DEPARTMENT OF STATISTICS

Overview

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 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, which are facilitated through their participation in RERF research cluster activities.

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 should result in improvement to dose estimates for specific organs and tissues.

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.

FY2021 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 FY2021 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 ongoing analyses and work on development of new research protocols.

Papers published or in press

Department members were authors on 23 peer-reviewed papers that were published or in press in 2021, 18 of which were primarily collaborative publications originating from the Departments of Epidemiology, Clinical Studies, or Molecular Biosciences, eight of which were previously reported as in press in 2020, and 10 of which represent papers newly published or in press (Amano, French, Sakata 2021, Brenner, Preston, Sakata 2021, Haruta, Landes, Hida 2021, Hayashi, Furukawa, Morishita 2021, Hida, Imaizumi, French 2021, Hu, French, Sakata 2021, Little, Wakeford, Zablotska 2021, Nakamizo, Cologne, Cordova 2021, Tatsukawa, Cordova, Yamada 2021, Ishihara, Kato, Misumi 2022). In addition, there was one letter of response to a previous collaborative publication (Yamada, Furukawa, Tatsukawa 2021).

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 selected of these not reported last year as in press are highlighted below.

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

Tatsukawa Y, Cordova KA, Yamada M, Ohishi W, Imaizumi M, Hida A, Sposto R, Sakata R, Fujiwara S, Nakanishi S, Yoneda M. Incidence of Diabetes in the Atomic Bomb Survivors: 1969-2015. Journal of Clinical Endocrinology & Metabolism. 2021; ***In Press****. [AHS]*

Ms. Cordova, with oversight from Dr. Sposto, was the primary statistician on a collaborative project with Dr. Tatsukawa and others in the Clinical Studies Department to assess radiation effects on incident diabetes among Adult Health Study subjects. The goals of the analysis were to determine whether there is a detectable radiation effect on incident diabetes, and whether that effect is modified by other factors including sex, city, and age at exposure (ageATB). After preliminary meetings focused on data preparation, management, and quality assessment, Ms. Cordova drafted the final statistical analysis plan and presented it for input from all collaborators. She completed the analysis in several stages with frequent collaborator feedback, applying Cox regression models to time-to-event data to assess radiation effects on diabetes incidence and potential effect modification by city and age at exposure. Ms. Cordova made major contributions to the writing of the manuscript and the response to the reviewer comments. The paper is now in press.

Nakamizo T, Cologne JB, Cordova KA, Yamada M, Takahashi T, Misumi M, Fujiwara S, Matsumoto M, Kihara Y, Hida A, Ohishi W. Radiation effects on atherosclerosis in atomic bomb survivors: A cross-sectional study using structural equation modeling. Eur J Epidemiol. 2021; 36(4):401-14. [AHS]

Ms. Cordova and Dr. Cologne collaborated with Dr. Nakamizo and others in the Clinical Studies Department on a project utilizing multiple indicator multiple causes (MIMIC) models to assess radiation effects on three distinct latent atherosclerotic pathologies (arterial stiffness, calcification, and plaque) measured in 14 correlated clinical markers in a cross-sectional sample of AHS participants. The analyses applied structural equation modeling methods and MIMIC models for latent factors to assess radiation effects on atherosclerosis. A unique aspect of the analysis was the computation of mediated effects of a covariate (radiation dose) on the indicators (clinical measurements) of the latent factors (categories of atherosclerosis), using the reduced form of the MIMIC model for the benefit of clinical practitioners who are more familiar with the clinical measurements than with the arbitrarily scaled numerical values of the latent factors. Ms. Cordova and Dr. Cologne provided the primary analysis and supplementary and sensitivity analyses and made major contributions to the writing of the manuscript and to responses to journal reviewers

Brenner AV, Preston DL, Sakata R, Cologne JB, Sugiyama H, Utada M, Cahoon EK, Grant E, Mabuchi K, Ozasa K. Comparison of all solid cancer mortality and incidence dose-response in the Life Span Study of atomic bomb survivors, 1958-2009. Radiation Research. 2021; ***In Press****. [LSS]*

Dr. Cologne met routinely with Dr. Brenner during the course of this research to discuss different aspects of the analysis, especially the treatment of high-dose adjustment in the ERR effect modification part of the dose response model, and to confer regarding the presentation of the confidence intervals for the dose response curvature parameters.

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. Radiation Research. 2022; ***197****(000-000). [AHS]*

In these analyses, NCQ scores from two surveys were used. Dr. Kato with Dr. Masumi 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 the measurements obtained from the same individuals. Parameters of random intercept models were estimated *via* Bayesian inference using OpenBUGS version 3.2.3 (http://www.openbugs.net); MCMC software for Bayesian inference and R version 3.5.3 for other statistical analyses.

Amano MA, French B, Sakata R, Dekker M, Brenner AV. Lifetime risk of suicide among survivors of the atomic bombings of Japan. Epidemiol Psychiatr Sci. 2021; ***30****(e43). [LSS]*

Hu A, French B, Sakata R, Bhatti P, Bockwoldt B, Grant EJ, Phipps A. The possible impact of passive smoke exposure on radiation-related risk estimates for lung cancer among women: The Life Span Study of atomic bomb survivors. Int J Radiat Biol. 2021; ***97****(11):1548-54. [LSS]*

These two publications arose 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.

Papers in development

Four additional collaborative papers are 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]. 2021; ***In Development.***

This study, which is based on the AHS Hepatitis Cohort Study, utilizes follow-up for incident primary liver cancer (hepatocellular carcinoma, HCC) from the tumor registry to assess joint effects of radiation and chronic infection with hepatitis virus (HBV or HCV). This draft manuscript is based on the first part of the analyses: mediation of radiation risk for HCC by HBV, which has a strong association with radiation dose and is therefore a mediator in principle (the second part will examine the joint effects on HCC of obesity and HCV, including their interaction and potential modification of radiation risk). Mediation was assessed with the mediation proportion, the ratio of indirect (mediated by HBV) to total effect of radiation on HCC risk, by using published equations for these effects on the log hazard ratio scale. The necessary parameters were derived from a logistic regression model for prevalence of the mediator (HBV) and a proportional hazards model for incidence of HCC. Dr. Cologne compiled the data from hepatitis cohort and AHS database sources, performed the analyses under Dr. Ohishi's guidance (and with the assistance of Dr. Kim in the estimation of the mediation proportion), and drafted the non-clinical aspects of the manuscript.

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. 2021; ***Submitted****. [AHS]*

This paper evaluates the effects of prenatal exposure to atomic bomb radiation on subjective neurocognitive function in aged survivors. Dr. Kato performed random intercept models to express intra-individual correlations, under the supervision of Dr. Misumi.

Yoshida K, Satoh Y, Uchimura A, Misumi M, Kyoizumi S, Taga M, Matsuda Y, Noda A, Kusunoki Y. Clonal hematopoiesis is prevalent in mice following whole-body X-irradiation. [Target Journal - TBD]. 2021; ***In Development****. [Mbs, AHS]*

Dr. Misumi has been involved in the clonal hematopoiesis program project from the initiation, and this is a manuscript based on the preliminary data of the 3rd project with an animal experiment. Dr. Misumi conducted statistical analyses to compare the clinical measurements, such as lymphoid cells, myeloid cells, and RDW, of mice between radiation exposed and non-exposed 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. 2021; ***Submitted****. [LSS]*

This paper also 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.

Research Proposals Approved

Radiation effects on the incidence of stroke in atomic bomb survivors Approved March 2021] (PI: T. Nakamizo):

This RP assesses radiation effects on incident stroke. Ms. Cordova actively collaborated on RP revisions and responses to reviewer comments while providing frequent input on the statistical aspects of the study, including the study design, calculation of power, and analysis plan. Dr. Sposto reviewed the RP in detail and suggested revisions to define more precisely some aspects of the proposal.

Roles of reduced lamin B1 and enhanced retrotransposon transcription in T-cell aging and inflammation Approved November 2021] (PI: K. Yoshida)

Dr. Sposto wrote the statistical considerations section for the two aims of this RP: (1) To validate the previous results for the aging-related change in lamin B1 expression in Tn cells, using PBMC samples preserved from 20 female non-AHS volunteers, and (2) To examine associations among lamin B1 expression, LINE-1 transcriptional activity, and age at the blood sampling in Tn, memory CD4 T (Tm), CD8 T, and monocyte fractions, using the same PBMC samples in Aim 1.

Feasibility of genomic analysis with DNA from stored blood smears and paper discs [PI: T. Hayashi]

This is a stand-alone proposal (Hayashi T, Ohishi W, Brenner A, Kato N, Cologne JB, et al: Preliminary study to determine the applicability of DNA extractable blood samples preserved in the past to GWAS) to assess the suitability for genomic analysis of Giemsa-stained and Wright-stained slides and blood-infiltrated paper discs collected in the AHS over the preceding decades by comparing concordance between SNP assays from DNA extracted from these samples to assays on DNA extracted from fresh blood to be collected from the same individuals.

Dr. Cologne, in collaboration with Dr. Brenner and Dr. Kato, helped with initial plans for the design of the study, in particular by drawing attention to needs for blinding, avoiding batch biases, and incorporating appropriate replicates. Dr. Kato performed sample-size estimation to achieve sufficient power with a non-inferiority analysis on the basis of information obtained from a previous pilot study that utilized stored specimens obtained from volunteers. This important study will provide critical information about the use of stored biospecimens, especially in terms of whether specimens stored far back in the past are usable, which will dictate the available population size for genomic studies in the AHS. The RP has been approved by the cancer cluster and is currently under IRB and Biosample committee review.

Research Proposals in Development

Investigation of hereditable genetic effects of radiation base on F1 family trios (PI: Noda)

Dr. Sposto, with the assistance of Ms. Funamoto and in collaboration with Drs. Noda and Uchimura of the Department of Molecular Biosciences, evaluated a study design and analytic plan for the proposed study of the relationship between parental radiation exposure and heritable mutations using parent/offspring trios. This work involved first assessing the existence of complete family trios with known DS02R1 estimated radiation doses and linking this to the inventory of specimens of the type required for sequencing of children and parents in order to identify the complete set of family trios that would be available for this study. Second, the distributional properties of the primary endpoints for this study, which are multi-site mutation, single nucleotide variants, and insertion/deletions, was derived from the existing literature, with particular attention to the expected extra-Poisson dispersion that will likely be encountered, leading to the adoption of a negative-binomial-based linear regression model of mutation rate on radiation dose. Simulations were performed based on the available trios and their associated DS02R1 doses to estimate the power of primary analyses that would be performed for each endpoint, including a subsampling scheme and sensitivity analyses in the event that cost prohibited assay of all possible trios, which would be the optimal approach. A detailed statistical analysis plan was written. The research proposal is now under review.

Longitudinal Analysis of thyroid disease incidence in young A-bomb survivors (PI: Imaizumi)

Previous research showed a relationship between radiation dose and thyroid cancer. However, only cross-sectional studies were evaluated for the relation between radiation dose and the other thyroid disease. In this RP, three examinations will be performed for each member of the AHS exposed at a young age to evaluate thyroid disease, especially solid thyroid nodules and cysts. Dr. Kato developed the statistical methods section for the RP, including estimation of the power of the various analyses, with oversight from Dr. Sposto, for an analysis of the relationship between radiation dose and growth and occurrence of thyroid cysts and nodules using Cox proportional hazards regression and logistic regression, respectively.

Screening of fusion genes and genomic mutations in autopsied cases with CML (PI: N. Yoshida)

Leukemia is one of the diseases caused by radiation dose. Especially, chronic myeloid leukemia (CML) was the most frequently developed type and CML which developed shortly after the bombing and may have produced characteristic genomic alterations. In this RP, we plan to extract DNA from the samples of autopsied CML participants and check the feasibility of applying high throughput sequencing analysis to FFPE tissue to detect fusion genes and genomic mutations. Dr. Kato estimated statistical power of the test of the relationship between

radiation dose and prevalence of fusion gene in acute myeloid leukemia (AML) using a logistic regression model, under the guidance of Dr. Sposto.

Ongoing analyses

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

Dr. Yamamura collaborated with Dr. Hida and others in the Department of Clinical Studies 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 probably weighting analysis to account for informative censoring due to cataract surgery. The manuscript for this project is now in preparation.

Chromosome aberrations scored using FISH

Ms. Cordova continued collaborative work with Dr. Kodama and Dr. Nakamura of the Department of Molecular Biosciences on an ongoing analysis assessing the relationship between DS02R1 estimated radiation doses and stable chromosome aberration frequency measured using the FISH method, overall and as a function of sex, city, age at exposure, and shielding type. As part of manuscript preparation, a supplementary analysis was requested to examine the roles of gamma and neutron dose components to the induction of translocations detected using FISH method. Given the observed city difference in the FISH dose response and differential exposure to neutrons (with substantial neutron exposure only in Hiroshima), the authors are investigating the impact of modeling the two types of doses separately, either by imposing an assumed linear dose response for neutrons (as informed by prior work) or by freely estimating the neutron effect. Given these alterations, we are exploring the change in gamma dose response, especially between cities. The analysis is currently ongoing and the results will be presented in a report to Dr. Kodama for use in the forthcoming manuscript.

Study of body weight trajectories and risk of subsequent mortality

This is a continuation of previously published work initially (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. A new research protocol (Ozasa K, 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 by applying innovative summaries of longitudinal BMI trajectories risk factors in joint models. We plan to eventually propose a new analysis (new RP) to study how changes in body weight affect radiation risk for 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 is collaborating with Dr. Misumi to conduct latent class analysis (primarily via growth mixture modeling) to identify BMI trajectory classes for use as risk factors in Cox regression. For this analysis, Dr. Cologne began testing latent class methods on the data. Dr. Ozasa, the project PI, along with members of the RERF Clinical Studies Department, will be primary collaborators in this part, and Ms. Cordova will help with structural equations and latent class analysis using the Mplus

software. The second part is a methodological study being conducted jointly with Dr. Araki of Shizuoka University in which we will compare various statistical approaches (functional and parametric) to joint modeling of latent classes and time to event (disease or death). The second part is described in detail below under Specific Aim 2.

Liver cancer risk in the AHS

This study focuses on joint effects of radiation and hepatitis viruses (HBV) on risk of hepatocellular carcinoma (HCC). Dr. Cologne has competed preliminary work on mediation of radiation risk by HBV, in collaboration with Dr. Young Min Kim (Kyungpook National University, Korea). Dr. Cologne and Dr. Sposto have begun work to analyze interaction between chronic hepatitis C virus infection and longitudinal trends in obesity (via BMI), and to assess whether and how that affects radiation risk for HCC. This is being investigated by using methods for joint modeling of longitudinal and event-time data with left truncation, which allow extending the longitudinal trajectories back in time to before start of follow-up for cancer incidence (the time of hepatitis virus measurements). This work is being conducted in collaboration with Dr. Ohishi (Chief of the Clinical Studies Department).

Association of immune-genome SNPs with solid cancers

This is a continuing analysis of data collected under now terminated (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, focusing 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. As the cancer data are based on tumor registry follow-up since the time of blood collection, they are also evaluating use of the glmnet R package for testing GxE interaction with Cox regression, as it will be especially useful for risk estimation in RERF cohorts when high-dimensional genomic features become available (such as the proposed genomic analyses in the AHS, pending the results of the newly proposed study "*Feasibility of genomic analysis with DNA from stored blood smears and paper discs*" described above). Dr. Cologne wrote and updated a reproducible research document in RStudio with LaTeX that will serve as an archive of this work.

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 urinary 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 was newly added as the statistical collaborator in 2021 and has been working to develop and finalize

the statistical analysis plan for this study. Data are currently being compiled and processed with analysis to begin in 2022.

Detecting onset of hematologic malignancies

Dr. Misumi started the analysis in December 2021 of DNA sequence data obtained with validation of the mutation calls by Dr. Miyazaki of Nagasaki University and Drs. Nanya and Ogawa of Kyoto University. Dr. Misumi will provide statistical data analysis to evaluate the associations among certain clones and clinical measurements such as red blood cell distribution width (RDW) and hemoglobin.

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 2021: The last four will be terminated during 2021. Please see the attached RP progress reports for updates. Papers published or in press

Of the 23 peer-reviewed papers on which Department members were authors, three reported development or application of novel statistical methods or techniques (Cologne, Sugiyama, Hamasaki 2021, Kaiser, Misumi and Furukawa 2021, Yamamura, Ohishi and Yanagihara 2021).

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. Radiation and Environmental Biophysics. 2021; ***In Press****.*

Dr. Cologne, having performed the analyses for the previous publication on the topic of the chromosome aberration (translocation) DS86 dose response among *in utero* exposed atomic-bomb survivors (Ohtaki K, Kodama Y, Nakano M, Itoh M, Awa AA, Cologne J, et al: Radiation Research 2004; 161(4):373-379), proposed in FY2019 this re-analysis with the updated DS02R1 dose estimates in response to discussions held between some ICRP members and RERF Chairman Niwa where it was suggested that smoking should be adjusted for. (Smoking had not been adjusted in the original study of Ohtaki et al). Dr. Cologne performed the analyses in collaboration with Dr. French and Dr. Misumi, with feedback from the other authors. The analyses were documented in a reproducible research document based on the Rmarkdown markup language in RStudio to facilitate sharing and archiving the methods and results. The manuscript was drafted primarily by Dr. Cologne and Dr. French, with input from the other authors.

Kaiser, J.C., M. Misumi, and K. Furukawa, Biologically-based modeling of radiation risk and biomarker prevalence for papillary thyroid cancer in Japanese a-bomb survivors 1958 - 2005. Int J Radiat Biol, 2021. 97(1): p. 19-30.

The original objective of this data sharing with Dr. Kaiser was an application of a model developed by Kaiser et al. (2016) to the LSS data. The result was very similar to that based on a descriptive model in Furukawa et al. (2013). That is, the radiation ERR was modified by the

age at exposure, and only the subjects with exposure in childhood showed strong association with radiation. This project did not initially make progress on developing a manuscript. Dr. Misumi discussed with Dr. Kaiser the inclusion of different perspectives taking account of possible biomarkers related to a papillary thyroid cancer.

Yamamura M, Ohishi M, Yanagihara H. Spatio-temporal adaptive fused lasso for proportion data. Intelligent Decision Technologies--Proceedings of the 13th KES-IDT 2021 Conference. 2021; (pp 479-89). [Spa]

Capturing changes in features over time is important for population-corrected rates, which are often used in statistical data. In this study, we proposed a method for analyzing the spatio-temporal effects on population-corrected rates in statistical data using the adaptive fused lasso method for the estimate of applicability. For the estimation, the analysis was conducted using the coordinate descent algorithm, which is regarded as accurate and fast. The results show that the proposed method is applicable to spatio-temporal analysis of statistical proportion data. Dr. Yamamura was in charge of all the work involved in preparing the paper.

Papers in development

Two additional papers are in development:

Misumi, M. and K. Furukawa, Multi-dimensional smoothing for age trends of radiation effects on the cancer risk of Japanese. [Target Journal - TBD], 2021. ***In Development.***

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.

Ohishi M, Yamamura M, Yanagihara H. Coordinate Descent Algorithm of Generalized Fused Lasso Logistic Regression for Multivariate Trend Filtering. Hiroshima Statistical Research Group Technical Report. 2021. [Spa]

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 update equations of a coordinate descent algorithm for solving the optimization problem in closed form. Moreover, we show an example for spatio-temporal data analysis. Dr. Yamamura checked the mathematical formulations and English description of the statistical theory.

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), 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 for presentation to the clinical collaborators. 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 Department of Clinical Studies. The working group recommendations on the analytic approach were accepted, and a formal analysis plan document is now being developed.

LSS colon cancer mechanistic modeling

Dr. Misumi had discussions via Zoom on the application of a model developed by Kaiser et al. (2013) to the latest LSS cancer incidence data. Although Dr. Casteletti and Dr. Simonetti, who played leading roles in this project, left Dr. Kaiser's group related to the COVID-19 pandemic, and the project has been suspended since then, Dr. Misumi has been involved in the discussion on the analysis of Bavarian colon adenoma data conducted by Dr. Kaiser, who suggested for Dr. Misumi to be involved to enable them to consider some comparison of colon carcinogenesis between different cohorts. Dr. Misumi has also started analyzing colon adenoma data of the LSS, which will provide further information for the mechanistic modeling, and will start mechanistic modeling in parallel with Dr. Kaiser, utilizing the R package Dr. Kaiser developed with advice from Dr. Misumi.

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 by Dr. Haeno of the University of Tokyo, conducted the 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. Misumi is writing a manuscript with Dr. Haeno based on the simulation studies, and they will consider further extension of their collaboration related to this topic while more information is provided from the Clonal Hematopoiesis RPs and other hematological studies.

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

Since Dr. David Pawel performed an empirical Bayes (EB) analysis of multiple cancer site ERR estimates several years ago (Pawel D, Preston D, Pierce D, Cologne J: Improved estimates of cancer site-specific risks for A-bomb survivors. Radiation Research 2008; 169(1):87-98) there has been interest within RERF to further utilize EB methods for multiple-site analyses of the LSS cancer incidence data. 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 radiation risk 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.

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. Dr. Cologne collaborated 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. Drs. Cologne and Misumi corresponded with Dr. Araki to discuss her proposal for using functional approaches to joint modeling. 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, and a paper on that work is expected around the spring of 2022.

Utilizing a structural equation modeling approach to investigate the magnitude of error in DS02 doses using biodosimetry data

In 2021, Ms. Cordova (with collaborative support from members of Statistics and MBS) launched a new analysis project which aims to combine various sources of information about physiological exposure among the Life Span Study survivor cohort in order to estimate the magnitude of dose error in RERF's DS02R1-estimated doses. Under the umbrella of the dosimetry RP, we plan to fit a structural equation model (SEM) which identifies true radiation dose as a latent variable indicated by DS02R1 dose. Existing data gathered from prior biodosimetry studies (presence of acute symptoms, electron spin resonance of tooth enamel, and chromosome aberrations detected using both Giemsa staining and FISH methods) will be jointly regressed on the latent, true dose while adjusting for other important covariates. From this model, we hope to derive an empirically driven estimate of the magnitude of dose error inherent in the DS02R1 estimated doses. Sensitivity analyses will be used to assess the impact of modeling assumptions (e.g., missingness) on the observed results, and if feasible, the proposed model may be extended to include radiation effects on relevant health outcomes, with physiological exposure variables included as instrumental variables of the latent true radiation dose. Over the course of 2021, the project was proposed and discussed among collaborators and within the department, followed by data acquisition and processing. Ms. Cordova presented background and preliminary modeling during an RERF colloquium in December 2021, with results from the full dose error SEM expected in 2022.

Effect of measurement error in the low dose range

Dr. Misumi conducted simulation studies under his Ministry of Education, Culture, Sports, Science and Technology (MEXT) grant to investigate effects of dosimetry errors on the shape of radiation dose response, focusing on low-dose estimation.

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." As part of this grant effort, Dr. Yamamura is currently also preparing a data-sharing RP on spatio-temporal statistical analysis, a joint project with Hiroshima University to obtain coordinate data such as latitude and longitude as the location of exposure, and explore mortality and cancer incidence with regional effects, in order to develop a statistical model of radiation exposure that includes regional effects. While this RP is being developed and going through the RERF review system, 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.

Dose response modeling

There are a number of issues related to dose response modelling where investigations were initiated.

Incidence vs mortality dose response. Discussion of analyses of cancer incidence and mortality raised the question of under what conditions the cancer incidence and cancer mortality dose responses should be similar in shape. Previously, Dr. Sposto showed, analytically, that even when post-incidence survival was not dependent on radiation dose, that LNT dose response in cancer incidence could lead to non-linear dose response in mortality and age-related effect modification, especially for less immediately fatal cancers. As a result, Drs. Brenner and Sposto discussed the possibility of modelling cancer mortality in terms of an integrated model of cancer incidence and post-incidence survival. In 2021 Dr. Sposto conducted an analysis of combined solid tumor post-incidence mortality, showing that when death is cause by the originally diagnosed solid tumor there is no evidence of a dose effect on post-incidence mortality, but when death is due to tumor unrelated to the original diagnosis or from non-cancer causes there is a dose effect. This is consistent with the idea that cancers occurring in individuals exposed to radiation do not have different prognosis compared to cancers in unexposed individuals. Hence post-diagnosis survival dose response would not be a major contributor to differences in mortality vs incidence dose response. A penultimate draft the paper reporting these results has been produced.

Bioinformatics

NAS and RERF successfully recruited a new member of the Department of Statistics. Dr. Zhenqiu Liu is scheduled to join the Department April 1, 2022. Dr Liu has a PhD in operations research with concentration on data mining and statistics, served post-doctoral research fellowships in bioinformatics and statistical genetics, and was until recently an Associate Professor of Biostatistics and Bioinformatics in the Department of Public Health Sciences at Pennsylvania State University. Dr. Liu has over 100 peer-reviewed papers, more than 30 of which are first author, and additionally has an MS degree in computer science. Prior to this

most recent appointment, Dr. Liu developed and directed for five years the bioinformatics department at the Samuel Oschin Comprehensive Cancer Institute in Los Angeles, California. Dr. Liu will take the lead role within the Department of Statistics in RERF genetics and genomics research, developing within the Department a group with the requisite faculty and staff and computer hardware and software resources (in collaboration with ITD) to support RERF research in this area.

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

Griffin, K.T., et al., Japanese pediatric and adult atomic bomb survivor dosimetry: Potential improvements using the J45 phantom series and modern Monte Carlo transport. Radiat Environ Biophys, 2021. 1-14.

In this paper, in order to evaluate the potential dosimetry improvements that would arise from the use of the new phantoms in a Dosimetry System (DS) at RERF, organ doses in the J45 series have been calculated using the environmental fluence data for twenty generalized survivor scenarios pulled directly from the current DS. Both Dr. Cullings and Ms. Funamoto critically reviewed the paper as it was being developed.

Papers in development

Paulbeck, C.J., et al., Fetal and maternal atomic bomb survivor dosimetry using the J45 series of pregnant female phantoms. Part 1: Analysis using DS02 exposure scenarios. [Target Journal - Radiation Environmental Biophysics], 2021. ***Submitted****.*

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 critically reviewed the paper as it was being developed.

Paulbeck, C.J., et al., Fetal and maternal atomic bomb survivor dosimetry using the J45 series of pregnant female phantoms. Part 2: Considerations of variations in fetal uterine position. [Target Journal - Radiation Environmental Biophysics], 2021. ***Submitted***

In this paper, the work in Part 1 (above) was extended to include additional models of the child both in a breach and in a transverse orientation at 15-weeks and 25-weeks post-conception. Both Dr. Cullings and Ms. Funamoto critically reviewed the paper as it was being developed.

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 (2021). "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." [Target Journal - Health Physics] ***In Development****.*

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 (2021). "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 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, which has resulted in the papers described above.

Finalization of organs sites for which new dosimetry will be computed.

Dr. Sposto coordinated, with assistance from Ms. Funamoto and Mr. Shimizu, a review of organ sites for which doses will be made available in the new revised organ dosimetry system in the likely event that it is adopted. Specifically, disparate but detailed organ and sub-organ and laterality information provided by the Organ Dosimetry Working Group (ODWG) for the different newly designed phantoms was organized into 14 organ systems and provided to an RERF wide committee comprising 11 senior investigators from the Departments of Clinical Studies, Molecular Biosciences, Epidemiology, and the Biosample Research Center. During an extended meeting, each organ system was reviewed in detail, and formal recommendations and requests were recorded and provided to the ODWG. The ODWG were able to accommodate the majority of the recommendations and request, and they provided alternative approaches to accommodate those for which it was infeasible to include. The list of organ sites was finalized during meetings of the ODWG on December 16, 2021, and January 7, 2022.

Implementation of new response functions and rotational code into existing dosimetry system.

As part of the preparation for implementation of the revised organ dosimetry, Ms. Funamoto and Mr. Shimizu have converted the current DS02 FORTRAN code from the obsolete Lahey FORTRAN compiler to the modern Intel FORTRAN compiler. This code is used to integrate the response function tables generated from the computational phantom models with the source terms and leakage files generated from the transport model and shielding models, which apply to the individual survival data on location, shielding, and orientation. This conversion was necessary because a much larger volume of data from the computational model is required to implement the new dosimetry, and this cannot easily be accommodated by the Lahey compiler without significant structural changes to the established FORTRAN code. The conversion of existing code was completed in early 2021. An additional module required to apply the response function tables was developed and verified during 2021 by Mr. Shimizu.

A detailed comparison of simulated doses and doses by the new module in the DS02 system was performed, revealing excellent agreement for standing posture. In addition, to save time to simulate response function for all orientations, code to rotate standing phantoms to the prone

and supine positions was implemented, and the resulting organ doses were compared to simulated doses, showing larger than expected differences between the directly simulated doses and those resulting from the rotational approximations. These results were presented at the December 16 meeting of ODWG. Reasons for and the significance of these differences were discussed further during the January 7, 2022, meeting of the ODWG.

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. The plan is to partner with institutions in Japan with strong statistics or biostatistics departments and invite interested doctoral students to develop methodologic or analytic research projects in collaboration with their faculty mentors, members of the RERF Department of Statistics, and other RERF researchers. Details of the program are as follows:

- The program is open to doctoral students in conjunction with their mentors.
- The program duration for a student is up to two years.
- Each year, the student and mentor will visit RERF for up to one week.
- The first-year visit will comprise classes describing RERF research and the statistical methods used, plus discussions with Department members and RERF researchers to identify a research project.
- The second-year visit will be to review progress and finalize details.
- The expectation will be that the research is published in a high-quality journal.

RERF provides the yearly funding to cover university tuition (when this is allowed) as well as transportation and lodging for the yearly visits to RERF for both the student and his/her mentor. Funding in the second year would be contingent on demonstrated adequate progress.

In the first year of the program, we were not successful in identifying an interested student, although we did have extended discussions with Dr. Satoshi Hatori at Osaka University about a potential student which unfortunately fell through. In 2021 we engaged in additional discussion with Kurume University Department of Biostatistics, with which the RERF Department of Statistics has had a long-standing formal relationship, and whose current chair, Dr. Kyoji Furukawa, is a former member of the RERF Department of Statistics. Dr. Furukawa is interested in participating in this program, although at present he does not have any PhD students who would be candidates for this program. We have recently consulted with Dr. Shigeyuki Matsui, Professor, Department of Biostatistics at Nagoya University Graduate School of Medicine and head of the Biometrics Society of Japan, on how best to move forward with this program, and Dr. Matsui advised that we should advertise the existence of this program to individual faculty members at major Universities throughout Japan to solicit interested students or faculty.

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. The postdoctoral fellowships are those that initially we will pursue. 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 available. The announcement is currently posted on the RERF website and on PROFELLOWS.COM. The continued inability for individuals to enter Japan and uncertainty as to when these restrictions will be lifted has prevented us from forcefully promoting this fellowship at this time.

University of Washington Partnership

The Department has in the past actively participated in the research and training partnership between the University of Washington (UW) and RERF, with the goal to encourage and facilitate scientific exchange and collaborations in epidemiology and biostatistics between RERF and UW and to develop and provide training opportunities in order to attract talented young investigators to careers in radiation science and to enhance and broaden the training of junior investigators at RERF and UW. The papers that have resulted from this have been discussed in the past and in this report. This program ended in 2021.

Other Outreach and Education Activities

Working group in radiation biology

Dr. Cologne organized and chaired a working group involving members of the Department of Statistics and the Department of Epidemiology to study the underlying principles of radiation biology. This group met monthly between February 2021 and November 2021, during which members took turns to review and present and lead the discussion of chapters of the book: Chadwick, K. H. *Understanding Radiation Biology : From DNA Damage to Cancer and Radiation Risk.* CRC Press, 2020. The working group was useful in providing a grounding in the basic concept of radiation biology.

Internal meetings and presentations

In 2021, we changed the format of internal Department presentation away from the previous Epidemiology-Statistics Science Thursday in order to allow the Department to focus more clearly on methodological issues that could not be discussed in the wider non-statistical audience of this previous series. Instead, the second semi-monthly meeting of the Department is 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. These talks during 2021 are listed below.

Speaker	Date	Venue	Title
M Yamamura	2021-01-27	Department of Statistics WIP	An overview of lasso estimation and its application to spatial analysis
R Sposto	2021-02-24	Department of Statistics WIP	Deconvolution of cancer incidence and mortality radiation risk
R Sposto	2021-03-10	Department of Statistics Educational Presentation	Components of an RP and statistical methods section
M Misumi	2021-04-28	Department of Statistics WIP	Multistate models of cancer incidence in the LSS
N Kato	2021-05-26	Department of Statistics WIP	Estimating ERR from individual data
K Cordova	2021-06-23	Department of Statistics WIP	Dose error quantification
R Sposto	2021-06-24	Epidemiology Science Thursday	Convolution Model of Cancer Mortality
J Cologne	2021-07-28	Department of Statistics WIP	Non-collapsibility of Effect Measures: Conventional Wisdom Not Applicable Beyond Ordinary Linear Regression (nonlinear or non-additive models)
M Yamamura	2021-08-25	Department of Statistics WIP	An overview of missing data analysis in cataract research
R Sposto	2021-09-29	Department of Statistics WIP	Further design considerations for the TRIO study
J Cologne	2021-10-07	Epidemiology Science Thursday	Reporting rate ratio estimates: How much precision. Considerations for analyses of risk at multiple cancer sites
S Shimizu	2021-10-27	Department of Statistics WIP	The comparison of organ doses between DS02 and new response functions
N Kato	2021-11-04	Department of Statistics WIP	Estimation of ERR using the proportional hazard model

Speaker	Date	Venue	Title
R Sposto	2021-12-09	Epidemiology Science Thursday	Effect of radiation exposure on survival after solid tumor diagnosis in A-bomb survivors
K Cordova	2021-12-22	Department of Statistics WIP	Project update: Dose error quantification.

We also participate in the institution-wide RERF colloquium. Department members' presentations in this forum were:

Speaker	Date	Title
K Cordova	12/17/2021	A comprehensive structural equation modelling approach to assess the magnitude of error in DS02 doses using biodosimetry

External meetings and presentations

Dr. Misumi organized and Dr. Sposto chaired an invited session titled "New direction in radiation epidemiology" for the Japanese Region of the Biometrics Society, WNAR, that was online in June 2021. The objective of this session was to familiarize the biostatistics community with RERF and the RERF Department of Statistics, and to describe statistical methods to investigate the role of radiation in disease development in the context of a radiation-exposed epidemiological cohort. The speakers and their talks were:

- Munechika Misumi, Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan. Title: *Radiation risk estimation and statistical methods for the long-term follow-up studies of Japanese Atomic bomb survivor*
- Carmen Tekwe, Department of Biostatistics and Epidemiology, Indiana University Bloomington, Bloomington, IN, USA. Title: *An application of multiple indicators, multiple causes measurement error models to adjust for dose error in RERF data*
- Jan Christian Kaiser, Institute of Radiation Medicine, Helmholtz Center Munich, Munich, Bavaria, Germany. Title: *Biologically-based risk models in radiation research*
- Kyoji Furukawa, Biostatistics Center, Kurume University, Kurume, Fukuoka, Japan. Title: *Statistical issues in estimating factors affecting the individual response to radiation.*

Department members also attended training for advanced statistical methods and other seminars applicable to RERF research. Specifically:

Member	Course/Symposium	Date	Location
M. Misumi	Japan Epidemiological Association Pre-Conference Seminar 2021	1/27/2021	Online
M. Yamamura	The Institute of Statistical Mathematics International Online Seminar	3/16/2021	Online
M. Yamamura	Women in Data Science Hiroshima Symposium	3/27/2021	Hiroshima Prefectural Office
K. Cordova	The 4th Gilbert W. Beebe Webinar Series	4/8/2021	Online
N. Kato	The 4th Gilbert W. Beebe Webinar Series	4/8/2021	Online
S. Shimizu	PHITS Online Seminar	5/21/2021	Online
M. Misumi	Hikone Data Science 2021: International Symposium on Casual Inference and Machine Learning	9/10/2021	Online
M. Misumi	The 2nd Meeting on Human Genome Research Ethics in 2021	10/29/2021	Online
R. Sposto	The 2nd Meeting on Human Genome Research Ethics in 2021	10/29/2021	Online

Department members also attended scientific meetings of relevance to RERF research. Specifically:

Member	Scientific meeting	Date	Location
M. Yamamura	Behaviormetric Society Okayama the 74th Online Meeting	3/6/2021	Online
M. Yamamura	The 15th Japanese Joint Statistical Society Spring Meeting	3/13/2021	Online
M. Misumi	The Biometric Society of Japan Annual Meeting 2021	5/13/2021~5/14/2021	Online
M. Yamamura	KES Intelligent Decision Technologies 2021	6/14/2021~6/16/2021	Online
M. Misumi	2021 WNAR/IMS/JR Annual Meeting	6/15/2021~6/17/2021	Online
R. Sposto	2021 WNAR/IMS/JR Annual Meeting	6/15/2021~6/17/2021	Online
M. Misumi	Japanese Joint Statistical Meeting 2021	9/5/2021~9/5/2021	Online
M. Yamamura	Japanese Joint Statistical Meeting 2021	9/5/2021~9/5/2021	Online

The Department has for the most part over the last two years been unable to participate in person in national and international meetings to the extent we have in previous years. We use such participation to increase the visibility of the Department and RERF and cultivate opportunities for collaborations that would be beneficial to RERF by direct interaction with participants at these meetings, something that cannot be done effectively in online meetings. Nevertheless, in 2021, Department members were presenters of or authors on talks at scientific meetings.

Authors	Title	Meeting Name	Date
Yamamura M*, Ohishi M, Yanagihara H	Spatio-temporal adaptive fused lasso for proportion data	Smart Digital Futures 2021	2021-06-14
Misumi M*	Radiation risk estimation and statistical methods for the long-term follow-up studies of Japanese atomic bomb survivor cohort	2021 WNAR Annual Meeting (Virtual)	2021-06-13
Taga M, Yoshida K, Kyoizumi S, Kato N, Sasatani M, Suzuki K, Ogawa T, Kusunoki Y	Cytokine expression and genomic damage analyses after in vitro X-irradiation of primary hepatic stellate cells isolated from 1-week-old mice	64th Annual Meeting of the Japanese Radiation	2021-09-22

Authors	Title	Meeting Name	Date
		Research Society	
Misumi M*	Methods for regression analysis with exposure uncertainty in radiation risk analysis	Japanese Joint Statistical Meeting 2021 (Virtual)	2021-09-05
Paulbeck CJ, Sato T, Funamoto S, Domal S, Correa C, Lee C, Griffin K, Cullings HM, Egbert SD, Endo A, Hertel N, Bolsh WE	Pregnant female computational dosimetry for the atomic bomb survivors of Hiroshima and Nagasaki	67th Annual Meeting of the Radiation Research Society	2021-10-03
Hayashi T, Kato N, Yoshida N, Ohishi W, Omae Y, Tokunaga K	Evaluation of the applicability of blood smear samples to genome-wide association study	44th Annual Meeting of the Molecular Biology Society of Japan	2021-12-01
Brenner AV, Grant EJ, Sugiyama H, Preston DL, Sakata R, Cologne JB, Utada M, Mabuchi K, Ozasa K	Age at exposure modification of radiation risk in the Life Span Study of Japanese atomic bomb survivors	67th Annual Meeting of the Radiation Research Society	2021-10-03
Ohishi M, Yamamura M, Yanagihara H	A coordinate descent method for Generalized Fused Lasso in logistic regression models	15th Japanese Joint Statistical Spring Meeting	2021-03-13
Dormal S, Correa C, Paulbeck C, Griffin K, Sato T, Funamoto S, Cullings HM, Egbert SD, Endo A, Hertel N, Lee C, Bolch W	Atomic bomb survivor dosimetry of Nagasaki factory workers	66th Annual Meeting of the Health Physics Society (US)	2021-07-25
Dormal S, Correa C, Paulbeck C, Griffin K, Sato T, Funamoto S, Cullings HM, Egbert SD, Endo A, Hertel N, Lee C, Bolch W	Fetal and maternal atomic bomb survivor dosimetry using kneeling and lying survivor postures of J45 pregnant female phantoms	63rd Annual Meeting of the American Association of Physics in Medicine	2021-07-25

*Presenter

DEPARTMENT OF STATISTICS

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.