is widely recognized that radiation exposure can induce leukemia. A study of leukemia morphological classification (French-American British classification) among A-bomb survivors in 1950-1980 revealed that chronic myeloid leukemia (CML) most frequently developed during the period. CML is currently diagnosed based on the presence of the fusion gene BCR-ABL1. We have conducted a preliminary study to assess whether formalin-fixed paraffin-embedded (FFPE) samples of 3 CML autopsy cases are available for molecular analysis. We performed pathological analysis and extracted DNA and RNA from the unstained slides. Using the extracted DNA and RNA, we evaluated the existence of BCR-ABL1 and several genomic mutations with a diagnostic value for hematological malignancies.

PCR /RT-PCR/droplet digital PCR (ddPCR) and pathological analyses indicated that extracted DNA and RNA from FFPE samples are suitable for traditional molecular analysis. Analysis of ddPCR identified BCR-ABL1 in 2 of the analyzed cases, but not in the other case, suggesting that CML diagnosed using pathological criteria alone may result in misdiagnosis. Review of autopsy reports suggested that all analyzed cases had myeloproliferative neoplasms including CML because all cases showed leukocytosis in the laboratory tests. We have also started another pilot-study related to the above to evaluate the feasibility of using DNA and RNA extracted from old FFPE samples for high throughput targeted sequencing.

- *F₁ cohort study (RPs 4-75, 18-61)*: Long-term studies of the F₁ cohort provide a framework for studying germline effects of radiation exposure and contribute important data to the largest study of its kind. After a major paper on mortality risk assessment was published in 2015, routine collection of case information is continuing. The individual doses of the parents of F₁ cohort members will be updated to DS02R1 by March, 2023 and the location at the time of bombing for the parents whose exposure status was unknown were investigated in the basic survey materials and updated (Sakata R). As residential information is essential for ascertainment of cancer incidence through the national cancer registry system, the information on participants in the F₁ Offspring Clinical Study (FOCS) has been collected and the record linkage will conduct (Sugiyama H, Kadowaki Y).
- An umbrella program project for comprehensive studies on F₁, including providing identification and availability of information of ‘trio’ members has been developed. In this program, the Dept. of Epidemiology will play a leadership role in a genotype/phenotype analyses. Dr. Noda of the Dept. of Molecular Biosciences leads this umbrella program.
- *Mortality surveillance (RPs 1-75, 2-61, 4-75)*: This is a primary responsibility of the department. Mortality follow-up for all cohorts (LSS, F₁, *in utero*) continues on a 3-year cycle. Mortality data are complete through 2017 and include underlying cause of death as well as associated causes of death. Archiving has been conducted of early-period materials (scanning and digitization) including questionnaires for the major cohorts and other subjects as part of the developing Research Resource Center (Sakata R).
- *Multi-state models for disease and mortality in the F₁ clinical study (FOCS)[RP4-10]*
Drs. Cologne and Yamamura led a working group comprising also Dr. Sposto and Ms. Funamoto to evaluate methods applicable to the F₁/FOCS analysis, which included illness-death models, multi-state models (MSM) with death as an absorbing state, and issues of interval censoring. This group met regularly during 2020 and 2021 to study these statistical methods and applicable software, applying these to preliminary data from the clinical follow-up study of offspring of atomic-bomb survivors. Focusing initially on the intermediate states of diabetes mellitus, hypertension, and dyslipidemia with mortality as a terminal state, Dr. Cologne played the leading role in conducting exploratory analyses and drafting a summary of the working group’s findings. This working group completed its work in 2021, having investigated MSM approaches for this analysis and presenting this to Drs. Tatsukawa, Ohishi, Hida, and other collaborators in the Clinical Studies Department. The working group recommendations on the analytic approach were accepted. During 2022 Dr. Cologne authored a comprehensive analytic plan for this project, which was reviewed by working group members and collaborators in the Clinical Studies Department. The plan was presented to and commented upon by the Scientific and Ethics Committee for the Clinical

Study of the F1 Offspring of A-Bomb Survivors in July 2022 and was then finalized and approved in late 2022. Dr. Cologne and Ms. Funamoto are currently finalizing the data and processing code necessary to perform these analyses, which should commence in Spring 2023.

3. Research to Elucidate Individual Doses and Effects from the A-bomb

- *Coordinating of Organ Dosimetry Working Group (ODWG) activities:* The Department of Statistics has continued its coordination and collaboration activities in the binational working group that is tasked with developing an improved approach to organ dosimetry by using existing, DS02-calculated shielded radiation fields with new response function tables calculated from new and improved computational phantoms. Dr. Harry Cullings, former chief of the Department of Statistics, and Ms. Sachiyo Funamoto, the member of the Department who is primarily responsible for overseeing the technical implementation of the dosimetry system at RERF, were and are ongoing contributors to this work.
- In order to evaluate the dose dependent effects of A-bomb radiation on humans, a cytogenetic biological dosimetry study has been conducted over several years for a subset of A-bomb survivors in the AHS cohort. A total of 1,868 survivors (1,179 in Hiroshima and 689 in Nagasaki) were examined using the 2-color-FISH method for detecting the frequency of stable translocations involving chromosomes 1, 2, and 4. The dose response from FISH data showed a wide scattering of individual translocation frequencies in both cities as we observed in the previous solid Giemsa staining study. Differences between the two cities remained significant but was much reduced suggesting the large city difference in the past study was mainly due to different aberration detection rates between Hiroshima and Nagasaki laboratories. The city difference was not significant when Nagasaki factory workers were excluded from the analysis. The results suggested that radiation-shielding was still a significant dose-effect modifier but neither sex, city, nor smoking was significantly associated with background rate. We published these analyses this year. Sposto et al., *Radiation Res.*, in press. (Kodama, Hamasaki, Cordova, Cullings, RP 8-93). PI; Kodama.
- Dr. Yamamura continues here collaboration with Dr. Hida and others in the Clinical Studies Department in a reinvestigation of the association between radiation and cataracts based on the new DS02R1 dosimetry and rigorously standardized cataract assessment using a new ophthalmic camera. Dr. Yamamura designed and performed the statistical analysis of the relationship between radiation exposure and prevalence of cataracts. The analysis utilized inverse probability weighting analysis to account for informative censoring due to cataract surgery. The manuscript for this project is now in preparation.
- This paper reports a pilot study for development of an integrated time and dose model to explore the dynamics of gene alterations of low and high dose irradiation with transcriptome datasets in Gene Expression Omnibus (GEO). Genes that are correlated with doses and time were identified, and it was observed that differentially expressed (DE) genes of low and high dose exposures are involved in similar pathways. Also, there were two clusters of genes that are either positively or negatively correlated with both dose and time based on the parameters of the model that may have long-term transcriptional alterations. The proposed model helps to understand the long-term effects of irradiation on gene expression. This work is the subject of a paper in development: *Liu Z, Cologne JB, Amundson SA, Noda A. Candidate Biomarkers and Long-term Transcriptional responses over low and high dose ionizing radiation. [Target*

Journal - TBD]. 2022; In Development. [No RP] [Smnos]

- The life span study (LSS) of A-bomb survivors provides a unique source for radiation risk estimation. Although there are many publications out of this study, the risk estimation is challenging and remains a focus of research. A linear dose-response model is often used for risk estimation. Nonlinear dose-risk associations are also investigated. The computational results of a parametric model usually depend on its model specification. Different parametric models may lead to inconsistent or contradictory results. Dr. Liu, with the help of Drs. Cologne, Misumi, Nakamizo, and Ono, has proposed a deep learning model with TensorFlow for nonlinear risk prediction with the life span cancer incidence data. This data-driven nonparametric method does not rely on any specific parametric settings, is easy to implement, and may perform significantly better than its linear counterpart with different metrics. This work has resulted in a paper in development: *Liu Z, Nakamizo T, Cologne JB, Misumi M, Ono S. Deep Learning for Radiation Risk Prediction of A-bomb Survivors. [Target Journal - TBD]. 2022; In Development. [RP 1-75] [Smnos]*
- The work of the ODWG is approaching completion. Four papers have been published on various aspects of the new organ dosimetry, two additional have been submitted and one other is in development. In addition we recently discussed the issue of how best to assign and assess uncertainty in fetal doses that arises because (a) fetal phantoms were made for several fixed gestational ages, but the actual gestational age may lie between that of two phantoms; (b) true gestational age is unknown, but can only be estimated from birth date; and (c) fetal phantoms exist for three fetal positions, but fetal position changes over time and in any case is unknown. The resolution of this issue by the working group will possibly lead to an additional paper.
- With respect to dosimetry error specifically, there are a number of potential issues with the current dose error corrections used at RERF that we plan to address. First, the current dose error adjustments are based only on a classical dose error model – e.g., errors due to misspecification of the location of the subject – but do not consider additional so-called Berkson type error – e.g., that due to the fact that individuals at far distances, and therefore with lower doses, do not have shielding histories, so that average transmission factors for the corresponding shielding scenarios (inside, outside, etc.) are assigned. Second, the current classical regression calibration dose error corrections are only applied at higher doses ($> \sim 500$ mGy in Hiroshima, $> \sim 700$ mGy in Nagasaki, shielded kerma). In addition, the recent analysis of chromosome aberrations points to a systematic overestimation of doses for Nagasaki factory workers. In light of these issues and also of the likely adoption of new organ dose estimates, a re-evaluation of the issue of dosimetry errors is warranted.
- RERF is conducting genomics and omics studies of animal experiments and planning those utilizing atomic bomb survivors samples. Drs Liu and Misumi are working with a single cell sequence data of mice experiment conducted by Dr. Yoshida and applying a standard pipeline to investigate differential expression of genes associated with radiation exposure. Also, Dr. Liu and other members of the Department of Statistics are collaborating with MBS and Dr. Ono of the ITD to find out the needs of our future bioinformatics capability including the computational infrastructure. Moreover, massive multi-omics data are available in public domain. Drs Liu, Misumi, and other members of Department of Statistics are considering exploring the potential of integrating public omics data with ongoing genetics and omics studies at RERF.

- The primary focus of our work on dosimetry during FY2023 is continued preparation for the implementation of the revised organ dosimetry using updated computational phantoms, as described above. Implementation of the revised organ dosimetry is planned for 2023.

4. Projects to Release Research Results and to Collaborate with Other Scientific Organizations

Crucial to the mission of RERF is the dissemination of results of our studies to survivors and their children and to the international community. Toward that end we interact with local liaison councils representing the communities of Hiroshima and Nagasaki and provide information via public lectures and other activities. These will be described later in another section of this report. With respect to the international community there are a number of activities. These include seminars, workshop, participation at international scientific conferences, and international publication of results. This year 3 seminars were held at RERF presented by national and international visitors to RERF and published more than 60 scientific papers.

Collaborative Research Projects

- Ongoing international collaborative research projects

In addition to the above activities the development of national and international collaborations is essential to help disseminate results and to enhance RERF research programs. A list of current collaborations is provided below:

- a. Partnership with the University of Washington
- b. Partnership with Kurume University
- c. Collaborations with the US National Cancer Institute
- d. Collaborations with the University of Florida
- e. Collaborations with Outside Investigators:
 - 39 Japanese Institutions
 - 7 North American Institutions
 - 8 European Institutions

5. Training Programs for Domestic and Overseas Specialists

- 1) RERF held an online epidemiological training course for radiation biologists to deepen the biologists' understanding of RERF's epidemiological research and to promote interaction among investigators working in radiation research institutes (August 22-23, 2022; 70 participants in total, including 40 and 30, respectively, from inside and outside RERF).
- 2) The Department of Epidemiology accepted a long-term internship student on the Hiroshima University phoenix leader education program from June 6 through July 1, 2022 and provided the student with online lectures and on-the-job training.
- 3) Due to the effects of COVID-19, acceptance of trainees from overseas through the Nagasaki Association for Hibakushas' Medical Care (NASHIM) and the like was completely canceled; however, the training of the International Council for Health Care of Radiation-exposed (HICARE) was resumed to provide online lectures.
- 4) There was no invitation for the MHLW-sponsored International Exchange and Research Program in FY2022 again, so we did not recruit trainees from abroad.
- 5) The Department of Statistics recruited investigators who would participate in the International Fellowships for Research in Japan program, sponsored by the Japan Society for the Promotion of Science (JSPS), on the RERF external website; there was a candidate

who considered applying in 2024-2025. However, there was no applicant in FY2022, and the department could not apply to the relevant program.

6. Public Information Programs

i) RERF public lecture series

RERF's new public lecture series, initiated in FY2019, targets peace volunteer guides among other such individuals, in partnership with external organizations such as the Hiroshima Peace Memorial Museum. In FY2022, due to effects from the coronavirus pandemic, this series was developed in limited numbers, involving Zoom meetings with the Hiroshima Peace Friendship Center as well as the United Nations through the Hiroshima Peace Memorial Museum.

ii) RERF Open House event

RERF held the 27th and 25th Open House event at its Hiroshima and Nagasaki laboratories. For the second year in a row, the joint Hiroshima and Nagasaki event was held using a virtual, online format, out of consideration for the effects of the persistent coronavirus pandemic. The total number of viewers who accessed the videos (in both English and Japanese) made specifically for the Open House events was 7,744, with the total number of page views reaching 9,565.

iii) Strengthening of social media-related activities

In FY2022, obtaining understanding from atomic bomb survivors, the second-generation of children, local communities, and the media was positioned as the most important task facing RERF, and social media was used to help reach that goal. RERF's follower numbers increased only slowly over that period, with the Facebook page reaching 862 followers as of March 31, 2023, and RERF's English and Japanese Twitter accounts totaling 599 followers by the same time. RERF paid particular attention to the creation of videos for posting on the website, Facebook page, and YouTube channel as part of our social media work. Videos made over the course of that fiscal year numbered 20, including those designed for the Open House event and the initial video of a series on the genome sequencing analysis research that RERF is planning.

iv) Promotion of public relations activities targeting media

In FY2022, RERF reinitiated gatherings and study sessions with the media to improve and strengthen relations, but such interactions were limited to one occasion, due to the coronavirus pandemic. Based on RERF's continued efforts to fully engage with the media and provide story ideas, the number of published articles featuring RERF in FY2022 totaled 105, with the plurality making up information about RERF's relocation, as of March 31, 2023.

v) Enhancement of RERF website

- During FY2022, the new homepage was regularly updated with revised information and the section on published scientific papers was enhanced for easier navigation and greater understanding of the RERF system of paper categorization.
- During FY2022, focus was placed on conveying readily understandable research-related and other information to the public through the utilization of more video and other methods, particularly at the time of the Open House event.
- Starting in FY2018, when papers are published in scientific journals, new easy-to-follow

synopses have been posted on the public website. That synopses were further refined in FY2022 for timely dissemination of information.

- The total number of RERF website hits, or page views, between April 1, 2022, and March 31, 2023, was 540,990, with the daily average being 1,482. The total number of website visitors for the same period was 246,389, with the daily average being 675.

vi) Enhancement of online news-delivery system

In FY2022, RERF's email magazine system, E-News, which replaced the printed *Update* newsletter, was terminated and changed to a video-production system for publicizing RERF research and other content in a more modern and visually pleasing way.

vii) School Visit Program

The RERF School Visit Program—which is an attempt to teach radiation health effects to school children using readily understandable language—was scheduled to continue in FY2022 but had to be canceled due to the coronavirus pandemic.

viii) Facility tours

Each fiscal year, RERF tries to handle the many requests for facility tours that come in, with the aim of introducing the foundation's history and research activities. In FY2022, facility tours were canceled because of the coronavirus pandemic, but the Hiroshima Laboratory was able to use outside lecture venues and RERF's Hijiya Hall during certain periods to introduce RERF and its research work to the public.

ix) Internship (work experience) project

RERF has been accepting interns, mostly those with scientific backgrounds, for some time. In FY2022, the plan was put on hold due to the coronavirus pandemic.

x) Other public relations activities

- RERF actively promoted the organization's important scientific papers to the media via press releases and remote press conferences.
- RERF worked to conduct training for staff to be able to provide RERF facility tours in English, but due to its desire to protect the aging A-bomb survivor participants in RERF studies from the coronavirus, RERF was unfortunately unable to provide sufficient practical experience in front of visitors to such staff.
- By increasing our effort at communicating RERF's research with the aim of improved transparency related to RERF research and establishment of good communication with the public, in particular A-bomb survivors, their children, and the media, the Public-Awareness Campaign (PAC) working group was formed in 2019. In FY2022, the PAC working group members formed the core of RERF's response to email inquiries from the public.
- RERF was unable to target small public groups of A-bomb survivors and their children to come to RERF and speak with directors and staff about ABCC/RERF history and research results, with the aim of achieving greater understanding about RERF, due to the coronavirus pandemic.

FY2022 RERF International Collaborative Activities

I. Participation in international collaborative activities by RERF directors and staff members		II. Acceptance of visitors from overseas for briefing and training	
WHO-related activity	3 people	(Hiroshima)	
UNSCEAR-related activity	3 people	Visitors related to HICARE	10 people
ICRP-related activity	2 people	Visitors related to RERF (International Exchange Research Program)	None
IAEA-related activity	None		
Medical checkup for A-bomb survivors residing in South Korea-related activity	None	Visitors related to MEXT	None
		Visitors related to JICA	None
Others	13 people	(Nagasaki)	
		Visitors related to NASHIM	None
Total: 21 people		Total: 10 people (Hiroshima: 10 people, Nagasaki: 0 people)	

I. Participation in international collaborative activities by RERF directors and staff members (excluding participation in international scientific meetings)

In italics: Funding Organization

1. World Health Organization (WHO)-related activity (3 people)

RERF (hereinafter, all titles represent those at time of participation)

- (1) Kazunori Kodama, Executive Director, and Misa Imaizumi, Assistant Department Chief of Clinical Studies (Nagasaki), participated in the 4th WHO Collaborating Centre collaboration meeting (April 26, 2022, Online).
- (2) Kazunori Kodama, Executive Director, gave a lecture entitled “Radiation Disaster Medical System in the World—WHO’s Radiation Emergency Medical Preparedness and Assistance Network (REMPAN) and Hiroshima” at the HICARE’s public lecture (February 2023).

2. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)-related collaborative activity (3 people)

1) *National Institute of Radiological Sciences*

Ritsu Sakata, Assistant Department Chief of Epidemiology, attended the UNSCEAR domestic committee meetings (July 22, October 17, 2022, and February 27, 2023, Online).

2) *RERF*

- (1) Alina Brenner, Senior Scientist, Department of Epidemiology, attended meetings as a lead writer for UNSCEAR Epidemiological studies of Radiation and Cancer (April 7, May 9-13, June 9, September 9, December 5, 2022, January 26, and March 29, 2023, Online, October 25-27 (IRSN, Paris in person)).
- (2) Satoshi Kurisu, Senior Scientist, Department of Clinical Studies, Hiroshima, attended the UNSCEAR CircuDis Expert Meeting (June 22, 2022, February 14, and February 28, 2023, Online).

3. *ICRP (International Commission on Radiological Protection)*-related activity (2 people)

- (1) Alina Brenner, Senior Scientist, Department of Epidemiology, attended meetings as a member of the ICRP Task Group 122 (Update of Detriment Calculation for Cancer) (January 4, March 6, 2023, Online).
- (2) Tomoki Nakamizo, Division Chief of Radiology of the Department of Clinical Studies, Nagasaki, attended meetings as a member of the ICRP Task Group 119 (Radiation Effects on Diseases of the Circulatory System) (June 16, September 26 and 28, 2022, January 31, March 29, 2023, Online).

4. *IAEA (International Atomic Energy Agency)*-related activity (0 person)

This activity was not done in FY2022.

5. Medical checkup for A-bomb survivors residing in South Korea-related activity (0 person)

This activity was not done in FY2022.

6. Others (13 people)

- (1) Eric Grant, Associate Chief of Research, attended the Workshop Jointly organized by Task Group 121 of the International Commission on Radiological Protection (ICRP) Committee 1 (May 31-June 2, 2022, Budapest, Hungary).
- (2) Eric Grant, Associate Chief of Research, attended the 44th Scientific Assembly of the COSPAR (July 16-24, 2022, Athens, Greece).
- (3) Osamu Tanabe, Chief Scientist, gave a lecture at the 67th Annual Meeting of the Health Physics Society (July 20, 2022).
- (4) Robert Ullrich, Vice Chair, and Eric Grant, Associate Chief of Research, attended the 68th Annual Meeting of the Radiation Research Society (October 16-19, 2022, Hawaii, USA).
- (5) Hiromi Sugiyama, Assistant Department Chief, Department of Epidemiology, attended a board meeting of international Association of Cancer Registries (IACR) (November 7, 2022, March 23, 2023, Online).
- (6) Hiromi Sugiyama, Assistant Department Chief, Department of Epidemiology, attended the annual meeting of international Association of Cancer Registries (IACR) (November 8-10, 2022, Online).
- (7) Kazunori Kodama, Executive Director, attended the re-designation ceremony of HICARE as a collaborating center for the International Atomic Energy Agency (IAEA) and discussed a work plan for the next four years as the liaison officer of HICARE (November 10, 2022).
- (8) Kazunori Kodama, Executive Director, participated as a lecturer in the IAEA-HICARE International Training Course on Advanced Radiation Therapy for Head and Neck, Lung, and Liver Cancer (November 15, 2022).
- (9) Robert Ullrich, Vice Chair, attended the NASA Human Research Program Investigators' Workshop (February 7-9, 2023, Houston, USA).
- (10) Robert Ullrich, Vice Chair, and Eric Grant, Associate Chief of Research, chaired sessions for the 59th Annual Meeting of the National Council on Radiation Protection and Measurements (NCRP) as the Program Committee (March 27-28, 2023, Bethesda, USA).

II. Acceptance of visitors from overseas for briefing and training (10 people)

Acceptance of trainees from overseas through the Nagasaki Association for Hibakushas' Medical Care (NASHIM) and the like, was completely canceled in FY2022 again; however, the training of the International Council for Health Care of Radiation-exposed (HICARE) was resumed to provide online lectures.

FY2022

Joint programs between RERF and overseas researchers/research organizations

In italics: Funding Organization

1. Collaborative studies between *RERF and US National Cancer Institute (NCI)*

- (1) Under the research contract entered into by and between RERF and the US National Cancer Institute (NCI), in which Kotaro Ozasa, Former Department Chief of Epidemiology, served as a responsible person of the RERF side, analysis of solid cancer incidence risks in the LSS cohort, site-specific cancer studies based on histopathological diagnoses were conducted based on this contract.

The following papers have been published (RERF authors underlined):

Yoshida N, Fujihara M, Preston DL, Ozasa K, Hida A, Ohishi W, Sakata R, Mabuchi K. Further analysis of incidence of multiple myeloma among atomic bomb survivors, 1950-1994. *Blood Advances* 2023/02/11 [Epub]:1-10 [RP-3-94]

Utada M, Brenner AV, Preston DL, Yamada M, Grant EJ, Sugiyama H, Sakata R, Cahoon EK, Ozasa K, Mabuchi K. The effect of prostate-specific antigen (PSA) test on radiation risk estimate for prostate cancer incidence among atomic-bomb survivors. *Radiat Res* [in press][RP-S5-19]

Note: The contract research agreement between RERF and NCI, dated May 20, 2019, expired on July 31, 2021.

- (2) Ritsu Sakata, Assistant Department Chief, and Alina Brenner, Senior Scientist, Department of Epidemiology, are joining with the data of tumor of the central nervous system from RERF as a part of the pooled analysis conducted by the scientists of Radiation Epidemiology Branch, NCI.
- (3) Ritsu Sakata, Assistant Department Chief of Epidemiology, is joining with the data of radiation-associated thyroid cancers from RERF as a part of the pooled analysis conducted by the scientists of Radiation Epidemiology Branch, NCI.

2. Collaboration between *RERF and the/Asia Cohort Consortium (ACC)*

Ritsu Sakata, Assistant Department Chief of Epidemiology, is joining the collaborative project with the ACC entitled: Tobacco smoking, alcohol drinking, body mass index and risk of rare cancers.

3. Collaboration between *RERF and Institute of Cancer Research, UK and US National Institute of Environmental*

Alina Brenner, Senior Scientist, Department of Epidemiology, is joining with premenopausal breast cancer data from RERF as a part of the pooled analysis conducted by Dr. Anthony Swerdlow of Institute of Cancer Research, UK, and Dr. Hazel Nichols of US National Institute of Environmental.

4. Collaboration between *RERF and University of Washington*

RERF entered into a research contract with the University of Washington (Department of Epidemiology and Department of Biostatistics), for which Richard Sposto, Department Chief of Statistics served as coordinator. Under this contract, RERF supported the training and education of MS and PhD students in epidemiology and biostatistics and conducted collaborative research with students and their advisors. Research projects focused on analyses of cancer incidence and mortality outcomes in the LSS, as well as the development of new statistical methods for analyzing LSS cohort data.

Note: The contract research agreement between RERF and the University of Washington, dated September 16, 2017, expired on December 31, 2021.

5. *RERF* international collaborative studies on statistical analyses

Munehika Misumi, Assistant Department Chief of Statistics, continued a collaboration study with the investigators at Helmholtz München on the mechanistic modeling of carcinogenesis having online meeting.

6. *RERF* international collaborative studies on radiation dosimetry.

Harry Cullings, Consultant, and Sachiyo Funamoto, Section Chief, Department of Statistics, collaborated with an international group of dosimetry experts in work to update RERF radiation dosimetry.

7. *University of Bern* international multi-institutional collaborative studies on thyroid

Misa Imaizumi, Assistant Department Chief of Clinical Studies (Nagasaki), Waka Ohishi, Department Chief of Clinical studies and Michiko Yamada, Division Chief of Radiology of Department of Clinical Studies are joining with Adult Health Study data from RERF as a part of the pooled analysis of thyroid conducted by Dr. Rodondi of University of Bern, Switzerland (Thyroid Studies Collaboration).

令和4年度 外部資金研究一覧表
FY2022 External Research Funds

外部機関名称 Name of Outside Organization	件数 Number of Grants	研究資金 (資金拠出機関からの入金額) Research funds (amount of funds from funding)
厚生労働省 Ministry of Health, Labour and Welfare (MHLW)	2	¥1,450,000
独立行政法人 日本学術振興会 (文部科学省所管の独立行政法人) Japan Society for the Promotion of Science (JSPS) [Independent administrative entity under the jurisdiction of the Ministry of Education, Culture, Sports, Science and Technology (MEXT)]	7	¥11,050,000
一般財団法人 土谷記念医学振興基金 Tsuchiya Memorial Medical Foundation	1	¥1,000,000
国立研究開発法人 国立がん研究センター National Cancer Center	1	¥0 *
総合計 Grand total	11	¥13,500,000

注)

- ・ 間接費を含む。
- ・ 研究分担者の配分額を含む。
- * 研究協力者として研究参画のため、配分資金の配分なし。

Notes)

- ・ These amounts include indirect cost.
- ・ These amounts include subsidies allocated to collaborators.
- * No research funds are allocated, because the RERF researcher takes part in the research as a cooperative investigator.

令和4年度 外部資金研究一覧表
FY2022 External Research Funds

研究のタイトル Title of Research	委託組織の名前と場所及び研究 グループのチーフ又は担当の主任研究者 Name and location of entrusting outside organization Chief of research group or principal investigator in charge	放影研における研究者の名前 Investigator(s) at RERF	研究資金(資金拠出 機関からの入金額) Research funds (amount of funds from funding organizations)	令和4年度 開始日 First project date in FY2022	令和4年度 終了日 Last project date in FY2022	関連RP Related RPs	関連性 Relationship to RERF's mission
疫学部 Department of Epidemiology							
1 社会経済的格差に着目したがん対策に資する空間疫学的ビッグデータ解析研究 Spatial epidemiological big data analysis research that contributes to cancer control focusing on socio-economic disparities	日本学術振興会・科学研究費助成事業 「基盤研究(B)」 研究代表者 伊藤 秀美 JSPS Grant-in-Aid for Scientific Research Scientific Research (B) Hidemi Ito	研究分担者 (Collaborator) 杉山 裕美 Hiromi Sugiyama	直接経費 (Direct cost) ¥200,000 間接経費 (Indirect cost) ¥60,000	April 1, 2022	March 31, 2023	RP-S2-17	日本人のがんの疫学研究 Epidemiological study of cancer in Japanese population
2 国際比較可能ながん登録データの精度管理および他の統計を併用したがん対策への効果的活用の研究 Studies on the quality control of internationally comparable cancer registry data and on the effective usage for cancer control using other statistics	厚生労働省・厚生労働科学研究費補助金 「がん対策推進総合研究事業」 研究代表者 松田 智大 国立研究開発法人国立がん研究センター がん対策研究所 国際政策研究部 部長 Health and Labour Sciences Research Grants (MHLW) Promotion of Comprehensive Research Project for Cancer Control Tomohiro Matsuda Chief, Division of International Health Policy Research, National Cancer Center, Institute for Cancer Control	研究分担者 (Collaborator) 杉山 裕美 Hiromi Sugiyama	¥600,000	April 1, 2022	March 31, 2023	RP-S2-17	日本人のがんの疫学研究 Epidemiological study of cancer in Japanese population
3 科学的根拠に基づくがんリスク評価及び予防ガイドライン提言に関する研究 Study for evaluation of cancer risk and proposal of cancer prevention guidelines on the basis of scientific evidence	国立がん研究センター・国立がん研究センター研究開発費 研究代表者 井上 真奈美 国立研究開発法人国立がん研究センター がん対策研究所 予防研究部 部長 National Cancer Center Funds for Cancer Research and Related Technology Development Manami Inoue Chief, Division of Prevention, National Cancer Center, Institute for Cancer Control	研究協力者 (Cooperative Investigator) 歌田 真依 Mai Utada	研究協力者のため、 研究資金の配分なし Since this person is a cooperative investigator, research funds were not allocated to her.	April 1, 2022	March 31, 2023	RP-A2-15	日本人のがんの疫学研究 Epidemiological study of cancer in Japanese population

令和4年度 外部資金研究一覧表
FY2022 External Research Funds

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臨床研究部 Department of Clinical Studies							
1 生涯にわたる循環器疾患の個人リスクおよび集団 リスクの評価ツールの開発及び臨床応用のための 研究 Assessments and clinical application of long-term predictability of cardiovascular risk factors in both individual and population levels	厚生労働省・厚生労働科学研究費補助金 「循環器疾患・糖尿病等生活習慣病対策総合研究事業」 研究代表者 村上 義孝 東邦大学医学部 教授 Health and Labour Sciences Research Grants (MHLW) Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus Yoshitaka Murakami Professor, Graduate School of Medicine, Toho University	研究分担者 (Collaborator) 立川 佳美 Yoshimi Tatsukawa 研究協力者 (Cooperative Investigator) 山田 美智子 Michiko Yamada 栗栖 智 Satoshi Kurisu	¥850,000	April 1, 2022	March 31, 2023	RP 2-75 RP 6-08 RP 1-15	広範囲な医学的調査 (生活習慣病) Broad-based medical research (Lifestyle disease)
2 被爆による造血器腫瘍発症に関する分子機構 の解明と今後への展望 Identification of molecular mechanisms related to development of hematological malignancies by atomic-bomb	日本学術振興会・科学研究費助成事業 「若手研究」 研究代表者 吉田 稚明 JSPS Grant-in-Aid for Scientific Research Early-Career Scientists Noriaki Yoshida	研究代表者 (P.I.) 吉田 稚明 Noriaki Yoshida	直接経費 (Direct cost) ¥0 間接経費 (Indirect cost) ¥0 補助事業期間延長により、令和3年度の未執行額(399,928 円)を使用。令和4年度に新たな助成金の交付はなし。 With extension of the funded term, the unexecuted amount for FY2021 (399,928yen) was used. No grant was provided for FY2022.	April 1, 2022	March 31, 2023	RP 6-70 RP 5-90 RP-S2-15 RP 5-02 RP-P2-19	がん研究 (被爆者がん研究への応用) Cancer research (Application to cancer research among A-bomb survivors)
3 被爆後早期に発症した白血病症例の分子病理学 的解析 Pathological and molecular characterization of leukemia developed shortly after A-bomb radiation exposure	一般財団法人 土谷記念医学振興基金 研究代表者 吉田 稚明 Tsuchiya Memorial Medical Foundation Noriaki Yoshida	研究代表者 (P.I.) 吉田 稚明 Noriaki Yoshida	¥1,000,000	April 1, 2022	March 31, 2023	RP 6-70 RP 5-90 RP-S2-15 RP 5-02	がん研究 (被爆者がん研究への応用) Cancer research (Application to cancer research among A-bomb survivors)

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統計部 Department of Statistics 1 Fused-lassoによる広島・長崎の被爆に関する時空間リスク推定モデルの開発 Development of a spatio-temporal risk estimation model for Hiroshima and Nagasaki exposures by Fused-lasso	日本学術振興会・科学研究費助成事業 「基盤研究(B)」 研究代表者 山村 麻理子 JSPS Grant-in-Aid for Scientific Research Scientific Research (B) Mariko Yamamura	研究代表者 (P.I.) 山村 麻理子 Mariko Yamamura 研究分担者 (Collaborator) 坂田 律 Ritsu Sakata	直接経費 (Direct cost) ¥3,700,000 間接経費 (Indirect cost) ¥1,110,000 広島大学の研究分担者への配分額は、上記の研究資金に含まれている。 The above amount includes funds allocated to the collaborators at Hiroshima University.	April 1, 2022	March 31, 2023	RP 1-75	LSS LSS
2 疫学データに基づく大腸がんの放射線発がん機序モデリングとその妥当性の検討 Biology-based mechanistic modelling of colorectal cancer based on epidemiological data and investigations of its validity	日本学術振興会・科学研究費助成事業 「基盤研究(C)」 研究代表者 三角 宗近 JSPS Grant-in-Aid for Scientific Research Scientific Research (C) Munehika Misumi	研究代表者 (P.I.) 三角 宗近 Munehika Misumi	直接経費 (Direct cost) ¥1,800,000 間接経費 (Indirect cost) ¥540,000	April 1, 2022	March 31, 2023	RP-S4-18 RP18-61	LSS LSS

令和4年度 外部資金研究一覧表
FY2022 External Research Funds

研究のタイトル Title of Research	委託組織の名前と場所及び研究 グループのチーフ又は担当の主任研究者 Name and location of entrusting outside organization Chief of research group or principal investigator in charge	放影研における研究者の名前 Investigator(s) at RERF	研究資金(資金拠出 機関からの入金額) Research funds (amount of funds from funding organizations)	令和4年度 開始日 First project date in FY2022	令和4年度 終了日 Last project date in FY2022	関連RP Related RPs	関連性 Relationship to RERF's mission
分子生物科学部 Department of Molecular Biosciences							
1 放射線の遺伝影響研究を目的として、マウス精原細胞の染色体に構造変異を持ち込む Introduction of chromosome structural changes into mouse spermatogonia cells for the analysis of their transmission to next generation	日本学術振興会・科学研究費助成事業 「基盤研究(C)」 研究代表者 野田 朝男 JSPS Grant-in-Aid for Scientific Research Scientific Research (C) Asao Noda	研究代表者 (P.I.) 野田 朝男 Asao Noda 研究分担者 (Collaborator) 濱崎 幹也 Kanya Hamasaki	直接経費 (Direct cost) ¥1,000,000 間接経費 (Indirect cost) ¥300,000	April 1, 2022	March 31, 2023	RP-P3-17	GS細胞染色体への構造変異導入 Introduction of chromosome structural changes by gene editing technology
2 ヒト造血幹細胞における放射線誘発変異の全ゲノムシーケンスによる解析 Whole-genome sequence analysis of radiation-induced somatic mutations in human hematopoietic stem cells	日本学術振興会・科学研究費助成事業 「基盤研究(C)」 研究代表者 田邊 修 JSPS Grant-in-Aid for Scientific Research Scientific Research (C) Osamu Tanabe	研究代表者 (P.I.) 田邊 修 Osamu Tanabe 研究分担者 (Collaborator) 松田 由喜子(分子生物科学部) Yukiko Matsuda (Dept. Molecular Biosciences) 吉田 健吾(分子生物科学部) Kengo Yoshida (Dept. Molecular Biosciences) 内村 有邦(分子生物科学部) Arikuni Uchimura (Dept. Molecular Biosciences)	直接経費 (Direct cost) ¥1,600,000 間接経費 (Indirect cost) ¥480,000	April 1, 2022	March 31, 2023	No RP	放射線被曝による晩発障害である白血病、固形腫瘍、循環器疾患などの分子メカニズムの解明と、それら疾患の予防法、治療法の開発に貢献 This study contributes to the elucidation of molecular mechanisms of the late-onset diseases by radiation exposure, including leukemia, solid tumors, and cardiovascular diseases, and contributes to the development of preventive and therapeutic measures for those diseases.

令和4年度 外部資金研究一覧表
FY2022 External Research Funds

研究のタイトル Title of Research	委託組織の名前と場所及び研究 グループのチーフ又は担当の主任研究者 Name and location of entrusting outside organization Chief of research group or principal investigator in charge	放影研における研究者の名前 Investigator(s) at RERF	研究資金(資金拠出 機関からの入金額) Research funds (amount of funds from funding organizations)	令和4年度 開始日 First project date in FY2022	令和4年度 終了日 Last project date in FY2022	関連RP Related RPs	関連性 Relationship to RERF's mission
情報技術部 Department of Information Technology 1 ワイヤレスセンシングと機械学習による猟師向けリアル タイム獣流推定に関する研究 Study concerning the use of wireless sensing and machine learning by hunters to estimate the movements of wildlife real-time	日本学術振興会・科学研究費助成事業 「若手研究」 研究代表者 小野 悟 JSPS Grant-in-Aid for Scientific Research Early-Career Scientists Satoru Ono	研究代表者 (P.I.) 小野 悟 Satoru Ono	直接経費 (Direct cost) ¥200,000 間接経費 (Indirect cost) ¥60,000	April 1, 2022	March 31, 2023	No RP	診療録を始めとする紙媒体のス キャンデータを分類するための 手法の構築には、本研究で用い る機械学習を用いた行動情報の 分類に関する研究が有用に機 能すると考えられる。 This research which will examine machine-learning-based dog's movement data classification, will expect to contribute to the creation of a best-fit classification method for medical charts and other paper documents.

令和4年度 特別会計一覧表
FY2022 Special Funds

資金拠出機関名称 Name of Funding Agency	件数 Number of Funds	資金合計 Amount of Funding Total
厚生労働省 Ministry of Health, Labour and Welfare (MHLW)	2	¥10,701,000
広島県 Hiroshima Prefecture	1	¥15,940,947
長崎県 Nagasaki Prefecture	1	¥8,700,000
総合計 Grand total	4	¥35,341,947

注)

- ・ 間接費を含む。
- ・ 研究分担者の配分額を含む。

Notes)

- ・ These amounts include indirect cost.
- ・ These amounts may include subsidies allocated to collaborators.

令和4年度 特別会計一覧表
FY2022 Special Funds

	研究のタイトル Title of Research	委託組織の名前と場所及び研究 グループのチーフ又は担当の主任研究者 Name and location of entrusting outside organization/Chief of research group or principal investigator in charge	放影研における契約者/ 研究者の名前 Investigator(s) at RERF	資金拠出機関か らの入金額 Amount of Funds from Funding Agencies	開始日 Initiation Date	終了日 Termination Date	関連RP Related RPs	関連性 Relationship to RERF's mission
1	放射線業務従事者の健康影響に関する疫学 研究 Epidemiological study of health effects in radiation workers	厚生労働省・労災疾病臨床研究事業費補 助金 研究代表者 大久保 利晃 独立行政法人労働者健康安全機構 労働安 全衛生総合研究所 労働者放射線障害防止 研究センター センター長 Research Grant for Clinical Studies of Work-Related Illness (MHLW) Toshiteru Okubo Director, Research Center for Prevention from Radiation Hazards of Workers, National Institute of Occupational Safety and Health, Japan Organization of Occupational Health and Safety	研究分担者 (Collaborative Investigators) 大石 和佳 Waka Ohishi	¥8,827,000	April 1, 2022	March 31, 2023	RP 6-15	東電福島第一原発事故処理緊 急作業従事者の長期疫学調査 Long term follow-up epidemiological study on emergency workers of TEPCO, Fukushima 1F Nuclear Power Plant accident.
2	原爆被爆者の生物試料の保管及び活用に関 する研究事業 Research Program on preservation and use of the A-bomb survivors' biosamples	厚生労働省・委託事業 丹羽 太貴 MHLW Entrustment Ohtsura Niwa	受託者 (Contractor) 丹羽 太貴 Ohtsura Niwa	¥1,874,000	December 19, 2022	March 31, 2023		原爆被爆者の生物試料の保管 及び活用 Preservation and use of the A- bomb survivors' biosamples
3	がん登録推進事業 Cancer Registry Promotional Project	広島県・委託事業 丹羽 太貴 Hiroshima Prefecture Ohtsura Niwa	受託者 (Contractor) 丹羽 太貴 Ohtsura Niwa	¥15,940,947	April 1, 2022	March 31, 2023	RP18-61 RP29-60 RPs18-61& 29-60附属書	がんの疫学研究、 LSS、胎内被爆者、 F1集団 Epidemiological study of cancer, LSS, in utero, and F1 populations
4	長崎県がん登録・評価事業 Nagasaki Prefecture Cancer Registry Program	長崎県・委託事業 丹羽 太貴 Nagasaki Prefecture Ohtsura Niwa	受託者 (Contractor) 丹羽 太貴 Ohtsura Niwa	¥8,700,000	April 1, 2022	March 31, 2023	RP18-61 RP29-60 RPs18-61& 29-60附属書	がんの疫学研究、 LSS、胎内被爆者、 F1集団 Epidemiological study of cancer, LSS, in utero, and F1 populations

II. Operation and management of RERF

1. Research Resource Center

In order to accomplish the Strategic Plan of RERF, it is planned that the Research Resource Center (RRC) will be established with the aims to modernize the research infrastructure of RERF and to facilitate collaborative studies by streamlining research management system. More specifically, the mission of the RRC is 3-fold as follows:

- (1) Preserve RERF's research assets and historical materials, which include various paper materials for research, photographs, films, paper manuscripts, and datasets.
- (2) Integrate all research data and biosample inventories to enhance the availability of those research resources, and for this aim, provide tools and systems for data visualization and data assembly.
- (3) Create an Office of Research Support to provide an efficient administrative framework to advance collaborative projects inside and outside RERF and facilitate applications for contracts and grants.

As the first of the two-step process to initiate the RRC under the recommendation of the Preparatory Committee for the Establishment of the RRC, the RRC Operating Committee was established in FY2021. With the retirement of Dr. Grant, Assistant Chief of Research, who was the chair from the time of the committee's establishment, Dr. Ono, Chief of Information Technology Department (ITD), assumed the chair's position in January 2023. In FY2022, the Research Resource Section, as the predecessor of the RRC, was newly established in ITD. As the endeavor to preserve RERF's research assets and historical materials according to the mission (1) above, microfilms kept by the Departments of Epidemiology and Clinical Studies were digitized over the two years from 2020. The physically degraded old microfilms needed to be dealt with urgently. Moreover, in FY2022, the Section undertook the digitization of photographs, videos, and films kept by the Library and Archives Section and the organization and digitization of inventories of pathological samples (such as paraffin blocks and slides) kept by the Department of Epidemiology, and initiated the digitization of negative films of chromosome images and their ledgers, which are kept by the Department of Molecular Biosciences. Furthermore, the preparation is being made to introduce a Content Management System for the centralized management of paper-based materials including paper manuscripts and research protocols. Further, according to the mission (2) above, the preparation is also being made to introduce a Data Management System to enhance the availability of RERF's research assets, and a pilot project involving the foundation's actual data has started. On the other hand, for the mission (3) above, the Office of Research Support aims to facilitate research activities through the support for research administrative procedures, the management and use of intellectual property, and the support for external grant application. To achieve this objective, the preparation is being made to introduce electronic workflow system for digitization of the foundation's decision-making processes.

2. Review on the relocation of the Hiroshima Laboratory

The candidate site for the Hiroshima Laboratory's relocation was narrowed down to the Hiroshima University's Kasumi Campus at the 12th Board of Councilors meeting in June 2022 (by mail ballot), and then the laboratory's relocation was finalized at the 31st extraordinary Board of Directors meeting in January 2023, and finally RERF submitted an application to Hiroshima University for acceptance of the relocation. RERF received a written approval of acceptance of the relocation from the university and carried forward the

plan to relocate the laboratory to the Hiroshima University's Kasumi Campus. In December 2022, the Cabinet approved the government budget for FY2023, which included part of the construction costs of the laboratory's new building at the relocation site, and the budget was passed in the Diet session on March 28, 2023.

3. Transition to a full audit

RERF has endeavored to undergo a voluntary audit (full audit) through an external auditing firm to supplement the audit conducted by its Auditors. In FY2022, the "FY2022 Beginning Balance Investigation" was conducted by Deloitte Touche Tohmatsu LLC. Tohmatsu's "Investigation Report," which was submitted in June 2022, concluded that Tohmatsu could undertake the voluntary audit. Accordingly, an audit contract was signed with Tohmatsu on September 1, 2022, and a voluntary audit for FY2022 was initiated. The voluntary audit has been conducted from the date of the contract and will continue through June 30, 2023.

The specifics of the voluntary audit, as of the end of March 2023, are as follows:

- First-round remote audit, December 12–14, 2022
 1. Assessment of preparation and implementation of internal control: Process for purchase, Process for fixed assets management, Inventory, Process for personnel affairs and salaries, Process for finance, Process for sales, and Business flow.
 2. Discussions with the Chairman: Gaining an understanding of the overall business environment and of the Directors' management processes.
- Second-round audit, March 30, 2023
Substantive procedures taken during the fiscal year: Substantive analytical procedures (procedures to determine any material difference between the expectation values and the book values)
- Third-round audit, March 31, 2023
Substantive procedures taken during the fiscal year: witnessing for stocktaking, physical inspection of cash, confirmation of bank balances, confirmation with a lawyer

Upon completion of the voluntary audit, the final report will be submitted to the Auditors by the regular meeting of the Board of Directors in June 2023.

4. Revision of the rules and regulations

RERF in FY2022 continued to review its regulations to enhance the public interest incorporated foundation's operational framework. The following are main regulations revised or established. As instructed by its auditing firm, the foundation also reviewed its system to clarify the associations and hierarchical relations among the regulations.

- Regulations Concerning Responses to Antisocial Forces [Effected on April 1, 2022]
Policy of RERF to prevent the damage by antisocial forces was developed, and at the same time, the regulations were established to block all associations with the antisocial forces including any transactions with them and to also include response at the time of occurrence of problems.
- Supplementary Regulations Concerning Organization of the Laboratory (Research Departments) [Effected on April 1, 2022]
Changes to the names of two of the Dept. of Molecular Biosciences' laboratories (Cellular

Genomics and Molecular Pathology) and changes accompanying the abolition of the NEWS Office in the Dept. of Clinical Studies were reflected into the regulations.

- Operational Administrative Regulations for the Core Administrative System under the Management of the Secretariat [Effected on April 1, 2022]
The rules for the core administrative system under the Secretariat's management were established.
- Regulations Concerning Internal Audit [Effected on April 1, 2022]
Overall review of the Regulations Concerning Performance of Internal Audit and the Detailed Regulations Concerning Performance of Internal Audit of External Research Funds was conducted to integrate the two regulations into the Regulations Concerning Internal Audit.
- Regulations on Handling of External Research Funds [Effected on April 1, 2022]
The Regulations on Handling of External Research Funds were established by merging of the administrative regulations on external research funds.
- Regulations of Safety and Health Committee [Effected on May 1, 2022]
The Safety and Health Committees in Hiroshima and Nagasaki reviewed the requirements for establishing a committee meeting, and based on the committees' decision, the Regulations of Safety and Health Committee were established.
- Regulations for Electronic Signature Management [Sept. 28, 2022 (applicability date: Sept. 1, 2022)]
The regulations pertaining to electronic signature including the administrator, authority holder, and handling of electronic signature were established to correspond to the use of electronic contracts requested from outside.
- Standards for Handling of Outside Congratulations/Condolences [November 1, 2022]
The standards were newly established by reviewing how the outside congratulations/condolences were being handled.
- Travel Reimbursement Regulations [December 1, 2022]
The Travel Reimbursement Regulations were revised following review of the regulations by the section in charge to facilitate the paperwork for the disbursement of official travel expenses and fair cost disbursement.
- Guidelines for Establishment of External Advisory Committee on Biosample Usage [Effective date: March 1, 2023]
With establishment of the "External Advisory Committee on Biosample Usage," these guidelines for the operation of the committee were established.

5. Facility upgrades

Nagasaki Laboratory replaced A/C units with FY2022 subsidy for major facility renovations including health and sanitation facilities from the Ministry of Health, Labour and Welfare.

Appended documents to FY2022 report of activities

There were no items considered to be important matters for supplementing the contents of the FY2022 report of activities.