Departmental Overview

The Department of Statistics supports the mission of RERF by collaborating in the design and analysis of all RERF research projects, developing and applying statistical methods in support of these projects, and managing the radiation dosimetry system.
Given the importance of sound statistical advice to the success of a research project, the Department devotes a majority of staff effort to our collaborative role, focused on study design, data analysis, and reporting. We have a proactive approach to collaboration, facilitated through research cluster activities and beginning with early involvement in study design. Our input provides critical information in evaluating how effectively a given project will be able to address its proposed scientific question, which in turn impacts its value to the RERF mission. We perform rigorous statistical analyses of data gathered by investigators in all research departments and assist with the effective communication of research results to the greater scientific community, stakeholders, and survivor groups.

The Department has historically led the development of analytical methods for major aspects of the RERF research program to estimate radiation risk for mortality and incident solid cancers. These methods have also been applied to numerous radiation studies of other cohorts. This includes the development of tools and methods to flexibly estimate radiation-associated excess relative and excess additive risks, and to handle various problem areas in the data collected on major RERF cohorts, such as error in exposure ascertainment, missing data on covariates, and unknown failures to register incident cancer cases due to undocumented out-migration from cancer tumor registry catchment areas, among others.

We also develop or adapt statistical methods to analyze the longitudinal data generated by the Adult Health Study and more recently by the F1 Clinical Study. We have evaluated or developed novel methods of sub-cohort sampling to maximize statistical power when studies cannot measure necessary covariates on the entire cohort, to address special issues related to variables that modify the radiation risk per unit dose or are intermediate steps on a causal pathway between radiation and the health outcome under study, and to accommodate correlated competing health outcomes that arise over long-term follow-up. We also develop many special methods to meet the requirements of RERF's basic-science research in genetics, immunology, radiation biology, and molecular epidemiology, notably applying new methods to analyze their high-dimensional data.

Work in radiation dosimetry, including investigation into dose uncertainty, is by definition central to the RERF mission of evaluating the effects of ionizing radiation on human health. The Department implements RERF dosimetry systems and maintains a database of DS02R1 survivor dose estimates, which requires developing methods to interpolate and extrapolate dose estimates from the coarse and limited-distance output of the dosimetry system, to provide dose estimates for survivors with incomplete data on shielding, and to correct for uncertainty in the dose estimates. The Department has an ongoing role with the binational working group of external scientists that seeks to quantify the improvements to dose estimates for specific organs and tissues that could be realized by new computational models of the human body and modernized transport calculations.

FY2018 Achievements

In the past year, members of the Department of Statistics have performed independent and collaborative research on a variety of topics regarding statistical methodology and radiation dosimetry, which is reflected in papers published in peer-reviewed journals (29 for which at least one Department member was listed as an author, including 14 originating in our Department) and presentations at scientific meetings (10 originating in our Department). In addition, members of the Department have been active collaborators on RERF studies, at all stages from proposal development within the research clusters, including experimental design and sample selection, to data analysis and manuscript preparation. Below, we provide details on methodological and collaborative research projects within several select initiatives. Additional details are provided in respective lists of presentations and publications.

Long-term follow-up studies
Follow-up of the LSS, the AHS, the *in utero* cohort, and the F1 cohort is central to RERF's mission to quantify the human health effects of radiation exposure. We collaborate closely with researchers in Epidemiology and Clinical Studies, as well as the U.S. National Cancer Institute, on studies regarding mortality and morbidity among these cohorts. Over the past year, statisticians have collaborated on studies regarding the incidence of solid cancer at specific sites, including lower digestive (Sugiyama/Misumi), liver (Sadakane/French), uterine (Utada/Cologne), urothelial (Grant/Cologne), and breast cancer subtypes (Sadakane/French), as well as pooled studies on leukemia (Little/French). These collaborations have motivated several methodological investigations regarding the statistical design and analysis of cohort studies, with focus on the shape of the radiation dose-response, including:

- Reasons for sex differences in the radiation dose-response for solid cancer (Cologne);
- Semi-parametric smoothing for joint effects of radiation and covariates (Misumi);
- Impact of adjustment for pre-bombing population density (French);
- Nonparametric methods for generating interpretable summaries of residual time acceleration by radiation dose and age at exposure (French/Cologne, with M Carone and a biostatistics PhD student, as part of the University of Washington partnership);
- Bayesian methods for flexibly estimating the low-dose response in excess relative risk and excess absolute risk models without using an assumed parametric dose-response function (Cologne/Misumi, with YM Kim and DL Preston).

We have developed and implemented novel methods for accommodating correlated competing health outcomes in aging RERF cohorts. Over the past year, we have implemented joint analyses that facilitate more detailed estimation of radiation risks and provide inference regarding differences in radiation effects, such as proximal versus distal colon cancer (Sugiyama/Misumi), liver versus intra-hepatic bile duct cancer (Sadakane/French), and dose-response modeling for mortality and groups of incident solid cancer (Brenner/Cologne). In addition, we have implemented joint regression models for longitudinal and survival outcomes in AHS studies regarding red blood cell distribution width (K. Yoshida/Misumi) and peripheral myeloid cells (K. Yoshida/French). We have continued research on joint regression models for longitudinal data with outcome-dependent observation times (French) and competing risks (Misumi). We have also initiated work on the use of functional

covariates as an alternative to the use of longitudinal outcomes as predictors in survival (time-to-event) analyses (Cologne/French/Misumi, with Y Araki at Shizuoka University).

We have also developed approaches for designing studies within these long-term follow-up studies, such as counter-matched nested case-control studies and stratified case-cohort studies, which are intended to reduce logistical effort and consumption of precious biological specimens, without suffering substantial loss of statistical efficiency. We are considering the use of exposure-enriched case-control studies for cross-sectional sampling in studies aimed at causal modeling or integrated analyses of molecular endpoints. Methods of analyzing data collected under these designs are constantly being updated, such as with two-phase analysis of nested case-control and case-cohort designs. We are keeping abreast of the evolution of these methods, and anticipate leveraging them as part of developing program projects.

Causal inference

In an observational study, treatment assignment (or, radiation dose) is typically assumed to be effectively random conditional on measured covariates. However, the presence of measured and unmeasured confounding can result in non-random treatment assignment, such that standard analysis methods can produce biased estimates of treatment effects. The potential for confounding motivates consideration of sensitivity analyses to assess how much bias, due to non-random treatment assignment, would be necessary to change the conclusions. We completed a manuscript that introduced new methods for performing sensitivity analyses based on evidence factors (French, with D Small). We developed approaches for combining the evidence from multiple correlated evidence factors in a single observational study, while controlling the family-wise error rate and maintaining statistical power.

Questions regarding the causal mechanisms of radiation effects can be addressed by quantifying the extent to which radiation-outcome associations are mediated by covariates that capture clinical or biological information. We completed work on estimating the mediation proportion with data collected under the counter-matched, nested case-control study design (Cologne, with YM Kim); this was the first examination of methods of inference for mediation in the nested case-control study design, and we showed that selecting controls by counter matching does not impact inference on mediation. We estimated mediation by viral hepatitis of the radiation risk for liver cancer using the AHS nested case-control study of liver cancer biomarkers. We began analyzing such mediation in the AHS hepatitis cohort follow-up study as well. We also performed an analysis of atherosclerosis risk involving latent clinical symptoms of atherosclerosis estimated with clinical indicators and structural equation models, and drafted a manuscript (I Takahashi/Cologne/Cordova/Misumi). We found that radiation is associated with latent factors for arterial calcification and plaque, and possibly arterial stiffness at high doses, even though it was not significantly associated with their clinical indicators individually. We also estimated the indirect effects of radiation on the clinical indicators as mediated by the latent factors. This study demonstrates that the use of MIMIC models (multiple indicators, multiple cause models allowing for latent factors) can have greater power than ordinary regression analyses applied to a large number of related endpoints.

Mechanistic models

We recognize the important need to complement clinical and epidemiological studies regarding radiation health effects with biologically-based models to elucidate the mechanisms of radiation-related carcinogenesis. A collaboration with the Institute of Radiation Protection, Helmholtz Zentrum Munchen (HGMU), Germany, was continued on biologically-based mechanistic modeling of radiation-related carcinogenesis for lung cancer, thyroid cancer, and colon cancer, with multiple manuscripts in preparation. In particular, a manuscript on the roles of smoking and radiation in molecular pathways to lung adenocarcinoma has been resubmitted (Misumi, with JC Kaiser and K Furukawa). We identified a new model that accurately reproduced the incidence of lung adenocarcinoma stratified by risk factor and molecular pathway, confirmed the existence of the two pathways, explained population differences in driver mutation frequencies, and provided the first direct epidemiological linkage of risk factors (smoking and radiation) with the two molecular classes of lung adenocarcinoma. A data-sharing agreement was executed to share LSS data on colon cancer with HGMU researchers. An international workshop on biologically-based modeling was co-organized with HGMU and held at RERF in March 2018, with 60 attendees.

High-dimensional data

Future RERF research requires maximizing the potential of longitudinal biosamples collected among the clinical cohorts, along with the application of state-of-the-art technologies in genomics, proteomics, and metabolomics. We collaborated with the Biostatistics and Informatics Resource at the University of Hawaii Cancer Center to complete and publish an analysis of SNP sets (pathways) in colon cancer demonstrating a practical approach to pathway analysis (Cologne/Misumi). We applied that methodology to analysis of immune-genome related SNPs in the Immunogenome Cohort Study (Cologne/Brenner/ Hayashi), and we began work on comparing methods of integrated analysis of multi-omics data using R and Bioconductor software (Cologne/Misumi).

Radiation dosimetry and dose error

Radiation dosimetry, including investigations into dose uncertainty, is by definition central to the RERF mission of evaluating the effects of ionizing radiation on human health, as such efforts provide individual dose information for measures of dose-response. We continued to investigate the information on the relative biological effectiveness of neutrons in the LSS solid cancer incidence data using the latest follow-up data and recently revised DS02R1 dose estimates, including most recently the contributing roles of shielding conditions and organ depth (Cordova, with H Cullings). We completed an analysis comparing ESR signals from tooth enamel to chromosome aberrations in blood lymphocytes among Nagasaki survivors to better understand the reliability and limitations of these biodosimetric methods (Hirai/Nakamura/Cullings/Cordova). We then began a new analysis of all currently available chromosome aberration data using fluorescent in situ hybridization (FISH), along with a revised and partially overlapping set of conventional Giemsa-staining data, to be compared to RERF's calculated DS02R1 dose estimates (Y Kodama/Cordova, with H Cullings).

Over the past year, we have supported and collaborated with an extramural working group that was formed to evaluate the effect of new computational models of the human body and new radiation transport calculations on the dose estimates for specific organs and tissues of

the body, including the 15 organs calculated by the current DS02 system and a larger set, as well as a pregnant-woman model and a complete pediatric series reflecting growth and development for survivors who were exposed *in utero* or at ages ranging from newborn to adult (under a contract with H Cullings). The working group has prepared two manuscripts. The first compares a new pediatric series of phantoms to the three (infant, child, adult) DS86/02 phantoms. The second compares a series of pregnant woman phantoms to the DS86/02 surrogate of the dose to the uterine wall of a non-pregnant adult DS86/02 phantom. A third paper for radiation transport computation is under preparation. The working group will present their results and recommendations for continued research at a meeting at RERF in February, 2019, which will be summarized at the SAC meeting in March.

We have ongoing research in dose uncertainty, stemming from Dr. Misumi's MEXT grant to investigate the impact of dose uncertainty on estimation of the radiation dose-response at low doses and to quantify uncertainty in the error-corrected estimates. A collaborative research project focused on dose-error correction is underway, in collaboration with CY Wang (University of Washington and Fred Hutchinson Cancer Research Center). Dr. Misumi recently submitted a supplement to his MEXT grant to support an international collaboration and exchange with Dr. Wang. In addition, we initiated collaborative work to incorporate alternative approaches to dealing with dose error in causal (MIMIC) models (Cologne/ Misumi/Cordova, with C Tekwe and R Carter).

Training, mentoring, and outreach

In addition to research, we have important roles in training, both as instructors and learners. In the past year, we provided lectures on radiation risk modeling for the RERF international exchange program and a lecture on statistical methods in radiation epidemiology at the Radiation Research Society's Scholars-in-Training program. We are active participants in the Hiroshima Statistics Study Group, which is held monthly at RERF in collaboration with Hiroshima University, and which we have leveraged as an opportunity to invite current and potential collaborators to RERF, including Yuko Araki (Shizuoka University) and Masao Ueki (RIKEN). Regular department seminars, now merged with Epidemiology, allow researchers to obtain feedback on work in progress and facilitate intra-departmental collaboration. We hosted an international workshop on biologically-based modeling in March, 2018. We expanded the University of Washington (UW) partnership to include biostatistics, recruited a biostatistics faculty member (Marco Carone), and identified a research project that is being led by a biostatistics PhD student, regarding nonparametric methods for generating interpretable summaries of residual time acceleration by radiation dose and age at exposure. Members of the department furthered their training by attending short courses in areas of interest to current and future research projects at RERF, including genomics (French, Cologne), multi-state modeling to address competing risks (Misumi), and structural equation modeling (Cordova).

We pursued several initiatives over the past year to increase our visibility and impact. As part of RERF's new website, the Department's page was updated such that all researchers have individual pages that list their expertise and key publications. We gave 3 national presentations, including at the Biometric Society of Japan, as well as 7 international

presentations, including at the International Society for Clinical Biostatistics, the Society of Risk Analysis, and the Conference on Radiation and Health.

With respect to staff recruitment, since revising and more broadly disseminating the job announcement, including internationally, we received 17 applications, interviewed 3 candidates (with a 4th interview scheduled for January, 2019), and successfully recruited a new scientist—Mariko Yamamura from Hiroshima University, with expertise in multivariate statistics and analysis of high-dimensional data. Although we extended an offer to an international applicant, the offer was not accepted due to our inability to negotiate outside RERF's salary regulations. An update on recruitment of a Department Chief will be given by the Chief of Research.