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Summary of Radiation Research Society Online 66th Annual Meeting, Symposium on "Epidemiology: Updates on epidemiological low dose studies", including Discussion

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Introduction

Cancer risk is thought to be the main health risk of low-level ionising radiation exposure (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation 2006; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008a). An increase in leukaemia was observed within 5 years of the Hiroshima and Nagasaki atomic bombings (Folley et al. 1952), but excesses of most other cancer types have also been observed in the Life Span Study (LSS) cohort of Japanese atomic bomb survivors (Grant et al. 2017; Ozasa et al. 2012) and elsewhere (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008a). An accumulating body of epidemiological evidence has made it clear that there are significant

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cancer risks at doses approaching or below 100 mGy both in the LSS and in other groups (Grant et al. 2017; Kendall et al. 2013; Little et al. 2018; Lubin et al. 2017; Richardson et al. 2015; Spycher et al. 2015); 100 mGy of low-LET radiation is the level which is often used to denote low dose (International Commission on Radiological Protection (ICRP) 2007). Circulatory disease used to be thought of as a so-called deterministic effect, only observed above high therapeutic levels of radiation dose (Adams et al. 2003). There is an accumulating body of data suggesting that excess risk of circulatory disease is associated with moderate doses (<0.5 Gy) of radiation (Little et al. 2008; Little et al. 2012; Little 2016; Little et al. 2020, submitted; McGale and Darby 2005, 2008; McMillan et al. 2010; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008b) although this remains controversial, with some suggesting that risk becomes negligible below about 0.5 Gy (International Commission on Radiological Protection 2012).

In this online symposium a number of talks were given dealing with various aspects of moderate and low dose risk for cancer and circulatory disease. Two invited talks by Drs Kendall and Cullings were given dealing specifically with the topic of low dose cancer risk. There were two other talks given, by Drs Arsham and Schöllnberger, the first dealing with methodological issues in measuring doses in a large study of background radiation in Great Britain, and the second dealing with low dose risk of circulatory disease in the LSS.

Summary of Talks and Discussion

Dr Gerald Kendall: Review of background radiation studies

Low doses of ionising radiation are conventionally defined as less than 100 mGy of low-LET radiation. However, interest extends well below 100 mGy, to the range of natural background radiation, very roughly 1 mGy a year from low LET radiation plus a high LET contribution mainly from radon (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1988).

Studies of childhood cancer and natural background radiation offer one of the better prospects of probing the effects of such low doses because of the elevated sensitivity of most cancers at young ages of exposure (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008a) and the absence of strong potential confounders for cancers in childhood (Amirian et al. 2018; Cerhan et al. 2018; Hjalgrim et al. 2018; Linet et al. 2018). Many studies of natural background radiation and childhood cancer have been undertaken (Kendall et al. 2020 submitted), although the majority have been underpowered, often severely so (Little et al. 2010). Power calculations show that many thousands of cases of childhood leukaemia are a realistic minimum for an effect of natural background gamma rays to be detected; for radon the predictions are much larger, if less certain.

Ecological studies are intrinsically less reliable than cohort or case-control studies (Greenland and Robins 1994). Conventional interview-based case-control studies have the significant advantage of allowing the prospect of direct measurements of radiation dose rates in the homes of study subjects. However, they are liable to participation bias, potentially seriously so, in particular that the families of childhood cancer cases are more likely to participate than the families of unaffected controls (United Kingdom Childhood Cancer

Study Investigators 2002). They are also very expensive, probably prohibitively so for studies of sufficient size. When assessing the weight to be given to small underpowered studies, particularly ecological studies which are relatively simple to carry out, reporting bias is a danger to bear in mind. It is plausible that those studies which found significant associations are more likely to overcome the various barriers to publication and citation. Moreover, an underpowered study which achieves a significant result is likely to report a higher risk factor than is really the case (Land 1980).

Record-based studies, in which no contact is made with study subjects, have distinct advantages over interview-based case-control studies. They are free of participation bias and much easier to scale to a large enough size to have a reasonable chance of detecting the small effects expected. Against that, no information can be gathered directly from the study subjects and, more importantly, radiation dose rates must be estimated from a model. The importance of reliable estimation of doses in unmeasured locations is, perhaps, a matter that has hitherto received insufficient attention, a matter also touched on in Dr Arsham's talk.

A number of national record-based studies of childhood cancer and natural background radiation have been undertaken. These have been reviewed by Mazzei-Abba *et al* (Mazzei-Abba et al. 2020). Since that review further studies have been published by Berlivet *et al* (Berlivet et al. 2020) and Nikkilä *et al* (Nikkilä et al. 2020). Results from these studies have been mixed. The results of five studies of childhood leukaemia and natural background radiation have been compared (Kendall et al. 2020 submitted; Mazzei-Abba et al. 2020). Two studies, from Britain (Kendall et al. 2013) and from Switzerland (Spycher et al. 2015) were positive and statistically significant. The study from Germany (Spix et al. 2017) was positive, but not significant; that from Finland (Nikkilä et al. 2016) was negative, but not significant. Nevertheless, the results of these four studies appear broadly similar, given the uncertainties that must be expected, and the small size of the some of the studies. The fifth study, set in France (Demoury et al. 2017) appears different, not so much because of its central estimate of risk (a relative risk 1.00, so no association between leukaemia rates and gamma-ray doses), but because of its exceptionally (and puzzlingly) tight confidence interval 0.99 – 1.01, while the distribution of gamma dose rates is much as in the GB study (Kendall et al. 2013). With these results it is hard to draw firm conclusions. More studies and perhaps pooled studies of those that have been published will hopefully make the picture clearer.

A question was asked whether Dr Kendall could further describe a European Union study mentioned briefly in his talk, and whether there were any plans for a pooling exercise of register-based studies in Europe. Dr Kendall indicated the two questions were linked; the EU study of radon involves half a dozen countries and will pool a number of published and forthcoming studies from these locations.

A question was asked whether dosimetric uncertainty in individual studies might introduce bias into pooled studies, even if individual cohorts are included as a factor in the model. Dr Kendall responded that researchers would need to answer questions about the compatibility of studies they were going to pool. Dr Cullings and Dr Little were asked the same question, and both indicated that such dose error would likely attenuate results if the error was of

classical type (Carroll et al. 2006; Thomas et al. 1993), but that a study would need to be conducted to truly determine how individual dosimetric uncertainty would impact a pooled analysis. If the error was of Berkson type the risk estimates would be approximately unbiased, but the CI would be inflated (Carroll et al. 2006; Thomas et al. 1993), and the effect of this could be estimated. However, in practice for most studies, adjusting for dose uncertainty was not associated with a large degree of correction, implying that the error in a pooled study might be minimal.

Dr Harry Cullings: Monograph on low dose cancer risk – a summary of the recent JNCI Monograph

Perhaps the most central question in contemporary radiation protection is whether low-level doses (< 100 mGy) causes harmful effects. The average annual dose received from all sources by people in the USA is on the order of 6.2 mGy (National Council on Radiation Protection and Measurements (NCRP) 2009) as a matter of comparison. Harmful effects at this dose level would generally be increased risk of leukaemia or solid cancer in the exposed individual's remaining lifetime. Since this question was last addressed by a large advisory body in 2006 when the National Academy of Sciences Committee on Biological Effects of Ionizing Radiation wrote its report BEIR VII (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation 2006), investigators from the US National Cancer Institute assembled an international panel of experts in 2018 to conduct a review of radioepidemiological studies published since BEIR VII (Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation 2006). The purpose of this review was to not only review the published studies, but to examine them in regard to potential sources of bias, and to perform a meta-analysis of the included studies.

To be included in this review, studies were required to be based on cumulative dose rather than dose rate, to have a mean cumulative dose among the study subject <100 mGy, and to have made estimates of risk with statistically estimated confidence intervals (Berrington de Gonzalez et al. 2020). The review included 26 studies that were published in the period from 2006 through 2017: 8 studies of environmental exposures, 4 of medical exposures, and 14 of workplace exposures (Berrington de Gonzalez et al. 2020). The studies were examined in regard to dosimetry error and whether it could have biased the results away from the null in a positive direction (Daniels et al. 2020), as well as potential confounding by other risk factors that might have been associated with the radiation dose, and selection bias, causing a bias in the results (Schubauer-Berigan et al. 2020), and other sources of potential bias associated with outcome assessment (Linet et al. 2020). Issues in interpreting studies, and in particular considerations of statistical power and possible applicability of the Bradford-Hill criteria (Bradford Hill 1965) were also assessed (Gilbert et al. 2020). In general, relatively minor potential bias was identified, and a few studies thought to potentially exhibit such bias were excluded from part of the meta-analysis. The aggregate data for the review included 91,000 solid cancers and 13,000 leukaemias, and only 5 of the included studies had any portion of the cohort with doses >100 mGy. For studies of solid cancer, 16 of 22 studies had positive risk estimates, for a *p*-value of 0.03, and when 4 studies with potential positive bias due to dose errors or confounding were excluded, the *p*-value was 0.12 (Hauptmann et al. 2020). For leukaemia, the corresponding numbers were 17 of 20 studies positive for a *p*-

value of 0.001, and a *p*-value of 0.02 when 5 potentially positive-biased studies were excluded (Hauptmann et al. 2020). The meta-analysis for solid cancer gave a $p<0.001$ when 1 of 14 studies was excluded for heterogeneity, and the one for adult leukaemia gave a $p<0.001$ as well (Hauptmann et al. 2020).

Dr Cullings was asked about two background studies that were excluded from the review: the Kerala India study, which had a non-statistically-significant negative risk estimate and was excluded because it had a mean dose of 161 mGy (Nair et al. 2009), and a French study (Demoury et al. 2017) that had a non-statistically-significant zero risk result and was excluded because it was based on dose rate and not dose. It may be worth noting, however, that of the 14 studies that were published in 2006–2017 but were excluded from the review, only 4 had negative or zero results, all of which were statistically non-significant, and most of the studies with positive results were statistically significant (Hauptmann et al. 2020).

Dr Cullings was asked whether the JNCI monograph calculated excess relative risks from data reported in each study, or whether they included only studies that reported excess relative risks (ERR), to which he responded that only papers with ERRs were used, as the original data was not available for this project.

Dr Cullings and Dr Little were both asked to comment on the Mayak studies excluded from the NCI review due to their mean cumulative dose >100 mGy, as Mayak was an influential study and this cumulative dose consisted of many small doses received at a low dose rate. Both Dr Cullings and Dr Little indicated that there were significant positive trends with dose in the Mayak analyses but did not anticipate that its inclusion would change the results of the meta-analysis substantially. Indeed, they indicated that it might strengthen their findings.

Dr Cullings was asked to comment on the type of bias that contributed the most to the studies with bias away from the null. Dr Cullings answered that studies were excluded from the analysis primarily due to confounding by indication. Several retrospectively analysed case-control studies, including those from three Chernobyl studies, had doses estimated based on information provided by the subjects, in which there was strong potential for dosimetric bias.

Dr Aryana Arsham: Machine learning methods applied to assessment of doses in a large background radiation case-control study

Ionizing radiation is one of the few established exogenous risk factors for childhood leukaemia (Linet et al. 2018); however, this evidence derives mainly from groups exposed to moderate or high doses and high dose rates (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008a). Importantly, the accuracy and precision of the dose rates in low exposure scenarios is essential for reliable cancer risk assessment. The work reported compared fits of three machine learning algorithms based on their resulting predictive performances for low dose radiation exposure. Two random forest approaches and the stochastic gradient boosting machine were applied to predict gamma dose rates in the UK background data.

The assumed hypothesis to be tested was that very low dose rate (~1–2 mGy/year) natural background radiation was associated with childhood cancer in Great Britain (GB) during 1962–2010. The large record-based GB study has ~55,000 cases and ~70,000 cancer-free controls, taken from the National Registry of Childhood Tumours. There was an additional set of ~10,200 indoor gamma measurements and various other socioeconomic and geologic variables. The talk described methods used to better estimate individual doses in the case control data of ~125,000 individuals from the set of ~10,200 indoor gamma measurements. The second part of the analysis, that would use these estimated doses to estimate radiation risk, was the subject of ongoing work.

Previous analysis by Kendall *et al.* (Kendall et al. 2013) assigned an aggregate measure of radiation exposure to all individuals in a specified location. The analysis was conducted on a subset of this data, during 1980–2006, and provided results consistent with extrapolation from high-dose rate risk models.

Several parametric models had been employed by Kendall *et al.* (Kendall et al. 2018) to estimate radiation dose rates. Compared to these parametric models the proposed machine learning methods were less prone to overfitting, avoided limiting parametric assumptions, could include variables of various types simultaneously, and flexibly modelled non-linearities. Exposure estimates from these models could in principle attain high accuracy and precision by partitioning individuals into similar groups defined by relevant characteristics.

Two random forest approaches were used, the first that of Breiman (Breiman 2001), who defined the stopping criterion of tree development in the forest by the size of parent nodes. The second random forest approach defined the stopping criterion by the size of terminal nodes (Arsham et al. 2020 submitted). The third approach used was the stochastic gradient boosting machine (GBM) (Friedman 2002). The three approaches were applied to ~10,200 indoor gamma measurements and their mean squared prediction errors (MSPE) compared. The predictive performance, using MSPE evaluated in a hold-out 30% sample after tuning of the model via minimizing cross-validated MSPE in the 70% training set, was best under the terminal node random forest approach, and the GBM model performed next best. Using the optimal terminal node random forest model geographical variables tended to be the most influential in predicting gamma dose rate compared to other variable types, specifically socio-demographic, geological, and geopolitical ones. Dr Arsham highlighted how visual aids in the form of partial plots, for variables being identified as highly influential, were relevant to understand the manner in which variables contributed to the model-predicted radiation dose rate. Predicted gamma dose rates from this work would shortly be applied to the case-control analysis for assessment of childhood cancer risk.

A question asked about the difference between model comparisons using the cross-validation and the hold-out approaches. Dr Arsham explained that selecting a model with machine learning required two steps: determining the optimal tuning parameters via cross validation (e.g. 5-fold) within the 70% training set, and a model performance evaluation stage evaluating MSPE for the tuned model in the 30% hold-out test set. The cross-validation analysis in the 70% training set demonstrated that the random forest terminal

node approach outperformed the random forest parent approach; the 30% hold-out set was then used to determine that the random forest leaf approach outperformed the GBM.

A question asked whether the methods Dr Arsham had described could be applied in situations where less was known about dose rates, to which it was replied that it depended on what was meant by “less.” A strength of machine learning was that this methodology could be applied to complex datasets as long as it could be reasonably assumed that the training and testing data were from the same population. The modelling requirement was that the variables in the testing data, used to measure model performance, were the same as those in the training data used to build the model. In the present data, the dose rates were needed in the 70% training set to create and tune the model and in the 30% hold-out testing set to assess model generalizability.

Dr Helmut Schöllnberger: Radiobiologically motivated models fitted to circulatory disease mortality data in the Japanese atomic bomb survivors LSS cohort

The LSS data are essential for estimating the biological effects of ionizing radiation. The person-year weighted mean dose within the whole cohort is 0.116 Gy, with a large number of survivors receiving near 0 dose, and a few receiving weighted absorbed doses of about 4 Gy. This cohort was therefore well-suited to investigate risks from low and medium dose exposures.

The latest publicly available LSS data for cerebrovascular diseases (CeVD) and heart diseases were analyzed by Schöllnberger *et al.* (Schöllnberger et al. 2018). In the primary analysis(using data of Shimizu *et al.* (Shimizu et al. 2010)), these data were analyzed using a stratified baseline model combined with LNT, quadratic, linear-quadratic and linear-threshold (LTH) models and implemented as excess relative risk (ERR) models. Their main results were based on the LNT model in line with the usual approach in radiation epidemiology.

In the present analysis, a larger series of radiobiologically motivated nonlinear dose response models were applied to the data in combination with a parametric baseline model either as ERR or EAR (excess absolute risk) models (Schöllnberger et al. 2018). The models described linear, sublinear and supralinear dose responses and could be justified from radiobiology (see Table 1 in Schöllnberger *et al.* (Schöllnberger et al. 2020)). For example, the use of the LNT and linear-exponential models was supported by data of Stewart *et al.* (Stewart et al. 2006) and Mancuso *et al.* (Mancuso et al. 2015), respectively. The LTH model finds support from the low dose and low dose rate studies of Mitchel *et al.* (Mitchel et al. 2011; Mitchel et al. 2013), Mathias *et al.* (Mathias et al. 2015), Le Gallic *et al.* (Le Gallic et al. 2015), and Ebrahimian *et al.* (Ebrahimian et al. 2018). The threshold dose parameter (D_{th}) contained in some models (LTH, step, smooth step, step-linear, sigmoid, hockey stick, hormesis, two-line spline) was optimized during the model fits. Subsequently, the models were weighted according to their quality of fit via multi-model inference (MMI) (Burnham and Anderson 2002; Claeskens and Hjort 2008; Walsh and Kaiser 2011). With MMI, the shape of the dose–response was more reliably determined than the shape for any individual dose–response because the MMI dose–response shape accounted for strengths of evidence for each of the contributing dose–response shapes (Schöllnberger et al. 2020). MMI also

provided a more comprehensive characterisation of model uncertainties by accounting for possible bias from model selection. It is a statistical method of superposing different models that all describe a certain data set about equally well.

It was found that for CeVD, the dose–response curve from MMI was located below the LNT model at low and medium doses (0–1.4 Gy) with a shallow dip below zero risk consistent with a threshold dose of 0.2 Gy. At higher doses MMI predicted a higher risk compared to the LNT model. A sublinear dose–response was also found for heart diseases (0–3 Gy) (Schöllnberger et al. 2018). However, due to the relatively large 95% confidence intervals associated with the dose responses from MMI the analyses provided no conclusive answer to the question whether there was a radiation risk below 0.75 Gy for CeVD and 2.6 Gy for heart diseases. Our results were consistent with those by Furukawa (work prepared for a forthcoming UNSCEAR report (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2019 in press)).

The sublinearity suggested that different biological mechanisms might operate at low and medium doses compared to high doses. The present study provided an elegant way to analyze radio-epidemiological data sets, which comprised a number of similar biological endpoints. Because the internationally applied guidelines for radiation protection largely relied on analyses of the LSS data and the LNT model, these findings had important implications for risk assessment of ionizing radiation in the context of medical applications (such as computerized tomography (CT) scans, radiotherapy and low dose anti-inflammatory radiotherapy), nuclear energy production, accident related long-term risks and international radiation protection practices in general.

Dr Schöllnberger was asked whether the analyses by Dr Furukawa mentioned in the talk used Bayesian Model Averaging (BMA), and whether these analyses were based on the same data used by Dr Schöllnberger. Dr Schöllnberger clarified that Furukawa used a semi-parametric Bayesian approach in combination with spline models, but not a BMA model in the sense commonly understood (Hoeting et al. 1999). The data used for Dr Furukawa's analysis were the same as the data used in the presentation.

Dr Schöllnberger was asked whether the additional LSS data published in Takahashi *et al* (Takahashi et al. 2017) might change the findings of Dr Schöllnberger's study. Dr Schöllnberger indicated that he had previously conducted a similar study (Schöllnberger et al. 2012) using an older dataset with follow-up until 1997; the present study with follow-up through 2003 (using data of Shimizu *et al* (Shimizu et al. 2010)) found similar patterns, even with an intentional change to more biologically realistic models. Therefore, he believed at least some results would be consistent after adding follow-up through 2008.

Dr Schöllnberger was asked about the influence of chronic rheumatic heart diseases on the LSS data. Dr Schöllnberger answered that the analysed data set did not contain information on subtypes of circulatory diseases and that therefore he could not comment on it.

Summary

The talks in this Symposium have given further evidence that radiation epidemiology was coming of age in that it was giving solid evidence on the carcinogenic risks of radiation down to the levels of a few tens of mGy. The data on circulatory disease risks in the LSS and in other groups also suggested that there may be risks at moderate doses, under 0.5 Gy. Of course, further work remains to be done, particularly as regards effects at even lower doses for cancer and circulatory disease endpoints. However, current and forthcoming studies, pooling and meta-analyses, offer the expectation that progress will continue.

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Aryana Arsham, Ph.D, obtained her doctorate from University of Maryland Baltimore Campus in 2019 and has been working for over a year since then at the National Cancer Institute in the Biostatistics Branch and the Radiation Epidemiology Branch as a post-doctoral fellow.

Helmut Schöllnberger, PhD, has worked in radiation research since the 1990s. He performed postdoctoral research at the University of North Carolina at Chapel Hill (1997–1999) and Lovelace Respiratory Research Institute (1999–2001). After a guest professor position at the University of Salzburg (2001–2002) he worked as EU Marie Curie Individual Fellow at RIVM, the Netherlands (2002–2004). In 2008 he habilitated at the University of Salzburg (*Venia* in Biophysics) and subsequently continued his research at Helmholtz Zentrum München.

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Mark P. Little, DPhil, joined NCI Radiation Epidemiology Branch (REB) in 2010, and was promoted to a Senior Investigator in 2012. Previously (2000–2010), he worked in Imperial College London, and before that (1992–2000) at UK National Radiological Protection Board (now part of Public Health England). He is a member of Council of NCRP, and has served as consultant to UNSCEAR, to IAEA, to ICRP (in particular as member of ICRP Task Group 91), to the UK COMARE, and to NCRP SC 1–21 and 1–26. In REB, Dr. Little is working on assessment of leukaemia risk in persons exposed at low doses and dose rates, cancer risk in various groups exposed as result of the Chernobyl accident, on risks of various health endpoints in the US radiologic technologists, and on treatment-related second cancer risks in various populations. He has particular statistical interests in machine learning algorithms and dose measurement error models. He has over 280 publications in the peer-reviewed literature.

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