

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 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, and will organize and lead a new working group of external scientists to provide an improved organ-dosimetry capability for DS02. The department does not undertake dosimetry-related research for its own purposes unless it stands to measurably improve the RERF dosimetry.

FY2015 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,
- participated in short courses on a variety of topics germane to improving themselves as consulting statisticians, including missing data analysis, use of simulation to evaluate statistical methods, and next-generation (DNA) sequencing,
- spent two months at a university medical center in the US learning methods of analysis for large-scale studies of genomics, GxE interaction, and cellular pathways in cancer (one member of the department),
- participated in initial meetings of the cancer, non-cancer disease, and genetics research clusters to encourage collaborative research and networking among departments at RERF,

Statistical Methodology

- completed a manuscript on effects of omitting covariates from generalized nonlinear models for binary data, including the ERR and general mixture models for case-control data,
- continued a study of an improved method of multiple imputation when a project contains missing data on variable(s) to be used in several analyses targeted for different subsets of the study subjects,
- published a methodological paper on a Bayesian semi-parametric model for radiation dose response estimation, applied the method to various outcomes of the LSS data, and gave invited talks on some results at the International Congress of Radiation Research in Kyoto,
- prepared a manuscript on modification of GEE1 and linear mixed-effects models for longitudinal heteroscedastic Gaussian data,
- prepared a manuscript on the effects of additive covariate error on parameters and covariates of a linear regression model,
- submitted a statistical manuscript on power analysis for mediated effects in studies with a dichotomous outcome,
- submitted a statistical manuscript on mediation analysis using conditional logistic regression in nested case-control studies,
- 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,

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 heteroscedastic, repeated-measures multivariate data, particularly longitudinal data, which are relevant to many studies in the AHS,
- performed analyses for the study of weight fluctuation and subsequent disease incidence/mortality in the AHS, including an analysis of interaction between weight change and radiation risk,, including more specific applications of techniques such as joint modeling described below,
- provided analytical support for a paper on analysis of mortality among the F1 cohort,
- gave a lecture on estimating Dose and Dose Rate Effectiveness Factor (DDREF) with the LSS data in a meeting of the epidemiological task group organized by Nuclear Safety Research Association,
- began initial analyses of the F1 Longitudinal Study, focusing on simple descriptions of crude rates or prevalence (to be compared to the earlier cross sectional study), and investigation of potential participation bias,
- analyzed data for a study of the risk of weight gain after smoking cessation on CVD incidence in the AHS,
- provided analytical support for an Epidemiology manuscript describing the F1 mail survey cohort in terms of demographics and self-reported health outcomes as a function of city, gender, and parental dose categories

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 a new mechanistic modeling study of combined effects of radiation exposure and smoking on lung cancer,
- 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

DEPARTMENT OF STATISTICS

Departmental Achievements

Page 4

populations, with a published paper titled “Nucleotide Excision Repair Gene ERCC2 and ERCC5 Variants Increase Risk of Uterine Cervical Cancer,”

- published a paper on evaluating the shape of the radiation dose-response for all solid cancer in the low-dose range by using restricted cubic splines,
- provided statistical analysis for a manuscript on a study of the effects of HLA-DRB1, -DQB1 and -DQA1 genotypes on risk of 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,
- provided statistical analysis for a new Clinical Studies paper on the effect of chronic atrophic gastritis on gastric cancer,

Radiation and Circulatory Disease

- provided statistical analysis for a manuscript on a study by 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 a manuscript on a study by the RERF CVD working group to evaluate the appropriateness of the spontaneously hypertensive rat (SHR) as an animal model for studies of radiation effects
- provided statistical support for a manuscript describing ERR for subtypes of cardiovascular disease deaths in the LSS mortality data

Radiation and Other Noncancer Conditions

- published a paper on the interpretation of risk modification by age in terms of the statistical distribution of age-at-onset, based on radiation accelerated menopause,
- provided statistical analysis for a manuscript on the relationship between body composition and development of diabetes in a Japanese population,
- provided statistical analysis for a Clinical Studies paper on atomic-bomb radiation and age-related macular degeneration (retina of the eye),
- provided statistical analysis for a Clinical Studies paper on atomic-bomb radiation and prevalence of thyroid nodules among survivors exposed as children,
- initiated development of a statistical approach using joint modeling for repeatedly measured bone mineral density data and time-to-event data of vertebral fracture in AHS cohort.
- started data analysis of a ophthalmological study on association between retinal vessel diameter and radiation among glaucoma patients in the AHS,

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 radiosensitivity as a function of gestation age, in mice,

DEPARTMENT OF STATISTICS

Departmental Achievements

Page 5

- continued collaboration with the RERF Genetics group on assay of *de novo* germ line mutations in relation to parents' gonadal radiation doses, in both animal models and human families, using both array CGH (comparative genomic hybridization using tiling arrays of oligonucleotide probes) and next-generation DNA sequencing, including the statistical analysis for a new manuscript on the results of a large array-CGH study in 200 mice,
- contributed the statistical analysis to a manuscript on an in vivo system of mutation detection (a mouse bearing a partial duplication of the HPRT gene marked with a green-fluorescent protein (GFP) and detection of revertant cells in situ as GFP-positive mutant cells),
- Provided the statistical analysis for a paper on progerin, a protein that increases unrepaired DNA damage from ionizing radiation,
- Continued collaboration with investigators in Molecular Biosciences on a study relating the XPA mutation of the xeroderma pigmentosum gene with skin cancer,

Radiation and Immunologic Effects

- provided statistical analysis for NIAID grant projects such as studies of the effect of radiation on hematopoietic stem cells, telomere length of granulocytes, counts of γ -H2AX foci, etc.,
- published a paper with a co-author from Clinical Studies on radiation-associated inflammation and adult-standing height,
- provided statistical analysis for a paper on an inverse association of obesity indicators and thymic T-cell production in aging survivors,
- performed statistical analyses for a study of T-cell receptor repertoires (diversity and clonality in healthy volunteers)
- provided statistical analysis for a paper on trajectories of cognitive function in dementia-free survivors,
- provided statistical analysis for a paper on cognitive function among survivors exposed during or after adolescence,

Radiation Dosimetry

- Completed and submitted a manuscript on a simulation-extrapolation (SIMEX) approach to evaluating and adjusting for random errors in survivor dose estimates in RERF studies,
- coauthored a manuscript with members of the RERF Epidemiology Department on the 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, and the resulting changes in survivors' DS02 dose estimates,
- coauthored a manuscript with members of the RERF Epidemiology Department on the analysis of acute radiation effects data in relation to reported exposure to rain after the atomic bombings,
- continued intramural work and extramural collaboration in dosimetry, including evaluating potential dose contamination from residual radiation,

DEPARTMENT OF STATISTICS

Departmental Achievements

Page 6

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- continued 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,
 - began a new study of the effect on model fit of varying the neutron multiplier in weighted doses, for risk of solid cancer incidence and mortality, as a measure of the information contained in RERF data on the relative biological effectiveness of neutrons, and
 - held two binational workshops on developing plans for improved calculation of organ doses by dosimetry system DS02.