DEPARTMENT OF STATISTICS

Mission and Specific Objectives

The mission of the Department of Statistics, which is to provide the expertise of its members for the advancement of research in the health effects of ionizing radiation, can be described in terms of the following four specific aims:

- Aim 1: Collaborate with RERF scientists in the conceptualization, design, analysis, and reporting of high-quality research projects relevant to the mission of RERF.
- Aim 2: Perform research to develop new, or extend and apply existing, statistical methods that are essential to the mission of RERF.
- Aim 3: Maintain and ensure the integrity of the RERF dosimetry system.
- 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.

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 communication of the research results to the greater scientific community, stakeholders, and survivor groups through peer-reviewed manuscripts and scientific presentations. Department members provide RERF researchers and leadership with critical information needed to evaluate the ability of proposed research to achieve its scientific objectives. The major portion of Department members' activities is devoted to these collaborations.

Members of the Department have in the past developed analytical methods for major aspects of the RERF research program to estimate radiation risk for disease mortality and incidence. These analytical methods 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 longitudinal analysis, joint modelling, causal inference/mediation analysis, biologically based models, spatial statistics, machine learning, and bioinformatics/omics.

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 that is developing and evaluating new computational models of the human body and modernized transport calculations that will result in improved organ dose estimates.

The collaborative role and the methods development role of the Department are intertwined. Collaboration with other departments may reveal the need for development or adaptation of

statistical methods relevant to the research problem. Since the majority role of Department members is collaboration with other RERF scientists, the priorities of the Department in these areas are dictated largely by the research priorities of RERF, with occasional adjudication by the Department chief. As for independent methodological research, individual Department members generally pursue different areas of research, so there is little need to prioritize these against one another. The criterion for pursuing a research area is that it is something worth pursuing as it addresses a current or future methodologic need at RERF.

Department Resources

- RERF dosimetry systems. The Department of Statistics is responsible for maintaining the RERF dosimetry systems. Ms. Sachiyo Funamoto and Mr. Shota Shimizu are responsible for the technical implementation of dosimetry, specifically maintaining and modifying when necessary the software required to compute individual subject doses based on shielding and other subject specific input data, carrying out these computations, and organizing and storing the resultant dose estimate in the RERF SQL research databases for use by RERF researchers.

Internal and External Collaborations

Internal collaborations. The Department of Statistics collaborates with all other research departments at RERF, namely Epidemiology (Acting chief: Ritsu Sakata), Clinical Studies (Chief: Waka Ohishi, Ayumi Hida), Molecular Biosciences (Chief: Asao Noda), Information Technology (Chief: Satoru Ono), and the Biosample Research Center (Chief: Osamu Tanabe).

External Collaborations. The Department of Statistics has ongoing and developing collaborations with the following institutions and individuals:

- Shizuoka University, Dr. Yuko Araki. “A methodological study to compare various statistical approaches (functional and parametric) for joint modeling of longitudinal trajectories (including latent trajectory classes) and time to event (disease or death).” (Cologne)
- Hiroshima University, Dr. Hirokazu Yanagihara. Development of methods for spatial-temporal analysis. (Yamamura)
- The Federal Office for Radiation Protection, Oberschleißheim, Germany, Dr. Jan Christian Kaiser. “Mechanistic modelling of the radiation risk for colon cancer in Japanese A-bomb survivors.” (Misumi)
- Tokyo University of Science, Dr. Hiroshi Haeno. Mathematical models for clonal hematopoiesis. (Misumi)
- Columbia University, Dr. Sally Amundson. Candidate biomarker discovery. Ongoing collaborations with Drs. Igor Shuryak and David J. Brenner focuses on accurate radiation risk estimation using deep learning, double/debiased machine learning, and causal gradient boosting. (Liu)
- University of South Carolina, Dr. Karl D. Gregory. “Advanced Statistics Models for Radiation Risk in RERF A-bomb Cohorts.” (Sposto)

- Kyungpook National University (Korea), Dr. Young Min Kim. Inference for the mediation proportion in causal models.

DEPARTMENT OF STATISTICS

FY2023 Department Highlights

Collaborations with RERF scientists

- F_1 Clinical Study (FOCS). Heritable effects of exposure to ionizing radiation are a public health concern, but no human data exist on the potential risk of adult-onset multifactorial diseases in the offspring of exposed persons. We have completed the first stage of the multi-state modelling longitudinal analysis of the F_1 Clinical Study aimed at investigating the association between parental A-bomb radiation dose and occurrence of multifactorial disease in the study cohort. The first stage of analysis included modelling of transitions between healthy, ill, death, and lost-to-follow-up states. Please see "Statistical methods and analysis for 'Longitudinal clinical study of the F_1 offspring of A-bomb survivors (RP 4-10)'."
- Cancer incidence/migration. Diagnosed cancers for LSS members who have migrated outside of Hiroshima and Nagasaki tumor registry catchment areas are not reflected in registries, resulting in underestimation and distortion of background cancer rates. We are therefore performing an indirect correction for non-residency. Based on analysis of Adult Health Study (AHS) contact and visit data, we are updating the estimates of probabilities of migration out of the cancer registry catchment area as a function of sex, city, age, and calendar year in anticipation of the upcoming reanalysis of cancer incidence to be led by the Department of Epidemiology. This new analysis is more sophisticated than those performed previously in that it accounts for the changes in the tumor registry catchment area over time. Please see "Correcting for Catchment Area Non-residency in Studies Based on Tumor-Registry Data (RP 18-61)."
- Non-cancer disease. We completed quality assessment of cytokine measurements that will be used to extend the previous analysis of radiation effects on atherosclerosis in the AHS by including measures of cytokines and inflammatory markers as potential mediators. Please see "Study of atherosclerosis in the AHS population: Part 2. Analysis of the cytokine network regulating differentiation of mesenchymal stem cells in artery (RP 2-11 and RP1-23-2)."
- Convolution Neural Networks. Recent studies have shown that CXR age obtained from chest x-ray images is a data-driven indicator of biological age that might more accurately reflect the effects of aging, disease, and mortality than chronological age. We have thus begun a collaboration with the Department of Clinical Studies and the Information Technology Department to apply convolution neural networks to assess biological age from such chest x-ray images. The initial work has involved development of the hardware and software capabilities to apply these methods and testing of the methods on publicly available data. Please see "Analytical support for 'Artificial intelligence-estimated Chest X-ray Age among atomic bomb survivors (RP 2-23)'."
- Cataract. Previous ophthalmological studies at RERF used non-standardized cataract evaluation methods, resulting in potential misclassification of outcomes. We have completed the primary re-analyses of the prevalence of cataracts using data from modern assessments of cataracts in AHS subjects in collaboration with the Department

of Clinical Studies. The reanalysis used generalized estimating equations (GEE) to account for cataract outcome in both eyes, and incorporated information on informative censoring due to individuals who had undergone eye surgery and could not be evaluated for cataracts. Please see "Statistical analysis in support of 'Ophthalmological Study of A-bomb Survivors Using a New Ophthalmic Camera (RP 5-15)'."

- Glucose and Lipid Metabolism. The association between radiation dose and insulin secretion, insulin resistance, and biomarkers related to inflammation and visceral fat accumulation is not well understood. We have completed the primary analysis of measures of glucose and lipid metabolism and their relationship to diabetes in a cross-sectional study in the AHS. The analysis utilized Multiple Imputation by Chained Equations (MICE) to accommodate multiple variables with missing or interval censored values. Please see "Statistical analysis in support of 'Effects of Ionizing Radiation on Impairments of Glucose and Lipid Metabolism and Impact on Risks of Arteriosclerotic Diseases and Cancers (RP 1-15)'."

Development or adaptation of statistical methods

- Joint modelling. We have investigated and submitted for publication analytic evaluations of features of joint modelling in excess relative and excess additive risk models of cancer incidence and mortality — i.e., analysis, within a single model, of multiple cancer types or causes of mortality. The evaluations focused on possible precision gains from parameter sharing and what types of shared parameters would lead to the largest precision gain, as well as the use of such models for analyzing aggregate endpoints, such as all cancer incidence or mortality, and the implication for utilizing organ-specific doses rather than a single surrogate dose (Sposto and Cullings 2023, Sposto, Misumi, and Cologne 2023). Please see "The Use of Joint Models in Analysis of Aggregate Endpoints in RERF Cohort Studies (RP 1-75 and RP 1-61)," and "Evaluation of Potential Gains in Precision of Radiation Risk Estimates from Joint Analysis (RP 1-27 and RP 18-61)."

- Spatial analysis. Geographical variation in incidence and mortality rates might remain even after controlling for known background, shielding, and effect modifying variables. Controlling for these effects could improve radiation risk estimates in A-bomb survivors. In collaboration with investigators at Hiroshima University, we are developing methods for spatio-temporal analysis of rates from count data using generalized fused-Lasso Poisson models (Yamamura, Ohishi, and Yanagihara 2023, Yamamura, Ohishi, and Yanagihara 2023). Please see "Development of a spatio-temporal risk estimation model for Hiroshima and Nagasaki exposures by fused-Lasso (MEXT Grant-in-Aid for Scientific Research B)."

- RNA-Seq pipeline development. In collaboration with Dr. Yoshida's lab for the mouse model study of the clonal hematopoiesis project (RP1-23-3), we have successfully developed two comprehensive pipelines tailored for bulk and single-cell RNA-seq analyses. These pipelines integrate innovative algorithms to ensure robust quality control, precise sequencing alignment, accurate gene calling, informative data visualization, reliable cell type detection, and various downstream functional analyses. These meticulously crafted pipelines serve as invaluable tools, not only for our current

project but also for potential future collaborations within RERF. Please see "Bioinformatics analysis in support of 'Mouse Model Study of Clonal Hematopoiesis including T-cell Aging and Inflammation (RP 1-23-3)'."

- Inference on mediation in causal models. We applied bootstrapping and confidence interval plots (also known as P-value functions) in a novel approach to assess the importance of proportion mediated in a causal model for joint effects of radiation and viral hepatitis B and C infections (Ohishi, Cologne, Kim, and others 2023). Please see "Study of liver diseases in the AHS sample: Relationship between radiation dose and infection by hepatitis B and C viruses (RP 9-92)."

RERF dosimetry system

- Organ Dosimetry. Department members have continued work with the international Organ Dosimetry Working Group in order to develop revised organ doses for RERF's epidemiological studies based on modern, sophisticated J45 computational phantoms. We have almost completed revision and quality control of the software necessary for the computations and are awaiting completion of the extensive simulations by means of which the necessary response functions for new organ dosimetry will be determined. Please see "Survey Shielding and Dosimetry Study (RP 18-59)."

- Relative Biologic Effectiveness (RBE). As a further investigation of the issue of RBE, recently studied in the context of all solid cancer incidence by Cordova, Cullings, et al.[1], we are collaborating with Dr. Sato at JAEA and Dr. Kai at Nippon Bunri University to utilize the J45 computational phantoms in conjunction with PHITS simulation software, currently used to compute the new organ dosimetry, to assess theoretically the RBE of neutrons in each organ for representative shielding categories for typical Life Span Study (LSS) subjects. A manuscript is currently in development. Please see "Calculations of neutron RBE using mean quality factors and their implications for analysis of radiation-related cancer risk in the atomic bomb survivors (RP 18-59)."

Education, outreach, and operational activities

- University outreach. Through attendance at domestic and international scientific meetings, also attended by heads of Japanese university statistics and biostatistics departments, we have successfully raised the profile of the RERF Department of Statistics with the intent of identifying potential Japanese candidates for research scientist positions that are soon expected to open up in the Department. Dr. Misumi introduced LSS statistical analysis at COMPSTAT 2024, the annual meeting of the International Association for Statistical Computing, which a number of groups of Japanese statisticians attend, and met with graduate students of both Japanese and overseas universities. In addition to such scientific meetings, Dr. Misumi visited

[1] Cordova, K. A. and H. M. Cullings (2019). "Assessing the relative biological effectiveness of neutrons across organs of varying depth among the atomic bomb survivors." Radiat Res **192**(4): 380-387.

Hokkaido University to introduce RERF's research to biostatistics researchers and graduate students there.

- Outside committee activities. Following the mission of RERF, we provide our expertise to the activities of external committees for promotion of nationwide collaborative research in Japan. Dr. Misumi works as a steering committee member of the Planning and Acting Network for Low Dose Radiation Research (PLANET) of the QST Institute for Radiological Science, headed by Dr. Michiaki Kai of Nippon Bunri University, which considers prioritizing research needs taking the potential of Japan into account and proposing strategies to improve the estimation of low-dose and low-dose-rate radiation risks. In addition, Dr. Misumi, as an expert advisor, provides advice to the basic survey and dose evaluation committee of Fukushima Medical University.