**Summary of Radiation Research Society Online 67th Annual Meeting, Symposium on “Radiation and Circulatory Effects”**

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**INTRODUCTION**

It has been established that high and moderate doses of ionizing radiation can cause non-cancer diseases including those related to cardiovascular disease (CVD). The related evidence was gained by analyzing cohorts of radiotherapy patients (Darby et al. 2013), animal experiments (Stewart et al. 2006) and epidemiological studies of various cohorts such as those of the Japanese atomic bomb survivors (e.g. Shimizu et al. 2010). Because CVD, such as ischemic heart disease (IHD) and stroke, is the leading cause of death worldwide the question of whether low doses of ionizing radiation pose a risk has high relevance for radiation protection. The International Commission on Radiological Protection (ICRP) currently assumes an effective threshold dose of 0.5 Gy (ICRP 2012). This is a matter of intense investigations. The current publication contributes to these debates and summarizes presentations and related discussions from the Symposium on “Radiation and Circulatory Effects” of the Radiation Research Society Online 67th Annual Meeting, held online 3-6 October 2021.

In this online symposium a number of talks were given dealing with various aspects of radiation-associated risk for circulatory diseases. Dr. Dauer presented an update of the U.S. Million Person Study with respect to cardiovascular disease risk from low-dose radiation exposures. Dr. Wakeford was invited to give a review of epidemiological findings of low-level exposure to radiation and diseases of the circulatory system and issues of interpretation. Dr. Schöllnberger presented his radio-biologically motivated mathematical modeling of radiation-risks of mortality from ischemic heart diseases in the Canadian fluoroscopy cohort study.

**SUMMARY OF SYMPOSIUM CONTRIBUTIONS**

***Dr. Lawrence Dauer: Radiation and Circulatory Effects in the Million Person Study***

The vision of the U.S. Million Person Study (MPS) is to provide broad scientific understanding of health effects following prolonged exposure to radiation (Boice et al. 2019; Boice et al. 2021a; Boice and Dauer 2021). The study is currently evaluating cancer and noncancer mortality following low-level low-linear energy transfer (LET) and high-LET exposure of over a million healthy American workers and veterans. The study is also evaluating rare cancers, intakes of radioactive elements, and differences in risks between women and men. (Boice et al 2021a). It consists of more than 30 cohorts of workers across seven categories of persons exposed to radiation from 1913 to the present: Manhattan Project and nuclear facilities of the U.S. Department of Energy, Atomic Veterans, nuclear power plant workers, industrial radiographers, medical radiation workers, nuclear submariners and other U.S. Navy personnel, and radium dial workers (Boice et al. 2021a). As a national effort, the MPS relies on the active cooperation and support of federal agencies (US GAO 2017). The key to high-quality epidemiology is comprehensive organ dose reconstructions for individuals and MPS dose estimates are performed according to methodologies described in National Council on Radiation Protection guidance (NCRP 2018; Dauer et al. 2018). Reconstructions have resulted in conversions of the badge and personal dosimetry readings into organ doses accounting for specific exposure scenarios, energies and orientation, for incorporating organ doses from the intakes of radionuclides, accounting for personal protective equipment (e.g., lead aprons on interventional radiographers and cardiologists) and for adding career doses for individual workers who were employed at multiple facilities.

The evaluation of radiation-related IHD is an important ongoing activity within the MPS. Over 515,000 workers have been evaluated and results published to date within distinct MPS cohorts. Table 1 provides a summary of the published standardized mortality ratios (SMRs) for IHD in seven MPS cohorts. MPS workers were significantly less likely to die than comparable persons in the general population likely because selection factors related to health can influence a person’s ability to work (Monson 1986; Checkoway et al. 1989; Buckley et al. 2015). Internal dose-response comparisons are conducted in the MPS to minimize this impact. In addition, adjustments for tobacco use (smoking) are implemented in various ways in the MPS depending on the information available for a specific cohort based on comprehensive interviews, education as a surrogate, pay type (white collar/blue collar), rank (officer/enlisted), or other measures of socioeconomic status (Boice et al. 2021a). Table 2 provides a summary of the mean (maximum) heart doses (mGy) for each cohort and lists the excess relative risk (ERR) at 100 mGy (95% CI). For the MPS, internal dose-response analyses found no evidence for an increase in IHD over categories of absorbed dose to the heart. The ERR at 100 mGy estimates of risk for IHD within seven MPS cohorts were mostly negative, but none were statistically significant. Dose-response evaluation for IHD among the MPS cohorts evaluated to date provide little consistent evidence for a statistically meaningful association with chronic radiation exposure at low levels.

Completion of the initial study of individual cohorts continues with plans to harmonize the data and combine (pool) the studies to provide detailed dose-response analyses for all organs and outcomes. Ultimately, continued vital status tracing and follow-up as well as the combined (pooled) all-cohort data within the MPS will provide a more powerful evaluation of the possible level of IHD risk following low-level radiation exposures received in the occupational setting over many years, especially in the dose range under 500 mGy. Future research opportunities of the MPS will be substantially enriched in that for upwards of 800,000 workers and veterans, cancer incidence and clinical diagnoses of nonmalignant conditions, such as heart disease not leading to death, will become available within the year via linkages with files from the U.S. Centers for Medicare and Medicaid (CMS 2018, 2021a). In addition, individual information will be available on important lifestyle factors, including those important for cardiovascular outcomes such as smoking and on individual characteristics and conditions such as obesity, hypertension, diabetes, and on many hundreds of other health conditions (CMS 2018, 2021a, 2021b). A National Center for Radiation Epidemiology and Biology (NCREB) is envisioned to provide continued support and guidance for addressing national needs (Boice et al. 2021a).

***Dr. Richard Wakeford: Cardiovascular disease following low-level exposure to radiation – some issues***

That low-level exposure to ionizing radiation could increase the risk of diseases of the circulatory system is one of the most important matters facing radiological protection today. In the current framework recommended by the ICRP, no account is taken of any risk of CVD (e.g., heart disease and stroke) consequent to the receipt of low doses or doses received at a low dose-rate. Recent data on CVD mortality among the Japanese atomic bomb survivors suggest that the radiation-related risk might extend to low doses, particularly for heart disease (Shimizu et al. 2010), although there are patterns in the data that encourage caution in interpretation (Ozasa et al. 2016), such as the effective absence of a radiation-associated risk of mortality from IHD (the most frequent cause of death from heart disease in the survivors) while the highest (and statistically significant) excess relative risk per unit dose (ERR/Gy) was found for rheumatic heart disease, which is caused by rheumatic fever in childhood.

Studies of those exposed in the workplace offer an important opportunity to examine the effect of protracted exposure to low dose-rates (Wakeford 2019). One such group is the Russian emergency and recovery workers (“liquidators”) who dealt with the consequences of the Chornobyl accident. Recent reports (Kashcheev et al. 2016, 2017) indicate highly statistically significant increases in ERR/Gy estimates that approach 50% for the incidence of both IHD and cerebrovascular disease (CeVD, e.g., stroke) and the assessed dose from gamma radiation in almost 54,000 liquidators. However, the level of incidence in the liquidators is surprisingly high – between 40% and 50% of liquidators were diagnosed with IHD or CeVD. Unfortunately, recent CVD mortality data for the liquidators have not been published. The possibility of “over-diagnosis” of these diseases, perhaps of the less severe types of CVD, especially among those with the highest assessed doses, must be borne in mind.

A further source of valuable information is the workforce of nearly 23,000 men and women of the Russian Mayak nuclear complex (Azizova et al. 2014, 2015). CVD mortality data are available throughout Russia, but incidence data are available only for Mayak workers in the neighbouring dormitory town of Ozyorsk. Almost 40% of all Mayak workers were diagnosed with CeVD and nearly 33% with IHD (while resident in Ozyorsk), which compares with just 7% and 13% dying of these respective diseases. The ERR/Gy estimates for the incidence of IHD and CeVD in terms of gamma ray exposure are both significantly raised, and particularly notable is the ERR/Gy for CeVD incidence, which approaches 50% and is highly statistically significant. In contrast, the ERR/Gy estimates for IHD and CeVD mortality were increased by just 5% and were not significantly different from zero, and the difference between the ERR/Gy estimates for CeVD incidence and mortality was highly significant. Could this pattern of results be due to the diagnosis of relatively minor or chronic conditions and more medical attention being paid to workers who had accumulated high doses?

Mortality among almost one-third of a million nuclear workers in the UK, USA and France has been investigated in terms of exposure to gamma radiation in INWORKS (Gillies et al. 2017). The ERR/Gy for CeVD mortality was significantly raised at around 50%, but that for IHD mortality was non-significantly increased at about 15%. However, the ERR/Gy estimates for CVD mortality by groups of workers in the three countries was significantly heterogeneous, largely due to the British Sellafield workforce; workforce heterogeneity has also been found by an extended study of heart disease mortality among British workers (Zhang et al. 2019a, 2019b). The effective absence of an increased radiation-associated risk of CVD mortality in US workers included in INWORKS has been confirmed by recent publications from the US Million Person Study (e.g., Boice et al. 2021b) for workforces not included in INWORKS.

An earlier study of British Nuclear Fuels Limited (BNFL) workers (McGeoghegan et al. 2008), an important component of the British nuclear workforce that includes Sellafield workers, found a significantly increased ERR/Gy for IHD mortality in relation to external exposure of 70%, but a non-significant increase of about 40% for CeVD mortality; there was significant heterogeneity in ERR/Gy for CVD mortality between socioeconomic groupings and internal exposure monitoring status. Mortality from IHD has been further investigated in a nested case-control study of workers at the two main BNFL sites (de Vocht et al. 2020, 2021). The impact of potential confounding factors that were included in this study was small, but an important influence on IHD risk was whether a worker had been monitored for potential internal exposure, with workers so monitored being at lower risk. There was, however, no effect of internal dose itself. The explanation for this monitoring effect is unclear, but could indicate some bias arising from selection of workers for internal monitoring. A similar internal monitoring effect was also apparent for digestive cancer mortality in the BNFL workforce (Gillies and Haylock 2014).

Observational epidemiological studies pose particular problems of interpretation, and studies of low-level exposure to radiation and the risk of CVD are no exception to this. This is undoubtedly an important issue for radiological protection, but the current findings of pertinent epidemiological studies pose questions that require answers before confident interpretation of reported associations can be made.

***Dr. Helmut Schöllnberger: Radio-biologically motivated modeling of radiation-risks of mortality from ischemic heart diseases in the Canadian fluoroscopy cohort study***

The Canadian Fluoroscopy Cohort Study (CFCS) data represent the largest cohort of patients exposed to fractionated low-to-moderate doses of fluoroscopic X-rays as part of treatment of tuberculosis (TB). It includes 63707 tuberculosis patients first exposed to fluoroscopic procedures in 1930–1952 and followed-up for death from noncancer causes in 1950–1987. The mean cumulative person-year-weighted lagged lung dose among exposed was 0.79 Gy (range, 0–11.6 Gy).

In the primary analysis, the data were analyzed using a stratified baseline model combined with a linear no-threshold (LNT) model implemented as ERR model. A significantly elevated risk for mortality from IHD was reported (Zablotska et al. 2014). The follow-up study (Schöllnberger et al. (2020) therefore focused on that detrimental health outcome. In addition, the assumption of linearity was scrutinized by analyzing a larger series of radio-biologically motivated nonlinear dose–response models to get a better understanding of the impact of radiation damage on IHD. The models describe linear, sublinear and supralinear dose responses and can be justified from radiobiology (see Table 1 in Schöllnberger et al. 2020). They were applied to the data in combination with a parametric baseline model as ERR models. 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 can be more reliably determined than the shape for any individual dose–response because the MMI dose–response accounts for the strength of evidence for each of the contributing dose–responses (Schöllnberger et al. 2020, Milder et al. 2021). MMI also provides a more comprehensive characterization 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.

For IHD, the dose response curve from MMI was consistent with the LNT model at low and medium doses (0–1.5 Gy). At higher doses (> 1.5 Gy) MMI predicted a higher risk compared to the LNT model. At 5 Gy, for example, the estimated radiation risks were fivefold higher compared to the linear no-threshold (LNT) model (Schöllnberger et al. 2020). The linearity at low and medium doses in combination with the supralinearity at doses > 1.5 Gy suggests that different biological mechanisms might operate at low and medium doses compared to high doses.

The authors of Schöllnberger et al. (2020) do not suggest to substitute the LNT model by the MMI approach when formulating radiation protection guidelines by analyzing radio-epidemiological data because MMI generally leads to much larger confidence intervals for its risk predictions compared to the LNT model (this usually does not allow to provide a conclusive answer to the question whether there is a radiation risk at low and medium doses; see e.g. Schöllnberger et al. 2018). Rather MMI should be applied in addition to an LNT-based analysis because MMI estimates the uncertainties more comprehensively than the LNT model and can provide hints to possible nonlinearities in the dose-response (Ulanowski et al. 2020).

Dr. Schöllnberger was asked whether the Canadian study took cigarette smoking history into account. He answered that a limited amount of smoking information is available for approximately 20% of the cohort (see Table 2 in Zablotska et al. 2014). However, separate analyses of IHD deaths among those who had information on smoking status showed similar radiation-related risks for smokers and nonsmokers, suggesting that smoking did not mask an association between radiation and IHD mortality (Zablotska et al. 2014).

It was stated that the Massachusetts TB fluoroscopy cohort did not report excess heart disease and Dr. Schöllnberger was asked whether he had any comment on these differences. This clearly refers to the study by Little et al. (2016). These authors report that over the full dose range, there was no overall radiation-related excess risk of death from circulatory diseases. However, under 0.5 Gy, there was a borderline significant increasing trend for all circulatory disease and for IHD (Little et al. 2016). Dr. Schöllnberger answered that the cohorts and analytical methods of the two studies (Zablotska et al. 2014, Little et al. 2016) differ in several ways: Different lag-times were used, the Canadian study used time-dependent annual lung doses, Little et al. (2016) relied on cumulative lung and thyroid doses, dose-rate was defined differently and the two populations also differ, e.g. the Canadian cohort has different calendar times of exposure compared to the Massachusetts cohort (Little et al. 2016).

It was commented that cor pulmonale (i.e. pulmonary heart disease) is an important cause of death among early TB patients due to pulmonary hypertension and not radiation. Dr. Schöllnberger was asked whether he had analyzed cor pulmonale deaths separately. He answered that neither Zablotska et al. (2014) nor Schöllnberger et al. (2020) had analyzed that endpoint.

**SUMMARY AND DISCUSSION**

The talks in this Symposium presented results related to the radiation and circulatory effects in occupationally or medically exposed populations as well as related radiobiological mechanisms. They also showed that low/moderate acute doses at low/moderate dose-rates can be associated with an increased risk of CVD, although some of the epidemiological results for occupational cohorts are equivocal. Earlier, Little et al. (2012) had suggested that radiation-associated risks of CVD mortality and cancer mortality are similar. Radiation-induced heart disease, which is a delayed effect of acute high-level exposure to ionizing radiation, can involve pericarditis, arrhythmias and valvular disease, early coronary artery atherosclerosis, and myocardial fibrosis that will lead to heart failure and death.

People at risk of radiation-induced heart disease include cancer survivors who received radiotherapy, survivors of nuclear accidents, and astronauts after extended space flights. For instance, the Life Span Study investigated the long-term effects of atomic bomb radiation on the causes of death and incidence of cancer. In the initial interview, Life Span Study cohort members described the circumstances of their exposure. It was estimated that they were exposed to radiation doses ranging from 0 to >3 Gy, and that 86% of participants received <0.2 Gy. Doses >0.5 Gy are associated with raised risk of stroke and heart disease, but the risk level associated with exposure to lower doses is still unclear. Among atomic bomb survivors, stroke and heart diseases together account for about one third of the radiation-associated excess deaths, similar to cancer (Shimizu et al. 2010). Other studies investigated mortality due to circulatory disease, ischemic heart disease and cerebrovascular disease as a function of the cumulative doses of external gamma radiation and internal alpha radiation (plutonium) over long follow-up periods in large cohorts of nuclear workers, such as the Russian Mayak Worker Cohort and the UK Sellafield Worker Cohort. The excess relative risk per unit liver absorbed dose (ERR/Gy) was significantly increased for the incidence of ischemic heart disease and cerebrovascular disease in 22,377 Mayak workers employed during the 1948-1982 period and followed up to the end of 2008 (Azizova et al. 2015), but not for mortality. For the U.S. Million Worker Study, the ERR at 100 mGy estimates of risk for IHD within seven MPS cohorts were mostly negative, and none were statistically significant (Boice et al. 2021a). Clearly, additional follow-up and careful dosimetric and outcome assessment are necessary. Epidemiologists are advised to be cautious and skeptical when analyzing data from nuclear workers from early years, because many data were mis-recorded or unavailable (Wakeford 2021).

This problematic subject can also be transposed to the risk assessment of medical radiation workers. One of the biggest issues is lead apron wearing. Dosimeters are often worn outside of the lead apron, which can bias results for dose. In addition, it is crucial to understand the specific exposure scenario. Therefore, all medical workers should not be pooled in a single group and dosimetry should be determined in each category of medical workers. Overall, the usually only limited availability of information on well-known risk factors for circulatory disease implies that this may have biased any observed association between radiation exposure and detrimental health outcome.

The main difficulty for epidemiologists is the lack of data related to the biological mechanisms associated with the observed findings. This is complicated by uncertainty on what are the doses to the relevant organs/tissues (e.g., brain, heart) that increase the incidence of CVD. Therefore, the doses to the heart, whole body, and other organs at risk should be compared to the available biological data or to relevant experimental data. For instance, radiation exposure to the heart induces specific and long-term alterations in the DNA methylome that may promote myocardial fibrosis and cardiomyopathy, providing a potential target for prevention or treatment. Thus, studying radiation-induced alterations in the DNA methylome may be a step towards a more integrated understanding of the effects of low-level exposure not just on cancer risk, but also on healthy tissues (with respect to CVD).

Finally, the possible risk of CVD resulting from low-level exposure to radiation is not included in the current system of radiobiological protection by the ICRP. In that context the question emerges whether this should be changed and how reliable the epidemiological evidence on the low-level radiation influence on CVD risk is. Epidemiological studies, mainly occupational ones, suggest that the risk of CVD following low-level exposure to radiation is increased, but the results are not always consistent and causative associations cannot yet be made because of unresolved interpretational issues. More epidemiological and experimental research is required before final conclusions can be drawn.

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**Conflicts of interest**

The authors declare no conflicts of interest.

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**Table 1. Standard Mortality Ratios (SMR) (95% CI) for ischemic heart disease (IHD) amongst cohorts of the Million Person Study (MPS) published to date.**

|  |  |  |  |
| --- | --- | --- | --- |
| Cohort | Reference | # IHD  Deaths | IHD  SMR (95% CI) |
| Atomic Veterans | Boice et al. 2020 | 16,704 | 0.85 (0.84, 0.86) |
| Nuclear Power Plant | Boice et al. 2021c | 5,410 | 0.80 (0.78, 0.82) |
| Industrial Radiographers | Boice et al. 2021a | 4,478 | 0.80 (0.78, 0.83) |
| Los Alamos Natl Lab | Boice et al. 2021b | 3,023 | 0.60 (0.58, 0.63) |
| Medical Workers | Boice et al. 2021d | 1,655 | 0.53 (0.51, 0.56) |
| Mallinckrodt Workers | Golden et al. 2019 | 521 | 0.92 (0.84, 1.00) |
| Mound Workers\* | Boice et al. 2014 | 753 | 0.81 (0.75, 0.87) |

\*For this cohort the SMR refers to all heart disease.

**Table 2. Mean heart dose and ERR at 100 mGy (95% CI) for ischemic heart disease (IHD) amongst cohorts of the Million Person Study (MPS) published to date\*.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Cohort | Reference | # Workers | Heart Dose mGy (max) | ERR at 100 mGy  (95% CI) |
| Atomic Veterans | Boice et al. 2020 | 114,270 | 6.1(953) | -0.01 (-0.12, 0.11) |
| Nuclear Power Plant | Boice et al. 2021c | 135,193 | 43.9(1,105) | -0.01 (-0.06, 0.04) |
| Industrial Radiographers | Boice et al. 2021a | 123,556 | 15.0(1,504) | -0.03 (-0.08, 0.03) |
| Los Alamos Natl Lab | Boice et al. 2020b | 26,328 | 13.5(8,970) | -0.06 (-0.16, 0.04) |
| Medical Workers | Boice et al. 2021d | 109,019 | 14.6(1,272) | -0.10 (-0.27, 0.06) |
| Mallinckrodt Workers | Golden et al. 2019 | 2,514 | 49.3(1,345) | 0.13 (-0.01, 0.28) |
| Mound Workers\*\* | Boice et al. 2014 | 4,954 | 24.3(941) | -0.14 (-0.43, 0.14) |

\*Some entries may differ slightly from those found in earlier summary articles which presented preliminary findings.

\*\*For this cohort the estimated ERR at 100 mGy refers to all heart disease.