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The U.S. Radiologic Technologists Study: cohort updates and opportunities for collaboration

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Abstract

Occupational doses to most medical radiation workers have declined substantially since the 1950s because of improvements in radiation protection practices and imaging equipment. However, recent preliminary data suggests different patterns for radiologic technologists working with nuclear medicine (NM) and fluoroscopically guided interventional (FGI) procedures because of the higher per-procedure doses and increasing workloads. This is particularly evident in the U.S., where these procedures are performed more frequently than anywhere else in the world. However, information on occupational doses and risks of radiation-associated cancers and other diseases in these workers has been limited. The U.S. Radiologic Technologists (USRT) is a large prospective cohort study of 146,000 medical workers with nearly 40 years of follow-up, objective badge dose records, and detailed work history information, including performance of NM and FGI procedures. We previously demonstrated that performance of NM procedures (by N=22,039 technologists) was associated with increased risk of squamous cell carcinoma of the skin, breast and lung cancer mortality, myocardial infarction, and cataracts, while performance of FGI procedures (by N=20,982 technologists) was associated with brain cancer mortality and incidence of breast cancer, melanoma, stroke, and cataracts. Because work history is an imprecise exposure metric, more reliable information on radiation-related risks from these procedures requires high-quality dosimetry to assess risk across a full range of exposures. To date, analyses of occupational dose-response have relied on a dosimetry system based on annual badge readings through the year 1997, supplemented by basic work history information (i.e., lead apron use) and literature review. However, these dose estimates did not account for the unique exposures received and radiation safety practices employed by workers conducting NM and FGI procedures. Therefore, we are updating the cohort dosimetry using an additional 23 years of badge readings obtained through a linkage with Landauer, Inc., the nation's largest commercial dosimetry provider, and detailed NM (based on work history data from N=9,400 technologists) and FGI (work history from N=12,500 technologists) procedure and radiation safety practice information obtained from work history surveys. In addition, we have extended the mortality follow-up and linked the cohort with the majority of U.S. state registries for more complete and reliable cancer incidence follow-up. These developments provide new opportunities to investigate associations of occupational radiation exposures with cause-specific mortality and cancer incidence by site and subtype.

Risk of central nervous system tumors in healthcare workers occupationally exposed to ionizing radiation: preliminary results of a French nested case-control study in the ORICAMs cohort

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Context
Medical personnel represent the largest group of workers occupationally exposed to ionizing radiation and their radiation-associated cancer risks are still debated. An excess of central nervous system (CNS) tumors has been reported in interventional cardiologists, but the link with their occupational exposure has never been demonstrated in a properly controlled epidemiological study.

Objectives
The ORICAMs (Occupational Radiation-Induced Cancer in Medical staff) nested case-control study's objective is to determine if there is an association between occupational exposure to external ionizing radiation and CNS tumor mortality among healthcare workers, considering potential confounders and effect modifiers.

Methods
All CNS tumor deaths occurring between 01/01/2002 and 31/12/2012 in the ORICAMs cohort of 164,015 healthcare workers (C70-C72, D32-D33, D42-D43 codes from the 10th revision of the International Classification of Diseases) were registered. Each case of death was matched to 5 controls alive at the time of death based on gender, year of birth, and date of enrollment in the cohort. All participants were monitored for external whole-body radiation exposure using badges throughout their careers. Conditional logistic regressions were used to analyze the dose-risk relationship between cumulative dose of ionizing radiation over the entire career and CNS tumor mortality, adjusted for gender, age, and medical profession.

Results
32 cases of CNS death and 160 controls were included (mean age: 53 years, 38% women). Among them, 68 (40%), 42 (25%), and 21 (12%) were nurses, physicians, and radiological technologists, respectively. Based on the mean cumulative occupational radiation dose, the cases were more exposed than the controls (5.7 mSv (max: 93.9 mSv) and 4.5 mSv (max: 113.8 mSv), p=0.74, respectively). Non-significant positive associations were found between external ionizing whole-body radiation exposure and CNS tumor mortality.

Conclusion
This study provides weak supports of an association between exposure and CNS tumor risk among healthcare workers. Nevertheless, analyses may suffer from low statistical power given the small number of CNS tumor deaths recorded. This cohort will be part of the international BECOME (Brain cancEr risk in pooled Case-cOntrol study of MEdical workers) project, which will increase the statistical power of the analyses, using a pooled dataset from France, South Korea, and the United States.

Lung cancer risk update in the US Radiologic Technologists Cohort: Can we revise sex-specific radiation-related risk estimates at low dose-rates?

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Background
Long-term follow-up studies of atomic bomb survivors have consistently shown greater radiation-related risk of lung cancer in females than males [1]. Based predominantly on these findings, NASA risk projections suggest female astronauts are more likely to die from radiation-induced cancer than their male counterparts [2]. However, small numbers of women, narrow dose distributions, absence of long-term follow-up, and lack of smoking data have precluded replication of a sex-specific lung cancer association in most radiation-exposed cohorts studied. The US Radiologic Technologists (USRT) cohort provides an opportunity to assess sex-specific lung cancer incidence and mortality in a large, US-based occupational cohort with detailed smoking information.

Methods
US radiologic technologists without prior cancers who responded to at least one of two baseline questionnaires were included in preliminary lung cancer mortality analyses through 2021. Annualized, cumulative individual lung doses were estimated from 1916-1997 and lagged 10 years. We determined smoking behavior from questionnaire responses. We used Poisson regression to estimate excess relative risk (ERR) of lung cancer mortality per 100 mGy, stratified on attained age, year of birth, and sex, and adjusted for smoking status (ever/never/former), pack-years, and years since quitting smoking (for former smokers). We tested dose-response effect modification by sex.

Results
A total of 555 and 1,128 lung cancer deaths occurred among 25,894 male and 80,183 female technologists, respectively. We found no evidence of increased lung cancer mortality risk with increasing radiation dose overall [ERR/100 mGy: 0.04, 95% Wald-confidence interval (CI): -0.11, 0.19]. When the ERR was allowed to vary by sex, the male ERR decreased with dose while the female ERR increased (male ERR/100 mGy: -0.14, 95% CI: -0.26, -0.12; female ERR/100 mGy: 0.18, 95% CI: -0.07, 0.43).

Conclusions and Future Directions
Consistent with the previous USRT lung cancer mortality study, we did not observe an increased risk of lung cancer mortality with increasing radiation dose overall [3], though there was some evidence for sex-specific differences in dose-response pattern. However, this analysis is preliminary and contains considerable uncertainty, particularly because dosimetry has only been updated through 1997. Ongoing analyses will include more detailed smoking data, job information, and population-based cancer registry-confirmed incidence. In addition to assessing whether the atomic bomb survivor findings are reproducible, we anticipate our results could contribute to future updates to lung cancer risk projections for astronauts.

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Updated findings from the International Nuclear Workers Study (INWORKS)

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Introduction
An update to the International Nuclear Workers Study (INWORKS) has been undertaken to strengthen direct assessments of the risks from low dose, low dose rate exposure to penetrating forms of ionizing radiation. Follow-up has been extended by 10 or more years in each partner country.

Materials and Methods
A pooled analysis of cohort mortality studies of nuclear industry workers in the United Kingdom, France, and the United States of America has been conducted. Individual annual estimates of whole-body dose due to external exposure to penetrating radiation were derived from personal occupational exposure monitoring data. Vital status was ascertained through 2012, 2014, and 2016 for workers in the United Kingdom, France, and the United States of America, respectively. Poisson regression models were fitted to quantify associations.

Results
The major aims of the project, findings to-date from the parent study, and report on the updated pooled study will be provided. The updated study includes 309,932 workers and 10.7 million person-years of observation. Over the period of follow-up, there have been 103,553 deaths observed, of which 31,009 are deaths due to cancer.

Conclusions
This presentation will describe the motivation and aims for an update of the INWORKS study, and the progress that has been made. The updated study encompasses an increase in person-time in INWORKS by a factor of 1.3 and an increase in the number of cancer deaths by a factor of 1.6. The updated INWORKS analyses will provide some of the most informative direct estimates of low dose radiation risks reported to-date.

Ionizing radiation exposure and cancer mortality: an update of the pooled US nuclear workers study

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Introduction
Studies of nuclear workers provide insights into the health effects of ionizing radiation at levels relevant to contemporary workers and the general public. We evaluated the association between penetrating ionizing radiation exposure and cancer mortality subtypes in a large pooled cohort of US nuclear workers. Follow-up was extended an additional decade to improve power and examine cancers with longer latency.

Materials and Methods
The pooled cohort includes 101,363 workers from five US Department of Energy and Department of Defense nuclear facilities, followed for causes of death between 1944 and 2016. Workers were individually monitored for ionizing radiation exposure with the use of personal dosimeter badges. The association between cumulative external penetrating ionizing radiation exposure and cancer subtypes were modeled as the excess relative rate per Sievert (ERR Sv^{-1}) using Cox regression.

Results
There were 13,568 cancer deaths during follow-up. We observed positive associations between ionizing radiation exposure and all solid cancer mortality (ERR Sv^{-1}=0.19; 95%CI: -0.10, 0.52), and all lymphatic and hematopoietic cancers (ERR Sv^{-1}=2.10; 95%CI: 0.97, 3.48). These associations were stronger among a contemporary sub cohort of workers first hired 1960 or later for both solid cancer (ERR Sv^{-1}= 2.23; 95% CI: 1.13, 3.49) and all lymphatic and hematopoietic cancers (ERR Sv^{-1}= 6.26; 95%CI: 2.86, 10.83). Additionally, we observed positive associations for several site-specific lymphatic and hematopoietic cancer types, as well as lung cancer. In some instances, we observed modification by time since exposure and age at exposure.

Conclusions
This analysis confirms the association between low dose, low dose-rate radiation and leukemias, and strengthens the evidence base supporting the radiogenic nature of some solid cancers. The extended follow-up, individual dosimetry, and precise estimates provided by this large pooled analysis can better inform current radiological protection models.

Updated Mortality Analysis of SELTINE, the French Cohort of Nuclear Workers, 1968–2014

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Abstract

Cohorts of nuclear workers are particularly relevant to study the health effects of protracted exposures to low doses at low dose-rates of ionizing radiation (IR). In France, a cohort of nuclear workers badge-monitored for external IR exposure has been followed-up for several decades. Its size and its follow-up period have recently been extended. The present paper focuses on mortality from both cancer and non-cancer diseases in this cohort. The SELTINE cohort of nuclear workers employed by CEA, Orano, or EDF companies was followed-up for mortality from 1968 to 2014. Mortality in the cohort was compared to that in the French general population. Poisson regression methods were used to estimate excess relative rates of mortality per unit of cumulative dose of IR, adjusted for calendar year, age, company, duration of employment, and socioeconomic status. The cohort included 80,348 workers. At the end of the follow-up, the mean attained age was 63 years and 15,695 deaths were observed. A strong healthy worker effect was observed overall. A significant excess of pleural cancer mortality was observed, but not associated with IR dose. Death from solid cancers were positively but non-significantly associated with radiation. Death from leukemia (excluding chronic lymphocytic leukemia) and from dementia and Alzheimer's disease were positively and significantly associated with IR dose. Estimated dose-risk relationships were consistent with those from other nuclear worker studies for all solid cancers and leukemia but remained associated with a large uncertainty. The association between IR dose and dementia mortality risk should be interpreted with caution and needs further investigation by other studies.

Radiation risk of thyroid cancer in the Life Span Study of Japanese atomic bomb survivors: 1958-2009

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Abstract

To study long-term risk of thyroid cancer risk in relation to radiation exposure from the atomic bombs, we extended follow-up for cancer incidence in the Life Span Study of Japanese atomic bomb survivors through 2009 (i.e., up to 64 years after the bombings). Between 1958 and 2009, 3.1 million person-years (PY) and 502 thyroid cancer cases were accrued among 105,444 LSS members (with DS02R1 dose estimates and not known to have cancer before 1958). Poisson regression methods were used to characterize the radiation-associated risks per Gy of weighted absorbed thyroid dose using excess relative risk (ERR) and excess absolute risk (EAR) models. Based on a linear dose response model with effect modification by sex, age at exposure, and attained age, the sex-averaged ERR and EAR at age 70 after exposure at age 30 were 0.33 per 1 Gy (95% CI: 0.10 to 0.81) and 0.85 cases per 10,000 PY-Gy (95% CI: <-0.19 to 1.81). Over the full range of doses, there was no evidence that a linear quadratic model described data better than a linear model (ERR or EAR). The ERR risk decreased sharply with increasing age-at-exposure (-58% per 10 years, 95% CI: -75% to -36%). Allowing for modification by age at exposure, the ERR did not vary by sex or attained age. Under preferred ERR model with effect modification, 28% of thyroid cancer cases were attributed to radiation exposure among survivors exposed to doses >5 mGy. More than 60 years after exposure to atomic bombs, thyroid cancer continues to demonstrate strong dose response with highest radiation risks among atomic bomb survivors exposed as children. Further follow-up in the LSS is important to fully characterize the lifetime risk of thyroid cancer following radiation exposure in childhood.

Genomic characterization of cervical lymph node metastases in papillary thyroid carcinoma following the Chornobyl accident

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Background
The 1986 Chornobyl nuclear accident deposited radioactive fallout in the surrounding region, resulting in the increased risk of developing papillary thyroid carcinoma (PTC) risk for children exposed to radioactive iodine (^{131}I). Presence of cervical lymph node metastases (cLNM) at diagnosis is well-recognized in pediatric PTC, and some studies have suggested that previous radiation exposure increases risk for cLNM, but the PTC metastatic process and potential radiation association are not well understood.

Methods
We extended a previous genomic landscape analysis (Morton et al., *Science* 2021) among 440 PTC samples with fresh frozen tumor samples from the Chornobyl Tissue Bank (^{131}I-exposed=359, Unexposed=81; mean age=28.0 years) by adding detailed clinical data to identify molecular and clinical predictors of cLNM occurrence, using both multivariable modeling approaches and stratification to disentangle the independent effects of patient, clinical, epidemiologic, and molecular characteristics. We further conducted a comprehensive genomic landscape analysis of 47 cLNM samples by profiling genomic, transcriptomic, and epigenomic characteristics in comparison to matched primary tumor samples.

Results
cLNM were more frequent in PTC with fusion (55%) versus mutation (30%) drivers ($P=5.8\times10^{-6}$), with heterogeneity by driver gene ($P=1.6\times10^{-19}$; *RET*-fusion=71%, *BRAF*-mutation=38%, *RAS*-mutation=5%). cLNM frequency was not strongly associated with other patient, clinical, epidemiologic, and molecular characteristics ($P>1.0\times10^{-4}$, including radiation dose P=0.32). Molecular profiling of 47 cLNM demonstrated 100% driver concordance with matched primary PTCs and highly concordant mutational spectra. Transcriptome analysis revealed 17 differentially expressed genes, including cLNM overexpression of the *HOXC* cluster ($P_{HOXC10}=6.4\times10^{-23}$; $P_{HOTAIR}=2.9\times10^{-17}$) and underexpression of *BRINP3* ($P=1.3\times10^{-17}$).

Conclusions
Our findings underscore the critical role of driver alterations in the development of PTC cLNM and suggest that prior reports of strong associations of age at PTC and prior radiation exposure with cLNM occurrence were likely confounded by the relationship of these variables with the PTC driver. Furthermore, these results highlight the importance of molecular subtyping in the clinical management of PTC across the age spectrum and inform approaches to patient risk stratification. Transcriptomic analyses demonstrating differences between cLNM and matched primary tumor samples provide promising candidates for elucidating the biological underpinnings of PTC cLNM.

What are differences in radiation dose, thyroid Hormone and IQ levels associations in children exposed in utero by the Chernobyl accident and controls?

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Introduction
Exposure by radiation in utero can occur because of natural (radon, NORM, etc..), medical (for diagnosis or treatment), professional or accidental exposure. To understand mechanisms of possible negative effects, the cohort studies are carried out. In one of the previous studies, in Belarus, it was examined psychological development in 250 children exposed in utero to radiation from the Chernobyl accident in 1986 and 250 control children of the same age and sex from areas with little or no contamination. Significant differences in IQ (Intellectual quotient) were reported at age 7 years, but not later. We used data from this study to further explore the possible relationship between dose, thyroid hormones levels and IQ (at the adolescent period).

Methods
The data set included information on radiation dose to the thyroid and gestation quarter at the time of the accident; thyroid hormones (T3 (triiodothyronine) and T4 (thyroxine)) levels and general IQ at three points of time (longitudinal). Descriptive and interference statistics (regression) was used to see the dynamic of changes through time and associations between main variables adjusted by sex in three time points: 1) 6-7 years old; 2) 11-12 years old and 3) 16 years old.

Results
IQ was significantly decreased in the highest dose category compared to the two lowest dose groups and was correlated with T3 in both the control and in utero exposed groups, though the direction of the correlation differed, and it was significant only in the control group. Other results are to be discussed during conference presentation.

Conclusions
This preliminary analysis suggests an association between dose and thyroid hormone levels and between these and IQ in our study population. Further in-depth analyses are underway to better characterize these, considering possible confounding factors.

ICRP Task Group 121 – Effects of ionising radiation exposure in offspring and next generations

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Abstract
The ICRP Task Group 121 is a task group under the Committee 1 of International Commission on Radiological Protection (ICRP), approved by the Main Commission on November 18th, 2021. The main goals of the Task Group 121 are to update the review of the scientific literature related to radiation-induced effects for the offspring of individuals exposed to ionising radiation for both human and non-human species; to discuss pre-conceptional and post-conceptional effects of radiation and related morbidity and mortality; and, to advise on the level of evidence and consideration of these effects in the system of radiological protection. The Task Group is reviewing the literature since the early 2000s on radiation-induced effects on future generations both in humans and non-human species. For the major publications, there will be critical examination of the approach used to produce and/or analyse data. Depending on the outcome of the review, the estimate of heritable risk calculated by UNSCEAR in 2001 would be revised. A review will be conducted on the way health effects in offspring and subsequent generations are considered in the current system of radiological protection and how these findings may influence the ICRP approach, for instance, in the radiation detriment calculation for human health. Finally, proposals to update the integration of health effects in offspring and next generations in the system of radiological protection will be derived. A Workshop, jointly organised by ICRP Task Group 121 and European Radiation Protection Research Platforms MELODI and ALLIANCE that took place in Budapest, Hungary, from May 31st to June 2nd, 2022, promoted discussions on four important topics: hereditary and epigenetic effects due to exposure of germ cell line (pre-conceptional exposure), effects arising from exposure of the embryo and fetus (post-conceptional exposure), transgenerational effects in biota, and potential impact on the system of radiological protection. A special issue of International Journal of Radiation Biology is in preparation for publication, which will contain the most important outcomes of the presentations and conclusions of the discussions during the Workshop. The main outcome of the Task Group will be an ICRP publication that reviews the scientific literature related to radiation-induced effects for the offspring of individuals exposed to ionising radiation, for both human and non-human species, including effects due to multigenerational (in utero and parent gonadal exposure) as well as transgenerational inheritance. Furthermore, this publication will also provide advice about possible ways to consider the impact of these effects in the system of radiological protection.

Effects of Ionising Radiation Exposure in Offspring and Next Generations: Dosimetric Aspects and Uncertainties

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Abstract
The impact of the exposure to ionising radiation in the offspring and next generation has been asked in the last decades and currently is the subject of study of the ICRP Task Group 121. This work presents the dosimetric aspects and uncertainties one must consider when studying such effects. Epidemiological and radiobiology studies are the two sources of information one can use to correlate the radiation dose to the human body and the resultant effects. To ensure reliability of these dose-response curves, and dose thresholds, it is necessary to trace and minimize all the source of uncertainties in epidemiological and radiobiology studies, including the dosimetric uncertainties. Already in 1992 a publication by Mole (Mole, R.H. 1992 Adv. Radiat. Biol. 15, 217–301.) pointed out deficiencies in numerous studies among those which laid the foundation of ICRP and UNSCEAR reports. Among these deficiencies are the lack of a proper description of how dose thresholds were determined, the fact that assumptions were made based on experimental studies with limited dose-dependence outcomes and the modality how the dosimetric calculations were performed. Even though over 30 years have passed, some of the issues remain present and some questions remain unanswered. A review of the scientific literature was conducted to evaluate how the dosimetry was performed in these key publications, and to point out the limitations observed, and improvements needed. The lack of information on the exposure scenario, type of data used, the type of dose being assessed, the dose units being used, are among the most common pitfalls encountered in the review. A poor description of the dosimetric information can be a challenge especially when studying the effects of radiation exposure in pre-conceptional and post-conceptional phases. In these scenarios, additional dosimetric peculiarities also include that, after intake by the mother, the embryo and fetus are irradiated by the radionuclides present in the mother's body, and these radionuclides can be transferred to the offspring and remain in its organism after delivery. Thus, the uncertainties on the pre- and post-conceptional incorporation of radionuclide should also be accounted for, and be well described. Potential effects to the fetus vary depending on the stage of fetal development and on the magnitude of the radiation doses received. Thus, reliable dosimetry techniques and accurate reporting are necessary, especially in radiobiology studies to ensure reproducibility of the results and proper evaluation of the outcomes of such studies.

Keywords
fetal dosimetry; uncertainties; pre-conceptional exposure; post-conceptional exposure; offspring.

A simulation-based method for estimating power and sample size for the linear excess relative risk (ERR) model

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Abstract

The linear excess relative risk (ERR) model is commonly used to quantify the association between ionizing radiation exposure and cancer risk. However, no software is available for calculating statistical power or sample size for the ERR model and model fitting is challenging when individuals can have multiple exposures over time. We developed a novel simulation-based method for estimating power and sample size for the ERR model for a variety of exposure distributions. These include distributions where subjects may have multiple exposures and the number and ages of these exposures varies across subjects. We demonstrate how to implement the method in SAS. In the simulation step, an exposure history is randomly sampled from a given joint distribution of the number of exposures (which may include 0), exposure ages, and radiation doses. Next, using inverse probability sampling, an event time is sampled from the time survival distribution for a given ERR model and the sampled exposure history. Finally, a censor time is sampled from a given censoring distribution. PROC NLMIXED is used to estimate model parameters and calculate likelihood ratio test *p*-values using a novel programming method where the likelihood function is explicitly constructed. The method is very flexible and can handle a large number of exposures in both the simulation step and the PROC NLMIXED parameter estimation step, with computer memory being the only constraint. The method can also be used for a variety of different ERR models, including those which have dose effect modification by age and/or time since exposure and any combination of continuous or categorical survival time, exposure age, and dose. Additionally, the model can incorporate stratification of baseline hazards on one or more variables. The method is illustrated using the age and dose distribution from the Risk of Pediatric and Adolescent Cancer Associated with Medical Imaging (RIC) study conducted in the U.S. and Ontario, Canada, which includes 801,259 subjects, some with over 200 exposures (at different ages).

Finite-sample bias of the linear excess relative risk in cohort studies of computed tomography-related radiation exposure and cancer

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Abstract

The linear excess relative risk (ERR) is the most commonly reported measure of association in radiation epidemiologic studies when individual dose estimates are available. While the asymptotic properties of the ERR estimator are well understood, there is evidence of small sample bias in case-control studies of treatment-related radiation exposure and second cancer risk (Roberti et al 2021). Cohort studies of cancer risk after exposure to low doses of radiation from diagnostic procedures, e.g., computed tomography examinations, typically have small numbers of cases and risks are small. Therefore, understanding the properties of the estimated ERR is essential for interpretation and analysis of such studies. We present results of a simulation study that evaluates the finite-sample bias of the ERR estimator and its confidence interval using simulated data, resembling a retrospective cohort study of radiation-related leukaemia risk following computed tomography examinations in childhood and adolescence. Preliminary results show upward bias for studies of typical size which decreases as the number of cases increases. A possible correction for the small-sample bias, Firth correction, will be evaluated. The results indicate the importance of conducting large studies and pooling those for unbiased risk estimates.

Taking into account exposure-related uncertainties in dose-response analysis of German commercial aircrew mortality 1960-2014

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Introduction
Aircrew are exposed to ionizing radiation of cosmic origin. With excess effective doses of 2-6 Millisievert (mSv) annually, and possibly more than 100 mSv cumulative occupational lifetime dose, aircrew have among the highest occupational radiation exposures. In a cohort of 26,804 German aircrew with follow-up from 1960-2014, we assessed potential health effects of this exposure, and studied the dose-response.

Methods
In previous follow ups, radiation dose had only been estimated for 6,054 cockpit crew until 2004. Since 2004, the German federal radiation registry (SSR) records calculated doses for both cockpit and cabin crew. To enable dose-response analyses for the 20,750 cabin crew prior to 2004, a statistical model predicted their annual dose for the years 1960-2003, and estimated the prediction error. The error for estimated cockpit crew dose prior to 2004 was evaluated by comparing estimated doses for 2004 to calculated doses from the SSR as a gold standard. In a dose-response analysis using Poisson regression, we assessed the dose-related mortality risk for the whole cohort. We took into account measurement uncertainty in dose as well as in person years by implementing an MCMC model with a Berkson error structure using information on the amount of dose uncertainty gained from the dosimetry study. As a sensitivity analysis, we fitted a Cox model with time-varying covariates to the individual survival data.

Results
Based on 55 years of observation time with 1,591 observed events and 750,227 person years, radiation dose was associated with an RR of 0.95 (95% CI 0.92-0.98) per 10 mSv for all cause mortality across the full cohort. Results from the Cox model (HR 0.94, 95% CI 0.91-0.98) agreed. Results for individual causes of death were also calculated.

Conclusion
Dose-response results were robust against regression model choice and measurement error. In the full cohort, there is a mild negative association of estimated radiation dose and mortality when dose uncertainties are accounted for.

Bayesian hierarchical approach to account for radon exposure measurement error when estimating the risk of death by lung cancer in an occupational cohort study

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Introduction
Despite its deleterious consequences for statistical inference and its ubiquity in observational research, exposure measurement error is rarely accounted for in epidemiological studies. Standard correction methods, like regression calibration or SIMEX, often lack the flexibility to account for complex patterns of errors whose type and magnitude may change over time.

Methods
We proposed several Bayesian hierarchical models, combining a survival submodel with time-dependent covariates, a measurement submodel and, when required, an exposure submodel, to obtain a corrected estimate of the potential association between chronic exposure to radon and lung cancer mortality in the French cohort of uranium miners. An adaptive Metropolis-Within-Gibbs algorithm was developed in Python to fit the proposed hierarchical models whose predictive performances were compared using the Widely-Applicable Information Criterion, A simulation study is underway to assess the impact of submodel misspecifications on risk estimates.

Results
In our application, one observed a marked increase in the excess risk estimate for lung cancer mortality when compared with an approach where radon exposure measurement error was not accounted for. As expected, the width of the credible intervals increased after accounting for measurement error but the estimated excess risk remained statistically significant. A sensitivity analysis showed that the posterior distribution of the excess risk were quite robust to the magnitude of the exposure measurement error.

Conclusion
Bayesian hierarchical models are an elegant way to account for exposure measurement errors in health risk estimates. Modelling exposure measurement error in a retrospective cohort study is often limited due to loss of information.

Keywords
Bayesian inference, Epidemiology, Hierarchical modelling, Measurement error, Survival model

The scientific basis for the use of the Linear No-Threshold (LNT) model in radiation protection

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Introduction
The Linear No-Threshold (LNT) model was introduced into the radiation protection system about 60 years ago, but this model and its use in radiation protection are still debated today.

Materials and Methods
The presentation summarises results in radiobiology and epidemiology accumulated over the last decade and discusses their impact on the use of the LNT model in the assessment of radiation cancer risks at low doses. It presents the IRSN position on the validity of the use of the LNT model in radiation protection.

Results
The knowledge acquired over the past 10 years, both in radiobiology and epidemiology, has reinforced scientific knowledge about cancer risks at low doses. In radiobiology, although certain mechanisms do not support linearity, the early stages of carcinogenesis comprised of mutational events, which are assumed to play a key role in carcinogenesis, show linear responses to doses from as low as 10 mGy. The impact of non-mutational mechanisms on the risk of radiation-induced cancer at low doses is currently difficult to assess. In epidemiology, the results show excess cancer risks at dose levels of 100 mGy or less. While some recent results indicate non-linear dose relationships for some cancers, overall the LNT model does not overestimate the risks at low doses. Current results, in radiobiology or in epidemiology, do not demonstrate a dose threshold below which the risk of radiation-induced cancer would be zero. Uncertainties persist but such a dose threshold, if any, could not be greater than a few tens of mGy.

Conclusions
The IRSN considers that the scientific knowledge currently available supports the use of the LNT model for the assessment of radiation-induced cancer risks, in support of the radiation protection system. The use of this model appears to be reasonable from a scientific point of view, and no other dose-response relationship seems more suitable or justifiable for radiation protection purposes.

Groundwork for a revision of radiation exposure assessments for the Japanese atomic bomb survivors

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Purpose
The Radiation Effects Research Foundation (RERF) has published two core dosimetry systems – Dosimetry System 1986 (DS86) and 2002 (DS02) – as part of their efforts to retrospectively calculate dose to the Japanese atomic bomb survivors. Both dosimetry systems were based on particle transport simulations coupled with virtual human models (phantoms). Due to computational limitations of the past, however, RERF modeled only three age groups to represent the entire Japanese population: the infant, child, and adult. These phantoms, developed in the early 1980s using simple geometrical shapes, are still in use at RERF. In 2018, a working group was formed to investigate the potential impact of using an updated phantom series in the dosimetry for the RERF cohort.

Methods
Two new high-resolution and age-expanded phantom series based on the Japanese population of 1945 have been developed; one covers six survivor ages of both sexes (the J45 pediatric and adult series), and another covers four gestational ages of the pregnant female survivor (the J45 pregnant female series). Consideration was given to the diversity of survivor postures at the time of exposure, with phantoms created in the standing, kneeling, and lying positions. Organ doses for the J45 phantom series were computed within Monte Carlo code using photon and neutron fluences for both Hiroshima and Nagasaki exposure conditions. These results were compared to the current estimates made by DS02, where certain organ doses that are unavailable from the system must be derived using a surrogate organ (e.g., fetal organ doses from in-utero exposures are estimated using the adult uterine wall dose).

Results
Overall, the updated phantom series were found to provide significant improvements to survivor dosimetry, primarily due to the more comprehensive and realistic modeling of the organs and tissues. These impacts have been tabulated for various survivor demographics, orientations, and locations relative to the bomb hypocenter. The most substantial changes were seen in the neutron component of the dose estimates, which are a vital source of data for radiobiological effectiveness studies.

Conclusion
The results of our working group have shown that the J45 phantom series will provide considerable advancements in the dose reconstruction for members of the atomic bomb survivors cohort. Work is currently underway to develop and test implementation of the J45 phantom series into a dosimetry system revision.

Imaging Utilization in Preterm Infants and Associated Radiation Exposure and Cancer Risk

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Background
Diagnostic imaging is used to assess preterm infants in the neonatal intensive care unit. No prior studies have quantified the frequency or type of imaging use in preterm infants or variation in use by gestational age. Neonates are more susceptible than older individuals to radiation-induced cancer due to active cell proliferation and long remaining lifespan. Given their small size, imaging in preterm infants may include all organs in the radiation field, resulting in a whole-body dose and higher effective dose than imaging in larger children. Therefore, it is important to quantify imaging utilization and associated radiation exposure in preterm infants to understand lifetime cancer risk from these exposures.

Methods
We examined utilization of medical imaging within the first 6 months of life among preterm and full-term infants born at a gestational age 24 weeks or older at 5 US healthcare systems from 1996-2016. Imaging examinations were identified from electronic health records in the U.S. and physician billing records in Ontario. For each modality, we calculated imaging utilization rates per infant, overall and by the severity of prematurity, ranging from extremely premature (24-27 weeks) to late preterm (34-36). A sample of imaging examinations were reviewed to determine the anatomic areas included and organ doses received. We will estimate cumulative exposure to ionizing radiation associated with imaging and project lifetime risk of cancer.

Results
Imaging use was common within the first 6 months of life and was strongly and monotonically inversely associated with gestational age. Preterm infants compared with full-term infants, depending on gestational age, were 2-11 times more likely to receive computed tomography (CT) imaging, 3-75 times more likely to receive radiographs, 2-13 times more likely to receive angiography/fluoroscopy, and 2-8 times more likely to receive nuclear medicine exams, with the highest rates in the most premature (24-27 weeks). CT imaging occurred in 0.8% of full-term infants vs. 7.0% of extremely preterm infants, radiography 13% vs. 91%, angiography/fluoroscopy 1.3% vs. 14%, and nuclear medicine 0.3% vs. 1.8%. Repeat imaging was common in preterm infants; 57% of extremely preterm infants received 10 or more radiographs. Estimated radiation exposure and projected lifetime radiation-induced cancer risk estimates are forthcoming.

Conclusion
Rates of imaging with ionizing radiation in preterm infants are high compared with full-term infants. Given neonates are particularly sensitive to radiation and are more likely to receive many exams, it is important to keep doses as low as possible.

Progress on establishing dose coefficients for common pediatric diagnostic fluoroscopic examinations in support of ICRP TG 113

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Abstract
The International Commission on Radiological Protection (ICRP) Task Group 113, a Task Group under Committee 2 and Committee 3, is responsible for developing reference organ and effective dose coefficients for common diagnostic x ray imaging examinations. Briefly, the task group recognizes that the primary dosimetric data available from diagnostic medical imaging procedures are entrance air kerma (for radiography), air kerma-area product (for fluoroscopy), and $CTDI_{vol}$ and DLP (for computed tomography, CT). While these dose metrics are useful in the establishment of Diagnostic Reference Levels, they are a limited surrogate for the quantity of effective dose. To date, the ICRP has not provided reference dose coefficients that would allow converting readily available dosimetric data reported from medical imaging equipment to estimates of effective dose, or a surrogate thereof, and organ absorbed doses. Consequently, disparate methodologies—often relying on older stylized hermaphroditic phantoms—are being used to estimate effective dose; thus, highlighting the need for standardization by way of ICRP reference dose coefficients.

To this end, we are developing ICRP reference dose coefficients for the most common pediatric diagnostic fluoroscopic examinations with the ultimate goals for clinical optimization and for radiological protection research. The major tasks of this effort are (a) to define representative imaging fields of the voiding cystourethrogram, lower GI series (commonly called the single contrast enema), upper GI series, and modified barium swallow examinations (b) to develop ICRP reference dose coefficients by performing Monte Carlo radiation transport calculations for each imaging field on each of the ICRP reference pediatric computational phantoms and (c) to report all methods, model assumptions, and results in a written report to the ICRP. The work done by this subgroup will be limited to those procedures previously listed, will not cover the full range of clinical practice, nor will it address variability in patient-specific anatomy and disease. Nonetheless, these reference imaging fields will be consistent with national and international imaging referral guidelines that outline typical techniques. These developments have the potential to assist low-dose research programs studying radiogenic health risks in cohorts of medically exposed patients.

Rapid dose calculation software for interventional cardiology

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Background
The HARMONIC study (health effects of cardiac fluoroscopy and modern radiotherapy in paediatrics) aims, among other goals, to study the relationship between ionising radiation received early in life, and subsequent cancer in children treated by interventional cardiology (IC). This requires the estimation of organ doses for 100000 cardiac procedures and at least as many procedures, potentially comprising millions of different exposure configurations.

Aim
A strategy to rapidly estimate patient-specific organ doses was therefore developed. This relies on a lookup-table containing thousands of pre-calculated conversion coefficients relating kerma-area product (KAP, a dose metric readily available in IC) to organ doses.

Materials and methods
Organ dose were calculated with the Monte Carlo particle transport code MCNPX. Ten paediatric and adult anthropomorphic phantoms were used. These represent patients of each sex and of age 1, 5, 10, 15 year old and adult. The X-ray field covered the phantom's heart and aortic arch. The X-ray tube was positioned according to the combinations of 19 beam primary angles (from -95° to 95°) and seven secondary angles (from -15° to 15°). Nine beam qualities were modelled, considering three filtrations (inherent and 0.6 and 0.9 mm added copper) and three tube voltages (60, 80 and 100 kV). The absorbed dose was computed for 61 and 62 organs, tissues and (sub)structures for the male and female phantoms, respectively. The calculated organ doses were normalised to the KAP value, resulting in KAP-to-organ dose conversion coefficients. These coefficients were extended by using radial basis function and linear kernel interpolation with Python library Scipy.

Results
Organ-dose conversion coefficients were simulated for 11970 configurations and extrapolated for 233730 additional configurations. The coefficients for 16 organs of interest for the epidemiology study were embedded in a rapid, user-friendly software program enabling the user to reconstruct organ doses in virtually any exposure conditions within the simulated parameter range. Work is ongoing to extend the simulation range, to include dose coefficients for the new-born and to investigate the effect of different degrees of collimation and translational shifts in the field position.

Conclusion
Organ-dose conversion coefficients were calculated for a wide range of exposure conditions relevant for IC procedures. The coefficients are available to the research community as a user-friendly software program.

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Risk of haematological malignancies after medical ionising radiation exposure from cardiac catheterisation during childhood: The French COCCINELLE cohort (follow-up 2000-2015)

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Introduction

Cardiac catheterization (CC) has largely improved the diagnosis and treatment of congenital heart disease in children over the last decades. Besides the large clinical benefit of CC, these procedures lead to an exposure to low dose ionizing radiation due to x-rays. Children have a greater radiation sensitivity and a longer life expectancy allowing the development of long-term radiation associated cancer risks. However, little is known about these health effects. This study aims to assess the risk of cancer and more specifically the risk of haematological malignancies among children diagnosed and/or treated with CC.

Methods

The COCCINELLE cohort includes children from 15 French paediatric cardiology departments who underwent a first CC between 2000 and 2013, before 16 years old. The cohort was linked with the national childhood cancer registry to identify cancer cases until the date of the 18th birthday or the end of 2015 and with the national Health Insurance database to collect information on predisposing factors to cancer (PF). Individual cumulative doses to active bone marrow (ABM) were calculated with the software PCXMC, based on detailed dosimetric information retrieved from reports of 1,139 CC procedures. Standardised incidence ratios (SIRs) were calculated comparing the

cancer incidence in the cohort and in the general population. Poisson regression was used to estimate the relative risks (RR) of haematological malignancies associated with the 2-year lagged ABM dose.

Results

The cohort included 17,104 children, followed 6.5 years on average, corresponding to 110,335 person-years. Among them, 7.5% presented PF. 22,227 CC procedures were collected, with a mean individual ABM cumulative dose of 3.0 mGy. A total of 59 cases of cancer, including 38 haematological malignancies was observed (23 lymphoma and 15 leukemia). A significant excess of cancer incidence was observed (SIR=3.8 [95% confidence interval 2.9;4.9]), which was anymore observed when excluding patients with PF (SIR=1.3 [0.6;2.7]). The ABM dose received was not significantly associated with the risk of haematological malignancies ($RR_{/mGy}$=1.00 [0.88;1.10]) or lymphoma ($RR_{/mGy}$=1.03 [0.90;1.14]) after adjustment for attained age, gender and PF. CT scan exposure didn't modify the risk.

Conclusion

No significant increase of cancer incidence was observed after excluding patients with PF and no dose-response relationship was observed between the risk of haematological malignancies or lymphoma and cumulative ABM dose arising from CC procedure in our study population. Larger studies as the European Harmonic project will help to better assess the potential health effects of CC exposure during childhood.

Organ dose calculation methods and tools for patients undergoing computed tomography, nuclear medicine, and fluoroscopy exams

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Abstract
Medical radiation sources, mainly composed of computed tomography, nuclear medicine, and fluoroscopy, contribute substantially to effective dose per capita worldwide. Although diagnostic radiology procedures provide inarguable benefits to patients, there are still concerns about potential risks associated with radiation doses, especially in pediatric patients who are more sensitive to radiation and have longer life expectancies than adults. Epidemiology is a way to quantify the risk but requires individualized organ doses as input data. In the past decade, researchers at the United States National Cancer Institute (NCI) have developed methods and tools to estimate individualized organ doses for patients who underwent computed tomography (CT), nuclear medicine (NM), and radiography/fluoroscopy (RF) examinations.

They have employed a library of realistic hybrid computational human phantoms, surrogates of patient's anatomy, combined with Monte Carlo radiation transport techniques to simulate radiations emitted from x-ray machines (CT and RF) or anatomical regions where radioisotopes are distributed (NM) and interact within the human anatomy models. Energy deposited to anatomical target regions is scored. The simulation results were used to derive organ dose conversion coefficients which were then converted to organ absorbed dose by using radiation measurements: Computed Tomography Dose Index (CTDI) in CT scans, Dose-Area Product (DAP) in RF exams, and administered activity in NM procedures.

A series of computer programs have been developed based on a comprehensive library of organ dose conversion coefficients: NCI dosimetry system for CT (NCICT), NM (NCINM), and RF (NCIRF). Doses calculated from the three dose calculation tools have been rigorously compared with experimental measurements (NCICT) and other existing dose calculation programs (NCINM with OLINDA and IDAC) and NCIRF with PCXMC). Organ doses obtained from the NCI dosimetry tools, based on the realistic hybrid computational human phantoms, showed substantial differences from those calculated by the existing programs based on the simplified mathematical phantoms.

The NCI dose calculators should be valuable resources for estimating individualized organ doses for epidemiological and clinical studies accurately. The computer programs are available free of charge for research purposes.

Complete patient exposure during paediatric brain cancer treatment for photon and proton therapy techniques including imaging procedures

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Abstract

Paediatric patients undergoing radiotherapy are subject to a wide range of doses of ionising radiation as a consequence of their radiotherapy treatment but also from complementing imaging procedures. However, only rarely data were complemented with doses from imaging. Until now, the imaging dose during radiotherapy was generally considered negligible in clinical practice because of its low magnitude compared to the therapeutic dose given during the treatment. Within the European project HARMONIC, a tool for calculating the dose from imaging procedures during radiotherapy has been explored. Furthermore, HARMONIC has substantial efforts into validating computational and analytical tools needed to estimate out-of-field organ doses in children treated with photon and proton therapy.

Aiming to simulate a realistic treatment of a brain tumor, a clinical proton plan was transferred to an anthropomorphic phantom (ATOM, Computerized Imaging Reference Systems (CIRS), Inc., Norfolk, VA) representing a five-year-old child (type 705D). A median dose of 50.4 Gy(RBE) with 1.8 Gy(RBE) per fraction was prescribed to the initial planning target volume (PTV), which was located in the cerebellum and had a volume of 195.2 cm^3.The proton treatment plan consisted of two ipsilateral oblique fields and a contralateral oblique field. The proton fields were delivered in a gantry room in pencil beam scanning delivery mode (PBS) employing a lucite range shifter. For comparison the anthropomorphic phantom was treated with photon therapy featuring the same cranial size and shape. Three radiotherapy techniques were applied, namely 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT). All photon irradiations for this article were done with a Varian TrueBeam STx linac operating with flattening filter at a nominal energy of 6 MV with the same dose prescription in Gy used for protons. Proton and photon plans were simulated with the Monte Carlo codes TOPAS and PRIMO, respectively. Also, imaging treatment doses were computed in all cases using the Monte Carlo code PENELOPE. All plans and imaging procedures were irradiated on the anthropomorphic phantom loaded with 180 thermoluminescent detectors and the obtained doses were used to validate the simulations.

Results indicate that the organ doses for organs far from the treated volume tend to be smaller in the case of proton irradiations than in the case of photons. However, the difference for these far from the field doses becomes smaller when imaging doses are taken into account.

Dose reconstruction for a large-scale retrospective study on late health effects following radiotherapy within the National Wilms Tumor Study

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Background and Purpose
As the survival rates of childhood cancer improve, it becomes increasingly important to study the impact of multi-modality therapies on long-term health. Radiotherapy has been implicated as a contributor to late toxicities such as second malignant neoplasms and cardiovascular disease; however, there are still significant gaps in knowledge. Indeed, survivors presenting with late health effects today were treated before the widespread availability of 3Dimaging and radiotherapy planning. However, without 3D organ dosimetry, it is difficult to translate the knowledge gained from past treatments into the dose tolerance criteria needed for improving outcomes for patients treated today. The National Wilms Tumor Study (NWTS) provides a unique opportunity to bridge this gap. In this paper we present the methods, workflow, and results of a multi-year effort to reconstruct radiotherapy organ doses for the NWTS cohort in support of late effects research.

Methods
We reconstructed 3D organ doses for 4716 pediatric patients in the NWTS cohort. As CT images were not available for theNWTS patients, computational phantoms were selected from the National Cancer Institute (NCI) body-size dependent phantom library to use as surrogate anatomy. Each patient was matched to a phantom in the library based on gender, height, and weight at age of Wilms tumor diagnosis. A DICOM CT image set and structure file for the matched phantom was then imported into a treatment planning system (TPS) for reconstruction of the radiotherapy fields according to paper medical records. The radiotherapy planning was performed by an experienced medical physicist under the supervision of a radiation oncologist familiar with protocols used during the NWTS trials. As the accuracy of the TPS is limited in the out-of-field region, Monte Carlo radiation transport calculations were also performed to improve the organ dose estimates. All calculations were performed on the NIH high-performance computing cluster.

Results
The patients were treated with a variety of photon energies: 4 MV (23%), 6 MV (48%), 10 MV (3%), Co 60 (23%), and other (3%). The most common treatment fields were left and right-flank, abdomen, and chest. The Monte Carlo dose calculations took approximately ~100 CPU hours (wall clock time ~2 hours) for a typical patient, resulting in approximately 0.5 million CPU hoursin total for the cohort. Mean organ dose and dose-volume metrics were computed for more than 100 organs or tissues.

Conclusion
This study represents the first time Monte Carlo methods have been directly applied on a large scale to reconstruct organs doses for an epidemiological cohort. The organ doses for the NWTS cohort will provide valuable information for developing dose tolerance criteria for mitigating radiotherapy toxicity.

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An innovative and versatile deep learning approach to estimate the out-of-field dose

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Abstract
Radiation therapy has common iatrogenic effects, including the development of radiation-induced lymphopenia, radiation-induced cancer, and cardiac and vascular complications. A growing body of scientific evidence reveals the potential effects of medium (Gy) and low doses (< 1 Gy) in particular on highly radiosensitive immune cells. Therefore, the assessment of low doses inevitably delivered outside the treatment field (out-of-field dose) is a topic of renewed interest at a pivotal moment in the development of combination therapies. In this work, we propose an original fast and versatile tool to estimate out-of-field doses for patients treated with external photon radiotherapy with energies above 1 MV based on a Deep Learning approach.

3152 pediatric patients from the French Childhood Cancer Survivor Study dataset who underwent 2D conventional and 3D conformational radiotherapies between 1953 and 2013 with accelerators operating with photons at energies higher than 1 MV were considered in this study (Table 1). A 3D U-Net architecture was investigated, considering in-field doses and patient geometries as inputs while using whole-body dose maps estimated with analytical models (Dos-EG) as ground truths. In addition to the traditional test set (test set), data from one specific center (center test set) and one specific linear accelerator (linac test set) were kept unseen during the neural network training. Data were split in 67%, 14%, 14%, 2% and 3% for the train, validation, test, center test and linac test set respectively.

Figure 1 shows an example of out-of-field dose prediction, and quantitative RMSD results can be found in Table 2. The results suggest that the initial hypothesis is validated, i.e. it is possible to estimate the out-of-field dose from the in-field dose map and the anatomy of the patient. The results on the test set, center test set, and linac test set seems to demonstrate good generalization performances, which is promising for large-scale applications on retrospective and prospective datasets.

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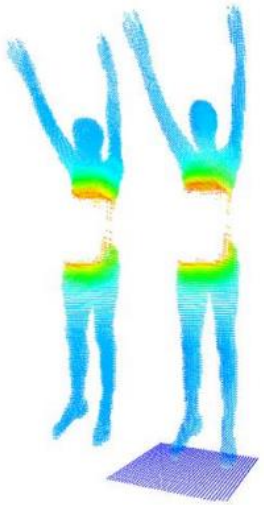

Figure 1: Example of predicted out-of-field dose map (with blue square) VS ground truth out-of-field dose map, for a male patient treated on a Co60 accelerator for a nephroblastoma

Table 1: Composition of work cohort

Center	Center 1	Center 2	Center 3	Center 4 (Center test)	Center 5
Number of accelerators	22 (5 Co^{60}, 13 linac, 4 betatron)	3 (3 Co^{60})	6 (4 Co^{60}, 2 linac)	4 (2 Co^{60}, 2 linac)	12 (8 Co^{60}, 4 linac)
Number of pathologies	37	7	20	13	22
Number of patients	2663	24	199	68	198

Table 2: Results at epoch 1975/2000 after a 160h training

RMSD	Validation	Test	Center test	Linac test
Out-of-field area	$2.33e^{-1}$ $cGy.Gy^{-1}$	$2.38e^{-1}$ $cGy.Gy^{-1}$	$3.18e^{-1}$ $cGy.Gy^{-1}$	$1.83e^{-1}$ $cGy.Gy^{-1}$
Near the field area (from isodose 5% to 0.1%)	$2.74e^{-1}$ $cGy.Gy^{-1}$	$2.78e^{-1}$ $cGy.Gy^{-1}$	$3.34e^{-1}$ $cGy.Gy^{-1}$	$1.99e^{-1}$ $cGy.Gy^{-1}$
Away from field area (beyond isodose 0.1%)	$0.98e^{-1}$ $cGy.Gy^{-1}$	$0.83e^{-1}$ $cGy.Gy^{-1}$	$2.01e^{-1}$ $cGy.Gy^{-1}$	$1.25e^{-1}$ $cGy.Gy^{-1}$

Radiation doses received by major organs in children and young adolescents treated for cancer with external beam radiation therapy: a large-scale study from 12 European countries

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Abstract

Childhood cancer survivors are at high risk of long-term iatrogenic events, in particular those treated with radiotherapy. The prediction of risk of such events is mainly based on the knowledge of the radiation dose received to healthy organs and tissues during treatment of childhood cancer diagnosed decades ago and who currently are at risk of long-term severe iatrogenic events. To date, no standardised organ dose table have been published. In the absence of this information, clinician in charge of long term follow-up of childhood cancer survivors may not anticipate.

We performed whole body dosimetric reconstruction for 2646 patients from 12 European Countries treated between 1941 and 2006. A patient specific voxel-based anthropomorphic phantom with more than 200 anatomical structures or sub-structures delineated as a surrogate of each subject's anatomy was used. The radiation therapy was simulated with a treatment planning system (TPS) based on available treatment information. The radiation dose received by any organ of the body was estimated by extending the TPS dose calculation to the whole-body.

By setting up the first large-scale European study including estimates of radiation doses to major body organs during childhood cancer radiotherapy, we have been able to detail dose estimates in a way that provides useful information to former patients or clinicians who have limited knowledge of radiotherapy protocols or techniques, but who know the type and site of the child's cancer, gender, age and year of treatment. These parameters accounted for about half of the variability of the organ dose. The country accounted for only 1% of this variability. The remaining variability was due to decisions by radiation oncologists, based on their own experience and patients' clinical characteristics not recorded in our study. We observed that the integral dose and normal-tissue doses to most of the 23 considered organs increased between the years of the 1950's to the 1970's and decreased or plateaued thereafter, what is due to a better knowledge of long term risk of radiation therapy and the need to reduce radiation dose to healthy organs.

The detailed dose estimates provide very useful information for former patients or clinicians who have only limited knowledge about radiation therapy protocols or techniques, but who know the type and site of childhood cancer, gender, age and year of treatment. This will allow better prediction of the long-term risk of iatrogenic events and better referral to long-term follow-up clinics.

Genetic susceptibility to radiation therapy side effects in childhood cancer survivors in Gene-FCCSS project

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Background
The French Childhood Cancer Survivor Study (FCCSS) is the French cohort focusing on the late effects of childhood cancer treatments with the longest follow-up (mean follow-up of 32 years). All patients included in FCCSS, have had radiation dose reconstruction per organ and detailed clinical, therapeutic, and follow-up data.

Objective
The Gene-FCCSS project was set up to sequence and analyze the genetic data from FCCSS, one of our main objectives is to analyze the genetic susceptibility to childhood cancer radiotherapy side effects, especially iatrogenic cancerous and non-cancerous radiation-related pathologies and propose polygenic risk scores (PRS) to better assess the individual risk associated with these side effects.

Methods
Whole genome sequencing will be performed on available saliva or blood samples from 2872 FCCSS patients. A minimum sequencing depth is fixed at 30X. Of them, 1518 have been treated with radiotherapy, and median doses in Gy were: 0.5 at the brain, 1.4 at the thyroid gland, 1.6 at the heart, 1.2 at the breast, and 3.0 at the kidney.
The analyses will investigate the genetic susceptibility to radiation therapy side-effects such as the risk of second primary neoplasm (n=440), severe cardiac disease (n=240), treated diabetes mellitus (320), severe ototoxicity (n=300), surgically treated cataract (n=60), chronic renal failure (n=70), and stroke (n=110). Interaction between genetic variants and radiation doses will be tested for each iatrogenic disease.

Conclusion
Gene-FCCSS will present a major European source of information about genetic susceptibility to radiation related pathologies.

Stroke after radiation therapy for a childhood cancer, the CerebRad Project

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Purpose
To quantify the cerebrovascular risk in yet treated childhood cancer patients and to anticipate the risk induced by new radiation therapy techniques, needs to establish reliable dose-response for radiation dose.

Methods
In the Frame of European CEREBRAD FP7 project, we set up a case-control study, including 394 validated cases of stroke reported 5 years or more following cancer treatment between 1945 and 2003 in France, Netherlands and UK before the age of x years. A total of 394 controls were matched by cohort, gender, age and date of childhood cancer, and length of follow-up. Half cases (199) occurred after a central nervous system (CNS) tumor. Using patient's medical records, a modified-treatment planning software permitting whole-body dose estimation and human voxelized phantoms in treatment position, we reconstructed cumulative radiation doses for each case and control who were treated with external radiation therapy. In Poisson regression models?, we considered mean radiation dose to all brain structures and cerebral arteries.

Results
Radiation dose received to the cerebral arteries (Willis circle and internal carotids) was the main risk factor for subsequent permanent stroke. Doses received to other brain structures did not play any significant role. Cisplatin was the only drug associated with an increased risk of stroke.
Averaged radiation doses lower than 1 Gy to the cerebral arteries (mean: 0.26 Gy) significantly increased the risk of ischemic stroke (odds-ratio=3.8, 95%CI 1.6-8.9), but not the one of hemorrhagic stroke. A linear model was the best one for the risk of hemorrhagic strokes, whereas the risk for ischemic stroke strongly increased at low doses and plateaued afterwards. Whatever the type of stroke, the EOR/Gy strongly increased with longer time since radiotherapy. Sex, age at radiotherapy and chemotherapy did not act as radiation dose effects modifiers.

Conclusion
In conclusion, this study, which is at our knowledge, the most important one aiming to quantify the role of radiotherapy in the long term risk of permanent symptomatic stroke after childhood cancer radiotherapy, emphases differences between ischemic and hemorrhagic radiation induced strokes.

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The risk of valvular heart disease in the French Childhood Cancer Survivors' Study: Contribution of Dose-Volume histogram parameters

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Background and purpose
Valvular Heart Disease (VHD) is a known complication of childhood cancer after radiotherapy treatment. However, the dose-volume-effect relationships have not been fully explored.

Materials and methods
We obtained individual heart Dose Volume Histograms (DVH) for survivors of the French Childhood Cancer Survivors Study (FCCSS) who had received radiotherapy. We calculated the Mean Dose to the Heart (MHD) in Gy, as well as the heart DVH parameters ($V_{d\,Gy}$, which represents the percentage of heart volume receiving at least d Gy), fixing the thresholds to 0.1 Gy, 5 Gy, 20 Gy, and 40 Gy. We analyzed them furtherly in the subpopulation of the cohort that was treated with a dose lower than 5 Gy ($V_{0.1Gy|V5Gy=0\%}$), 20 Gy ($V_{5Gy|V20Gy=0\%}$), and 40 Gy ($V_{20Gy|V40Gy=0\%}$), respectively. We investigated their role in the occurrence of a VHD in this population-based observational cohort study using the Cox proportional hazard model, adjusting for age at cancer diagnosis and chemotherapy exposure.

Results
Median follow-up was 30.6 years. Eighty-one patients out of the 7462 (1%) with complete data experienced a severe VHD (grade ≥3). The risk of VHD increased along with the MHD, and it was associated with high doses to the heart (V_{40Gy} <50%, hazard ratio (HR) = 7.96, 95% CI: 4.26-14.88 and $V_{20Gy|V40Gy=0\%}$ >50%, HR=5.03, 95% CI: [2.35-10.76]). Doses 5-20 Gy to more than 50% ($V_{5Gy|V20Gy=0\%}$ >50%) of the heart induced a marginally non-significant estimated risk, that becomes significant when 90% of the heart volume is affected. We also observed a 2-fold ERR increase when attained age is over 40, and 3-fold when attained age is over 50 years old.

Conclusions
Our results provide new insight into the VHD risk that may impact current treatments and long-term follow-up of childhood cancer survivors.

Risk of haematological malignancies in relation to radiation dose from paediatric scanning: results from the European EPI-CT study

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Abstract

Ionising radiation exposure in childhood is known to increase the risk of haematological malignancies. The magnitude of risk at dose levels typical of computed tomography (CT) is uncertain, however. This is an important issue given the rapid increase in CT usage in healthcare since the 1970s.

We followed-up a European multinational cohort (EPI-CT) of 948,174 individuals from nine European countries who underwent a CT scan before the age of 22 between 1977 and 2014 and had no previous diagnosis of cancer. Participants were identified through the Radiology Information System in 276 hospitals and followed-up through linkage with national or regional cancer and vital status registries. Radiation doses to the active bone marrow were

estimated based on body part scanned, patient age, time period, and technical parameters of the scans. Dosimetric estimates considered shared and unshared uncertainties.

Analyses included 876,771 individuals, alive and cancer free two years after their first CT, who underwent a total of 1,331,896 CT-scans. These individuals contributed 6,863,833 person-years of follow-up. The average bone marrow dose was 20 mGy (maximum 286). An association between cumulative dose (lagged by 2 years) and risk of all haematological malignancies was observed, with an excess relative risk (ERR) of 1.96 (95% CI 1.10–3.12), based on 790 cases. Similar results were observed in analyses of lymphoid neoplasms (577 cases) and myeloid neoplasms (203 cases) separately. A statistically significantly increased risk was also seen for Hodgkin lymphoma (190 cases). Results were generally robust to different analytical strategies. Excluding 5 and 10 years of follow-up after the 1st CT increased the estimated ERR for all haematological and for lymphoid neoplasms, as did exclusion of subjects with the highest doses. Lagging doses by 5 years instead of 2 reduced the risk estimates though the increases were still statistically significant for all haematological malignancies and for lymphoid neoplasms.
Our results suggest radiation exposure from paediatric computed tomography is associated with an increased risk of haematological malignancies. They strengthen the body of evidence that low to moderate doses of radiation can cause cancer and underline the need for strict justification of paediatric CTs.

Dose estimation for the European Epidemiological Study on Pediatric Computed Tomography (EPI-CT)

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Abstract

Reliable estimation of organ doses is vital for unbiased estimation of the dose-response relationship in epidemiological studies. In the EPI-CT study, careful estimation of radiation doses to individual organs of roughly 1,000,000 paediatric to young adult patients who underwent computed tomography (CT) examinations was essential to quantify the radiation-associated cancer risks. We developed a strategy to estimate, on an individual basis, absorbed organ doses and characterise the uncertainty resulting from (a) lack of knowledge of the true but unknown values of dose-model parameter values and (b) the necessity of applying the same estimated value of parameters to individuals within groups of patients with similar exposure attributes.

There are three main components in the dose reconstruction. First, we gathered exposure-related data from the Radiology Information System and, for more recent time-periods, from the Picture Archiving Communication System of participating hospitals. Second, organ doses were calculated from the collected data using National Cancer Institute dosimetry system for CT (NCICT), a program based on detailed Monte-Carlo radiation transport calculations combined with realistic computational human phantoms and several scanner models used in the participating countries over time. The third and most unique aspect is that we accounted for the many individual exposure-related data not available, particularly for early years when only sparse information on implemented protocols was available.

Our approach produces alternative sets of doses for the entire cohort (each called a 'realization'), thus, not only characterizing the uncertainty of individual doses but, also producing numerous plausible dose sets, each suitable for use in a single dose-response model. Doses in each realization maintain proper correlations among persons with similar (shared) exposure-related attributes, e.g., having been scanned in the same hospital. To accomplish this, missing parameters were constructed in the form of probability density functions (PDFs) representative of the state-of-knowledge for the relevant time-period. Parameter values were selected for each realization from the appropriate PDFs for the entire group of subjects to which it applies.

Relatively high doses were received by the brain from head CTs in the early 1990´s, with individual mean doses (mean of 200 simulated values) of up to 70 mGy per scan. Optimization strategies and technology improvements have resulted in an overall decrease in doses over time, with mean brain dose from head CTs in newborns decreasing from 45mGy in the late 1980´s to 35mGy in recent years. The impact was greater in chest CTs with, for instance, active bone marrow doses dropping from over 15 mGy prior to 1991 to about 5 mGy/scan after 2001. Our findings illustrate patterns of age-specific doses and their temporal changes and provide suitable dose estimates for radiation-associated risk estimation in epidemiological studies.

Results from the EPI-CT cohort study: risk of brain cancer after radiation exposure from CT examinations of children and young adults

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Abstract

EPI-CT is a European cohort study that aims to quantify cancer risks from CT examinations of children and young adults. Here, we assess the risk of brain cancer. Using a common core protocol, we pooled individual patient data from existing and extended cohorts in nine European countries. Eligible participants had at least one CT examination before age 22 years recorded between 1977 and 2014, had no previous diagnosis of cancer or benign brain tumour, and were alive and cancer-free at least 5 years after the first CT. We identified participants through the Radiology Information System in 276 hospitals and then linked with national or regional registries of cancer and vital status. Eligible cases were patients with brain cancers according to WHO International Classification of Diseases for Oncology. We analysed gliomas separately to all brain cancers. Organ doses were reconstructed using historical machine settings and a large sample of CT images. Excess relative risks (ERRs) of brain cancer per 100 mGy of cumulative brain dose were calculated with linear dose-response modelling. For this analysis, the outcome was the first reported diagnosis of brain cancer after an exclusion period of 5 years after the first electronically recorded CT examination. EPI-CT cohort includes 948,174 individuals, of whom 658,752 (69%) were eligible for our study. Among all patients included in the analyses, 73% received at least one head/neck CT examination. During

a median follow-up of 5·6 years (IQR 2.4–10.1), 165 brain cancers occurred, including 121 (73%) gliomas. Mean cumulative brain dose, lagged by 5 years, was 47.4 mGy among all individuals and 76.0 mGy among people with brain cancer. A significant linear dose-response relationship was observed for all brain cancers (ERR per 100 mGy 1.27 [95% CI 0.51–2.69]) and for gliomas separately (ERR per 100 mGy 1.11 [0.36–2.59]). Relative risk for all types of malignant brain tumours was 5.9 [95% CI 3.1-11.2] among those who received four or more head/neck CT examinations compared to no head/neck CT. Results were robust when the start of follow-up was delayed beyond 5 years and when participants with possibly previously unreported cancers were excluded. The observed significant dose-response relationship between CT-related radiation exposure and brain cancer in the largest international study to date with individual dose evaluation emphasises careful justification of paediatric CTs and use of doses as low as reasonably possible.

Accounting for organ dose uncertainties on childhood cancer risk estimates in the French CT cohort

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Background

Computed tomography (CT) has been used increasingly worldwide over the last decades. However, concerns have been raised about potential radiation-related cancer risks, particularly after exposure to CT in childhood, due to the greater radiation sensitivity of children and to their longer life expectancy allowing to develop radiation associated late health effects. Several CT cohort studies aim at understanding the relationship between CT organ dose and cancer incidence. However, several sources of uncertainty coming from CT acquisition parameters and patient's morphology exist but have sparsely been accounted for in risk estimates. This may lead to biased risk estimates and misleading conclusions. In this work, the aim is to study the impact of CT organ dose uncertainties on the risk of central nervous system (CNS) tumors and leukemia in the French CT cohort.

Methods

The French CT cohort includes almost 100,000 children who received at least one CT between 2000 and 2011 in one of the 21 participating university hospitals. Patients were followed until the first diagnosis of cancer, the death, the 18th birthday or the 31st December 2016. Examinations and radiological protocols were retrieved to estimate cumulative absorbed doses to the brain and the red bone marrow (RBM) with NCICT 1.2. Sensitivity analysis indices were computed to identify the most influential input parameters in the estimation of organ doses. A first submodel was proposed to describe the discrepancy between the CT values provided by the French radiological protocols for these input parameters and their "true" values. A second submodel was proposed to describe the discrepancy between the NCICT estimated organ doses and "true" dose values accounting for patients' morphology. Cox and excess hazard ratio survival models were considered as two alternative dose-response models. The submodels were combined into a unique framework and fitted simultaneously using a Bayesian learning algorithm to estimate cancer risks. PACS data (Picture archiving and communication system) were used to learn about dosimetric uncertainties.

Results and discussion

When not accounting for dosimetric uncertainties, a Cox model-based frequentist estimation, with asymptotic 95% confidence intervals, showed statistically significant dose-response relationships for CNS tumors and leukemia. Bayesian risk estimates were similar but with wider credible intervals which seems to call into question the use of any statistical estimation approach based on asymptotic assumptions, in this context of weak signal data. Moreover, we will show how dose uncertainties impact cancer risk estimates and compare the fitting abilities of several models.

A nested case-control study on cancer risks from paediatric CT scans – protocol and illustration from Sweden

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Abstract

Diagnostic imaging modalities involving ionising radiation (IR), e.g. computed tomography (CT), play an essential role in modern healthcare. Although doses from individual CT scans are relatively low (a few mGy to few tens of mGy), patients with repeated CTs may receive cumulative doses of several hundred mGy, reaching levels known to increase cancer risk. Given that 12 to 15 million young persons aged 0-20 years undergo a CT in Europe every year, any increased cancer risk from this exposure could translate into many additional cancer cases. In the last decade, large-scale cohort studies have been conducted in children/young adults exposed to IR from CT scans and reported increased cancer risk. These studies have been criticised as potentially subject to biases related to exposure misclassification, confounding by indication, and potential effect modifiers (in particular increased cancer susceptibility).

We designed a case-control study, nested within the Spanish, French and Swedish EPI-CT cohorts, to improve current risk estimates from medical diagnostic IR exposure in young populations by addressing these potential biases. The study involved collection of detailed information (by questionnaire and from clinical and radiological records) on potential confounding and effect modifying factors, including other radiological examinations, that cannot be obtained in large-scale cohort studies. Analyses of the Swedish nested case-control study, focusing on impact of exposure misclassification (due to missing doses from additional radiological procedures), was conducted. The study included 40 cases of haematological malignancies and 81 matched controls. An increased OR was observed among subjects who received cumulative doses (all radiological procedures) of 50 mGy or more (OR 4.3, 95% CI 1.2-16.1, based on 8 cases). This OR is compatible with, though higher than, that found in the analysis of the Swedish cohort (RR 2.4, 95% CI 0.5-7.2, based on 4 cases) restricting to doses from CT scans. These results suggest that missing doses from other radiological procedures might affect the risk estimates in cohort studies where that information is not available, thus contributing to the ongoing debate about the impact of dose misclassification in record-linkage based cohort studies. These results will be verified with the integration of data from France and Spain.

Radiation Dose Associated with Common CT Examinations Over Time in the US and Ontario Canada

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Background
The Radiation-Induced Cancers (RIC) Study is quantifying the association between cumulative radiation exposure from medical imaging in children and cancer in retrospective cohorts assembled from 6 U.S. healthcare systems and the province of Ontario, Canada from 1996 to 2017. Individual patient doses by age, calendar year, and type of computed tomography (CT) scan are described.

Methods
The cohort includes children born into the health system and followed while continuously enrolled. Technical parameters including CT scanner manufacturer, and machine model, x-ray tube current (mAs), mA, rotation time, tube potential (kV), scan length, and whether the scan was performed using a fixed mA or under tube current modulation for each CT examination were manually abstracted for older examinations (generally prior to 2005 but varying across site), and electronically abstracted using Radimetrics radiation dose software for recent examinations. All scans were mapped to the closest body morphometry-matched phantom in the University of Florida/National Cancer Institute expansive library of hybrid computational human phantoms based on patient sex, age, height, and weight. Technical parameters from each scan were used to calculate organ doses using Monte Carlo simulations. Organ doses were summed across multiple series to obtain a single dose for each examination.

Results
Individual dosimetry was calculated for 30,212 CT examinations. Slightly more scans were obtained in boys. Across most body regions, including head CT, organ doses consistently declined over calendar year, but remained highly variable across patients and facilities through 2017. For head CT, the most common exam type accounting for approximately 60% of all scans, mean doses declined consistently over time. Among children <4 years of age who underwent head CT, average brain doses for decreased from 70 mGy in 1996 to 35 mGy in 2017 and average bone marrow doses decreased from 26mGy to 12 mSv. For abdomen CT, the next most common scan type, in children <4 years of age, average colon doses decreased from 26 mGy to 7 mGy from 1996-2017.–

Conclusion
Radiation organ doses from CT imaging have significantly decline over time but remain highly variable across patients and facilities.

Dysfunction of the salivary and lacrimal glands after radioiodine therapy: 6-month follow-up results of a self-controlled study in France

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Keywords
Salivary dysfunctions, lacrimal dysfunctions, radioiodine, thyroid cancer, epidemiology

Abstract
Following radioiodine therapy (RAI) of differentiated thyroid cancer, salivary and lacrimal glands may be injured, leading to dysfunctions. The incidence of these dysfunctions after RAI is poorly known, and no risk factors have been identified to date to define at-risk patients. The aims of this study are to characterize the dysfunction of salivary and lacrimal glands after RAI, and to identify risk factors of such dysfunctions.

START (Salivary dysfuncTion After Radioiodine Treatment) is a prospective study launched in 2020, including 139 thyroid cancer patients, candidates for a RAI (45 and 94 patients received 1.1GBq and 3.7GBq ^{131}I activity, respectively) in Pitié-Salpêtrière hospital, Paris, France. Follow-up was based on 3 scheduled visits: immediately before RAI (T0), 6 months (T6) and 18 months (T18) later. At each visit, questionnaires on salivary disorders (validated French tool), dry eye (OSDI© Questionnaire), and anxiety/depression symptoms (HAD scale) were administered. At T0 and T6, individual salivary flow measurements (with and without salivary gland stimulation) were performed. The doses to the salivary glands were evaluated through a dosimetric reconstruction based on recordings from thermoluminescent dosimeters directly positioned on the patients.
In the present work, data for the T0 and T6 visits were analysed based on descriptive analyses and random-effects logistic and linear regressions.

Complete information was provided for 136 patients (71% women, mean age=47.1 (±14.1) y). Mean doses to the salivary glands were 0.7 (±0.2) and 2.3 (±0.9) Gy for the 1.1GBq and 3.7GBq ^{131}I-activity groups, respectively. At T6, 18% and 22% of the study population without any symptoms at T0 reported dry eye and/or dry mouth feeling, respectively. Stimulated saliva flow rate significantly decreased from T0 to T6 (2.14 (±0.86) and 1.93 (±0.78) mL/min, $p<10^{-3}$, respectively). Univariate analyses allowed to highlight age, menopause, depression and anxiety symptoms, history of systemic disease, and not taking painkillers in the last 3 months as risk factors or variables significantly associated with salivary or lachrymal disorders. Multivariate analyses adjusted on the previous variables showed significant dose-responses relationships between doses to the salivary glands and dry mouth

sensation or stimulated saliva flow rate, as well as between administered activity and dry mouth sensation or lachrymal disorders.

This work presents the 6 months follow-up results of the START study, showing higher salivary and lacrimal gland disorders after RAI. Further analyses will include saliva biochemical concentrations, genetic and epigenetic variants as risk factors, and quality of life of patients at T6 and T18.

Thoracic soft tissue sarcoma risk following breast cancer treatment in two US retrospective cohorts

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Abstract

Survivors of breast cancer who received radiotherapy are at high risk of developing subsequent thoracic soft tissue sarcomas (STS). Compared to other radiation-related subsequent malignancies, these cancers occur with a shorter latency period and risk did not decline with increasing age at exposure, which raises interesting questions about potential co-factors. We evaluated the risk of subsequent thoracic STS among breast cancer survivors in two complementary cohorts.

Eligibility criteria in both cohorts were female breast cancer cases (stage I-III) aged 20-84 years who had survived at least 1 year since diagnosis. The Kaiser Permanente (KP) cohort included 16,004 women diagnosed 1990-2016, with detailed treatment data, and co-morbidities (including hypertension and diabetes at or before breast cancer diagnosis). The SEER 13 registries cohort included 457,300 women diagnosed 1992-2016 with initial treatment data. The outcome of interest was any second thoracic STS (angiosarcomas and other subtypes). Risk factors for thoracic STS were assessed using multivariable Poisson regression models.

In the KP cohort there were 19 thoracic STS (11 angiosarcomas, 8 other sub-types) after a median follow-up of 9.3 years. The median latent period for developing a thoracic STS was 5.5 years (IQR:3·8–7·5) and most (95%) thoracic STS occurred in women treated with radiotherapy (RR=8.1; 95%CI:1.1-60.4). We found no relationship with radiotherapy prescribed dose, number of fractions, or receipt of boost radiation. For thoracic angiosarcomas, anthracyclines were associated with a 3.6-fold increased risk (RR=3.6, 95%CI:1.0-13.3) and history of hypertension and diabetes were associated with approximately 5-times increased risk (RR=4.8, 95%CI:1.3-17.6 and 5.3, 95%CI:1.4-20.8, respectively). In the SEER cohort there were 430 subsequent thoracic STS (268 angiosarcomas) after a median follow-up of 8.3 years. The median age at thoracic STS diagnosis was 74 years (IQR:62–79) and most (78%) cases occurred after radiotherapy (RR=3.0; 95%CI: 2.4-3.8), with an increased risk of thoracic angiosarcoma for patients who underwent breast-conserving surgery+radiotherapy vs mastectomy+radiotherapy (RR=1.9: 95%CI:1.1-3.3). By 10 years after radiotherapy, cumulative incidence of thoracic STS was 0.20% in the KP cohort and 0.15% in SEER.

Radiotherapy was the strongest risk factor for thoracic STS in both cohorts with a short latency for development. Of clinical relevance, we observed an increased risk of thoracic angiosarcoma with anthracycline receipt and with a history of hypertension or diabetes at or before breast cancer diagnosis. The potential role of these comorbidities warrants further investigation, to reveal possible targets for future prevention strategies and increased surveillance for this highly fatal disease.

Radiation dose-response for cardiac events in breast cancer patients in Germany treated with 3D-conformal radiotherapy: a nested case-control study of the ESCaRa project

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Abstract

Background: Heart disease is a potential late toxicity after breast cancer (BC) radiotherapy (RT). Previous studies with the majority of BC patients treated up to the year 2000 provided evidence that radiation dose to the heart from RT was linearly associated with increasing risk for long-term cardiac disease. In the late 1990s, RT switched from conventional 2D RT to 3D-conformal RT based on computed tomography scans.
While this resulted in a reduction of radiation exposure to the heart, the heart typically remains exposed. This study investigated the dose-dependent cardiac risk in German BC patients treated with more contemporary RT.

Methods: In a cohort of 11,982 BC patients diagnosed in 1998–2008, we identified 494 women treated with 3D-conformal RT who subsequently developed a cardiac event, including incident events of cardiac morbidity and cardiac death. Using a nested case-control approach, these cases were matched to 988 controls based on age and year of BC diagnosis, study center, and cardiac comorbidities. Controls were patients without a cardiac event after RT until the index date of the corresponding case. Separate multivariable conditional logistic regression models were used to assess the association of radiation to the complete heart and to the left anterior heart wall (LAHW) with cardiac events.

Results: More than 75% of cases and controls were treated after the year 2000. The retrospective dosimetry showed a mean dose to the heart of 4.27 Gy (1.21 Gy-11.98 Gy) for left-sided RT in cases and 4.31 Gy (0.80 Gy-13.56 Gy) for controls and 1.64 Gy (0.44 Gy-6.10 Gy) and 1.66 Gy (0.56 Gy-13.56 Gy) for right-sided RT respectively. The dose-response analysis for the complete heart did not reveal any association with cardiac events (OR per 1 Gy increase 0.99, 95% CI 0.94-1.05, p=.72). Likewise, the analysis for the LAHW did not reveal any

dose-response relationship for cardiac events (OR per 1 Gy increase 1.00, 95% CI 0.98-1.01, p=.68). Results were consistent across all analyses when comparing risk estimates and corresponding CI for adjusted and unadjusted models.

Conclusions: Contrary to previous studies, our study provided no evidence that radiation dose to the heart from 3D-conformal RT for BC patients treated between 1998–2008 was associated with an increased risk for cardiac events. Besides the different treatment period, comparability to previous studies is hampered by heterogeneity in aspects of study design including the definition of the endpoint, inclusion criteria, matching criteria and the use of latency time.

Keywords: Breast cancer, Radiotherapy, Cardiac mortality, Cardiac morbidity, Nested case-control study

Risk of second primary malignancies after radioactive iodine treatment for thyroid cancer in patients younger than 45 years: a SEER (1975-2017) database analysis

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Abstract

Differentiated thyroid cancer (DTC), the second most common cancer in adolescents and young adults, is commonly treated with radioactive iodine (RAI) following total thyroidectomy. RAI treatment exposes many radiosensitive organs to doses >100 mGy and has been associated with increased leukemia risk about 2-3 years after exposure. However, because of the lack of studies with long-term follow-up the risks of solid malignancies remain unclear, and few studies have quantified second malignancy risks in young patients who are more susceptible than adults to radiation-related effects. We estimated risks of second malignancies after RAI treatment for pediatric/young-adult DTC in a large U.S. study.

Using data from 9 U.S. Surveillance, Epidemiology, and Results cancer registries (1975-2017), we estimated relative risks (RRs) for solid and hematopoietic malignancies associated with RAI treatment (yes versus no/unknown) for non-metastatic DTC before age 45, using Poisson regression among 27,050 5- and 32,171 2-year survivors, respectively.

Over a median follow-up of 15 years (maximum=43 years), RAI therapy was associated with an increased risk for solid cancer ($RR_{overall}$=1.23; 95% CI:1.11-1.37) with a strengthened association beginning >20 years after DTC diagnosis ($RR_{>20\ years}$=1.47; 95% CI:1.24-1.74). A similar pattern was observed for female breast cancer, the most common second cancer in this population ($RR_{overall}$=1.18; 95% CI:0.99-1.40; $RR_{>20\ years}$=1.46; 95% CI:1.11-1.95). Positive associations were also observed for uterine cancer (RR=1.55; 95% CI:1.03-2.32) and leukemia (RR=1.92; 95% CI:1.04-3.56). We estimated that 6% of solid and 14% of hematological malignancies that occurred in 1+ year pediatric/young-adult DTC survivors during 1975-2017 may be attributable to RAI.

RAI treatment for DTC in patients under 45 years of age was associated with increased risks of leukemia and several types of solid malignancies, including breast cancer. These results reinforce the need to carefully weigh the benefits versus risks of RAI treatment for DTC, especially in younger patients.

Risk of therapy-related subsequent cancers in individuals with germline *TP53* variants

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Background
Based primarily on *in vitro* and animal studies, germline *TP53* variants are considered to confer sensitivity to ionizing radiation-induced DNA damage, but data in humans are sparse. We sought to quantify risk of developing radiotherapy and chemotherapy-related subsequent neoplasms by pooling individual-level data from seven cohorts of individuals with confirmed pathogenic/likely pathogenic germline *TP53* variants.

Methods
Individuals were followed from six months after first cancer until death or date of last study follow-up. Analyses of subsequent breast cancer risk censored follow-up at the date of bilateral mastectomy. Radiotherapy (yes/no) and chemotherapy (yes/no) for each cancer were considered as time-dependent covariates in Cox regression models with age as the time-scale, adjusted for sex and occurrence of prior malignant or benign tumors. Subsequent cancers were classified as in- or out-of-field based on the body region of previous cancers.

Results
Among 522 individuals, 354 (67.8%) were female and 285 (54.8%) were diagnosed with a first cancer before age 30 years. Breast cancer was the most commonly diagnosed first cancer (N=184, 35.2%), followed by central nervous system (CNS) cancers (N=99, 19.0%) and soft tissue sarcomas (STS; N=81, 15.5%). First cancer treatment included radiotherapy for 123 (23.9%) and chemotherapy for 233 (44.6%) individuals. During a median follow-up of 6.1 years (inter-quartile range 2.5-14.3), 272 (52.1%) developed at least one subsequent cancer, most commonly breast cancer (N=106), STS (N=97), gastrointestinal tract cancer (N=49), and CNS cancer (N=44).

Radiotherapy was associated with increased risk of developing any subsequent cancer in the same body region (in-field: hazard ratio [HR]=1.6, 95% confidence interval [CI]=1.1-2.3) but not in other body regions (out-of-field=0.6, 0.4-1.0). Chemotherapy was associated with borderline increased risk of developing any subsequent cancer (1.3, 0.95-1.7). These risks varied substantially by subsequent cancer type, with in-field radiotherapy-related risks significantly elevated at least >4-fold for cancers of the bone, CNS, and thyroid as well as STS, but not for breast cancer, and chemotherapy-related risks significantly elevated for gastrointestinal cancers only (2.8, 1.3 -6.2).

Conclusions

Our initial results support the important contribution of radiotherapy to the increased risk of certain subsequent cancers among individuals with germline *TP53* mutations. Additional analyses will consider more detailed treatment data, a lag period, and inclusion of additional individuals.

Introduction for patients/families (2-3 sentences) in plain language to depict the study's purpose

Patients with Li-Fraumeni syndrome are at risk of developing multiple tumors. It is not known how much of this risk, if any, is contributed by cancer therapies themselves. We have collected detailed cancer and therapy data from many centres around the world, in order to answer the question of whether cancer therapies increase the risk of subsequent cancers in patients with LFS. Knowing the magnitude of this risk will help doctors and patients make informed decisions about their cancer management.

Main take home points (2-3 sentences) in plain language for patients and family members

In this early analysis, there is some evidence that radiation therapy may contribute to the development of certain subsequent tumors in patients with LFS. Our future work, which will include more patients and detailed treatment data, will help us to confirm our initial results and to provide more nuanced analyses and interpretation.

A review of current evidence on skin cancer and ionizing radiation

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Abstract

Cancer of the skin represents a challenge for radiological protection: it involves the largest organ of the human body which is exposed to many different possible radiation sources. At the same time, it includes common subtypes such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) with very low mortality, and the rare subtype malignant melanoma (MM) with a generally poor prognosis. Current consideration of skin cancer in radiological protection is mainly based on data from the 1990s, which indicate that BCC may be induced by ionizing radiation, SCC is only weakly associated with ionizing radiation, and MM is not considered as radiation-induced. We performed a semi-systematic review of the current evidence on ionizing radiation and skin cancer in order to assess the potential implications for radiological protection.

Advantages of Japanese nuclear workers cohort J-EPISODE

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Objective
The aim of the study is to clarify advantages of the Japanese nuclear workers cohort study, J-EPISODE.

Methods and Materials
J-EPISODE has been conducted between 1991 and 2010 with ~200,000 participants. Results of the last follow-up study suggested the confounding by smoking in the association between radiation and cancer mortality in a subset of ~70,000 lifestyle survey respondents in the entire cohort. Between 2015 and 2019, a re-set-up of a cohort was performed with ~80,000 participants, all of those consented to participation in the cohort and responded to the baseline survey on smoking, alcohol consumption, education, and work. It re-started the follow-up of mortality since 2015. Identification of the underlying cause of death was done by linkage with the death certificate of the vital survey. The follow-up of cancer incidence was made possible using newly established National Cancer Registry from 2016. Most exposure doses since 1957 have been from nuclear power plants, where photon exposure was dominant, and neutron dose and internal exposure were rare. A radiation risk assessment plan based on organ doses was determined.

Results
Reconstruction of annual organ dose from the normal work doses during operation, maintenance and inspections was completed in 2020. Reanalysis results of the prior cohort showed that the ERR/Gy of 1.00 (90%CI: -0.55, 2.82) decreased to 0.25 (-1.16, 1.92) with smoking adjustment for deaths from all cancers excluding leukaemia among 72,000 males during the 1991-2010 follow-up, which was consistent with the previous results using recorded dose; ERR/Sv of 0.80 (90%CI: -0.49, 2.00) to 0.29 (-0.90, 1.40). J-EPISODE included ~4,000 emergency workers who were exposed to external and internal radiation as a result of working at the Fukushima Daiichi Nuclear Power Plant accident occurred in 2011. The conversion from the emergency work dose to organ dose will be completed soon. The risk analysis of mortality 2015-2020 and cancer incidence 2016-2020 will be conducted in 2024.

Discussion
The risk estimates to be conducted within a few years will have many uncertainties due to the small number of person-years and cases, however, further continued follow-up will contribute to the elucidation of dose-response relationships for low-dose and low-dose-rate exposures, and allow comparison with preceding studies. An advantage of J-EPISODE is having individual lifestyle information, including smoking. Less uncertainty in dosimetry is another advantage compared to preceding nuclear workers cohort studies including nuclear weapons manufacturing workers.

This study was funded by the Nuclear Regulation Authority, Japan.

Anatomical predictive extension of partial-body CT scans for assessing organ dose in support of epidemiological studies on late effects following radiotherapy

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Purpose

Patient anatomy is critical for the assessment of radiotherapy organ dose. The typical radiotherapy planning CT, however, only covers the region of the body near the target volume, whereas for late effects research we are often interested in scatter radiation to organs located partially or fully outside the available CT scan. Our previous work has shown that the dose to organs distant from the radiotherapy field edge can be accurately calculated by Monte Carlo radiation transport simulation if the extended anatomy is modeled. Therefore, to support epidemiological research on the late effects of radiotherapy we have developed a method to extend partial-body CT scans.

Methods

A MATLAB function was written which takes as input a user-provided partial-body DICOM CT scan and associated DICOM structure file containing organ contours. The output is an extended DICOM CT and structure file which we refer to as the Anatomically Predictive Extension (APE). Our method uses a library of 359 pediatric chest-abdomen-pelvis or abdomen-pelvis CT scans from which surrogate images are selected. The library is equally distributed in gender with patient ages ranging from 5 daysto 16 years. Each patient CT scan also comes with an associated structure file containing expert contours for up to 29 organs. Image registration is performed by comparing skeletal images obtained by thresholding with allowance for transformations such as scaling, rotation, and translation. The transformed images showing closest similarity are appended to the original CT and a new structure file is written combining contour information from the original patient with that of the surrogate patient. To test the CT extension method, we identified patients having CT images with a large scan range. Subsets of these CT scans were extracted for applying the APE extension method, with the original patient images serving as ground truth for comparison.

Results

We used our method to create three APE examples: (1) head CT for brain radiotherapy extended to chest for calculating dose to heart and lungs; (2) superior chest CT for axilla irradiation extended to inferior chest region for calculating dose to lungs, kidneys, and gonads; (3) pelvic CT for Wilms tumor treatment extended to superior chest for calculating dose to heart and lungs. The resulting extended CT scans showed good agreement with the original patient images. Comparison of the organ doses for the APE patients with the original patient CT images is part of our on-going work.

Conclusion

When fully automated the APE method will be useful for estimating dose for organs peripheral to the treatment fields in support of epidemiological research on late effects following radiotherapy.

Cancer risks after low-dose exposure to ionizing radiation: IARC perspectives

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Abstract
International Agency for Research on Cancer (IARC) is a specialized institution of the World Health Organization focused on prevention, early detection, and causative cancer research. Environmental and Lifestyle Epidemiology Branch (ENV) of IARC is at the forefront of identifying modifiable cancer risk factors and protective factors to support the IARC vision of a world where fewer people develop cancer. Environmental and lifestyle factors are considered by IARC and ENV to comprise potentially carcinogenic substances in any medium – including soil, water, food, and air – that expose humans in their workplace, at home, and in the general environment. These factors include all types of radiation (ionizing, optical, and non-ionizing), as well as lifestyle factors such as habits or behaviours that are due to individual choice and to life circumstances within a socioeconomic and cultural context. The scope of ENV ionizing radiation research includes long-term cancer risks in various groups of population, namely *in utero* exposed, offspring to exposed parents, residents of radioactively contaminated territories, occupationally exposed professionals, patients underwent medical diagnostic irradiation (computer tomography). ENV scientists actively collaborate with international experts in dosimetry, radiobiology, clinical medicine, epidemiology, and risk communication to study the consequences of the Chernobyl radioactive fallout, nuclear weapon tests in the Semipalatinsk nuclear test site in Kazakhstan, radioactive contamination of the Techa River from activities of the "Mayak" plutonium production association in the Southern Urals of Russia. Special attention is given to cancer research in relation to uranium exposure from gold mine tailing in the South Africa residents living in the proximity to the tailings. ENV and IARC act as an observer and play an active role in the meetings and task group activities carried out by the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) and, recently, the International Commission on Radiological Protection (ICRP).

Dose Reconstruction for Epidemiological Studies among Chernobyl Cleanup Workers

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Abstract

After the Chernobyl (Chornobyl) accident occurred on April 26, 1986, more than 300,000 Ukrainian cleanup workers took part between 1986 and 1990 in decontamination and recovery activities at the site of the Chernobyl Nuclear Power Plant. The U.S. National Cancer Institute in collaboration with the Ukrainian National Research Center for Radiation Medicine conducted several epidemiological studies in this population. An important part of these studies was the reconstruction of the radiation doses for cleanup workers along with the assessment of uncertainties in doses.

A method called RADRUE (Realistic Analytical Dose Reconstruction with Uncertainty Estimation) was used to calculate the doses due to external irradiation to cleaning workers during their missions, which was the main exposure pathway for most workers. At the initial phase of the accident during the atmospheric releases of radioactivity from the destroyed reactor, the cleanup workers also received doses due to inhalation of radionuclides. In addition, the cleanup workers received doses at the places of residence, especially those who lived in highly contaminated areas.

The radiation doses estimated for the cleanup workers included in the NCI-coordinated studies varied widely: (i) bone-marrow doses due to external irradiation in the case-control study of leukemia ranged from 3.7×10^{-5} mGy to 3.3 Gy (mean=92 mGy); (ii) thyroid doses in the case-control study of thyroid cancer due to all exposure pathways combined were from 0.15 mGy to 9.0 Gy (mean=199 mGy); (iii) gonadal doses in the study of germline mutations in the offspring ranged from 0.063 mGy to 4.1 Gy (mean=390 mGy) and from 0.013 to 550 mGy (mean=27 mGy) for male and female cleanup workers, respectively; and (iv) lungs doses in the study of germline genetic variants associated with host susceptibility to COVID-19 were from 0.02 mGy to 2.5 Gy (mean=150 mGy).

The uncertainties assessed for the dose estimates included two components: (i) inherent uncertainties that arise from the stochastic variability of the parameters used in exposure assessment and from a lack of knowledge about the true parameter's values and were considered in stochastic dose calculations using the Monte Carlo method; and (ii) human factor uncertainties due to poor memory recall resulting in incomplete, inaccurate, or missing responses during personal interview with cleanup workers conducted long after exposure.

The presentation will provide an overview of methodologies and results of the reconstruction of radiation doses for cleanup workers along with an assessment of the uncertainties and discuss further developments in this area.

Haematological malignancies in the most contaminated regions of Belarus and Ukraine after the Chernobyl accident: Ecological study

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Background
There is a lack of consistency regarding the risk of malignancies, other than thyroid cancer in the residents of territories contaminated from the Chernobyl radioactive fall-out.

Materials & methods
We study a risk of hematological malignancies (HM) in the residents of Gomel and Mogilev regions of Belarus, and Kyiv, Zhytomir and Chernihiv regions of Ukraine, most radioactively contaminated after the Chernobyl nuclear power plant accident, using an ecological study design. The HM incidence follow-up period was from 1978 through 2018. The data on HMs by disease type (ICD-10 disease codes: C81-C96) were received from the national population-based cancer registers. The disease-specific HM cases and population size data were tabulated over administrative raion, urban status, gender and attained age categories. Raion-average age-specific annual absorbed doses to the red bone marrow (RBM) were estimated for the period of 1986-2018 from external irradiation and ingestion of long-lived radioisotopes of caesium (Cs-134, Cs-137) and strontium (Sr-90) with the locally produced foodstuff. We applied a 2-year lag period in the cumulative raion-average age-specific absorbed RBM doses, as a minimal period for induction of radiogenic leukemia. We excluded people who were born after 1986 to avoid confusion with potential effect of intrauterine exposure. We use Poisson and logistic regression models to assess "dose-effect" relationship between various HM groups and estimated raion-average absorbed RBM dose.

Results
We report first the results for Belarus. A total of 16,982 HM cases were registered in the period of 1986 – 2018, namely 8,758 leukemia (ICD-10 codes: C91-C95), 6,405 lymphoma (ICD-10 codes: C81-C85) and 1,753 multiple myeloma (MM) (ICD-10 code: C90). Among leukemia, the most frequent cell-types were lymphoid (64%) and myeloid (32%) leukemia. Hodgkin's lymphoma (ICD-10 code: C81) represented 32% of the total lymphoma cases. Maximum raion-average RBM doses accumulated by 31 December 2018 were 60 mGy and 37 mGy in Gomel and Mogilev region residents, respectively. Positive although non-significant association between non-Hodgkin lymphoma, MM and all leukaemia incidence rates and 2-year lagged rayon-average cumulative RBM dose used as continuous variable, was found in the residents of Mogilev region. Analysis of association between the HM incidence and raion-average 2-year lagged cumulative RBM dose in the residents of the most contaminated regions of Ukraine is ongoing.

Conclusion

The results are important for health monitoring of the affected populations, and for improvement of radiation protection measures of people at risk in case of potential future nuclear accident.

Increased Cardiac Risk After a Second Malignant Neoplasm Among Childhood Cancer Survivors, a FCCSS Study

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Background
Advances in cancer treatment have significantly improved childhood cancer survival, with five-year survival exceeding 80% in most European and North American countries today. The adult population of childhood cancer survivors (CCS) exceeds 300,000 people in Europe, and is growing. Many late-effects have been observed at a higher rate than the general population. Cardiac disease (CD) and second malignant neoplasms (SMN) are among the most serious and life-threatening late adverse effects experienced by CCS. Previous work has identified important risk factors of CD, but the impact of other late-effects as SMN have been ignored. We have studied the effect of a SMN on both the cumulative incidence and the instantaneous risk of CD accounting for the competing risk of death.

Methods
Analysis included 7670 CCS diagnosed between 1945 and 2000. To account for the time-dependance of the occurrence of SMN, we employed the landmark approach considering an additive regression model for the cumulative incidence of CD. Next, the effect of SMN on the instantaneous risk of CD was estimated using a proportional cause specific hazard model considering SMN as a time-dependent exposure while adjusting for treatment information (age at diagnosis, radiotherapy doses, anthracyclines, ...). In both models, we included death as a competing event.

Results
Overall, after a median follow-up of 30 years, 369 CDs including 49 experimenting a SMN were identified. An increased cumulative incidence of CD was estimated for patients experimenting a SMN before they reached 35 years old. This increase was of 3.0% [95%CI: 0.1-5.8%] at 30 years old, with a cumulative incidence of 6%. No increase in the cumulative incidence of CD was observed for later landmark times. SMN has been estimated to multiply the cause-specific-hazard by a 2.0 fold [95% CI: 1.5-2.8].

Conclusion
Our results provide new insight into the CD risk after a SMN that may impact long-term follow-up of CCS.

LySAIRI research program: towards lymphocyte-sparing radiotherapy

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Abstract
In the short - to mid-term after treatment, external beam radiotherapy (EBRT) can be associated to haematological toxicities, including lymphopenia (i.e. decreased lymphocyte counts in the peripheral blood). This detrimental effect is in competition with the immune-stimulatory effects of radiotherapy, which has been described in the early 2000s as a synergy between radiation and checkpoint blockers, and can thus have an impact on treatment outcomes. In adult patients, lymphopenia has been found to be associated with EBRT for a very wide range of cancer types, including glioblastoma, lung, oesophageal or head and neck cancers, treated or not with prior or concomitant chemotherapy. The mechanisms by which EBRT can induce lymphopenia are not currently known, but several hypotheses have been proposed. Post-EBRT lymphopenia could be due to irradiation of in field and out-of-field lymphoid organs, circulating lymphocytes in the peripheral blood and/or intra-tumoral lymphocytes. A strong correlation between the grade of lymphopenia and response to treatment, including progression free survival (PFS) and overall survival (OS), has been demonstrated in adult patients. To study the risks of radiation-induced lymphopenia and to understand the cause of this radiation-induced toxicity in both adult and paediatric patients, a large research program has been funded at Gustave Roussy (RHU LySAIRI). The dosimetry part is based on the development of 2 main tools: a Monte-Carlo-based bi-compartmental tool that aims to evaluate the dose received by the circulating blood and an algorithm allowing to extend the dose maps in the field provided by the TPS to the whole body dose maps using deep-learning. First results for brain irradiation indicate that conventional IMRT irradiated about 30% of the lymphocytes (dose > 0 Gy) at a mean dose of the order of 50 mGy. Computation of whole-body dose maps by a convolutional neural network has been favourably implemented, showing the ability of such tool to generalize to unseen accelerators in an external test set of paediatric patients. Experimental measurements are in progress to evaluate performances on modulated irradiation technics. This presentation will provide an overview of current knowledge of radiation-induced lymphopenia, including dosimetric constraints already established in the literature. The current research program and the tools developed and their utility for epidemiological research will also be presented. The application of these tools on large retrospective cohorts will provide information on the clinical impact of lymphocyte sparing dosimetric strategies.

Preliminary Results from a Mortality Study of Rocky Flats Nuclear Workers: a Million Person Study cohort

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Background
The Million Person Study (MPS) is a retrospective mortality study of one million US workers and veterans with chronic low-dose radiation exposure. The MPS is comprised of numerous individual cohorts updated utilizing standardized, advanced methods for tracing, dosimetry, and analyses to achieve harmonization for pooling. This paper highlights the results from the most recently updated cohort, the Rocky Flats (RF) plant, a US Department of Energy (DOE) plutonium processing facility that operated near Denver, Colorado from 1951 until 1989. The site's primary mission was to create nuclear and non-nuclear weapons components through processes that resulted in exposures to many substances including plutonium, uranium, and beryllium. Prior studies by Gilbert et al. (1993) were utilized to identify the cohort for inclusion in the MPS.

Methods
A total of 9,397 workers who were first employed before 1980 and who worked at least 30 days were followed for mortality outcomes through 2017. Organ doses were calculated from internal and external radiation monitoring sources and included exposures from photons, neutrons, Pu-238, Pu-239, Pu-241, Am-241, Am-241 progeny, and uranium. As beryllium is considered an important co-exposure for the RF cohort, data from the DOE Beryllium Surveillance Program was obtained for evaluation. Vital status was ascertained through multiple sources including the National Death Index, Social Security Administration, and state death files. Statistical analyses include standardized mortality ratios and Cox proportional hazard models.

Results
The majority of RF workers were white (95.7%), male (83.5%), and with high school education or less (60.0%). Approximately 89.9% (n=8445) had radiation monitoring with mean doses (radiation dose weighting factor = 1) of58.2 mGy (SD: 109.4) for lung, 54.4 (SD: 102.6) mGy for bone, 51.3 mGy (SD: 96.3) for liver, 51.6 mGy (SD: 97.9) for colon, 46.7 mGy (SD: 88.1) for brain, and 50.8 mGy for heart (SD: 96.2). A total of 5,049 (53.2%) workers were deceased. Most common causes of death included ischemic heart disease (n=999), non-malignant respiratory disease (n=436), lung cancer (n=361) and cerebrovascular disease (n=237). Preliminary dose-response analyses indicate little evidence for increased risk from fractionated, low doses. Nearly 40% of workers were monitored for beryllium, with indication of beryllium sensitization or disease for 6% (n=563). A non-significant indication of confounding by beryllium exposure was observed for lung cancer risk.

Conclusion
Additional analyses are needed to assess the risk of mortality from radiation exposure in the RF cohort, with particular attention to potential confounding by beryllium exposure.

Radiation exposure and mortality in a cohort of Korean radiation workers

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Abstract

The effects of exposure to ionizing radiation have been found in a number of published studies, primarily of populations exposed to moderate-to-high rate ionizing radiation. The Korean Radiation Workers Study (KRWS) was established to construct a cohort of Korean radiation workers and assess health effects of chronic low-dose radiation exposure. This study aims to determine whether prolonged exposure to low doses of ionizing radiation is associated with cancer and non-cancer mortality. The KRWS cohort comprised 196,379 radiation workers registered in the National Dose Registry (NDR) and their radiation doses was linked to the National Vital Statistics Registry (1992-2020). We compared mortality in the Korean general population with that in this cohort and undertook a dose-response analysis. Most workers were men (84.0%) and nuclear power plant workers (32.5%), and 64.1% of workers were born before 1980. The mean cumulative radiation dose (standard deviation) was 4.48 mSv (17.09) for all workers and was higher in men (5.28 mSv) than women (0.55 mSv). In total, 4709 workers (2.4%) deceased during the follow-up period. The causes of death were cancers (33.1%), external causes (29.6%), circulatory diseases (14.8%), and digestive diseases (5.4%). The standardized mortality ratio (SMR) from all causes of death was 0.60 (95% CI 0.58 to 0.61). No statistically significant risk associated with ionizing radiation was observed in the dose-response analysis. The excess relative risks (ERR/Sv) for infectious disease (ERR/Sv=3.61, 95% CI -10.6 to 17.81), all cancers (ERR/Sv=0.90, 95% CI -1.99 to 3.78), circulatory disease (ERR/Sv=0.17, 95% CI -3.96 to 4.30), respiratory disease (ERR/Sv=7.17, 95% CI -5.75 to 20.09), and digestive diseases (ERR/Sv=4.15, 95% CI -3.736 to 12.02) tended to increase but were not statistically significant. Further studies are needed to investigate the dose-response analysis using organ doses including more varied confounders such as smoking habits, alcohol consumption, and social economic status.

Synthesis of recent results from the literature on heritable effects of radiation exposure among humans

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Introduction

Exposure of a population to ionising radiation can induce adverse health effect in offspring and next generations as a consequence of mutations induced in the germ cells. The first evidence of a genetic effect was demonstrated in 1927 by Muller in experiments with *Drosophila melanogaster*. Next, the radiation-induced heritable consequences were studied in the mice by Russell and Russell where the dose-rate effect was discovered. The Japanese A-bomb survivors constitute one of the largest irradiated human populations studied carefully for heritable effects. However, no significant increase in genetic diseases was found in children whose parents had received significant amount of radiation.

The fundamental mechanisms underlying potentially radiation-induced genetic diseases remain poorly understood, as well as the contribution of epigenetic processes in the occurrence of adverse outcomes, if any. Also, there is compelling evidence that radiation causes heritable effects in experimental animals. Consequently, detecting radiation effects in human germ cells remains a difficult task.
Therefore, this paper aims to conduct a review of the epidemiological literature related to radiation-induced effects in the offspring of human individuals exposed to ionizing radiation and contribute to the revision of the consideration of these effects in the radiological protection system.

Methods

The systematic review began in early 2022. The main inclusion criteria are: (i) articles published from 2018 to 2022; (ii) epidemiological studies carried out on parents exposed to ionizing radiation and offspring of exposed parents; (iii) all types of ionising radiation; (iv) cohort, case control, longitudinal, retrospective, prospective or cross-sectional epidemiological studies of people exposed to ionizing radiation.
The primary outcome is the determination of genetic effects in offspring from preconceptional exposure to ionizing radiation in human population. Genetic effects includes but are not limited to prematurity, chromosome aberration, neonatal death, perinatal mortality, major birth defect, cancers, multifactorial disease, modification of the sex ratio, mortality of any cause, lifespan.

Results

Descriptive analyses of all studies are performed, considering different exposure situations, e.g. Chernobyl and Fukushima nuclear accidents, diagnostics, occupational exposure… in offspring of exposed parents compared with unexposed subjects or age-gender-matched general population.

Conclusion

Nevertheless, the potential of ionizing radiation to induce adverse health outcomes in offspring and next generations is a recurring issue for the general public and a major concern for parents exposed to radiation due to occupational, medical or environmental reasons. The characterization and quantification of these effects is a major issue for the radiological protection system.

Assessment of medical radiation exposure within the German National Cohort (NAKO) - results, current work and outlook

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Funded by the Federal Office for Radiation Protection (BfS)

Background
Few large general-purpose population-based cohort studies collect data on diagnostic medical ionizing radiation exposure among study participants. However, besides being a health risk factor on its own, ionizing radiation may also be a confounder for other exposure-disease relationships. In Germany, a large prospective cohort, the German National Cohort (NAKO, "NAKO Gesundheitsstudie"), offers an opportunity to assess diagnostic medical exposure.

Methods
Retrospective and prospective assessment of medical radiation exposure was performed within the NAKO. Examinations with comparably high dose potential were focused on, dental X-rays were excluded. Retrospective assessment including questions on the respective medical indications was done by a self-administrated touchscreen questionnaire within the NAKO baseline survey in participants aged 18+ years. Two follow-up waves were performed through a postal questionnaire. Four of 18 study sites of the NAKO were involved.

Results
3,923 persons participated between October 2017 and August 2018 (response 82%). Having received at least one examination in their lifetime was reported by 69% of the participants (2,717). CT (41%), conventional X-ray (25%) and nuclear medicine diagnostics (14%) made up 80% of all reported examinations. Baseline and follow-up did not show sex differences but age-specific differences in indications. The age group 40-50 years and >50 years stated more often prolapsed disc, spine-pain and cardiovascular diseases as indications. In Follow-up, conventional X-rays were reported the most.

Conclusion, current work and outlook
This assessment of medical radiation exposure within a large population-based cohort study is unique. CT examinations account for a major proportion of all radiological examinations. Age-specific health burdens are reflected in the medical indications. An expansion of the cohort to 7,500 participants is ongoing since August 2021. Follow-up is ongoing since March 2022. Furthermore, three tasks are planned with health insurance claims data from the participants: current data validation, development of a "best-off" data set with complimentary data from the questionnaire and claims data, and feasibility testing of a claims data-based follow-up for the total NAKO cohort of more than 200,000 participants. Administrative preparations are completed, with data delivery expected in 2023. Through integration of the assessment within the NAKO, it is possible to quantify medical radiation exposure in the general population. By expansion of the cohort quantification of radiation-associated risks and consideration as a confounder for other risk relationships will be possible in the long term.

Brain CancEr risk in joint cOhort of MEdical workers exposed to ionizing radiation in France (BECOME)

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Context
Among medical professionals, there is some evidence that protracted exposure to ionizing radiation (IR) is associated with risk of certain cancers. Some publications have reported an excess of brain tumor in interventional cardiologists. However, few epidemiological studies have been performed to examine brain cancer risk with organ dose assessment in cohort of medical radiation workers.

Objectives
The objective of the BECOME (Brain CancEr risk in joint cOhort of MEdical workers exposed to Ionizing radiation in France, USA and Korea) project is to conduct an international nested case-control study to quantify the radiation-induced risk of death from central nervous system (CNS) cancer, using estimated cumulative IR occupational doses in 3 cohorts of medical professionals exposed to IR in France, USA and Korea.

Methods
The study is based on 3 national cohorts, aiming at analyzing the risk of radiation-induced diseases in medical professionals: the French O'RICAMs (Occupational Radiation-Induced Cancer in Medical Staff) cohort, which follows 227,000 individuals since 2002, the USRT (U.S. radiological technologists) cohort, which includes about 110 000 medical workers exposed from 1920 to through the 2020s, and the Korean cohort, which includes 94,394 individuals followed since 1996. At the end of follow-up, 193, 67 and 25 deaths by CNS tumors were reported in the US, French and Korean cohorts, respectively. For each case, five controls will be randomly selected in the country-specific cohort and matched according to year of birth and sex.Organ doses for individuals of the USRT cohort have already been calculated and published. Organ doses for French and Korean cohorts will be estimated based on passive dosimetry, accounting for uncertainties. Conditional logistic regression models will be used to estimate the dose response relationship, taking into account potential confounding factors.

Expected results and conclusion
The inclusion of 285 cases and 1425 matched controls will allow detecting at least an odds ratio of 1.66 for a statistical power of 80% (alpha significance level 5%). The study will quantify the relationship between occupational exposure to low doses of IR and CNS tumor mortality risk in medical workers. Our joint approach could be extended to assess the dose-response for other type of cancers and non-cancer outcomes, and
it will increase the knowledge on health effects of protracted low-dose exposures to IR.

Identification of rare variants involved in the risk of second cancer following radiotherapy and chemotherapy treatment of pediatric cancer

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Background
Survivors of childhood cancer are at risk for therapy-related subsequent malignant neoplasms (SMN). Exposure to radiation therapy and certain chemotherapy molecules are known risk factors for SMN development. However, there remains inter-individual variability in these treatment related SMN that is attributed to genetic variations.

Objective
The aim of our study is to identify genetic rare variants associated with risk of second cancer and their interactions with treatment of the primary cancer in childhood.

Methods
We conducted nested case-control study of SMNs within the French Childhood Cancer Survivors Study (FCCSS) cohort with 163 cases and 287 controls. Whole exome sequencing was realized on these 450 survivors. The mean radiation dose at SMN sites, spleen and active bone marrow were estimated. Rare variants associated with SMN outcomes were identified using SKAT, burden, and skat-o adjusting for sex, year and age at first cancer diagnosis, type of first cancer, length of follow-up and associated first four principal components to account for potential population. Genes significantly associated with SMNS outcomes will be analyzed in gene-radiation doses interactions models.

Results
The mean age at diagnosis of the first cancer was 7 years for cases and controls. The length of follow-up is similar for cases and controls with a median of 24 years. A total of 151 cases (92,7 %) and 194 controls (67,5%) had received radiation therapy. Association analysis tests identified 19 genes enriched in rare variants in cases with promising associations with the risk of second cancer. Further analysis of these genes is underway, as well as analysis focusing on the most common second cancers type (thyroid: 41% and breast: 29%). Interaction studies with these spleen, active bone marrow and radiation dose received at the site of the second cancer will be performed. The results of this gene-radiation interaction will be available for the conference.

Discussion
This study will provide new evidence regarding the involvement of genetics in the development of second cancers in interaction with the first cancer treatment received. This could allow the identification of survivors at higher risk for SMN development in order to adapt treatment and/or follow-up.

Cancer effects of low to moderate doses of ionising radiation in young people with cancer predisposing conditions: A systematic review

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Abstract

Moderate to high doses of IR have been consistently shown to increase the risk of cancer. An ongoing concern, however, is characterizing and quantifying the effects of low doses (less than 100 mGy) and determining the role of cancer predisposing factors (CPFs) (genetic disorders, immunodeficiency, mutations/variants in DNA damage detection or repair genes) on radiation-induced cancer (RIC) risk.

We conducted a systematic review of evidence that CPFs modify RIC risk in young people. Factors considered included: cancer predisposing conditions, immunodeficiencies, mutation in DNA damage detection or repair genes and family history of breast cancer. Searches were performed in PubMed, Scopus, Web of Science, and EMBASE for epidemiological studies of cancer risk in humans (<25 years) with a CPF, exposed to low-moderate IR. Fifteen articles focusing on leukaemia, lymphoma, breast, brain, and thyroid cancer were included. Risk of bias was assessed in each study. We found *inadequate* evidence that CPFs modify the risk of radiation-induced leukaemia, lymphoma, brain/CNS, and thyroid cancers and *limited* evidence that *BRCA* mutations modify radiation-induced breast cancer risk. In general, the studies identified in this systematic review were too limited – mainly because of low statistical power – to adequately address the question of whether CPFs modify the risk of RIC. Further studies with more appropriate study designs and sufficient power are needed to better identify cancer predisposing conditions / variants that may increase the risk of RIC.

Given the rarity of CPFs in the general population, informative studies should be based either on 1) cohorts of persons who are carriers of mutations of interest – e.g. *BRCA1/2, AT* heterozygotes- in which detailed information regarding radiation exposure can be obtained and doses estimated either at the level of the cohort or in a nested case-control study; or 2) general population/patient studies with adequate individual dosimetry, focusing on common variants using PRS. If such children can be identified, personalised screening, surveillance, management and treatment can be offered to reduce their risk of RIC.

Changing Patterns of Irradiation In Conditioning Regimens for Allogeneic Hematopoietic Cell Transplantation (HCT) for Hematologic Malignancies and Implications for Subsequent Neoplasm (SN) Risk: Preliminary Analyses Within A Novel Linked Dataset of Center For International Blood And Marrow Transplant Research (CIBMTR) and California Cancer Registry (CCR) Data

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Abstract

Hematopoietic cell transplantation (HCT) is a curative treatment for a number of hematologic malignancies. However, subsequent neoplasms (SN) represent a leading cause of non-relapse mortality among HCT survivors. Historically, increased risk of SNs have been observed among patients receiving myeloablative conditioning regimens, often including high-dose total body irradiation (TBI). The introduction of reduced-intensity conditioning regimens in recent years has changed the landscape of potential SN risk factors and expanded the eligible patient population, but changes in SN risks over time are poorly understood. In preliminary analyses presented below, we aimed to describe the calendar-year patterns of conditioning regimens, with a focus on radiation dose and field.

Analyses were conducted within a novel dataset including patients reported to the Center for International Blood and Marrow Transplant Research (CIBMTR) who resided in California and were linked to the California Cancer Registry (CCR) to increase ascertainment of SNs in subsequent risk analyses. CIBMTR collects extensive patient, procedure, and outcome data from HCT centers in the United States, and the population-based CCR captures all incident cancers in the state. The study population included 8,232 patients of all ages who received allogeneic HCT for a hematologic malignancy diagnosed between 1991 and 2016. Information about conditioning regimens, including chemotherapy type, intention for myeloablation, and prescribed radiation dose and field, was available from pre-HCT forms reported to the CIBMTR.

In preliminary analyses, the conditioning regimen (+/- irradiation) was non-myeloablative for 2266 (27.5%) patients, increasing from 1.2% for $HCT_{1991\text{-}1999}$ to 37.5% for $HCT_{2010\text{-}2016}$. Conditioning regimen included planned irradiation for 4087 (49.6%) patients. Among irradiated patients, the proportion receiving total body irradiation (TBI) decreased from 99.9% ($HCT_{1991\text{-}1999}$) to 85.3% ($HCT_{2010\text{-}2016}$), while receipt of more limited fields, including total lymphoid- or nodal- irradiation, increased from 0.14% ($HCT_{1991\text{-}1999}$) to 14.7% ($HCT_{2010\text{-}2016}$). Radiation dose was largely unavailable prior to 2008. During 2008-2016, the median total prescribed dose was 1200 cGy (range 165–3655), higher in patients receiving myeloablative (median 1320 cGy; 98% received TBI) versus non-myeloablative conditioning regimens (median 800 cGY; 48% received TBI).

In this novel linked dataset, we observed a decrease in the use of myeloablative conditioning regimens and a shift from TBI to more limited field irradiation. Our future analyses will evaluate the impact of these treatment changes on SN risk to improve understanding of SN risk factors among the growing population of HCT recipients.

DICOMInspector: Collection and analysis of exposure data from clinical procedures

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Abstract
Radiology related epidemiological investigations of cancer risk following medical exposure often starts with the collection of data from Hospital Information Systems (HIS) like Radiology Information Systems (RIS) and Picture Archiving and Communication Systems (PACS). While RIS data is easy to access, the access to PACS data is more challenging. On the other hand, the use of Digital Imaging and Communications in Medicine (DICOM) metadata brings massive benefits, as it contains more complete and comprehensive dosimetry information, especially after the introduction of Radiation Dose Structured Reports (RDSR).

DICOMInspector is a software system that allows an automatic collection of DICOM metadata including image data from PACS. The easy-to-install package includes all needed components: A DICOM server/node that communicates with the PACS, a database for the collected data in the server package and an R-based interactive Graphical User Interface (GUI) to facilitate data exploration and analysis.

The software works in 4 straight-forward steps. First, the user defines the research question, including patient characteristics and other parameters like radiological modality type and period of the study. All parameters can easily be configured in the GUI. Second, the PACS is queried for the available patient data and next, the metadata is collected. In the fourth step, the user can extract the desired data. This is done using reports in the form of R markdown. More than 10 different report types are available today that address different modalities, research questions and study designs. Is it easy to create new or adapt existing reports thanks to the powerful R syntax.
The software operates locally: no data is exposed to the Internet or transferred. There are options to analyze patient data for applications where this is needed, but most of the available reports work with anonymous data.
The DICOMInspector platform facilitates the secure collection and analysis of DICOM metadata for multipurpose clinical (cohort) studies without the need to introduce complex and expensive Dose Management Systems (DMS) into clinical routine. All reports are open source and can be shared conveniently between installations. For other study designs, the software can be used as well, as it can work with a patient list or even without a connection to a PACS system.

The system has applications in epidemiological studies, quality assurance and optimization of radiological procedures. DICOMInspector is successfully used for data collection within the HARMONIC project to extract data for organ dose reconstruction following cardiac catheterization.

Dosiomics-based prediction algorithms of radiation-induced valvulopathy after treatment for childhood cancer

Stefania Chounta

Background and purpose
Valvular Heart Disease (VHD) is a known late complication of radiotherapy for childhood cancer (CC). An important medical challenge is correctly identifying high-risk survivors and providing them with early diagnosis and treatment. While data-driven clinical predictions are an ancient practice in medicine, machine learning algorithms with the right choice of variables could improve accuracy and become a useful asset in late-effects prediction.

Materials and methods
From the 7488 5-year survivors of the French Childhood Cancer Survivors' Study (FCCSS) with complete data, 3902 had been treated with radiotherapy. From their voxelized dosimetric data, we used the dosiomics method to extract 98 first order and spatial features. We then trained weighted (wtRF) and Balanced Random Forests (BRF) after rigorous variable selection. Models were also adjusted on clinical variables (year and age of CC diagnosis, biological sex, and chemotherapy (y/n)). We compared them in terms of their predictive power. Models were compared to the baseline model, where the radiation-induced risk is obtained by the mean heart dose (MHD). Sensitivity analyses were conducted for the sub-population of survivors with heterogeneous heart doses.

Results
Eighty-one of the survivors (1%) had experienced a severe VHD. Models based on the dosiomics features outperform MHD-based models both when trained in the entire cohort or in the subpopulation exposed to heart radiation. In the subpopulation exposed to heart radiation clinical variables improve the MHD-based model impressively. A smaller improvement is observed in the dosiomics-based BRF and no improvement in the wtRF. The adjusted MHD-based BRF, trained on the sub-population that was exposed to heart-radiation seems to outperform all of the other models. The adjusted dosiomics-based BRF performs almost as well.

Conclusions
When clinical variables are available, the MHD seems like a sufficient predictor. Alternatively, a selection of dosiomics features can perform an almost equally well prediction.

Organ Doses Associated with Diagnostic Computed Tomography (CT): Results from the UCSF International CT Dose Registry

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Background
Individual organ doses associated with routine CT are not well known.

Objective
To describe representative organ doses for common CT examination types in children and adults, using data prospectively collected from the UCSF International CT Dose Registry on CT exams assembled from 156 hospitals and imaging facilities in 7 countries.

Methods
Technical parameters including CT scanner manufacturer, x-ray tube current (mAs), tube potential (kV), scan length, and whether the scan was performed using tube current modulation for each examination were extracted using Radimetrics. All scans were mapped to the closest body morphometry-matched phantom in the University of Florida/National Cancer Institute library of hybrid computational human phantoms based on patient sex, age, or size. Technical parameters from each scan were used to calculate organ doses using Monte Carlo simulations. Organ doses in adults were stratified by patient diameter (small <25th percentile, average 25-75%, large >75%) and in children by age. Mean organ dose (in milliGray, mGy), standard deviation (SD), and range in means (R) across size or age strata were calculated.

Results
The study includes 130,170 CT examinations in children ages 0-21 years and 814,375 in adults older than 21 assembled between 2015-2020. For the most common exam type in adults, abdomen and pelvis (41% of all scans), the colon dose was 20 mGy (SD=11 mGy, R=17-23 mGy). For adult chest CT, the lung dose was 18 mGy (SD=15, R=17-20), thyroid dose was 28 mGy (SD=23, R=26-33), and breast dose was 18 mGy (SD=15, R=16-21). For adult head CT, the brain dose was 39 mGy (SD=16, R=33-41), and lens dose was 49 mGy (SD=21, R=41-54). For adult neck CT, the mean thyroid dose was 51 mGy (SD=37, R=46-53). The most common CT scan type in children was head (58% of all scans). The brain dose was 37 mGy (SD=19, R=32-42), bone marrow dose was 9 mGy (SD=7, R=8-18), and lens dose was 38 mGy (SD=22, R=35-44). For pediatric abdomen and pelvis, the colon dose was 13 (SD=66, R=12-14). For pediatric chest, the lung dose was 12 (SD=8, R=10-14), thyroid dose was 16 mGy (SD=11, R=13-21), and breast dose was 10 mGy (SD=7, R=9-12.) For pediatric neck CT, the thyroid dose was 29 mGy (SD=18, R=20-33).

Conclusion
These organ doses reflect current CT exposures and can be used to counsel patients and provide typical values for epidemiological studies. For patients who undergo multiple scans, the organ doses should be summed accordingly.

Meta-GWAS identifies the heritability of acute radiation-induced toxicities in head and neck cancer

On the behalf of the Radiogenomics Consortium
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Abstract

Background and purpose: We investigated the genetic composition of acute radiation-induced toxicities (RITs) in patients with head and neck cancer (HNC). We estimated RIT's specific heritability, polygenic risk scores (PRSs) and sought to identify RIT's specific risk variants.

Materials and methods: We performed the largest meta-GWAS of seven European cohorts consisting of 4,042 patients who were scored weekly during radiotherapy for acute RITs including dysphagia, mucositis, and xerostomia. We analyzed the effect of variants on the average burden (measured as the area under the curve, AUC) per RIT, and standardized total average acute toxicity ($STAT_{acute}$) score using a multivariate linear regression. We tested suggestive variants with a $p<1.0x10^{-5}$ identified in discovery set (three cohorts; n=2,640) in an independent replication set (four cohorts; n=1,402). We meta-analysed the entire cohorts together to calculate RITs specific SNP-based heritability, and PRSs, and genetic correlations among RITS.

Results: The SNP-based heritability (±standard error) was 29±0.08% for dysphagia, 9±0.12% (mucositis) and 27±0.09% ($STAT_{acute}$). Positive genetic correlation was rg=0.65 (p=0.048) between dysphagia and $STAT_{acute}$. PRS_s explained limited variation of dysphagia (3%), mucositis (2.5%), and $STAT_{acute}$ (0.4%). From 393 suggestive SNPs identified in the discovery set; 37 were nominally significant ($p_{replication}<0.05$) in the replication set, but none reached genome-wide significance ($p_{combined}<5\times10^{-8}$). *In-silico* functional analyses identified "3'-5'-exoribonuclease activity" (FDR=$1.6e^{-10}$) for dysphagia, "inositol phosphate-mediated signalling" for mucositis (FDR=$2.20e^{-09}$), and "drug catabolic process" for $STAT_{acute}$ (FDR=$3.57e^{-12}$) as the most enriched pathways by the RIT specific suggestive genes.

Conclusion: In HNC patients, acute RITs are modestly up to, 30% heritable, sharing 10% genetic susceptibility, when PRS explains <3% of their variance. We identified numerous suggestive SNPs, which remain to be replicated in larger studies.

Keywords: Head and neck cancer, radiation-induced acute toxicity, meta-GWAS, SNP-based heritability, polygenic risk score.

The impact of baseline cancer rates on lifetime risk estimates of space radiation-induced cancer

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Abstract

Astronauts face many hazards during spaceflight, including exposure to the space radiation environment. The NASA Space Cancer Risk (NSCR) model was developed to estimate astronauts' risk of exposure induced cancer (REIC) and risk of exposure induced death (REID) due to space radiation exposure. Currently, the model incorporates background cancer and mortality rates from the U.S. population, and epidemiologic evidence from Japanese atomic bomb survivors is translated to the U.S. population. Astronauts are considered healthier than the general U.S. population because of the competitive selection process and training required to become an astronaut. Hence, rates within the NSCR model are also adjusted to reflect a never-smoking population that may better forecast rate of cancer in the healthier astronaut population. In the recent International Commission on Radiological Protection (ICRP) publication 152, the ICRP identified the need to determine if updating baseline cancer rates would affect the REIC estimates within their radiation detriment calculations. Results from a sensitivity analysis using a variety of different baseline cancer rates to calculate REIC and REID for an example male and female astronaut using the NSCR model will be presented. Variations will include trends over time and rate adjustments to represent a healthier never-smoking population.

A case-control study to identify potential genetic biomarkers related to cardiac diseases occurrence in childhood cancer survivors

Naïla Aba

Background
Cardiac Disease (CD) is the most common non-cancerous long-term adverse effect in childhood cancer survivors. Exposition to anthracyclines and chest radiations is significantly associated with CD. These treatments alone cannot, however, explain the individual variability in the prevalence and severity of CD.

Objective
The current study aims to identify genetic biomarkers associated with CD occurrence after childhood cancer treatment, and to build a genomic signature linked to this cardiotoxicity.

Materials and Methods
We conducted a case-control study nested in the French Childhood Cancer Survivors Study (FCCSS) cohort. A total of 165 validated cardiac cases and their individually matched controls on gender, age at first primary cancer diagnosis (± 3 years), type of first primary cancer diagnosis, and follow-up duration. The expression of 33.000 genes was obtained through a transcriptome microarray. Clinical and detailed therapeutic information was retrieved in hospital records. For all patients who had received radiotherapy, the radiation dose to the heart and its structures were estimated. Dose-volume metrics (ex: V20 volumes receiving at least 20Gy) were calculated. The Lasso approach extended to the conditional logistic regression was used for gene selection. We also used the BoLasso, SubLasso and Percentile Lasso to obtain a robust selection of genes. The intersection of these three approaches formed our genomic marker selection. The interactions with cancer treatments received and selected genes have also been investigated.

Results
For both cases and controls, median age at first cancer diagnosis was 6 years (IQR 2 – 11), and the median follow-up was 20 years (IQR 13 – 29) in case, and their median age when developing CD was 28.6 years (IQR 36.56 – 20.15). The mean radiation dose received to the heart is 9.46 Gy in cases and 5.74 Gy in controls. We identified 5 promising genes differentially expressed between cases and controls. Gene expression-heart radiation doses interactions will be conducted and their results will be available for the conference. The addition of these genes in a prediction model with clinical risks factors discriminated better between case and controls than clinical factors alone (AUC = 0.41 vs. 0.90, $P < 2.2e\text{-}16$). We will complete this approach with other methods such as random forest or gradient boosting.

Conclusion
In summary, we identified five genes that may be involved in the risk classification of CD. Coupled with clinical risk factors, knowledge of the expression levels of these genes can help to identify survivors most at risk of developing CD.

A descriptive analysis to aid discovery of relationships between radiotherapy for childhood cancer and neurocognitive outcomes

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Purpose
Advanced radiotherapy techniques can be used to limit toxicity by reducing exposures of normal tissues below threshold levels, but relevant thresholds are not always precisely known. Image-based data mining (IBDM) is a voxel-based analysis method to investigate spatial correlations between radiotherapy dose and toxicity. However, correlation does not indicate causation and so further causal understanding of dose response is required to translate IBDM discoveries into clinical practice. In this study, we performed a descriptive analysis to aid IBDM dose-response assessment in medulloblastoma survivors by testing the contribution of common clinical and treatment factors to neurocognitive decline.

Methods
We considered data from 101 children aged < 21 years treated for medulloblastoma and who are under investigation in an IBDM analysis. Children received neurocognitive assessments for working memory capacity (WM), processing speed (PS) and perceptual speed (PeS) at baseline and annually for up to five years post treatment. A multidisciplinary team created a preliminary causal diagram for causal inference analysis (directed acyclic graph: DAG) considering clinical and treatment covariates of dose response. We tested univariable associations using Kruskal-Wallis tests between continuous and categorical variables, and Pearson's chi-squared tests between categorical variables. We also considered the competing risk of an intervention for hydrocephalus.

Results
Age at treatment, tumour volume, risk classification, hydrocephalus and hydrocephalus management were chosen as important clinical and treatment variables by an expert panel. PeS, PS and WM were significantly associated with each other ($p<0.05$). There were no associations between clinical variables and WM decline. Younger age at treatment and a high-risk classification (residual primary tumor > 1.5 cm and/or neuraxis metastases) were associated with declining PS and PeS. Unexpectedly, tumour volume and hydrocephalus status were not associated with neurocognitive decline. The use of a shunt in the management of hydrocephalus was associated with declines in PeS and PS, but not WM.

Conclusion
We identified important covariates to associate dose and neurocognitive decline. Expert team recommendations were generally supported by the data. The unexpected absence of associations between neurocognitive decline and tumour volume or hydrocephalus status could suggest the presence of other correlations unmeasured here, such as dose. Decline in WM was less influenced by baseline clinical and treatment variables than were PeS and PS declines, despite association between scores. The DAG developed here, combined with the parallel IBDM analysis of dose, will inform guidelines to avoid toxicity and improve cognitive outcomes for survivors of childhood medulloblastoma.

Breast doses received by young women treated for lymphoma between 2005 and 2021: a single institution study

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Background
Young women receiving radiotherapy to the chest have a greater risk of breast cancer (BC) later in life and enhanced breast screening is recommended. However, individual exposure (i.e. radiotherapy (RT) dose to breast tissue) is rarely taken into consideration in such screening programmes. In this work, we explored the variation in dose to breast tissue in a large cohort of young women treated for Hodgkin Lymphoma (HL) and non-Hodgkin lymphoma (NHL) with modern RT techniques.

Methods
All female HL patients treated with supradiaphragmatic RT from 2005 to 2021 aged ≤ 36y were included. For each patient, breast tissue was contoured using a deep learning segmentation algorithm and the following dose metrics were extracted for a structure combining both breasts: V4Gy (total breast volume receiving ≥4Gy, cm^3) reflecting exposure to low doses of RT, V20Gy, reflecting exposure to high doses of RT, and mean breast dose (MBD, Gy).

Results
All data are reported as median (range). Individual treatment plans for101 patients with median age 23 (13-35) years at the time of RT were available for analysis. Across the cohort, the prescribed dose of RT to the tumour was 30 Gy (20-50) and breast volume (BV) was 1400 cm3 (364-4504). Extracted dose metrics showed large variations between patients: MBD was 8.4 Gy (2.0-16), V4Gy was 110 cm3 (3-605), V20Gy was 52 cm3 (0-352).

No significant correlation was observed between breast dose (any metric) and year of radiotherapy. Age at treatment was weakly correlated (Pearson r=0.2) with V20Gy, but not MBD or V4Gy. Prescribed dose to the tumour showed a weak correlation with MBD (r=0.2) and V20Gy (r=0.3), but no correlation with V4Gy.
BV was moderately correlated with V4Gy (r=0.4) and V20Gy (r=0.4). but showed no significant correlation with MBD. Accordingly, correlations between BV and V4/20Gy were lost when V4/20Gy were expressed as percentages of BV. Age and BV showed a weak positive correlation (r=0.3).

Conclusion
Despite the global trend to use smaller fields and lower doses in the treatment of HL and NHL, our results give no evidence of overall reduction in breast dose since 2005 2005 at this tertiary Cancer Centre.
Our data also suggest that prescribed dose of RT to the chest is a poor surrogate for individual breast tissue exposure. The large range of breast doses in this cohort supports the need to develop individualised BC screening strategies through initiatives such as the Breast screening After Radiotherapy Dataset (BARD).

A twin study on the genetic component of acute toxicity after radiotherapy-related radiation exposure

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Abstract

How far the risk of radiation-induced toxicity is genetically determined is still unknown, despite many studies on host-related factors using various assays and methods. We capitalized on the rare occasion of metachronous double radiotherapy to different body parts to evaluate the genetic contribution to radiatheraphy-related toxicity in a twin study design. We collected information about demographics, lifestyle, radiotherapy and toxicity of several tissues for 99 patients who underwent two metachronous radiotherapeutic treatments of different body areas. We consider as genetic component the variation of toxicity that is not explained by radiation dose to the tumour (in Gy), age at radiotherapy (in years), sex, smoking status, and whether the patient has undergone surgery. We identified and applied three statistical approaches to assess whether tissue reactions are more similar within the same patient versus between different patients, accounting for the effects of the abovementioned factors. Preliminary results provide no evidence of a genetic contribution to adverse tissue reactions.

Radiation-induced neurotoxicity assessed by spatio-temporal modelling combined with artificial Intelligence after brain radiotherapy: the RADIO-AIDE project

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Context
Radiotherapy (RT) is one of the most important treatments of brain tumors. However, its potential toxicity on the central nervous system is a highly relevant clinical issue as cognitive dysfunction, mainly related to radiation-induced leukoencephalopathy (RIL), may alter the quality of life of patients. However, the physiopathology of post-RT brain injuries in normal tissues and organs is complex, multifactorial and partly understood as well as its potential links with the initiation and temporal progression of cognitive dysfunctions. Moreover, the knowledge about the radiosensitivity of the brain structures implied in cognitive processes must be improved.

Objectives
The RADIO-AIDE project is a multidisciplinary project of 4 years, that started in April 2022. It aims to develop spatio-temporal (ST) models and artificial intelligence (AI) tools to : a) generate new knowledge about the underlying neurotoxic mechanisms implied in the initiation and temporal progression of cognitive dysfunctions following brain RT and the radioresistance of targeted brain structures, while accounting for the tumor-response status; b) predict individual cognitive impairment at early stage after brain RT to set up mitigation measures and preserve the patients' quality of life; c) provide to clinicians a usable academic tool to perform an automated longitudinal extraction of clinically relevant image-based biomarkers - like white matter hyperintensities (WMH), vascular lesions, brain tissues volume quantification, tumoral lesions - from Magnetic Reasonance (MR) brain images acquired in clinical routine.

Methods
The project will be guided by the rich and multimodal data from the prospective EpiBrainRad cohort including patients treated by RT for a high-grade glioma. Fully automated segmentation algorithms based on deep learning architecture will be developed. ST models and AI tools will be proposed to extract, if it exists, a set of ST features which characterize WMH of different nature that may be associated either to post-RT side-effects (RIL, radio-necrosis, post-RT oedema) or to treatment responses (brain tumor progression, peritumoral oedema). Finally, dose-response analyses and individualized predictions of cognitive dysfunctions following brain RT will be performed.

Results and perspectives
An update of the EpiBrainRad cohort is in progress. New patients will be included from 2023. An annotated dataset including ground truth labels for post-RT WMH, vascular lesions and tumoral lesions as well as many brain regions of interest implied in cognitive functions is being produced from the MR brain images of the EpiBrainRad cohort. This large and well curated data set will feed the ST models and AI tools subsequently developed.

Changes in risk perception over time among residents of a town affected by the Fukushima nuclear accident

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Abstract

This study examined changes in risk perception over time and the intention to return (ITR) among evacuees from a town (Tomioka) affected by the Fukushima disaster. All residents evacuated until April 2017. The town office commenced decontamination efforts to facilitate the return of its residents, but only 11% wanted to return. Although exposure doses among evacuees measured four months after the accident were limited and no appreciable radiation-related health effects were expected, risk perception of living in Tomioka (regarding food consumption, drinking tap water, health effects and genetic effects) remained high. As risk perception plays a role in decision-making, such as the ITR, this research can refine risk communication strategies and rehabilitation of Tomioka.

Responses to two questionnaires distributed in 2017 (response rate 27%) and 2021 (response rate 34%) were compared regarding demographic information, intention to return to Tomioka, desire to consult radiation experts, and risk perception such as anxiety about food consumption, drinking tap water, self-health, and genetic effects.

The proportion of residents who returned/wanted to return (ITR+) and who did not want to return (ITR -) increased by 3.2% and 6.8% respectively and those unsure about returning (ITR unsure) decreased by 10.1%. In 2017, significant characteristics associated with returnees were sex (male), not living with children and being interested in consulting radiation experts. Only sex remained significant in 2021.

From 2017 to 2021, anxiety about the effects of radiation on health, food consumption and genetic effects reduced by 15.4%, 24.4% and 30.9% respectively. Compared to ITR + residents, multinomial regression analysis revealed that ITR unsure and ITR – residents were 3.4 and 7.3 times more likely to be anxious regarding the health effects of radiation in 2017. This was not significant in 2021. For anxiety regarding the consumption of Tomioka-produced food in 2017, ITR unsure and ITR - residents were 2.5 and 4.0 times more likely to perceive risk. In 2021, these odds were reduced to 1.5 and 1.4. For anxiety regarding the genetic effects of radiation in 2017, ITR unsure and ITR - residents were 2.8 and 4.6 times more likely to be anxious. In 2021, only ITR unsure residents were 1.4 times more likely to perceive this risk.

Risk perception for food and genetic effects remained associated with ITR unsure and ITR - residents. There is a need to address these specific topics in risk communication sessions and to target communication strategies according to demographic groups.

Impact of potential confounders for occupational radiation exposure and cancer incidence among radiologic technologists

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Background
Confounding is important consideration in observational epidemiology, particularly in low-dose radiation studies. The confounding effects have been observed differently for each population group. We examined the impact of potential confounders on cancer risk from occupational radiation exposure, and the magnitude and direction of these potential confounding estimates among radiologic technologists.

Methods
The study included 4,308 radiologic technologists who participated from the questionnaire survey-based cohort study (2012–2013) that investigated non-radiation factors, and 19,408 radiation technologists from the registration-based cohort study (1996-2011) enrolled in the National Dose Registry that obtained non-radiation factors by multiple imputation. Non-radiation factor items including smoking status, alcohol intake, body mass index (BMI), exercise, sleep duration, shift work, personal medical examination, and past medical history were selected as potential confounders. We quantified the confounding effects of cancer risks on radiation exposure based on a linear dose-response model. To determine whether a given risk factor caused confounding on the estimate of the baseline model, we compared the estimated measure of association before and after adjusting for non-radiation factors.

Results
In the questionnaire survey-based cohort, the ERR per 100 mSv of the baseline model for the association between radiation dose and cancer risk was 0.58 (95% CI: -0.91, 2.07, 10-years lagged) after adjusting for sex, attained age, birth year, and years of employment duration. Directly adjusted for confounding by smoking (ERR/100mSv=0.58), alcohol intake (0.57), BMI (0.64), exercise (0.55), sleep (0.62), shift work (0.53), personal medical examination (0.52), and past medical history (0.70), but the trend was not statistically significant. In the registration-based cohort, the baseline ERR per 100mSv estimate was 0.12 (95% CI: -0.34, 0.57). After indirectly adjusting for the imputed non-radiation factors by smoking (ERR/100mSv=0.13), alcohol intake (0.12), BMI (0.11), exercise (0.12), sleep (0.13), and shift work (0.13), there was no significant difference compared to the estimation of the baseline model.

Conclusions
We found little evidence of factors with statistically significant confounding effects on risk per unit dose of cancer between directly and indirectly confounder-adjusted effects. However, cautious interpretation is needed due to the possibility that these results from biases and unmeasured or insufficiently measured confounding factors cannot be excluded.

Thyroid Nodules and Cancers in Fukushima: An Analysis with Updated UNSCEAR Thyroid Dose Estimates

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Background/Aim
After the Fukushima–Daiichi nuclear power plant (NPP) disaster, thyroid ultrasound examination (TUE) was performed in subjects who were aged ≤18 years. In the first round of TUE (October 2011 to March 2014), 115 malignancies (including suspicious cases, "malignancies," hereafter) were detected. Beside malignancies, 1,713 nodules with a diameter ≤5 mm and 2,275 with nodules larger than 5mm were detected among 300,472 participants. They comprise 0.039%, 0.57%, and 0.76% of participants, respectively. In the second round of TUE (April 2014 to March 2016), while much less malignancy was expected, additional 71 malignancies, 1,570 nodules with a diameter ≤5 mm, and 2,219 with nodules larger than 5mm were detected among 270,522 participants. They comprise 0.026%, 0.58%, and 0.82% of participants, respectively. Following to previous study (Hamaoka, 2021), I analyzed the same data with updated thyroid absorbed dose estimates (UNSCEAR 2022).

Data and Methods
A critical literature review of studies that analyzed Fukushima TUE was conducted, and two limitations were identified. (1) Most studies segment 59 municipalities into three to nine regions that affect results. (2) Although analysis of a-bomb survivor identified radiation cause thyroid nodule and cyst, most studies neglect them. To overcome these limitations, an alternative analysis was conducted for the ^{second} round of results. The relationship between thyroid dose and the number of participants with a thyroid nodule, with whom fine needle aspiration test (FNA) was conducted, and with malignancy were analyzed using publicly available municipality-level data *without* regional grouping (N=59). A Poisson regression model with log(Thyroid dose for ten years old) and age at TUE was applied.

Results
UNSCEAR(2022) re-estimated thyroid dose incorporating the latest information on the ingestion of contaminated food, the flow of radiation plumes, and other factors. The estimates were reduced by 1/8 lower than the previous estimates (UNSCEAR 2013). Although magnitudes were reduced, previous and re-estimated thyroid dose have a positive and significant correlation of 0.44. The coefficient of log (Thyroid dose for ten years old) was positive and significant for small nodules (β= 0.112, p=0.008), FNA (β= 0.514, p=0.000), and malignancy (β= 0.36, p=0.077).

Conclusions
Although this was an ecological study, health follow-up for children in Fukushima is urgent. Since the third screening, municipality-level data has been undisclosed because of privacy concerns. Data disclosure is necessary to understand the effect of the Fukushima disaster.

Incidence and characteristics of multiple myeloma among A-bomb survivors

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Abstract
Multiple myeloma (MM) is a plasma cell malignancy characterized by clonal proliferation of plasma cells and the presence of monoclonal immunoglobulins (M-protein) from the tumor cells. MM accounts for approximately 1-2% of all malignancies and has a distinctly late age of onset with a median age at diagnosis of around 70 years. The Life Span Study (LSS) is a cohort study of 120,321 atomic-bomb (A-bomb) survivors, followed up for investigating effects of radiation exposure on malignant and other diseases. In general, epidemiological studies have provided inconsistent results on relationship between radiation exposure and MM. The LSS of A-bomb survivors has not shown a statistically significant radiation risk for MM. We studied previously reported MM cases diagnosed between 1950 and 1994 in the LSS and assessed diagnostic certainty based on histological and clinical features. Among 122 incident MM cases, 67 were classified as definite, 23, probable and 32, undetermined. The incidence rate increased with attained age and was highest in the oldest age group of over 70 years. For definite MM, Poisson regression dose response analysis showed an elevated, though not statistically significant, radiation risk with an estimated excess relative risk (ERR) per Gy of 0.44 (95%CI:<-0.02, 2.4), which was markedly higher than the previously reported ERR/Gy of -0.02 (95% CI: -0.24,0.75) that included cases with undetermined diagnostic certainty.

During 1979-1981 and 1985-1987, M-protein screening was offered to a clinical sub-cohort of 24,358 adult health study (AHS) members as part of biennial health examinations. Twenty-four survivors with MM had participated in the screening and they were not known to have had MM before the screening except for a case. We further examined the first opportunity for MM diagnosis among definite and probable MM cases, including those diagnosed after M-protein screenings outside the AHS. Nine (82%) of the 11 definite MM cases among participants of AHS M-protein screening were diagnosed with MM based on M-protein screening results and 5 (9%) of the definite MM cases, who were not screened at AHS, were diagnosed by the screening conducted outside AHS.

In the present study, the large number of survivors (n=46,220) exposed at ages younger than 20 years (41%) had not reached age 70 years at the end of follow up in 1994. These young survivors will enter into the oldest age groups in the next few decades. Future follow-up will be informative of long-term radiation effects on MM in this cohort.

Importance of educational dialogue in public perception of low dose radiation risks

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Abstract

Public perception of nuclear radiation depends on how risk is measured and managed, and how this is communicated. Reports of nuclear accidents and radiation leaks at Fukushima nuclear facility in Japan following the 2011 earthquake/tsunami triggered concern and panic among the public has emphasized the importance of incorporating aspects of science-technology-society (STS) into medical education. Radiation and Society is a seminar-style module at the Tembusu College, National University of Singapore, made up of weekly 3-hour interactive discussions which runs for 13 weeks. Undergraduate students from various faculties were exposed to themes and concepts related to radiation and society. Student numbers were restricted to 15 enrolments per group to ensure effective interactions. A variety of topics included nuclear fall-out, historical contextualization of nuclear fear/stigma, STS and science communication and most importantly, the uses of radiation in biomedicine., Field visits were arranged – one to a research reactor and a radiation oncology department at the hospital to enable students to understand the various peaceful uses of nuclear radiation. Expert guests were invited to share their perspectives on related matters, such as ongoing technological developments and societal impacts of radiation. I have facilitated this course since 2015 at Tembusu College, National University of Singapore, which over 100 students attended in the past 5 years. This seminar-style module has equipped students with the tools required to analyse evidence sources and critically assess social perceptions of radiation. Such educational efforts enable future leaders to have a deeper understanding of the uses and effects of nuclear radiation.

The Global Register of Low Dose Research Projects

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Introduction

Epidemiological and radiobiological studies of health effects of low dose ionizing radiation and associated mechanisms are the primary source of information for understanding and assessing radiation-induced health risks for human and non-human species Such studies and projects are often expensive and planning, execution and making the results available via peer-review publications is time consuming. Subsequently, research communities, advisory and regulatory bodies, and other stakeholders are poorly informed about these Low Dose Research (LDR) projects at their early stages. This can impede international collaboration, as well as effective funding decisions whereas more efficient coordination would allow for example, to avoid duplication of effort and spending.

Methods

To address this issue, an international expert group has developed the concept of a global register of LDR research projects (LDR register). The idea is to provide a simple system for collecting and disseminating key information on current and upcoming LDR research projects. This initiative is being implemented by a Topical Group within the High-Level Group on LDR (HLG-LDR) under the auspices of the Organisation for Economic Co-operation and Development, Nuclear Energy Agency (OECD-NEA). The register is a searchable library of LDR projects with a broad coverage of disciplines: epidemiology, radiobiology, dosimetry, ecotoxicology, social sciences and humanities. The main criterion for inclusion is addressing issues associated with radiological protection via original research in the field of low doses and low dose rates. Each project entry in the LDR register contains 30+ fields such as principal investigators name and contact, funding agency, partners, type of study, type of radiation used, dose and dose-rate range used, experimental model, endpoints. A dedicated field addresses availability of samples or data for collaboration. Another field indicates whether a project deals with the development of Adverse Outcome Pathway (AOP) as (one of the) objective(s).

Results

The LDR register initiative has been implemented in 2022, through two pilot phases. The first was to test the performance of the register using a limited number of pilot entries, and the second was to open the register to all HLG-LDR members and start communicating on the LDR register. An updated version of the LDR register will be opened to all in 2023. The presentation will provide details on the organization of the LDR register and the process of project submission and review. The goal is to attract attention of all relevant communities and encourage active participation at both institutional and individual research group levels.

Radiological component of the exposome and risks of chronic diseases in the Constances cohort (CORALE)

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Context
The whole population is exposed to ionizing radiation (IR) at varying levels, via multiple natural and artificial sources, whether in the context of residential environment, personal and professional activities or healthcare. The carcinogenic effects of IR are well documented, but there is still controversy about the shape of the relationships between exposure and cancer risks at low doses (less than 100 milliGrays). In addition, quantification of the effects of multiple exposures to IR and other cancer risk factors is poorly documented, apart from the interaction between tobacco and radon on lung cancer risk. Potential associations between low IR dose and non-cancer chronic diseases also require further research.

Objectives
The objectives of the CORALE project are: 1/ to carry out the broadest possible IR dose reconstruction from environmental (radon, terrestrial and cosmic radiation, food, anthropogenic sources), medical (diagnostic and therapeutic procedures) and occupational (workers in nuclear and other industries, health professionals) sources, received by 80,000 volunteers from the French Constances cohort (https://www.constances.fr/index_EN.php) since birth, following the logic of the exposome concept;2/ to estimate the risks of cancers and other chronic diseases potentially associated with the cumulative IR doses taking into account the potential influence of multiple exposures to other risk factors.

Methods
Reconstructions related to environmental, medical and occupational exposures will be performed by IRSN in collaboration with the Constances cohort team. In parallel to several record linkages which will be performed to estimate doses, a questionnaire will be sent during year 2023 to cohort members who have already provided their residential histories to gather complementary data on radiation exposure. The statistical analyses will be carried out at the IRSN epidemiology laboratory and will benefit from the expertise of radiobiologists. The use of innovative regression methods on exposure profiles will be explored.

Results and perspectives
Dose calculations are already in progress for several sources of radiation exposure. Preliminary epidemiological results from the CORALE project are expected in year 2024.

The use of radiophotoluminescent (RPL) glass dosimeters for out-of-field dose measurements, in vivo, during external beam radiotherapy

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Background and Purpose
Comparing out-of-field dose calculations with in-vivo measurements in a wide range of clinical situations is a decisive step to achieve. This study aimed to derive an accurate estimate of individual patient organ dose from in-vivo skin dose measurements.

Materials and Methods
All measurements were performed at a linac, Varian Clinac 2300/CD, operating at 6MV photons. The AGC Techno Glass Corporation system (RPL of models GD-302M and GD-352M and a FDG-1000 readout system) was investigated. The uniformity and reproducibility were tested. The changes with out-of-field distance of the beam effective energy was assessed through the linear attenuation coefficient of the filter (90% Sn, 10% Pb) integrated in the GD-352M holder. We were thus able to establish appropriate values for radiation quality correction factors. The RPL response was modelled as a function of out-of-field distance, at the surface of the phantom and at different depths, for different field sizes. In-vivo skin doses measurements were performed for a series of patients. A comprehensive whole-body dose distribution was obtained from detectors located at the forehead, sternum, left and right axillary, lower left thorax, umbilicus, right inguinal, left knee and right foot.

Results
The number of RPL elements were 98 and 60 for types GD-302M and GD-352M, respectively. The uniformity was ±1.2% for both types, at one standard deviation level. The reproducibility was ±0.3% for GD-302M and ±0.8% for GD-352M. For distances ranging from 10 to 40 cm from the beam central axis, our evaluations of the radiation effective energy, out-of-field, led to values ranging from 130 to 1350 Kev, the energy being the lower, the greater the distance. Evaluations of the additional factor required to properly correct for the varying beam quality out-of-field was ranging from 0.90 to 1.12 and 0.77 to 0.97, for GD-302M and GD-352M, respectively. At this stage in-vivo skin dose measurements have already been achieved for 6 patients, all treated for a head and neck cancer. Depending on the detector location, the measured skin doses for one radiotherapy session ranged from 0.3 mGy to 60 mGy.

Conclusions
Our results support that RPL glass dosimeters are well suited for accurate and reproducible in-vivo evaluations of out-of-field doses during radiotherapy.