FY2019 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 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 major areas of emphasis are radiation dosimetry, dosimetry error/measurement error, dose-response modelling, longitudinal analysis, causal inference/mediation analysis, biologically based models, and spatial statistics.

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.

FY2019 Departmental Achievements

During FY2019 members of the Department played an essential role in collaborations with RERF scientists and also made important contributions in each of its seven areas of emphasis.

Publications

During 2019, Department members were authors on 30 peer-reviewed papers that were published or in press, with 14 originating from department-based(Cologne, Furukawa, Grant 2019, Cologne, Kim, Sugiyama 2019, Cologne, Takahashi, French 2019, Cordova and Cullings 2019, Griffin, Paulbeck, Bolch 2019, Jazic, Haneuse, French 2019, Karmakar, French and Small 2019, Paulbeck, Griffin, Lee 2019, Cologne, Sugiyama, French 2020, French, Sadakane, Cologne 2020, Kaiser, Misumi and Furukawa 2020, Kim, Cologne, Jang 2020, Little, Pawel, Misumi 2020, Sato, Funamoto, Paulbeck 2020), six of which with Department members as first author (Cologne, Furukawa, Grant 2019, Cologne, Kim, Sugiyama 2019, Cologne, Takahashi, French 2019, Cordova and Cullings 2019, Cologne, Sugiyama, French 2020, French, Sadakane, Cologne 2020). The remaining 16 publications are collaborations with Departments of Epidemiology, Clinical Studies, or Molecular Biosciences (Castelletti, Kaiser, Shimonetto 2019, Hirai, Cordova, Kodama 2019, Kiuchi, Yanagi, Itakura 2019, Okubo, Akashi, Ohishi 2019, Ozasa, Cullings, Ohishi 2019, Sadakane, French, Brenner 2019, Sadakane, Landes, Sakata 2019, Sakata, Preston, Brenner 2019, Yamada, Landes, Hida 2019, Yoshida, French, Yoshida 2019, Brenner, Sugiyama, Preston 2020, Satoh, Asakawa, Nishimura 2020, Sugiyama, Misumi, Brenner 2020, Takahashi, Misumi, Murakami 2020, Takahashi, Misumi, Niwa 2020, Ueda, Ohishi, Cullings 2020)

Eight papers are in development, three originating from the Department:

- Little MP, French B, Borrego D and others, "Lymphoma and plasma cell malignancies among cohorts of persons exposed to low and moderate doses of external ionising radiation in childhood". [RP-A1-16]

- Misumi M, Furukawa K. "Multi-dimensional smoothing for age trends of radiation effects on the cancer risk of Japanese". [RP1-75]

- Paulbeck CJ, Sato T, Funamoto S, Lee C, Griffin K, Cullings HM and others, "Fetal and maternal atomic bomb survivor dosimetry using the J45 series of pregnant female phantoms. Part 1: Analysis using DS02 exposure scenarios". [RP18-59]

Some of these papers are highlighted further below.

Radiation dosimetry

The Department of Statistics coordinated and collaborated in the work of the binational working group that was 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. This work has resulted in a series of papers comparing new sets of phantoms, designated as "J45," to DS86/02 phantoms, using idealized irradiation geometries, i.e., all neutrons and gamma-rays arriving from the same direction, e.g., antero-posterior, or at random from all directions (isotropic). The first paper (Griffin, Paulbeck, Bolch 2019) evaluated the dosimetric differences from using an updated and age-expanded J45 phantom series. The second (Paulbeck, Griffin, Lee 2019) extended this work by examining the atomic bomb photon and neutron field incident upon the adult pregnant female. The third paper, currently in review (Sato, Funamoto, Paulbeck 2019) investigated the potential impact of introducing not only the J45 series but also radiological physics methodological upgrades into the dosimetry system. A fourth paper, currently in development, (Paulbeck, Sato, Funamoto, in development) expands upon the initial study (Paulbeck, Griffin, Lee 2019) by performing survivor dose reconstructions with the J45 PF phantom series using DS02 specific particle fluences in terms of particle type, energy, and direction at both cities and for five localized shielding exposure scenarios. A white paper is being developed by Dr. Cullings that will provide a suggested 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 has 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.

Ms. Cordova and Dr. Cullings completed work that assessed information about the relative biological effectiveness (RBE) of neutrons in organs of varying depth using the LSS solid cancer incidence data with separate neutron and gamma-ray doses (Cordova and Cullings 2019). This work suggests that the colon may be too deep an organ to be used as the whole-body representative for all solid cancer, and that the weighted dose with neutron RBE of 10 currently used in RERF studies could underestimate the impact of neutrons.

Ms. Cordova and Dr. Cullings collaborated with Dr. Hirai of the Department of Molecular Biosciences and others in an analysis comparing two biological estimates of radiation exposure, gathered from electron spin resonance (ESR) of tooth enamel and chromosome aberration (CA) frequency scored using the FISH method, to DS02R1 doses in a sample of Nagasaki atomic bomb survivors (Hirai, Cordova, Kodama 2019). They found no evidence of systematic discrepancies between estimated DS02R1 doses and doses estimated from these biological dosimeters.

Ms. Cordova collaborated with Dr. Kodama of the Department of Molecular Biosciences to complete an analysis assessing the relationship between DS02R1 estimated radiation doses and stable CA frequency measured using the FISH method, overall and as a function of sex,

city, age at exposure, and shielding type. This is an update of previous work (Kodama et al., Radiat Res. 2001; 156(4):337-46) wherein CA frequency was assessed by older Giemsa staining technology.

Dosimetry error/measurement error

The topic of measurement error, particularly with respect to random errors in dose estimates, has been and continues to be an important focus of the Department of Statistics.

Drs. French and Misumi have organized a measurement error / dosimetry error symposium to be held in Hiroshima in March 2020. This two-day symposium will bring together international experts in measurement error – including Paul Albert (US National Cancer Institute), Veronica Deffner (University of Munich), Masahiko Gosho (University of Tsukuba), Mark Little (US National Cancer Institute), Victor Kipnis (US National Cancer Institute), Dale Preston (Hirosoft Inc), Pamela Shaw (University of Pennsylvania), Noriko Tanaka (Tokyo Metropolitan Institute of Gerontology), Carmen Tekwe (Indiana University), and Daniel Stram (University of Southern California) – 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.

Ms. Cordova, along with Drs. Cologne and Misumi, and with collaborative support from Drs. Carmen Tekwe and Randy Carter, began initial work on a new research project to evaluate the use of MIMIC ME models as an approach to adjust for measurement error, extending previous collaborative work (Stat Model. 2016; 16(2):140-59; Stat Med. 2014; 33(10):4469-81).

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. A manuscript summarizing this work will be written shortly.

Drs. French and Cologne submitted a paper, now in second review, on misclassification of primary liver cancer (French, Sadakane, Cologne 2019). They concluded 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.

Drs. Misumi and Cullings collaborated on a submitted paper on mortality risk prediction using a Bayesian approach to account for dosimetry error (Little, Pawel, Misumi 2019), with particular attention to the effect of dosimetry error on the shape of the dose response.

Dose-response modelling

Analyses of mortality and disease incidence in RERF long-term follow-up studies have relied primarily on Poisson regression excess relative risk (ERR) and excess absolute risk (EAR) modelling of these endpoints. Department of Statistics research in this area focuses on

understanding some of the implications of the use of these models as well as exploring alternative approaches to analysis.

Drs. Cologne, French, and Cullings, in collaboration with the Department of Epidemiology and others, published a paper (Cologne, Kim, Sugiyama 2019) on heterogeneity in background incidence, concluding that this heterogeneity is a potential cause of bias in inference about the shape of the radiation risk dose response for solid cancer incidence, and that joint analysis with suitable choices of cancer groups that allows background-rate heterogeneity across sites might be preferable to analysis based on all solid cancers as a single outcome in assessment of radiation risk for solid cancer in the Life Span Study.

Drs. Cologne and Furukawa, in collaboration with Dr. Grant, published a paper investigating the effect of omitted covariates on bias and precision of risk estimates from ERR models, (Cologne, Furukawa, Grant 2019) concluding that previous work on the existence of bias in other contexts is applicable, but that possibly more bias may exist in the context of ERR models.

Dr. French, in collaboration with investigators at University of Washington as part of the UW-RERF partnership, received approval of a data-sharing research proposal, RP-S1-19, to provide individual-level data to UW investigators for the purpose of methodological research focusing on establishing model-free functional summaries of residual lifetime acceleration as a function of radiation dose and age at exposure. These data were sent on April 18, 2019, with the goal of publication of a first manuscript in FY2020.

Dr. Yamamura, a recent addition to the Department, submitted a MEXT grant application titled “Development of sparse estimation methods for Poisson regression models with optimal categorization of explanatory variables” that will extend statistical methods in sparse estimation to Poisson regression analysis, a primary method for analysis of RERF radiation risk data from the LSS and AHS cohorts.

Dr. Misumi has continued work with Dr. Furukawa on multi-dimensional smoothing in the context of age trends and radiation risk of cancer.

Longitudinal analysis

The RERF Adult Health Study (AHS) and F1 Clinical Study (FOCS) are unique resources in that data on front-end characteristics (e.g., subject and exposure data at the time of the bombing), and endpoint occurrences (mortality, disease incidence) is complimented by biennial or quadrennial serial data on clinical and other subject characteristics. Understanding of and application of efficient longitudinal analytic methods is important to take full advantage of this rich resource.

Drs. Cologne, French, Misumi, and Cullings, in collaboration with Dr. Takahashi and others in the Department of Clinical Studies, published a longitudinal analysis that assessed whether extreme body weight variation is associated with mortality after controlling for

nonlinear weight change, concluding that an association exists between weight variation and heart disease mortality (Cologne, Takahashi, French 2019).

Dr. French collaborated with Dr. K. Yoshida and others in the Department of Molecular Biosciences in an application of joint modelling of longitudinal and survival outcomes, concluding that peripheral monocyte trajectories differed by sex, age, and radiation dose, and increases in monocyte percentages and counts were associated with higher risk of all-cause mortality (Yoshida, French, Yoshida 2019).

Dr. Misumi is currently collaborating with Dr. K. Yoshida and others on a complementary analysis and manuscript, in development, of the association between red blood cell distribution width trajectories and all causes mortality (Yoshida, Misumi, Kusunoki, in development).

Dr. French collaborated with Dr. Ina Jazic of Harvard University in methodological work developing a general framework for the design of nested-case-control studies in the presence of recurrent and terminal events, research that is directly relevant to studies conducted at RERF (Jazic, Haneuse, French 2019).

Causal inference/mediation analysis

We have continued our effort to incorporate methods for causal inference into radiation epidemiology research conducted by RERF.

Dr. Cologne, Ms. Cordova, and Dr. Misumi are collaborating with Dr. Nakamizo of the Department of Clinical Studies on a manuscript, in development, reporting an analysis that utilizes MIMIC models to assess radiation effects on latent atherosclerotic pathologies measured in correlated clinical markers (Nakamizo, Takahashi, Cologne, in development).

Dr. Cologne and Ms. Cordova are collaborating with Dr. Nakamizo in the Department of Clinical Studies and investigators in the Department of Molecular Biosciences to develop a project within a program project research proposal investigating intermediating factors (inflammation, t-cell aging, and clonal hematopoiesis) as potential mechanisms through which observed radiation effects on latent atherosclerotic pathologies (described above) are propagated.

Dr. French collaborated with Drs. Karmakar and Small of the University of Pennsylvania to investigate the use of evidence factors as an approach to conduct sensitivity analyses for unmeasured confounding with multiple comparisons (Karmakar, French and Small 2019). They showed that the Bahadur efficiency of combined evidence factors is greater than either evidence factor alone. They illustrated the method using data on radiation exposure and risk of cancer.

Biologically based models

The Department has continued to investigate the use of biologically-based models to elucidate the mechanisms of radiation-related carcinogenesis as a complement to clinical and epidemiological studies regarding radiation health effects.

Dr. Furukawa collaborated with Dr. Castelletti and others at Helmholtz Zentrum München to develop a molecular mechanistic model of lung adenocarcinoma and applying this to incidence data from atomic bomb survivors (Castelletti, Kaiser, Shimonetto 2019).

Drs. Misumi and Furukawa have further collaborated with these investigators to extend this work to the context of thyroid cancer in a paper that is currently in peer review (Kaiser, Misumi and Furukawa 2019).

Dr. Misumi is the principal investigator on a project in Dr. Yoshida's developing program project research proposal on clonal hematopoiesis in which he proposes to use mathematical and computational models to examine the effect of radiation on clonal hematopoiesis.

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. This is a developing area of research in the Department.

Dr. French has continued to collaborate with the Department of Epidemiology to enhance the ability to incorporate higher-resolution and more accurate demographic data through residence locations, in work that will refine his previous collaborative work on the effect of population density on radiation risk estimates (French, Funamoto, Sugiyama 2018) and extend this to other spatially-related subject features.

Dr. Yamamura has submitted a MEXT grant application for development of spatial statistics methods applicable to RERF research titled "Development of a spatio-temporal risk estimation model for Hiroshima and Nagasaki exposures by Fused-lasso" in which she will develop efficient ways to incorporate high resolution geographical data into the traditional Poisson regression models.

Other methodologic/applications work

Dr. Kato, a recent addition to the Department, has implemented R packages for high-dimensional gene-radiation interaction analyses (GxEScanR, and iSKAT), and has performed analyses of association between colon and breast cancer and SNPs from the Immunogene cohort (a subcohort of the AHS on which blood samples were obtained between 1981 and 2002) using PLINK software and R glmnet package.

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. In this regard, members of the department contributed to collaborations resulting in papers published, in press, submitted, or in development. We contributed to work with the Department of Epidemiology in analyses of the LSS, specifically central nervous system tumors (Brenner, Sugiyama, Preston 2019), smoking and lung cancer (Hu, French, Sakata, in development), prostate cancer (Mabuchi, Preston, Brenner 2019), liver, biliary, and prostate cancer (Sadakane, French, Brenner 2019), medical radiation exposure (Sadakane, Landes, Sakata 2019), upper digestive track cancer (Sakata, Preston, Brenner 2019), and colorectal cancer (Sugiyama, Misumi, Brenner 2020). We contributed to work with the Department of Clinical Studies on analyses of the AHS, specifically radiation and glaucoma (Kiuchi, Yanagi, Itakura 2019), chronic atrophic gastritis as an effect modifier for gastric cancer (Ueda, Ohishi, Cullings 2019), and neurocognitive complaints in the elderly (Yamada, Landes, Hida 2019). We contributed to work with the Department of Molecular Biosciences, specifically in vivo research on induced mutations in offspring (Satoh, Asakawa, Nishimura 2019) and effect of radiation on stroke (Takahashi, Misumi, Murakami, in development), and blood pressure and body weight (Takahashi, Misumi, Niwa 2019).