Departmental 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, 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.

FY2020 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 FY2020 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 20 peer-reviewed papers that were published or in press, 14 of which were primarily collaborative publications with the Departments of Epidemiology, Clinical Studies, or Molecular Biosciences (Bockwoldt, Sugiyama, Tsai 2020, Brenner, Sugiyama, Preston 2020, Grant, Yamamura, Brenner 2020, Mabuchi, Preston, Brenner 2020, Satoh, Asakawa, Nishimura 2020, Sugiyama, Misumi, Brenner 2020, Sugiyama, Misumi, Sakata 2020, Takahashi, Misumi, Murakami 2020, Takahashi, Misumi, Niwa 2020, Ueda, Ohishi, Cullings 2020, Utada, Brenner, Preston 2020, Yamada, Furukawa, Tatsukawa 2020, Yamada, Kato, Kitamura 2020, Yoshida, Misumi, Kusunoki 2020).
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 are highlighted below.

1Drs. 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.

Gastrointestinal cancer survival (Bockwoldt, Sugiyama, Tsai 2020)
This publication arose from the RERF/University of Washington partnership. Dr. French was the RERF Department of Statistics statistical mentor for the epidemiology MPH student who performed this research.

Colorectal cancer incidence in the LSS (Sugiyama, Misumi, Brenner 2020)
Dr. Misumi led and provided statistical analysis of this project including the tables and descriptive statistics. This study updated the follow-up period of the LSS cohort and took account of smoking and other lifestyle factors in the analysis. An effect of screening by colonoscopy was indicated and calendar year was used as a surrogate for that in addition to and as an alternative to the conventional temporal patterns. Also, the colon cancer cases were separately and jointly analyzed by the location of the tumors with comparison of the radiation risks among the cancer sites. Radiation risk was increased in colon cancer but was not observed in rectal cancer. The analysis revealed that the estimated radiation ERRs decreased gradually by the site from the upper colon to rectum although the differences among the sites were not statistically significant.

Mortality among individuals exposed to atomic bomb radiation in utero (Sugiyama, Misumi, Sakata 2020)
Dr. Misumi led the statistical analysis of this project and provided statistical advice on the methods to be used and presentation of the results. This project comprehensively investigated mortality risks of cancer and non-cancer diseases in the *in-utero* cohort of RERF. The radiation risks were estimated similarly to those in the previous report for cancer mortality. However, there were several factors reported elsewhere related to non-cancer mortality risks of *in utero* exposure, such as birth weight and small head size at birth, and those factors were mostly post- exposure variables. Therefore, we reported the non-cancer mortality risks without adjustment for those variables and added information after the adjustment for those variables with explanation for the interpretation of the results.

Radiation and onset of stroke in rat a model (Takahashi, Misumi, Murakami 2020)
Dr. Misumi provided statistical advice on the experiments and analyzed the data of time-to- stroke for multiple experiments conducted with different radiation doses (vs. control). The analysis was conducted for each experiment separately as well as combining all the experiments
– i.e., the results of multiple experiments were combined with a frailty model to estimate the relative risk at low dose exposure taking into account the heterogeneity among experiments.

Radiation and hypertension in a rat model (Takahashi, Misumi, Niwa 2020)
Dr. Misumi provided statistical advice on the experiments and analyzed the data on longitudinal follow-up of body weight and blood pressure of rats, organ weights of rats at death, and pathological measurements of liver at death.

Radiation risk of ovarian cancer in A-bomb survivors (Utada, Brenner, Preston 2020)
Dr. Cologne assisted Dr. Utada with the analyses of ovarian cancer, providing advice on fitting risk models with the Epicure software, including how to avoid convergence problems arising from negative ERR estimates, and offering guidance on how to deal with multiple tumor site in a joint analysis. He checked Dr. Utada's analysis scripts and re-ran some of the analyses to independently confirm the results.
He also proposed a permutation test to assess the difference in radiation ERR between tumor sites, collaborating with Dr. Kato, who carried out that test.

Cognitive function among elder A-bomb survivors (Yamada, Kato, Kitamura 2020)
Dr. Kato performed the linear regression analysis of log transformed CASI scores on radiation dose adjusted for sex, city, age, education, and gestational age.

Untoward pregnancies outcome in children of A-bomb survivors (Yamada, Furukawa, Tatsukawa 2020)
Dr. Furukawa designed and performed the analysis of the effect of maternal and paternal dose on the incidence of congenital malformations and perinatal death in children born to A-bomb survivors. Ms. Funamoto verified the dataset used in this analysis and made comparisons of these results with previous studies. Dr. Sposto independently recapitulated the statistical analysis and verified the results that were reported and provided substantive comments on the penultimate version of the manuscript.

Radiation and red blood cell distribution width in the AHS (Yoshida, Misumi, Kusunoki 2020)
This research investigated the association of longitudinal trajectory of red blood cell distribution width (RDW) with radiation exposure in AHS participants. This study was initiated by Drs. Yoshida and Misumi. Dr. Misumi conducted the statistical analysis utilizing a joint model of longitudinal and survival process to take into account informative censoring due to death. That is, the association between RDW and radiation was evaluated utilizing methodology to avoid possible bias due to dropout of participants which might be highly influenced by the past radiation exposure. The biological mechanisms of RDW increase related to radiation exposure were unclear. However, the result was supported by appropriate application of a complex statistical method despite the difficulty of the interpretation of the effect of radiation exposure more than 50 years ago.

Papers in development
Seven additional collaborative papers are in development.

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. [Target Journal - Radiation Research]. *2020; In Development.* [Lss]
Dr. Cologne met routinely with Dr. Brenner during the course of this research to discuss different aspects of the analysis and to provide advice.
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. [Target Journal - Radiation and Environmental Biophysics]. *2020; In Development.* [Lss]
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 update 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). A working group that included all authors of the manuscript deliberated the sources and utilization of auxiliary data in a series of meetings organized by Dr. Cologne, and data coordination was managed by Ms. Funamoto. Dr. Cologne then performed the analyses in collaboration with Dr. French and Dr. Misumi, with feedback from the other working group members. The analyses were documented in a reproducible research document based on the Rmarkdown markup language in RStudio, created by Dr. Cologne, to facilitate sharing results with the working group. The manuscript was drafted primarily by Dr. Cologne and Dr. French, with input from the other members of the working group.

Hu AE, French B, Sakata R, Bhatti P, Bockwoldt B, Grant EJ, Phipps AI. The potential impact of passive smoke exposure on radiation-related risk estimates for lung cancer among women: The Life Span Study of atomic bomb survivors. [Target Journal - Radiation Research]. *2020; In Development.* [Lss]
This publication arose from the RERF/University of Washington partnership. Dr. French was the RERF Department of Statistics statistical mentor for the epidemiology MPH student who performed this research.

Hida A, Imaizumi M, French B, Haruta D, Eguchi K, Nakamura H, Kawakami A. Association of human T-cell leukemia virus type 1 with prevalent rheumatoid arthritis. [Target Journal - Medicine]. *2020; In Development.* [Ahs]
Dr. French performed the Firth bias-reduced penalized likelihood adjusted cross-sectional logistic regression analysis of the association between HTLV-1 positivity and odds of RA. He also contributed to multiple revisions of this paper.
Little MP, French B, Borrego D, Zablotska LB, Adams MJ, Allodji RS, de Vathaire, Lee C, Brenner AV, Miller JA, Campbell DK, Pearce MS, Doody MM, Holmberg E, Berrington de, Lundell M, Sadetzki S, Wakeford R, Linet MS. Lymphoma and plasma cell malignancies among cohorts of persons exposed to low and moderate doses of external ionising radiation in childhood. [Target Journal - TBD]. *2020; In Development.* [Lss]
Dr. French was the principal investigator on the research proposal that enabled participation of RERF in this pooled analysis.
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. Target Journal - European Journal of Epidemiology]. *2020; Submitted.* [Ci]
Ms. Cordova and Dr. Cologne continued collaborative work 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. In early 2020, Dr. Nakamizo rebuilt the data set using consistent and justifiable criteria for eligibility and measurement. Following this rebuild, Ms. Cordova and Dr. Cologne worked together to re-run the full analysis and revise the drafted manuscript to reflect the changes in the presentation of the results. The analyses involve learning and newly applying to RERF data 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 numerical values of the latent factors. The indirect, or reduced-form, effects of covariates on the latent-factor indicators is generally not of primary interest in applications of MIMIC models. We therefore discussed plans for drafting a future paper on this targeted at a clinical audience. Currently, the paper is undergoing the second round of peer review at the *European Journal of Epidemiology*. Both Ms. Cordova and Dr. Cologne have provided frequent statistical support when revising the manuscript, conducting supplementary and sensitivity analyses, and responding to comments throughout the review process.
Hayashi T, Furukawa K, Morishita Y, Hayashi I, Kato N, Yoshida K, Kusunoki Y, Kyoizumi S, Ohishi W. Intracellular reactive oxygen species level in blood cells of atomic bomb survivors increased due to aging and radiation exposure. [Target Journal - Free Radical Biology and Medicine]. 2021; In Development. [Ahs]
Dr. Furukawa performed the primary multiple linear regression of O2.- and H2O2 in immune cells on radiation dose in 2495 A-bomb survivors. Dr. Kato performed supplementary analyses.

Research Proposals in Development / Design Activities

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. We plan to test the relationship between radiation dose and their growth and occurrence using Cox proportional hazards regression and logistic regression, respectively. Dr. Imaizumi of the Department of Clinical Studies proposed the RP. Dr. Kato is developing the statistical methods section for the RP, including estimation of the power of the various analyses, under the supervision of Dr. Sposto.

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 A- bomb 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. Yoshida of the Department of Clinical Studies proposed the RP and Dr. Kato estimated statistical power under the supervision of Dr. Sposto.

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. From this a simulation was 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 trios. A detailed statistical analysis plan was written that summarized this work.

Feasibility of genomic analysis with DNA from stored blood smears and paper discs [PI: T. Hayashi]
This is a new stand-alone proposal under development (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 recently 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 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.

Radiation effects on the incidence of stroke [PI: Nakamizo]:
This newly proposed RP assessing radiation effects on incident stroke has proceeded through noncancer cluster review over the course of 2020 and was approved at the end of September. It is now under review by a panel of outside experts. 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.

Clonal Hematopoiesis Project 1: Evaluation of radiation-associated clonal hematopoiesis among atomic-bomb survivors [PI: Yoshida]
This project evaluating radiation-associated clonal hematopoiesis among atomic bomb survivors was approved by the noncancer research cluster and a panel of external reviewers in 2019. During review by various internal committees throughout 2020, Ms. Cordova and Dr. Cologne assisted with modifications to the RP to address reviewer comments. Dr. Cologne performed a power calculation that confirmed the adequacy of the proposed sample size.

Clonal Hematopoiesis Project 2: "Evaluation of radiation-related changes in clonal hematopoiesis, inflammation, and atherosclerosis indicators among A-bomb survivors" [Co- PIs: Nakamizo, Yoshida]
This project, investigating intermediating factors (inflammation, t-cell aging, and clonal hematopoiesis) as potential mechanisms through which observed radiation effects on latent atherosclerotic pathologies are propagated, proceeded through reviews by the noncancer research cluster, external reviewers, the IRB, and other committees throughout 2020. Throughout the review process, Ms. Cordova assisted with responding to reviewer comments and incorporating suggestions into the revised RP during frequent contact with collaborators. Dr. Cologne, in collaboration with Ms. Cordova, began considering aspects of the sampling design, such as the use of propensity score matching coupled with similarity matching on the most important covariates.

Clonal Hematopoiesis Project 3: “Mouse models to enable assessments of clonal hematopoiesis, hematologic indicator changes, and pro-inflammatory phenotypes following radiation exposure”[PI: Kusunoki]
This project aims to establish one or more mouse models that can test the hypothesis that clonal hematopoiesis in irradiated mice is involved in pro-inflammatory phenotypes that promote atherosclerosis formation, evaluating the extent to which clonal hematopoiesis following radiation exposure leads to the accumulation of pro-inflammatory monocytes in the periphery. Because this study is still under a preliminary exploration of the candidate mouse model, several preliminary studies were conducted to obtain preliminary data for the RP development. Dr. Misumi provided several graphs of the results for the presentation on the RP, and he will provide statistical advice on the design of experiments when this study proceeds to the stage of evaluating radiation effects once the candidate mouse has been fully decided.

T-cell aging [PI: K. Yoshida]
This is a confirmatory study of the association between age and Lamin B1 and LINE-1 expression as indicators of T-cell aging in a group of healthy volunteers of disparate ages to confirm the results of a previous study in which these two genes were identified as possible markers. Dr. Sposto wrote the statistical considerations section for this and confirmed that the proposed sample size provided adequate power to detect subtle and biologically plausible associations between age and gene expression as measure by RT-PCR.

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 Study 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 generalized estimation equations in order to account for possible correlation between left and right eye cataract assessments. This project is now proceeding to the manuscript preparation phase.

Relationship of radiation to the incidence of diabetes in A-bomb survivors

Ms. Cordova, with supportive oversight from Dr. Sposto, contributed as 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 participants. Initially, 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. Over the course of 2020, Ms. Cordova 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. After compiling and presenting a report of the results to study collaborators, Ms. Cordova solicited further feedback from RERF colleagues during an interdepartmental presentation of the study. The study collaborators are now transitioning to the manuscript preparation stage, and Ms. Cordova continues to provide statistical support with supplementary and sensitivity analyses to clarify interpretation of the primary results. Meanwhile, the next stage of the analysis is currently being planned for 2021, wherein potential mediation of the observed radiation effect on diabetes by body mass index will be investigated.

Chromosome aberration scoring using FISH

Ms. Cordova continued collaborative work with Dr. Kodama 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 impact of shielding type on solid cancer incidence risk estimates (similar to the previous Giemsa-staining chromosome aberrations paper, Kodama et al., 2001, Table 5). After receiving approval to use the data for this purpose, Ms. Cordova conducted the required data management and statistical analysis. In brief, the FISH study data was used to characterize the extent to which the chromosome aberration frequency dose-response differed depending on DS02 shielding type (inside 9-parameter structures, outside globe terrain, Nagasaki factory workers, etc.). These shielding- specific estimates were then used to scale the radiation doses for all LSS members in order to determine the impact on radiation risk estimates for all solid cancer incidence (using the most recently compiled data available from Grant et al., 2017). The results were 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 work initially published in the previous year (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, with a view towards eventually proposing 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 a substantive 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 body weight (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 to compare various statistical approaches (functional and parametric) to joint modeling of latent classes and time to event (disease or death) in this somewhat unique design (uncommon in typical application of joint modeling), which includes a separate 20-year baseline period prior to incidence and mortality follow-up. The second part is described in detail below under Specific Aim 2.

Liver cancer risk in the AHS

This study focuses on mediation of radiation risk by HBV and the joint effect of obesity and HCV on radiation risk. Nearly 20 years of follow-up for liver cancer have accrued since the conduct of the hepatitis study in the AHS cohort (Ohishi W, Cologne JB, et al: Study of liver diseases in the Adult Health Study sample: Relationship between radiation dose and infection by hepatitis B and C viruses). Dr. Cologne performed preliminary work, in collaboration with Dr. Sposto, to implement methods to address two mechanistic aims under the guidance of Dr. Ohishi (Chief of the Clinical Studies Department). The primary aim is to estimate the proportion of total radiation-related risk of hepatocellular carcinoma mediated by chronic hepatitis B virus infection (the prevalence of which is itself causally related to radiation dose). This is being investigated by using methods for inference on indirect effects in discrete survival models with the Mplus software. The secondary aim is to assess interaction between obesity and chronic hepatitis C virus infection and whether that affects radiation risk. 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).

Association of immune-genome SNPs with colorectal cancer

This is a continuing analysis of data collected under now terminated a certain research protocol (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. Dr. Cologne and Dr. Kato analyzed individual SNP associations (using PLINK) and performed gene-set and pathway analyses (using the SKAT package in R) for colorectal cancer, breast cancer, and all solid cancer combined. They also analyzed interactions between radiation dose and (i) individual SNPs, (ii) gene groups, and (iii) pathways as assessed with the GxEScanR R package for gene-environment (GxE), and iSKAT R package for pathway-environment,

interaction analysis. They began to evaluate use of the glmnet R package for testing GxE interaction, as it will be especially useful for risk estimation via Cox regression in RERF cohorts when high-dimensional genomic features become available. Dr. Cologne built a reproducible research document in RStudio with LaTeX that will serve as an archive of this work.

Association of immune-genome SNPs with colorectal cancer

This is a continuing analysis of data collected under now terminated a certain research protocol (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. Dr. Cologne and Dr. Kato analyzed individual SNP associations (using PLINK) and performed gene-set and pathway analyses (using the SKAT package in R) for colorectal cancer, breast cancer, and all solid cancer combined. They also analyzed interactions between radiation dose and (i) individual SNPs, (ii) gene groups, and (iii) pathways as assessed with the GxEScanR R package for gene-environment (GxE), and iSKAT R package for pathway-environment, interaction analysis. They began to evaluate use of the glmnet R package for testing GxE interaction, as it will be especially useful for risk estimation via Cox regression in RERF cohorts when high-dimensional genomic features become available. Dr. Cologne built a reproducible research document in RStudio with LaTeX that will serve as an archive of this work.

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 2020: The last four will be terminated during 2021. Please see the attached RP progress reports for updates.

Papers published or in press

Of the 20 peer-reviewed papers on which Department members were authors, four reported development or application of novel statistical methods or techniques (French, Sadakane, Cologne 2020, Kaiser, Misumi and Furukawa 2020, Kim, Cologne, Jang 2020, Little, Pawel, Misumi 2020). There was also an editorial response to a letter about a previous Department paper (Cologne, Sugiyama, French 2020).

Misclassification of primary liver cancer (French, Sadakane, Cologne 2020)

Dr. French completed publication of the evaluation of misclassification in primary liver cancer, concluding that radiation risk estimates for primary liver cancer are sensitive to death-certificate inaccuracies, with attenuation on average by 13–30% after correcting for misclassification. Dr. Cologne, having worked several decades earlier on misclassification of liver cancer diagnoses in the tumor registry due to diagnoses based solely on death records, collaborated closely with Dr. French in the conduct of this research and in the writing of the manuscript.

Biologically based model of thyroid cancer (Kaiser, Misumi and Furukawa 2020)
Dr. Misumi led discussions on thyroid cancer mechanistic modeling to write a manuscript based on the analysis of an LSS thyroid cancer data with Dr. Kaiser of Helmholtz Zentrum Munchen and Dr. Furukawa of Kurume University. The original objective of the data sharing with Dr. Kaiser was just 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). 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. This work subsequently was published in *International Journal of Radiation Biology*.

Causal mediation analysis in case-control studies (Kim, Cologne, Jang 2020)
Dr. Kim performed the bulk of this work, under the guidance of Dr. Cologne, while he was a member of the Statistics Department at RERF. Ideas for mediation analysis at RERF had their beginning with a now terminated research protocol (Cologne JB, Kim YM, et al: Methods for assessing joint effects of radiation and intermediate risk factors in nested case control studies), upon which this paper is in part based. Dr. Cologne helped review the literature, checked the simulation results, and participated in drafting the manuscript and responding to journal reviewers.

Lifetime mortality risk and dosimetry error (Little, Pawel, Misumi 2020)
The first draft of this manuscript was written by Dr. Mark Little of US NCI, who applied a Bayesian method for dose error correction utilizing grouped data of LSS report 14. Dr. Misumi pointed out possible effects of members who had dose estimates greater than 4 Gy on the shape of radiation dose-response and provided unadjusted untruncated DS02R1 colon dose estimates with advice and suggestions on the Bayesian MCMC results of the LSS data analysis. Then, Dr. Little conducted risk predictions based on the result of the LSS analysis for the information of an ICRP task group led by Dr. Werner Ruhm of Helmholz Zentrum Munchen. Dr. Misumi also proactively joined the discussion and wrote the manuscript with Dr. Little and others. The manuscript has been published in *Radiation Research*.

Background heterogeneity (Cologne, Sugiyama, French 2020)
This letter to the journal Radiation Research was written in response to a letter submitted by Walsh and Schneider that commented on our paper, published in 2019, dealing with curvature in the LSS cancer incidence analyses (Cologne et al: Effect of heterogeneity in background incidence on inference about the solid-cancer radiation dose response in atomic-bomb survivors. Radiation Research 2019; 192(4):388-398. DOI: 10.1667/RR15127.1). Dr. Cologne drafted the response in consultation with the other authors. Dr. Cologne also led a discussion on the Walsh- Schneider letter, our response to it, and more general issues related to the needs of radiation protection organizations vis-à-vis the RERF research mission, at the bimonthly RERF Epidemiology-Statistics Science Colloquium on 12 December 2019.

Papers in development
One additional paper is in development:
Misumi M, Furukawa K. Multi-dimensional smoothing for age trends of radiation effects on the cancer risk of Japanese. [Target Journal - TBD]. *2020; In Development.* [Drm, lss]
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 will complete the manuscript on multi-dimensional smoothing as applied to age trends and radiation risk by the end of FY2021.

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 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, 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 the project is now proceeding to the stage of definitive analysis planning.

LSS colon cancer mechanistic modeling

Dr. Misumi provided advice for the R programming for the mechanistic modeling when he visited Munich in 2019. Then, Dr. Kaiser and his group developed an R package msce for their mechanistic modeling in 2020. Dr. Misumi had e-mail discussions on the application of a model developed by Kaiser et al. (2013) to the latest LSS cancer incidence data. Although Dr. Casteletti, who played a leading role 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.

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.

Detecting onset of hematologic malignancies

Dr. Misumi started this investigation on the methodology for the analysis of DNA sequence data obtained 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. He applied a causal discovery approach to the AHS data of RDW to obtain a causal diagram during the analysis of the AHS RDW study (Yoshida, Misumi, et al. *British Journal of Hematology* 2021), and will consider expanding the approach to longitudinal data.

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 collaborated with members of the RERF Epidemiology Department in joint analyses of multiple cancer site risks by using stacked person-year data in traditional Poisson regression analysis. When it became apparent that the method is computational difficult with many sites of cancer due to the large dimension of the stacked data, he began implementing the EB approach, which only requires a single record for each stratum in the person-year data, in collaboration with Dr. Pawel (at the US Environmental Protection Agency). Dr. Cologne made a presentation to the RERF NCI contract working group to explain this approach, in which he described his preliminary experiences with the method. He and Dr. Brenner (RERF Epidemiology Department) began 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.

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 a certain research protocol. 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. Dr. Cologne performed an exhaustive literature search and began fitting standard latent class models to the data for exploratory purposes. He also began working with Dr. Misumi to consider implementing parametric models for joint modeling with left truncation (allowing longitudinal trajectories to be estimated in the past, before the start of event follow-up), and together they corresponded with Dr. Araki to begin making plans for developing functional approaches to joint modeling.

MIMIC models incorporating measurement error

Ms. Cordova, with collaborative support from Dr. Cologne and Dr. Misumi, furthered work on an independent project aiming to evaluate the use of multiple-indicators-multiple-causes- measurement-error (MIMIC ME) models as an approach to adjust for measurement error in radiation doses. Using the previously established MIMIC model for detecting radiation effects on atherosclerotic pathologies in a cross-sectional sample of Adult Health Study participants, assumed values of radiation dose error were introduced to assess changes in the observed associations of interest and global model fit. Ms. Cordova tested the MIMIC ME approach across a range of modeling assumptions in comparison to simple, unadjusted doses, and submitted an abstract describing the preliminary results of this project to the first meeting of the International Society of Radiation Epidemiology and Dosimetry (ISORED) in Sitges, Spain. The abstract was accepted for oral presentation, but the conference was unfortunately cancelled.

Residual time acceleration

In this project related to the RERF/University of Washington partnership, Dr. French, former member of and now expert advisor to the Department, continues as a mentor to Mr. Eric Morenz, biostatistics PhD student, for his dissertation that arose from this RP titled “Quantifying residual time among A-bomb survivors”. This work continues, with three papers planned – one on parametric and semi-parametric methods, one on non-parametric methods, and one on application.

Dosimetry error/measurement error symposium

Drs. French and Misumi had organized a measurement error / dosimetry error symposium to be held in Hiroshima in March 2020. This two-day symposium was to bring together ten international experts in measurement error from Europe, Japan, and the United States to present their latest research, discuss its relevance to radiation dosimetry and other measurement error issues that arise in analyses of RERF data, and explore the possibility of collaborations in these areas. Unfortunately, the conference had to be cancelled, although we intend to reapply for funding for this symposium.

Effect of measurement error in the low dose range

Dr. Misumi has continued work on 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 incudes regional effects. While this RP is being developed and going through the RERF review system, Dr. Yamamura is doing initial methods development on spatio-temporal statistical analysis using a dataset on crime statistics that has analytic features in common with analytic problems related to RERF research.

Dose response modeling

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

ERR vs EAR modeling. Past RERF publications and others publications in the field analyzing radiation risk have fit both excess relative risk (ERR) and excess absolute risk (EAR) models to the same data. As these models have become increasingly complex, especially with respect to background models and effect modification, one or the other scale may or may not be clearly a better or more parsimonious description of the data. In addition, the tendency has been, even within a particular form of the model, to report results from multiple versions of the model that may omit known significant covariates in order to derive aggregate estimates – e.g., "sex averaged" effects – rather than fitting a single best or at least admissible parametric model and deriving the aggregate measures directly from this. The result has been the fitting and reporting of results from multiple models within the same report. Dr. Sposto advocated against this approach as being incoherent in that the various models do not describe the data identically or some not necessarily well, and the practice results in an overly complex presentation of the results. In addition, there has been the practice of performing multiple analyses over restricted dose ranges, for example to obtain a "minimal significant dose", which is a completely data driven and biologically meaningless quantity. Dr. Sposto plans to develop a position paper discussing these and other similar conceptual issues.

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. 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, 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. This also suggests the possibility of applying contemporary cancer survival estimates to RERF incidence radiation risk models to predict cancer mortality in a way relevant to a contemporary population.

Bivariable dose modelling. In analyses of the F1 cohort of patients – e.g., F1 mortality, F1 untoward pregnancy outcome (UPO), F1 TRIO studies – a question arises about what the best way is to model the joint effect of maternal and paternal doses. In the untoward pregnancy outcome manuscript (Yamada, Furukawa, Tatsukawa 2020), maternal and paternal doses were modeled separately in a linear excess relative risk (ERR) model, with significance judged by likelihood ratio tests of the maternal and paternal slopes in the context of the bivariable model, without Bonferroni correction. A reviewer of this paper commented that this was not an optimal way to test for radiation effects, suggesting instead that maternal and paternal doses should be weighted equally in a single dose variable (i.e., summing the doses), as this would be a more sensitive test to detect any radiation effect. Dr. Sposto's initial investigations of this recommendation tended to support this view, but on further investigation in the context of the TRIO study bivariate dose distribution it was clear that this approach to inference was not uniformly optimal, suggesting instead that equal weighting may be far superior, in terms of efficiency or power, to Bonferroni adjusted or bivariate testing when there are roughly similar contributions to dose effect by both parents, but can be far inferior when one parental dose effect dominates over the other. This problem is related to the concept of maximum efficiency robust tests (MERT) or maximum optimum test (MX) procedures discussed in (Freidlin B et al, Biometrics. 1999; 55(3):883-6). This issue will be investigated further in the coming year.

Flexible dose response modelling. In (Furukawa, Misumi et al, Risk Anal. 2016; 36(6):1211- 23), Dr. Furukawa and Misumi developed a Bayesian semiparametric model that used a connected piece-wise-linear dose-response function with prior distributions having an autoregressive structure as a way to flexibly model dose response to more correctly reflect the precision of low dose radiation risk estimation compared to a traditional highly structured parametric model. Their approach has good statistical properties but is computationally intensive and hence does not easily lend itself to facile data analysis. In an attempt to identify similar approaches that were computationally more feasible, Dr. Sposto, in consultation with Drs. Misumi and Cologne, investigated the use of various other methods, including B-splines, fractional polynomials, isotonic regression, piecewise linear models with random effects, and monotonic cubic splines. Unfortunately, in these initial investigations these methods all suffered from edge effects resulting in unrealistic low-dose dose response or other undesirable properties. Whether a computationally facile flexible approach for RERF analyses can be developed will be the subject of future research.

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

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

Papers published or in press

Dosimetric influence of new computational phantoms(Sato, Funamoto, Paulbeck 2020)
This is another paper in a series of papers that have been published or are in development arising from the organ dosimetry reevaluation project, in which Dr. Cullings (former chief of and now expert advisor to the Department of Statistics) and Ms. Funamoto have been directly and non- trivially involved. Dr. Cullings has continued to contribute his expertise in radiation physics and dosimetry. Ms. Funamoto provided the fluences which are coupled with PHITS software calculation after considering the shielding scenarios and provided technical details of the DS02 dosimetry system to the working group, e.g., kerma approximations, groups of gamma/neutron, the calculation of each shielding type, and angular-fluence systems to match with organ leakage file. She also provided the computer program to rotate angular fluences to correspond with phantoms rotation, thus avoiding calculating organ doses of each orientation by PHITS. Ms. Funamoto was also consulted about the features of general LSS cohort. Both Dr. Cullings and Ms. Funamoto critically reviewed the paper as it was being developed.

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. Part 1: Analysis using DS02 exposure scenarios. [Submitted – Radiation Environmental Biophysics]. *2020; In Development.* [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. Dr. Cullings' and Ms. Funamoto's contribution is the same as described above.
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. Part 2: Considerations of variations in fetal uterine position. [Target Journal – Radiation Environmental Biophysics]. *2020; In Development.* [Dos]
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. Dr. Cullings' and Ms. Funamoto's contribution is the same as described above.
Griffin KT, Sato T, Funamoto S, Chizhov K, Domal S, Paulbeck C, Bolch W, Cullings H, Egbert S, Endo A, Hertel N, Lee C. Japanese pediatric and adult atomic bomb survivor dosimetry using the J45 phantom series: comprehensive source term modelling. [Target Journal -TBD]. 2021; In Development. [Dos]
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. Dr. Cullings' and Ms. Funamoto's contribution is the same as described above.
Completed and Ongoing work

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.

As part of this effort, Dr. Cullings developed a white paper outlining a plan for adopting the new set of computational models of the human body (phantoms) for use with Dosimetry System DS02, with discussion of the models currently in use, the advantages of a newer set of phantoms that have been developed, the method for implementing the new phantoms, the anticipated cost and justification for the replacement of the current set of phantoms with the newer set, and a proposed timeline for implementation.

As part of the preparation for implementation of the revised organ dosimetry, Ms. Funamoto has been converting 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 is 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 to Intel FORTRAN requires fewer code changes, which primarily consist of revising native function calls. The code revision and testing will be completed in early 2021. An additional module will be required to apply the response function tables, but this should also be completed during 2021.

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 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. This program would complement our current US partnership program with the University of Washington, which is supported by the US Department of Energy. Details of the proposed program are as follows:

- The program would be open to doctoral students in conjunction with their mentors.
- The program duration for a student would be up to two years.

- Each year, the student and mentor would visit RERF for up to one week.
- The first-year visit would 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 would be to review progress and finalize details.
- The expectation will be that the research is published in a high-quality journal.
- The program will be limited initially to one student.

RERF will provide the yearly funding to cover university tuition 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.

Our initial outreach was to 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. While Dr. Furukawa was and is interested in participating in this program, at present he does not have any PhD students who would be candidates for this program, although he may in the future. We recently discussed with Dr. Furukawa the possibility of engaging some of his master's students who intend to proceed to the PhD program in RERF projects, outside of the program described here, as a way to identify possible future candidates.

Our second outreach was to Dr Satoshi Hattori, Professor of Biomedical Statistics in the Department of Integrated Medicine at Osaka University. Dr. Hattori identified a student candidate for this program, and we proceeded to develop a formal agreement to proceed, but unfortunately administrative complications arose at Osaka University that ultimately prevented Dr. Hattori from participating in the program.

Our current plan is to advertise the existence of this program to other major Universities throughout Japan to solicit interested students or faculty.

International Partnerships

The Department has received approval to develop 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.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, which have deadlines in May and June 2021. 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 have evaluated this proposed program and consider it feasible given the JSPS funding available. The announcement is currently posted on the RERF website (https://www.rerf.or.jp/en/information/9803-2/).

University of Washington Partnership

The Department continues to actively participate 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 program were described under Specific Aim 1 above.

Other Outreach and Education Activities

Dr. Misumi contributed an article to the regular newletter of the Biometrics Society of Japan titled "Introduction of radiation epidemiology and a Japan-US research institute". The purpose of the article was to raise awareness within the Japanese biostatistics community of RERF and the RERF Department of Statistics.

During 2020 we hosted, jointly with the Department of Epidemiology, a semi-monthly EPI/STAT seminar which allows researchers to obtain feedback on work in progress and facilitate inter- and intra-departmental collaboration. Department members' presentations in this forum were:

Speaker	Date	Title
M. Yamamura	1/23/2020	Current Progress of Cataract Study
R Sposto	3/19/2020	F1 Trio Study Design
B. French	3/26/2020	Update on suicide risk analysis in LSS
N. Kato	4/16/2020	Candidate SNP Study of Breast Cancer in the IMG Cohort
J. Cologne	6/4/2020	Follow-up Analysis of Hepatocellular Carcinoma (HCC) in the AHS Hepatitis Cohort
R. Sposto	7/30/2020	Low dose risk estimation
E. Morenz	9/18/2020	Analyzing the Residual Lifetime of Atomic Bomb Survivors
M. Misumi	10/22/2020	Data-driven causal exploration in RERF studies?
K. Cordova	11/19/2020	Assessing Radiation Effects on Diabetes Incidence: Preliminary Results

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

Speaker	Date	Title
Cologne	8/21/2020	Re-analysis of In Utero Survivor Chromosome Aberration Data
Sposto	12/08/2020	Observations on current RERF approaches to analyzing radiation risk

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

Member	Course/Symposium	Date	Location
Cordova	Longitudinal Data Analysis using Structural Equation Modeling (Instructor: Paul Allison)	November 30-December 18, 2020	Statistical Horizons LLC (via Zoom)
Kato	Special Lecture on Data Science II	August 27 – September 1, 2020	Center for Mathematical Modeling and Data Science, Osaka University
Misumi	Short course "Absolute Risk Methods and Applications in Clinical Management and Public Health" (Ruth Pffeiffer, Mitchell Gail)	August 23-27, 2020 August 23, 2020	41st annual meeting of the International Society for Clinical Biostatistics Krakow, Poland (via Zoom)
Misumi	"Meta-analysis and network meta-analysis"	December 19, 2020	Japanese Biometric Society (via Zoom)
Misumi	"Causal Inference and Mediation Analysis (Tomohiro Shinozaki, Masataka Taguri)	January 27, 2021	Japanese Epidemiological Society (via Zoom)
Yamamura	"Recent Progress in Spatial and/or Spatio-temporal Data Analysis"	October 20, 2020	Center for Data Science and Service Research, Tohoku University
Whole Department	"3rd Beebe Webinar on Commemorating the 75th Anniversary of the Atomic Bombings"	November 10, 2020	National Academies of Sciences
Whole Department	"ELSI workshop toward RERF future genome studies on atomic bomb survivors and their children"	December 10-11, 2020	Radiation Effects Research Foundation

The Department has for the most part over the last year been unable to participate 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. However, in 2020 Department members were authors on two scientific presentations at international meetings, on six presentations at national meetings, and had two invited oral presentations at universities or peer institutions.