DEPARTMENT OF STATISTICS

The Department of Statistics has historically led in the development of analytical methods for major aspects of the RERF research program of radiation risk estimation, which have also been applied by others to numerous radiation studies of other cohorts. This includes the development of tools and methods to flexibly estimate radiation-associated excess relative and additive risk of cancer and other adverse health outcomes and to handle various problem areas in the data collected on major RERF cohorts, such as missing data on various covariates, or unknown failures to register incident cancer cases due to undocumented out-migration from cancer tumor registry catchment areas, among many other examples. 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 special methods of sub-cohort sampling to maximize statistical power when studies cannot measure necessary covariates on the entire cohort, and 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 a health outcome under study. 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.

Unlike other departments, we engage in both consulting and research and devote a majority of staff efforts to our consulting role. Given the crucial importance of sound statistical advice in the design, analysis, and conduct of studies, the Department of Statistics seeks to adopt a proactive approach to consulting, beginning with early involvement in study design, and estimation of the statistical power of potential studies. This proactive approach is facilitated significantly through research cluster activities associated with research project development. This is 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. Our second major responsibility is to provide sound statistical analyses of data gathered by investigators in all the research departments.

Work in dosimetry, including investigation 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. The Department implements RERF dosimetry systems and maintains a database of survivor dose estimates, presently using the DS02 system developed by a combined external and internal scientific working group, and provides key statistical and dosimetric support to RERF projects in biodosimetry. The Statistics Department in collaboration with Epidemiology played a major role in the recent revision of survivor input data, including a much-improved implementation of individuals' terrain shielding. Statistics staff organized two meetings of a binational working group of external scientists, culminating in co-authorship of a white paper for RERF management on the subject of an improved organ-dosimetry capability for DS02. It is expected that the Department will be actively involved in a new project to evaluate the feasibility of improved organ dose calculations and the extent to which they would differ from the existing ones. The department does not undertake dosimetry-related research for its own purposes unless it stands to measurably improve the RERF dosimetry.

FY2016 Statistics Department Achievements

Members of the Department have

- consulted at the inception of numerous studies and provided analytical support for a large number of other RERF studies in the past year, including various published or submitted manuscripts and numerous presentations at scientific meetings,
- performed both individual and collaborative research on a variety of topics in statistical methodology and dosimetry, which are reflected in a number of presentations at scientific meetings and published papers; details are given below and in the respective lists of presentations and publications,
- participated in short courses on a variety of topics germane to improving themselves as consulting statisticians, including,
- organized and attended a one-day short course on counter-factual statistical approaches to casual inference, presented by a Danish statistician whom we invited to RERF, who is a well-known innovator in the field,
- as in previous years, presented a two-day series of lectures on environmental statistics at Kurume University, in cooperation with a member of the RERF Epidemiology Department,
- provided intensive lectures and workshops on statistical methods used in risk analysis, for the benefit of trainees as part of the International Exchange Program,
- participated in all meetings of the cancer, non-cancer disease, and genetics research clusters to encourage collaborative research and networking among departments at RERF,

Statistical Methodology

- continued a study of an improved method of multiple imputation when cohort data are missing for some subjects, on variable(s) to be used in several analyses targeted for different subsets of the study subjects,
- applied a new approach to radiation dose-response estimation using a Bayesian semi-parametric model to various outcomes of the LSS data,
- revised a manuscript on the effects of additive covariate error on parameters and covariates of a linear regression model,
- continued work on development of bootstrap methods for survival models with a high percentage of censoring,
- continued work on development of bootstrap methods for rare events in logistic regression,
- co-authored a published paper with an external collaborator on a generalization of Multiple Indicators Multiple Causes dose error models,
- submitted a manuscript on the selection of an unexposed reference group in the analysis of cohort data, using the LSS as an illustrative example,
- started a study on biology-based modeling of the joint effect of radiation and smoking on lung cancer,

- continued work on development of joint regression models for longitudinal and survival outcomes when observation times are dependent on outcome values,
- continued work on development of prediction accuracy methods for survival outcomes with continuous competing risks; preliminary results presented at the Kurume Biostatistics Forum,
- continued work on development of statistical methods for integrating the evidence from multiple dependent tests that may be sensitive to unmeasured confounding, using the LSS as an illustrative example,

Platform Protocols and Data Collection/Processing Protocols

- continued collaborative research on causal models, including the effects of visceral fat in the association between radiation dose and cardiovascular disease, with the Clinical Studies Department,
- performed research on new methods for analyzing heteroscedasctic, repeated-measures multivariate data, particularly longitudinal data, which are relevant to many studies in the AHS,
- started analyses of the F1 Longitudinal Study, focusing on effects of parental exposure on incidence of hypertension, and investigation of potential participation bias,
- provided statistical support for on-going studies of cataract and heart disease in the AHS,

Radiation and Cancer

- participated in collaboration with the Epidemiology Department and the U.S. National Cancer Institute on an extensive new analysis of cancer incidence, including methodology for imputation of missing smoking data, updating of residence probabilities for estimating the effect of out-migration from tumor registry catchment areas, and various methods for risk estimation such as models for joint effects of smoking and radiation and non-parametric smoothing of the dose-response, with a dosimetry manuscript and a manuscript on all-solid cancer completed and under internal review, and several related manuscripts in preparation,
- continued collaboration with external investigators in several areas related to new radiation risk models, including mechanistic modeling of leukemia and multi-model inference for circulatory disease outcomes, including a new collaboration with the German Institute of Radiation Protection on mechanistic modeling studies of thyroid cancer after childhood exposure and combined effects of radiation exposure and smoking on lung cancer,
- analyzed the bivariate effect modification of radiation risk by age-related variables, by applying multidimensional smoothing methods including uncertainty estimation, and presented the result at the Conference on Radiation and Health 2016,
- initiated discussions for new collaborative studies with computational biologists of Kyushu University to develop methods to investigate radiation carcinogenesis applying a model based on an evolutional theory, and gave a related invited talk at the mini-symposia of the annual conference of Japanese society for mathematical biology,

- continued participation in a joint research project under the Korea-Japan basic scientific cooperation program, on a molecular epidemiological study of gynecologic cancer and its correlation with radiotherapy outcome in Korean and Japanese populations, with a published paper titled "Nucleotide Excision Repair Gene ERCC2 and ERCC5 Variants Increase Risk of Uterine Cervical Cancer,"
- initiated a new collaborative study of leukemia after childhood exposure to low and moderate radiation doses, with RERF Epidemiology and the U.S. National Cancer Institute,
- continued collaborative research on mediation of radiation risk for liver cancer by viral hepatitis and chronic liver diseases assessed via serum biomarkers,
- initiated analyses of data on pathways (SNP sets and gene sets) in colon cancer,
- provided statistical support for a new collaborative project to study the onset of hematological malignancy of atomic bomb survivors utilizing stored samples with next-generation sequencing technologies,

Radiation and Circulatory Disease

- provided statistical analysis for an ongoing project in the RERF CVD research cluster to investigate the effect of low-dose radiation on the time to stroke in the stroke-prone hypertensive, spontaneously hypertensive rat (SPSHR),
- provided statistical analysis for an ongoing project in the RERF CVD working group to evaluate the appropriateness of the spontaneously hypertensive rat (SHR) as an animal model for studies of radiation effects,
- continued collaborative research on atherosclerosis using structural equation models to assess radiation effects on intermediate clinical endpoints, provided statistical consultation for a new study examining updated ischemic heart disease risk among Adult Health Study participants,

Radiation and Other Noncancer Conditions

- initiated development of a statistical approach using joint modeling for repeatedly measured red blood cell data and time-to-event data for outcomes such as all-cause mortality in the AHS cohort. in collaboration with the departments of Clinical Studies and Molecular Biosciences,
- continued data analysis of a ophthalmological study on association between retinal vessel diameter and radiation among glaucoma patients in the AHS,
- started data analysis of longitudinal T-cell subset measurements to investigate the association with various time-to-event outcomes and the modification of the association due to past radiation exposure,

Radiation and Genetic Effects

- continued collaboration with the RERF Genetics group on radiation effects in cellular mutation rates of various organs (2 manuscripts under review/revision), and on radio-sensitivity as a function of gestation age, in mice,
- completed statistical analysis for investigators in Molecular Biosciences on a study relating the XPA mutation of the xeroderma pigmentosum gene with skin cancer,
- provided analytical support for a paper on analysis of untoward pregnancy outcomes among atomic bomb survivors,

Radiation and Immunologic Effects

- updated statistical analyses for a study of T-cell receptor repertoires, (diversity and clonality in healthy volunteers)

Radiation Dosimetry

- published a manuscript with members of the RERF Epidemiology Department, culminating more than six years' work on DS02R1, a major revision of DS02 dose estimates for members of the LSS, including revised location estimates for individual survivors resulting from recent map work by the Master File Section, revised and improved input data on terrain shielding at those new locations, many other improvements to methods of implementing dosimetry system DS02, and an evaluation of the effect on risk estimates,
- continued intramural work and extramural collaboration in dosimetry, including evaluating potential dose contamination from residual radiation, continuing support of Molecular Biosciences Department analyses of ESR measurements in donated teeth to estimate radiation doses, including the first analyses of Nagasaki teeth,
- continued active collaboration with several teams of external investigators on statistical methods for dealing with errors in dose estimation, which resulted in a new manuscript again this year,
- conducted an examination of the empirical information available in the LSS cohort data about the relative biological effectiveness of neutrons, both constant and variable across the dose range, as a function of city and gender subgroups, and presented elements of this analysis at two conferences for feedback, and
- completed a white paper on recommended research related to improved calculation of organ doses by dosimetry system DS02, based on the results of two binational working group meetings held in the previous year.