DEPARTMENT OF STATISTICS

The mission of the RERF Department of Statistics is to provide the expertise of its members for the advancement of research in the health effects of ionizing radiation. Department members do this by developing or extending statistical methods that are relevant to RERF research as well as more generally, by applying or adapting existing methods to RERF research, and by designing, analyzing, and reporting RERF research studies in collaboration with and in support of RERF researchers. The Department's expertise is an essential component of modern epidemiological and biomedical research. The Department in addition takes responsibility for managing and ensuring the integrity of the RERF dosimetry system. Department members also engage in education and outreach activities that cultivate opportunities for outside collaborations that are beneficial to RERF.

Members of the Department have in the past developed analytical methods for major aspects of the RERF research program to estimate radiation risk for mortality and incident solid and hematologic cancers, and that have also been applied to numerous radiation studies of other cohorts. These include the development of tools and methods to flexibly estimate radiation-associated excess relative and excess additive risks, methods to account for errors in radiation dose estimates, and methods to account for the underreporting of incident cancer cases due to undocumented out-migration from cancer tumor registry catchment areas, among others. The Department's current methodological focus includes continued development in these areas along with research in new areas. Current and future major areas of emphasis are radiation dosimetry, dosimetry error/measurement error, dose-response modelling, longitudinal analysis (including joint modelling), causal inference/mediation analysis, biologically based models, spatial statistics, and bioinformatics/omics.

In addition to work in these methodologic areas, Department members collaborate closely with RERF researchers in all phases of RERF research projects: study conceptualization and design; development of rigorous statistical analytic plans; execution of the analytic plan; and communicating the research results to the greater scientific community, stakeholders, and survivor groups through peer-reviewed manuscripts and scientific presentations. This collaborative work is informed by the Department's above-mentioned research in applicable statistical methods. Through their close involvement in the development of RERF research projects, Department members also provide RERF researchers and leadership with critical information needed to evaluate the ability of proposed research to achieve its scientific objectives. The major portion of Department members' activities is devoted to these collaborations.

In addition, the Department implements, manages, and ensures the integrity of the RERF dosimetry system. Department staff are responsible for computing organ doses for RERF cohort subjects by applying individual location, shielding, orientation, sex and age data as input to the DS02 software system that translates raw neutron and gamma fluences at the location to appropriately attenuated values for each individual. The Department also has an ongoing role with the binational working group of external scientists that is developing and evaluating new computational models of the human body and modernized transport calculations that will result in improved dose estimates, with doses to the pregnant mother and fetus being completely revamped as well as extensions to new organs and tissues not previously covered.

Through these various activities and involvements, members of the Department of Statistics play a central role in and make important contributions to RERF's research mission.

The mission of the Department of Statistics can broadly be described in terms of the following four specific aims:

- ***Specific Aim 1: Collaborate with RERF scientists in the conceptualization, design, analysis, and reporting of high-quality research projects relevant to the mission of RERF.***
- ***Specific Aim 2: Perform research to develop new, or extend and apply existing, statistical methods that are essential to the mission of RERF.***
- ***Specific Aim 3: Maintain and ensure the integrity of the RERF dosimetry system.***
- ***Specific Aim 4: Participate in education, outreach, and operational activities to increase visibility, enhance opportunities for external collaboration, and contribute to the functioning of RERF as a research organization.***

Recent activities and future plans in each of these four areas are described in the following sections.

FY2022 Departmental Achievements

Specific Aim 1: Collaborate with RERF scientists in the conceptualization, design, analysis, and reporting of high-quality research projects relevant to the mission of RERF.

During FY2022 members of the Department[1] played an essential role in collaborations with RERF scientists. These activities are reflected in published papers and papers in development, as well as in ongoing analyses and work on development of new research protocols.

Papers published or in press.

Department members were authors on 11 peer-reviewed papers that were published or in press in 2022, six of which were primarily collaborative publications originating from the Departments of Epidemiology, Clinical Studies, or Molecular Biosciences(Brenner, Preston, Sakata 2022, Hamasaki, Matsumoto, Cologne 2022, Ishihara, Kato, Misumi 2022, Little, Brenner, Grant 2022, Tatsukawa, Cordova, Yamada 2022, Yoshida, Satoh, Uchimura 2022), two of which were previously reported as in press in 2021, and four of which represent papers newly published or in press

For all of these publications, Department members participated actively in discussions about and provided input on the focus of the research, the design and analytic plan and the presentation of the results in the manuscript. Department member contributions for those not reported last year as *in press* are highlighted below.

Little MP, Brenner AV, Grant EJ, Sugiyama H, Preston DL, Sakata R, ***Cologne JB****, Velazquez-Kronen R, Utada M, Mabuchi K, Ozasa K, Olson JD, Dugan GO, Pazzaglia S, Cline JM,*

[1]Drs. Harry Cullings, Benjamin French, Kyoji Furukawa, Young-Min Kim, and Ms. Kismet Cordova, former members of the Department of Statistics, may be cited because they contributed to work that was initiated while they were members of the Department.

Applegate KE. Age effects on radiation response: Summary of a recent symposium and future perspectives. Int J Radiat Biol. 2022; 1-34.

In this report summarizing presentations made at the 67th annual meeting of the Radiation Research Society in October 2021, Dr. Cologne collaborated with Dr. Alina Brenner of the Epidemiology Department in the analysis of age-at-exposure and attained-age modifications of radiation risk in the Life Span Study.

Hamasaki K, Matsumoto T, ***Cologne JB****, Mukai M, Kodama Y, Noda A, Nakamura N. Translocations are induced in hematopoietic stem cells after irradiation of fetal mice. J Radiat Res. 2022; rrac078:1-6.*

Dr. Cologne performed the statistical analysis of this *in vivo* experiment on irradiated pregnant mice to shed light on the finding that an increased frequency of translocations are not observed in lymphocytes from individuals exposed *in utero* but examined in adulthood. The results indicate that cells with translocations can arise in mouse fetal HSCs but exist at a lower frequency than in the mothers and disappear with aging.

Yoshida K, Satoh Y, Uchimura A, ***Misumi M****, Kyoizumi S, Taga M, Matsuda Y, Noda A, Kusunoki Y. Massive expansion of multiple clones in the mouse hematopoietic system long after whole-body X-irradiation. Scientific Reports. 2022;* ***12****(1):17276. [Mbs]*

Dr. Misumi has been involved in the clonal hematopoiesis program project from its initiation. This manuscript is based on preliminary data from the third project. Dr. Misumi conducted statistical analyses to compare clinical measurements, such as lymphoid cells, myeloid cells, and red cell distribution width (RDW), between radiation exposed and non-exposed mice.

Ishihara K, ***Kato N****,* ***Misumi M,*** *Kitamura H, Hida A, Yamada M. Radiation effects on late-life neurocognitive function in childhood atomic bomb survivors: A Radiation Effects Research Foundation Adult Health Study. Radiat Res. 2022; 197(4):403-7. [Ahs].*

In this paper, Dr. Kato, with guidance from Dr. Misumi, analyzed neurocognitive questionnaire (NCQ) scores by applying random intercept models of linear and generalized linear mixed effects models for continuous and binary responses to express the within-participant correlation induced by replicate measurements. The parameters of the random effects models were estimated via Bayesian methods.

Papers submitted or in development.

Three additional collaborative papers have been submitted (Kitamura, Ishihara, Kato 2022, Matsuda, Uchimura, Satoh 2022, Tsai, Brenner, Sugiyama 2022).

Kitamura H, Ishihara K, ***Kato N****,* ***Misumi M****, Hida A. Neurocognitive Function in Aged Survivors Exposed to Atomic Bomb Radiation in Utero: The Radiation Effects Research Foundation Adult Health Study. Radiation Research. 2022; Submitted. [Ahs]*

This paper evaluates the effects of prenatal exposure to atomic bomb radiation on subjective neurocognitive function in aged survivors. As in the published NCQ paper above, Dr. Kato and Dr. Misumi applied random intercept models of linear and generalized linear mixed effects models for continuous and binary responses to express the within-participant correlation induced by replicate measurements.

Matsuda Y, Uchimura A, Satoh Y, ***Kato N****, Toshishige M, Kajimura J, Hamasaki K, Yoshida K, Noda A, Tanabe O. Spectra and characteristics of somatic mutations induced by ionizing radiation in hematopoietic stem cells. PNAS. 2022; Submitted. [Mbs]*

Dr. Kato performed the Poisson regression and other analyses of somatic mutations detected *via* whole-genome sequencing induced in long-term hematopoietic stem cells in irradiated mice.

Tsai K, Brenner A, Sugiyama H, Utada M, Morenz E, Carone M, ***French B,*** *Phipps A. Effect Modification by Reproductive Factors on Radiation-Related Lung Cancer Risk among Atomic Bomb Survivors. Radiation Research. 2022; Submitted. [Lss]*

This paper arises from the RERF/University of Washington partnership. Dr. French was the RERF Department of Statistics statistical mentor for the epidemiology students who performed this research. It has been resubmitted for publication in *Radiation Research*.

Two additional papers which are in development (Nakamizo, Cologne, Kishi 2022, Ohishi, Cologne, Kim 2022) are discussed further below.

Research Proposals Approved

The following are collaborative research protocols approved in 2022 for which members of the Department are co-investigators.

RP#	Title	Investigator(s)	Department
RP	Radiation effects on the incidence of myocardial infarction in atomic bomb survivors	Kurisu S, Yamada M, Arakawa S, Misumi M, Sposto R, Kadowaki Y, Sakata R, Tatsukawa Y, Nakamizo T, Yoshida N, Imaizumi M, Hida A, Ohishi W, Nakano Y, Maemura K	Clinical Studies
RP	Estimate solid cancer risk based on radiation-associated immunological changes in A-bomb survivors: Cancer incidence follow-up among Adult Health Study participants based on the relative number of naïve T cells and the diversity of T-cell receptor repertoire in peripheral blood CD4 T lymphocytes	Kusunoki Y, Misumi M, Sugiyama H, Kyoizumi S, Yoshida K	Molecular Biosciences
RP	Preliminary study to determine the applicability for GWAS of DNA extractable blood smears and blood-infiltrated paper discs preserved in the past	Hayashi T, Ohishi W, Brenner AV, Kato N, Cologne JB, Yoshida N, Hamasaki K, Kodama Y, Tokunaga K, Ueki	Molecular Biosciences

		M, Matsuura S, Yoshida K, Tanabe O, Noda A	
RP	Feasibility of applying high throughput targeted sequencing technology to DNA and RNA extracted from stored FFPE samples of CML cases	Yoshida N, Kato N, Sugiyama H, Imaizumi M, Ohishi W	Molecular Biosciences

Research Proposals in Development

The following are collaborative research protocols that were in development in 2022 for which members of the Department are co-investigators.

Title	**Investigator(s)**	**Department**
Roles of hepatic stellate cells and macrophages in the course of liver carcinogenesis in X-irradiated mice	Taga M, Yoshida K, Ito R, Kyoizumi S, Kato N, Cologne JB, Ohishi W, Tanabe O, Sasatani M, Suzuki K, Kusunoki Y	Molecular Biosciences
A Longitudinal Thyroid Survey of Young A-bomb Survivors in the Adult Health Survey (Amendment RP)	Imaizumi M, Oishi K, Yamada M, Tachikawa Y, Nakamizo T, Yoshida W, Kato N, Sposto R, Usa T, Horie I, Sugino K, Tobita A	Clinical Studies
Study of the association between parental radiation exposure and occurrence of de novo germline mutations in their offspring	Uchimura A, Satoh Y, Noda A, Ohishi W, Hida A, Terao C, Nakagawa H, Berrington de Gonzalez A, Chanock SJ, Ono S, Sposto R, Sakata R	Molecular Biosciences
Artificial intelligence-estimated "Chest X-ray Age" among atomic bomb survivors	Nakamizo T, Liu Z, Ono S, Yamada M, Kurisu S, Tsuruyama T, Misumi, M, Sposto R, Sugiyama H, Imaizumi M, Hida A, Ohishi W	Clinical Studies

Ongoing analyses

Multi-state models for disease and mortality in the F1 clinical study (FOCS)

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.

Relationship of radiation to prevalence of cataract in A-bomb survivors

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.

Mediating effect of HBV and HCV on hepatocellular carcinoma in the AHS

Chronic infection with hepatitis B (HBV) or C (HCV) virus, and exposure to ionizing radiation, are established risk factors for liver cancer (hepatocellular carcinoma, HCC), and as association between radiation exposure and chronic HBV infection has been established. An important mechanistic question is to what extent HBV (and possibly HCV) mediate the risk via an indirect pathway between radiation and HCC. We estimated the mediation proportions for HBV and HCV in a prospective clinical cohort study of 4,345 atomic bomb survivors with 111 cases of HCC identified through local cancer registries in Hiroshima and Nagasaki, Japan. Association parameters were estimated via a proportional hazards model for HCC incidence and logistic regression models for HBV and HCV carrier status. Estimated mediation proportions were 11% for HBV and 33% for HCV. Sensitivity analysis using E-values suggested that associations in indirect and direct pathways are unlikely to be explained solely by an uncontrolled confounder. Strengths of this study include prospective follow-up with clinical measurement of key variables and reliable indicators of HBV and HCV carrier status. Limitations include the small number of HCC cases, lack of precision estimating the mediation proportion and its uncertainty, and inability to determine HCV carrier status among a small subset of the study cohort. This work, conducted in collaboration with Dr. Ohishi, Chief of the Clinical Studies Department, and Dr. Young Min Kim (Kyungpook National University, Korea) has resulted in a paper currently in development: *Ohishi W, Cologne JB, Kim YM, Fujiwara S, Tsuge M, Chayama K. Mediation by Hepatitis Viruses of the Radiation-related Risk of Liver Cancer. [Target Journal*

- International Journal of Cancer or European Journal of Epidemiology]. 2022; In Development. [Ahs]

Association of immune-genome SNPs with solid cancers

This is a continuing analysis of data collected under now terminated RP (Hayashi T, Yoshida K, Kusunoki Y, Kyoizumi S, Ohishi W, Hida A, Imaizumi M, Cologne JB, Misumi M, et al: Relationship between cancer development and genetic polymorphisms among A-bomb survivors. This RP focused on immune-related genes) in which about 370 single nucleotide polymorphisms (SNPs) at candidate genes related to immune function, inflammation, DNA repair mechanisms, and metabolism were genotyped by Dr. Hayashi of the Molecular Biosciences Department. Drs. Cologne and Brenner conducted preliminary QC checking of the genotypes. Dr. Cologne and Dr. Kato are analyzing individual SNP associations with logistic regression (using PLINK) and gene-set and pathway analyses (using the SKAT package in R) for colorectal cancer, breast cancer, and all solid cancer combined. They are also assessing interactions between radiation dose and (i) individual SNPs, (ii) gene sets, and (iii) pathways as assessed with the GxEScanR R package for gene-environment (GxE), and iSKAT R package for gene-set/pathway interaction with radiation. This analysis continues with plans to prepare a manuscript in 2023.

Radiation association with chronic kidney disease in atomic bomb survivors

In this study, cross-sectional data collected in 2008-2012 are being used to examine whether radiation exposure is associated with the development of chronic kidney disease (as identified using updated criteria including eGFR and urine albumin), and whether any observed association is modified by other factors such as city, sex, or age at exposure or mediated by clinical factors such as obesity, hypertension, dyslipidemia, or diabetes. Ms. Cordova had been working to develop and finalize the statistical analysis plan for this study. With Ms. Cordova's departure, Dr. Yamamura has taken over this project. Finalization of the data for this project and initiation of analysis will proceed in 2023, after completion of the cataract study discussed above.

Longitudinal trajectories for genomic alterations in MDS

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.

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.

Reliability and stability of serum/plasma cytokines after long-term storage

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. [Ahs]*

AHS Report 9

In late 2022 regular joint monthly meetings were initiated between Dr. Kurisu and members of the Clinical Studies Department with Dr. Sposto, Dr. Misumi, Ms. Funamoto, and Mr. Shimizu of the Department of Statistics to begin discussions and planning for the 9th report on non-cancer disease incidence in the Adult Health Study. In the two meetings thus far, the criteria for inclusion in the study cohort and the ICD definitions of the diseases that will be studied were discussed. These meetings will result in the writing of a detailed analysis plan, after which formal analysis will begin. We anticipate the formal analysis will begin in the 2nd or 3rd quarter of 2023.

Prevalence of Diabetes

As a follow-up to the recent report on the incidence of diabetes in the Adult Health Study (Tatsukawa, Cordova, Yamada 2022), Dr. Tatsukawa and other members of the Clinical Studies Department, and Dr. Sposto and Ms. Funamoto from the Department of Statistics, have begun preparing for an analysis of the prevalence of diabetes in the AHS. At present the analytic cohort has been defined and the data necessary for this analysis are being finalized. We anticipate that the formal analysis will begin in the 2nd or 3rd quarter of 2023.

Incidence of Thyroid Disease

Dr. Kato of the Department of Statistics has worked with Dr. Imaizumi and members of the Clinical Studies Department to update RP2-99 in preparation for an analysis of the associations between incidence of thyroid diseases and A-bomb radiation exposure in younger and in utero

exposed survivors and to study effects of radiation on the increase in size of thyroid nodules. This RP revision is in final review, and analysis will commence in 2023.

Neural-network assessment of biological age from chest x-rays.

Dr. Liu of the Department of Statistics has worked with Dr. Nakamizo and other in the Clinical Studies Department to develop a research proposal that will study the utility of biological age estimated from chest x-rays (CXR) as an alternative or adjunct to chronological age. In this study, initially, a previously published convolution neural network (CNN) developed in the United States to estimate biological age will be applied to CXRs from Adult Health Study subjects. If it is determined that the performance of this previously published CNN is unsatisfactory, an attempt will be made to update the CNN via transfer leaning using CXRs from the AHS cohort. This RP is currently undergoing final scientific review.

Specific Aim 2: Perform research to develop new, or extend and apply existing, statistical methods that are essential to the mission of RERF.

Research Proposals

The following RPs originating from the Department were active in 2022. For the last, Dr. Misumi assumed the role of PI, replacing Dr. Ozasa, former chief of the Epidemiology Department.

Papers published or in press.

Of the 11 peer-reviewed papers published or in press on which Department members were authors, five originated in the Department of Statistics and reported development or application of novel statistical methods or techniques(Cologne, Sugiyama, Hamasaki 2022, Noma, Misumi and Tanaka 2022, Ohishi, Yamamura and Yanagihara 2022, Sposto, Cordova, Hamasaki 2023, Sposto, Sugiyama, Tsuruyama, Brenner 2023).

***Cologne JB**, Sugiyama H, Hamasaki K, Tatsukawa Y, **French B**, Sakata R, **Misumi M**. Chromosome aberrations among atomic-bomb survivors exposed in utero: Updated analysis accounting for revised radiation doses and smoking. Radiat Environ Biophys. 2022; **61**(1):59-72. [Ahs]*

This paper reports a re-analysis of chromosome aberrations occurring in peripheral blood lymphocytes in individuals exposed to A-bomb radiation *in utero.* Compared to the previous analysis, this updated analysis accounted for smoking behavior and medical radiation exposure, and also used the most recent DS02R1 dosimetry. The analysis suggested a low dose increase in aberration frequency that is not sustained over the entire dose range.

*Noma H, **Misumi M**, Tanaka S. Risk ratio and risk difference estimation in case-cohort studies. J Epidemiol. 2022; **1-15**. [Sd]*

This paper provided pseudo-Poisson and pseudo-normal linear regression methods for estimating risk ratios and risk differences in analyses of case-cohort studies, which compared to the odds ratio, are more favorable outcome measures that are directly interpreted as effect measures without the rare disease assumption. The multivariate regression models are fitted by

weighting the inverses of sampling probabilities. Computational code in R (R Foundation for Statistical Computing, Vienna, Austria) were developed to easily apply these methods.

*Ohishi M, **Yamamura M**, Yanagihara H. Coordinate descent algorithm of generalized fused Lasso logistic regression for multivariate trend filtering. Japanese Journal of Statistics and Data Science. 2022; **1-17**. [No RP] [Smnos]*

This paper deals with an optimization problem for Generalized fused Lasso (GFL) logistic regression. Model parameters for the generalized linear model including the logistic regression model are usually optimized by minimizing a linear approximation of an objective function because the minimizer of the objective function cannot be obtained in closed form. In this paper, we propose an algorithm for solving the optimization problem for GFL logistic regression without approximating the objective function, for the purpose of optimizing fast and accurately. Specifically, we derive updated equations of a coordinate descent algorithm for solving the optimization problem in closed form. Moreover, we show an example for spatio-temporal data analysis.

***Sposto R, Cordova KA**, Hamasaki K, Nakamura N, Noda A, Kodama Y. The association of radiation exposure with stable chromosome aberrations in atomic bomb survivors based on DS02R1 dosimetry and FISH methods. Radiat Res. 2023; 1-12. [RP8-93]*

In this paper we analyzed the relationship between the frequency of stable chromosome aberrations (sCA) detected by FISH and radiation exposure as estimated by the latest RERF DS02R1 dosimetry in blood lymphocytes collected from atomic bomb survivors. The major foci of the analysis were the strength and shape of the dose response and factors that appear to modify the effect of radiation exposure on induction of stable chromosome aberrations. We found that based on FISH methods and recent dosimetry, the relationship between radiation dose and sCA frequency is largely consistent with previous findings, although the lesser importance of city as an effect modifier may reflect better dosimetry as well as more reproducible scoring of sCA. The persisting difference in sCA dose response by shielding category points to remaining problems with the accuracy or precision of radiation dose estimates in some A-bomb survivors. Ms. Cordova performed the initial analyses and Dr. Sposto produced the definitive analysis and authored the paper.

***Sposto R**, Sugiyama H, Tsuruyama T, Brenner A. Effect of radiation exposure on survival after solid tumor diagnosis in A-bomb survivors. Cancer Epidemiology. 2023; In press. [RP1-75, RP18-61]*

In this paper we investigated whether pre-diagnosis radiation exposure affects survival after solid cancer diagnosis by analyzing post-diagnosis survival and its relationship to radiation exposure in subjects diagnosed with solid cancers in the LSS from 1958 to 2009 with specific attention to differences in dose response for different causes of death. As opposed to the Bockwoldt *et al. (Cancer Epidemiol Biomarkers Prev. 2021; 30(2):412-8)* recent analysis that included post-diagnosis survival in 7,728 LSS subjects with gastrointestinal cancer who died of this cause, we include all first primary solid cancers in a single analysis and investigate differences in the association of prior radiation exposure to survival for different causes of death. This approach provides a more sensitive analysis of the association of radiation dose to post-diagnosis survival, especially in those who died from the originally diagnosed cancer. We

concluded that there is no detectable large effect of pre-diagnosis radiation exposure on post-diagnosis death from the first primary cancer in A-bomb survivors, so that direct effect of pre-diagnosis radiation exposure on cancer prognosis is ruled out as an explanation for the difference in incidence and mortality dose response in A-bomb survivors. Dr. Sposto conceived and carried out the analysis and was the primary author of the paper.

Papers submitted or in development.

Four papers are in development (Cologne, Misumi, Kadowaki 2022, Liu, Cologne, Amundson 2022, Liu, Nakamizo, Cologne 2022, Misumi and Furukawa 2022) and are described in the next section.

Ongoing analyses

Mechanistic modelling of colon cancer incidence

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.

Multidimensional Smoothing

Dr. Misumi applied a generalized additive model to the LSS cancer incidence data to flexibly model the temporal trend of radiation risks. The method to evaluate the model fit *via* the comparison to the conventional parametric models is under investigation. The draft manuscript was written with an evaluation based on ratios of expected cases based on the model to the observed cases. Dr. Misumi is currently revising the manuscript considering further improvement of the radiation dose-response under the GAM framework. This work is the subject of a paper in development: *Misumi M, Furukawa K. Multi-dimensional smoothing for age trends of radiation effects on the cancer risk of Japanese. [Target Journal - TBD]. 2022; In Development. [RP1-75] [Drm, lss].*

Candidate biomarker discovery

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]*

Deep learning for radiation risk prediction

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. [Smnos]*

Development of mathematical and computational models to examine the effects of radiation exposure on clonal hematopoiesis. [Related to Clonal Hematopoiesis RPs in development]

Dr. Misumi proposed this project to apply a computational biology approach to an investigation of clonal hematopoiesis development. Simulations including radiation effects were conducted. One of the scenarios considered as a possible radiation effect on the stem cells was the reduction of the number of stem cells due to radiation exposure and recovery from it. Dr. Misumi, with the help and advice of Dr. Haeno of the University of Tokyo, conducted simulations assuming different ages at exposure. The frequency of clonal hematopoiesis was higher when the age at exposure was older if they did not consider adding mutations by radiation exposure. The frequency of clonal hematopoiesis increased when DNA mutations were added by radiation exposure at younger ages. Dr. Haeno is currently drafting a manuscript based on this work, and Dr. Misumi plans to visit Dr. Haeno in Tokyo in late February 2023 in order to complete the manuscript.

Empirical Bayes analysis of radiation risk for multiple cancer sites (joint analysis)

Dr. Cologne is working with members of the RERF Epidemiology Department and collaborators at the US NCI to conduct joint analyses of multiple cancer site risks by using the EB approach. He and Dr. Brenner (RERF Epidemiology Department) are studying the utility of the EB method for making inference about heterogeneity of background incidence and heterogeneity of radiation risk (including curvature and effect-modification) in the joint

analysis of six groups of cancers not covered under the individual site-specific analyses. As the numbers of these cancers are mostly relatively small, they are currently assessing how best to deal with numerical problems related to the hyper-prior distributions of precision parameters in the prior distributions for the background-rate parameters.

Use of historical data as adjunct to RERF data in risk estimation.

Related somewhat to the joint analysis approach above, the advantage of this approach comes from the ability to identify commonalities in the background or radiation effect parameters among different diseases as a way to increase precision compared to completely independent analysis of each endpoint. Such a joint analysis is also being considered by Dr. Sakata for the analysis of morality in the LSS as a part of the planned LSS report 15. In order to inform where such commonalities may exist in background cancer mortality outcome, Dr. Sposto used Japanese national cancer mortality data based on the entire Japanese population to compare background model cancer mortality for different cancer types based on attained age (0 to 85+ years), sex, and era (1950 to 2020). Some commonalities were discovered which could inform the future joint analysis. But two questions arose during this investigation, which will be pursued further: (1) What in fact would be the expected gain in precision for risk estimation that can be achieved in such joint analyses, and (2) rather than joint analysis, can precision be increased by utilizing national mortality data as a fixed background, and modelling the difference in background between the national data and LSS, which may require estimation of fewer background parameters than use of LSS data alone. Some initial work was presented at the RERF Colloquium on 20 January 2023.

Study of body weight trajectories and risk of subsequent mortality

This is a continuation of previously published work (Cologne J, Takahashi I, French B, Nanri A, Misumi M, et al: Association of weight fluctuation with mortality in Japanese adults. JAMA Network Open 2019; 2(3):e190731. DOI:10.1001/ jamanetworkopen. 2019.0731) under a now-terminated protocol. The research protocol (Misumi M, Cologne JB, et al: Longitudinal weight fluctuation and cancer and cardiovascular disease mortality in Japanese atomic bomb survivors) was prepared to allow continuation of this multi-departmental and multi-institutional collaborative study. The primary objective is to study how best to assess the association between body weight variability and subsequent disease incidence and mortality There are two parts to the current study. The first part is an analysis of risk for weight fluctuation, in which Dr. Cologne and Dr. Misumi are conducting latent class analysis (primarily via latent class mixed models) to identify BMI trajectory classes for use as risk factors in Cox regression. This work has resulted in a paper currently in development: *Cologne JB, Misumi M, Kadowaki Y, Nakamizo T, Araki Y. Association of Adult Body Weight Trajectories with Mortality in a Japanese Clinical Cohort: Analysis via Joint Latent Class Mixed Models. [Target Journal - TBD]. 2022; In Development. [Ahs]*.

The second part, a methodological study being conducted jointly with Dr. Araki of Shizuoka University in which we will compare various statistical approaches (functional and parametric) for joint modeling of longitudinal trajectories (including latent trajectory classes) and time to event (disease or death), is described below.

Methodological comparison of functional and parametric approaches to latent class analysis and their application to joint modeling of longitudinal and event-time analysis

This is the methodological component of the work related to RP. Dr. Cologne and Dr. Misumi, collaborating with Dr. Y Araki at Shizuoka University (formerly of the Kurume University Biostatistics Center), an expert in functional data analysis, to consider methods of incorporating functional estimates of BMI trajectories into Cox regression models for mortality risk due to extreme weight fluctuation. Dr. Araki has been working with a student of hers to implement a functional cluster analysis to relate weight fluctuation trajectory classes to total mortality. Dr. Cologne visited Dr. Araki in late 2022 to discuss progress on the manuscript reporting these methods, which is expected to be submitted in 2023.

Spatial statistics

Features of the RERF long-term follow-up cohorts that have not been extensively explored to date relate to heterogeneity in incidence, mortality, or radiation risk induced by spatial differences in demographic or topologic effects that are likely not accounted for in the current modelling approaches. Dr. Yamamura was awarded MEXT(B) grant funding for five years for "Development of a spatio-temporal risk estimation model for Hiroshima and Nagasaki exposures by Fused-lasso." Dr. Yamamura developed initial methods for spatio-temporal statistical analysis using a dataset on crime statistics that has analytic features in common with analytic problems related to RERF research and is currently conducting research on the analysis of individual LSS data including geographic information using publicly available person-year LSS data.

Bioinformatics

Dr. Zhenqiu Liu joined the Department on April 25, 2022. Dr Liu has a PhD in operations research with concentration on data mining and statistics, and served post-doctoral research fellowships in bioinformatics and statistical genetics. Dr. Liu will be taking the lead role within the Department of Statistics in RERF genetics and genomics research and implementation of machine learning methods, developing within the Department a group with the requisite faculty and staff and computer hardware and software resources (in collaboration with Dr. Ono of ITD) to support RERF research in this area.

On August 30, 2022, Drs. Liu, Sposto, and other members of the Department of Statistics met with RERF scientists representing all other RERF departments to assess generally upcoming needs in this area. This meeting identified a number of upcoming and future research areas that would utilize these techniques. Among these more immediate projects are (1) the research by Dr. Nakamizo to predict the biological ages and radiation effects with chest X-ray images and convolution neural networks (CNN). This project is based on a previously published CNN model with known network structures and pretrained with chest X-ray images from US cohorts. The goal is to investigate the applicability of the current model to RERF cohort and fine-tune the model with transfer learning if necessary. This project RP is currently in final scientific review; and (2) The TRIO study, which has an approved RP and is currently undergoing IRB review. This latter is a collaboration between RERF, the US NCI, and RIKEN. The aim of this project is to study the association between parental radiation exposure and occurrence of *de novo* germline mutations in their offspring. Dr. Sposto will lead the effort in providing data

analysis support. Other potential research areas discussed include the integrated analysis of proteomics, metabolomics, lipidomics, and image data of fixed tissue and the integration of omics and non-omics data, but these have not yet reached the level of conceptual maturity sufficient to make definitive plans for these needs. However, it is recognized that we will need to develop pipelines for data preprocessing before analysis and will require some high-performance computing (HPC) resources, either in house or subscribed to. Dr. Ono from ITD is providing three HPC servers with CPU for immediate computing needs. In addition, specifically as related to the TRIO study, on December 12, 2022, Drs. Sposto, Liu, and Misumi met with Drs Noda and Uchimura of Molecular Biosciences to begin to work out the details of the division of labor for various tasks, specific requirements for pipeline development and computation, and the responsibilities of Department of Statistics in genome data analysis.

Besides these collaborative projects, as mentioned above, Drs. Liu and Cologne are collaborating with Dr. Noda from RERF and Dr. Amundson from Columbia University to investigate the possibilities of identifying candidate dosimetry biomarkers from multiple whole genome expression datasets in public domain. Drs. Liu, Misumi, and Cologne, in collaboration with Drs. Nakamizo and Ono are also developing data-driven deep learning methods for radiation risk estimation with Life Span Study (LSS) cohort data and exploring the potential of AI in radiation effects research.

Specific Aim 3: Maintain and ensure the integrity of the RERF dosimetry system.

Current work in this area is primarily related to the Department of Statistics involvement in the organ dosimetry reevaluation project.

Papers published or in press.

None

Papers in development

Paulbeck CJ, Sato T, Funamoto S*, Lee C, Griffin K,* Cullings HM*, Egbert SD, Endo A, Hertel N, Bolch WE. Fetal and maternal atomic bomb survivor dosimetry using the J45 series of pregnant female phantoms with realistic exposure scenarios. [Target Journal – Radiation Environmental Biophysics]. 2022; Submitted. [RP18-59] [Dos]*

In this paper previous work [Radiat Res 192, 538-561 (2019)] was extended using realistic angular fluences from the DS02 system for up to nine different radiation dose components and five shielding conditions. Both Dr. Cullings and Ms. Funamoto's critically reviewed the paper as it was being developed.

Domal SJ, Correa-Alfonso CM, Paulbeck CJ, Griffin KT, Sato T, Funamoto S, Cullings HM, Egbert SD, Endo A, Hertel NE, Lee C, Bolch WE. Fetal and maternal atomic bomb survivor dosimetry using the J45 series of pregnant female phantoms: Consideration of the kneeling and lying posture with comparisons to the DS02 system. Health Physics. 2022; Submitted. [Dos].

Domal, S. J., C. M. Correa-Alfonso, C. J. Paulbeck, K. T. Griffin, T. Sato, S. Funamoto*, H. M.* Cullings*, S. D. Egbert, A. Endo, N. E. Hertel, C. Lee and W. E. Bolch (2022). "A reassessment*

of the partial body shielding of the Nagasaki factory workers in the LSS cohort using the J45 computational phantoms." [Target Journal - Radiation Research] In Development.

In these two papers, issues surrounding dosimetry for subjects in non-standing positions and for Nagasaki factory workers are explored.

Completed and Ongoing work

Coordinating 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, which has resulted in the papers described above.

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.

On April 8, 2022, a meeting was held between ODWG members, RERF leadership, and representatives of the Japanese Ministry of Health Labor and Welfare (MHLW) and the US Department of Energy (DOE). The ODWG presented an overview of the evolution of RERF dosimetry and described the recent work that created the modern sophisticated phantoms, the likely changes in dosimetry that would be expected if these new phantoms were utilized and plans and timeline for implementing the new organ dosimetry.

Ms. Funamoto and Mr. Shimizu of the Department of Statistics have completed the work of converting the current dosimetry system computer code to a modern software platform, and in addition have integrated new software that is necessary to compute organ doses using the new phantoms. We are now awaiting completion of the extensive simulations that are being performed by Dr. Lee's group at NCI, by means of which the necessary response functions for the new organ dosimetry will be determined. The response functions are essentially massive data tables for each combination of phantom type, orientation, radiation type, and other parameters. Once these response functions are computed and delivered to us, Ms. Funamoto and Mr. Shimizu will use these to determine the organ doses for all possible RERF cohort subjects for which DS02R1 doses can be computed. We expect that this work can be completed in 2023.

Specific Aim 4: Participate in education, outreach, and operational activities to increase visibility, enhance opportunities for external collaboration, and contribute to the functioning of RERF as a research organization.

Domestic Partnerships

The Department received continuing approval and funding from RERF to proceed with a program to collaborate with Japanese universities to impact the quantity and quality of Japanese research statisticians with expertise in methods that are relevant to the research mission of RERF. Unfortunately, the plan as originally envisioned, whereby RERF would offer tuition remission to PhD students pursuing dissertation topics of interest to RERF, turned out to be unworkable due to regulatory issues related to the use of funds granted to RERF by the Ministry of Health, Labor, and Welfare.

In October 2022, we obtained permission from RERF to transform this program into a student research opportunity. Under this new program, the RERF Department of Statistics will recruit student researchers to assist senior researchers in the Department in the application of or development of statistical methods in the realm of biomedical and epidemiological research that is relevant to RERF's research mission. To qualify, we require that interested post-graduate students are in a master's or PhD degree program in statistics, biostatistics or related programs from Japanese universities and have completed at least one-year of post-graduate classroom training in these fields. The student will be employed as a student researcher during which time the student researcher will assist in the completion of methodologic or analytic research projects in collaboration with RERF researchers and under the supervision of a senior scientist in the RERF Department of Statistics. The duration of the appointment will be determined based on the student's availability and level of training and the needs of the specific project being considered.

Dr. Misumi has begun outreach, having introduced and discussed this program with the directors of Japanese university departments in September 2022 at the Japanese Joint Statistics meeting in Tokyo, and also in December 2022 at the Biometrics Society of Japan Biometrics Seminar in Tokyo.

International Partnerships

The Department had received approval to continue an international exchange program based on the Japan Society for Promotion of Science (JSPS) International Fellowships for Research in Japan mechanism, [https://www.jsps.go.jp/english/e-inv_researchers/index.html, and we have received continuing approval from RERF. This program provides funding for postdoctoral fellowships of 12-to-24-month duration or invitational fellowships for established researchers of 2-to-10-month duration. Preference will be given to researchers who have background and interest in statistical genomics, genetic epidemiology, or bioinformatics. Funding will come from the JSPS award, with RERF serving as the host institution and providing administrative support to interact with the applicant researcher in preparing and filing the applications, monitor its status, and if granted, work with researcher to facilitate the transition to Hiroshima, including applying for any necessary work authorization and helping to identify acceptable housing. RERF administration and the Department of Statistics evaluated this proposed program and consider it feasible given the JSPS funding availability. The

announcement is currently posted on the RERF website and on PROFELLOWS.COM. We have had one applicant about a sabbatical stay at RERF from a U.S. scientist at RERF relevant to this program which we are currently evaluating.

Other Outreach and Education Activities

Internal meetings and presentations

The Department holds semi-monthly meetings dedicated to work in progress (WIP) presentations on a rotating basis. In addition, we still participate in the now-titled Epidemiology Science Thursday when we have a topic to present to a wider audience and also make presentations at the RERF Monthly colloquia. These talks during 2022 are listed below.

Speaker	Date	Venue	Title
J Cologne	2022-03-09	Department of Statistics WIP	GAMLSS (Generalized Additive Models for Location, Scale, and Shape): An Application in the AHS Atherosclerosis Cytokine Validity Study
M Yamamura	2022-03-23	Department of Statistics WIP	Overview FOCS & multi-state models
K Cordova	2022-04-13	Department of Statistics WIP	FISH Study: Updated Analysis Report with Revised Testing of Effect Modification
N Kato	2022-04-27	Department of Statistics WIP	Detecting Cancer Relevant SNPs Using Bayesian Lasso Model
R Sposto	2022-05-11	Department of Statistics WIP	Radiation transmission factors, and implications for dosimetry error
M Misumi	2022-05-25	Department of Statistics WIP	An introduction to mechanistic model in radiation epidemiology
Z Liu	2022-06-08	Department of Statistics WIP	Radiation Sensitivity and Dose-Response Assessment with Omics Data from Cell Lines
S Shimizu	2022-06-22	Department of Statistics WIP	Issues to be considered : New organ doses of a pregnant woman and a fetus
J Cologne	2022-07-13	Department of Statistics WIP	Joint Modeling of Weight Fluctuation and Mortality in the Adult Health Study: Phase 1 - Methodological Collaboration
J Cologne	2022-07-15	133rd RERF Colloquium	Analysis Plan for the F1 Clinical Study (FOCS)
N Kato	2022-07-27	Department of Statistics WIP	Spike and slab variable selection for ERR model

Speaker	Date	Venue	Title
M Yamamura	2022-08-10	Department of Statistics WIP	Current Status of Cataract Research in 2022
R Sposto	2022-08-24	Department of Statistics WIP	The Association of Radiation Exposure with Stable Chromosome Aberrations in Atomic Bomb Survivors based on DS02R1 Dosimetry and FISH Methods
M Misumi	2022-09-14	Department of Statistics WIP	An update of the LSS colorectal cancer incidence data analysis
Z Liu	2022-09-28	Department of Statistics WIP	Candidate Biomarkers and Long-term Transcriptional responses over Low and High Dose Ionizing Radiation
Benjamin French (Visiting former acting Department chief)	2022-10-12	Department of Statistics WIP	Acceleration of residual lifetime among survivors of the atomic bombings of Japan
S Funamoto	2022-11-02	Department of Statistics WIP	The structure of acute effects table in ONDO [SQL Database]
J Cologne	2022-11-09	Department of Statistics WIP	Assessing Variability Within and Between Clinical Laboratory Assay Batches: Inference for the Coefficient of Variation (CV). Application to the RERF Atherosclerosis Study Cytokine Assay Quality Assessment (QA).
N Kato	2022-11-21	Department of Statistics WIP	Group variable selection for ERR model

External meetings and presentations

During 2022, Department members attended scientific meetings and educational sessions of relevance to RERF research.

Member	Scientific meeting	Date	Location
M Misumi	2022 Annual Meeting and Tutorial of the Biometric Society of Japan	2022-05-13 to 2022-05-14	Online
M Misumi	2022 Japanese Joint Statistical Meeting	2022-09-04 to 2022-09-08	Tokyo
Z Liu	The 68th Annual International Meeting of the Radiation Research Society	2022-10-16 to 2022-10-19	Hawaii, USA
M Misumi	2022 Biometric Seminar	2022-12-08 to 2022-12-09	Tokyo

Member	Educational meeting	Date	Location
M Misumi	2nd Biostatistics and Informatics Seminar 2022, "Fundamentals of Meta-Analysis"	2022-07-22	Online
M Misumi	1st Webinar on Medical and Health Data, "Challenges of effect heterogeneity in Statistical Casual Inferences" by Dr. K. Shiba (Boston Univ.)	2022-10-04	Online
S Shimizu	the 81 Annual General Assemblies of the Japan Industrial Safety and Health Association	2022-10-19	Online
M Misumi	2nd Webinar on Medical and Health Data, "Fundamentals of statistical machine learning and neural networks" by Dr. K. Matsui (Nagoya Univ.)	2022-11-25	Online
M Yamamura	GIS Day in Chugoku 2022	2022-12-08	Hiroshima University
M Misumi	3rd Webinar on Medical and Health Data, "Method and practice of machine learning for effective use of small data" by Dr. K. Matsui (Nagoya Univ.)	2022-12-19	Online
S Shimizu	DPC++ Programming Introductory Workshop	2022-10-05, 2022-10-13	Online
M Yamamura	ArcGIS Introductory Workshop	2022-10-17 to 2022-10-28	Tokyo

In addition, Department members were presenters of or co-authors of 15 RERF presentations at scientific meetings. These are listed in the appendix.

Outreach to junior and high schools in Hiroshima.

On January 6, 2022, Ms. Funamoto participated in a meeting between a science instructor for Hiroshima junior and high school students. The purpose of the meeting was to provide the instructor with a firm grounding of the issues surrounding radiation and radiation dosimetry in atomic bomb survivors so that he could develop a teaching plan for this topic.