MEMORANDUM

A Report from the 2013 International Workshop: Radiation and Cardiovascular Disease, Hiroshima, Japan

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MEMORANDUM

A Report from the 2013 International Workshop: Radiation and Cardiovascular Disease, Hiroshima, Japan

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Abstract
Two longitudinal cohort studies of Japanese atomic bomb survivors—the life span study (LSS) and the adult health study (AHS)—from the Radiation Effects Research Foundation (RERF) indicate that total body irradiation doses less than
1 Gy are associated with an increased risk of cardiovascular disease (CVD), but several questions about this association remain.

In particular, the diversity of heart disease subtypes and the high prevalence of other risk factors complicate the estimates of radiation effects. Subtype-specific analyses with more reliable diagnostic criteria and measurement techniques are needed. The radiation effects on CVD risk are probably tissue-reaction (deterministic) effects, so the dose–response relationships for various subtypes of CVD may be nonlinear and therefore should be explored with several types of statistical models.

Subpopulations at high risk need to be identified because effects at lower radiation doses may occur primarily in these susceptible subpopulations. Whether other CVD risk factors modify radiation effects also needs to be determined. Finally, background rates for various subtypes of CVD have historically differed substantially between Japanese and Western populations, so the generalisability to other populations needs to be examined.

Cardiovascular disease mechanisms and manifestations may differ between high-dose local irradiation and low-dose total body irradiation (TBI)—microvascular damage and altered metabolism from low-dose TBI, but coronary artery atherosclerosis and thrombotic myocardial infarcts at high localised doses. For TBI, doses to organs other than the heart may be important in pathogenesis of CVD, so data on renal and liver disorders, plaque instability, microvascular damage, metabolic disorders, hypertension and various CVD biomarkers and risk factors are needed. Epidemiological, clinical and experimental studies at doses of less than 1 Gy are necessary to clarify the effects of radiation on CVD risk.

1. Introduction

An international workshop was held on 5–6 February 2013 at the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan, entitled ‘Radiation and Cardiovascular Disease’. After opening remarks by the RERF Chairman Dr Toshiteru Okubo, Dr Waka Ohishi from the RERF posed several key research questions.

(1) What are the consistencies and inconsistencies in studies of radiation-associated cardiovascular disease?

(2) What mechanisms are responsible for low- and high-dose radiation effects on the development of cardiovascular disease?

(3) What measurements would provide more insights into understanding radiation-associated cardiovascular disease?

(4) What additional statistical analyses might be useful in assessing the relationships between radiation and the risk of cardiovascular disease?

Presentations were made by nine Japanese and international scientists with a wide range of expertise. The group discussion focused on identifying and recommending important research directions.
2. Session I. Update on assessing the risk of radiation-related cardiovascular disease

Chair, Dr Kazunori Kodama, Chief Scientist, RERF

Presentation 1. Review of studies on radiation and risk of cardiovascular disease

Dr Fred A Mettler, Department of Radiology, University of New Mexico, New Mexico, and Federal Regional Medical Center, Albuquerque, New Mexico, USA

The epidemiological cohort studies on CVD and radiation exposure have used data from those exposed through radiation therapy [1–6], occupational or environmental exposures [1, 6–14] and the Japanese atomic bombs [15–19]. In most of the radiotherapy studies, where exposures are local rather than total body, the rate of myocardial infarction did not noticeably increase at doses less than 1.5 Gy. Increased risks of CVD have been documented in atomic bomb survivors exposed to doses greater than 0.5 Gy [20]. Studies of CVD among radiation workers have shown inconsistent results, probably owing to the relatively low doses, limited statistical power and potential confounding by other risk factors. Animal studies have revealed cardiac effects [6], but most involve acute doses well above 1 Gy. The degree of CVD risk associated with low-dose exposure has major implications for the citizens of Fukushima and for occupational and medical exposures, but several issues and questions need to be addressed.

High doses of radiation have specific, pathological effects on the circulatory system, such as damage to arterial walls [6, 21]. In contrast, lower dose total body irradiation (TBI) has pathologically non-specific effects on CVD, potentially including disorders related to stroke, heart disease (20 or more subtypes), hypertension and atherosclerosis. Furthermore, different subtypes of CVD may derive from exposures to different target organs or tissues. A dose-related excess of haemorrhagic stroke, which was seen more in the early years of the A-bomb study, may have been associated with microvascular disease. Many epidemiological studies have not adequately specified the subtypes of disease or their diagnostic criteria and have not controlled for potential confounding factors, such as smoking, diet and genetics [22].

Another important question is the degree to which the results of risk estimation among atomic bomb survivors generalise to other populations. Unlike the causes of death in most Western nations, more deaths are caused by stroke than heart disease in Japan, and more deaths are caused by haemorrhagic stroke than by ischaemic stroke among atomic bomb survivors [17]. The A-bomb survivors have substantial excess relative risks (ERRs) for rheumatic heart disease, hypertensive heart disease and heart failure, but not for ischaemic heart disease or myocardial infarction (figure 1). These findings contrast with those in other exposed populations that typically show associations of radiation dose with ischaemic heart disease.

Epidemiological studies of broad populations sometimes overlook susceptible subpopulations at high risk among whom the lower dose effects may tend to occur. For example, survivors of childhood cancers treated with radiation therapy appear to be a sensitive subpopulation at high risk for CVD. Though there are limitations to the lower dose studies, they are nevertheless of importance for informing radiation protection practices, decisions about patient compensation and future management of exposed populations.

Presentation 2. Epidemiological studies of cardiovascular disease in the life span study

Dr Kotaro Ozasa, Department of Epidemiology, RERF

Recent data from the LSS show dose–response relationships between radiation and mortality from stroke and heart disease; the relationship is approximately linear for heart
Figure 1. Radiation risks for circulatory disease from the life span study of atomic bomb survivors. Per cent excess relative risks (ERRs) based on radiation dose–response analyses for selected circulatory diseases. Bars are 95% confidence intervals [15].

disease and linear–quadratic with upward curvature for stroke [15]. However, an important issue concerns subtype-specific ERRs (figure 1). ERRs were not seen for ischaemic heart disease, including myocardial infarction, or for cerebral infarction or haemorrhage, but they were significantly higher for rheumatic heart disease, hypertensive heart disease, heart failure and stroke of unspecified subtype.

To interpret these complicated results, the different coding rules and causal backgrounds during different periods in Japan must be considered. Compared with Western countries, Japan has higher mortality rates for stroke, especially intracerebral haemorrhage [23], than for heart disease [24, 25], although death rates from stroke (especially for cerebral haemorrhage) have fallen sharply over time while those for heart disease (especially heart failure) have increased. Claims that types of heart disease were misclassified are supported by the marked increase (more than 30%) in the recording of mortality rates for ischaemic heart disease and cerebral infarction in Japan between 1994 and 1995 and by a corresponding decrease in reports of heart failure (<50%). This probably occurred because in 1995, when ICD-10 replaced ICD-9, physicians were instructed to use ‘heart failure’ sparingly as an underlying cause of death (www.who.int/healthinfo/paper12.pdf).

To clarify these classification issues, subtype-specific CVD-related mortality rates were examined by dose categories over three time periods: 1950–1967, 1968–1994 and 1995–2003 (unpublished data from analysis of LSS mortality data) that coincide with the introduction of new ICD versions. These periods also reflect changes in the causes of CVD in Japan [26, 27], especially a decline in population blood pressure levels and the prevalence of hypertension [28]. In these period-specific mortality rates, overall heart disease and stroke showed consistent dose–response trends during each period. However, the temporal patterns in dose–response associations for specific subtypes of CVD were less consistent, though one interesting finding was that dose-dependent risk of rheumatic heart disease was limited to the early period (1950–1967). At RERF we have begun to examine CVD subtype results in more depth, including the uncertainties in the diagnoses listed on death certificates.

Dr Peter Jacob, Institute of Radiation Protection, Helmholtz Zentrum München, Germany

The LSS provides data for analysing the risk of cardiovascular disease after acute, whole-body, moderate exposures (0.1–1.0 Gy) to ionising radiation. Using primarily the ERR model, Shimizu et al found an approximately linear dose–response for heart disease but a linear–quadratic dose–response for stroke risk [15]. There was no clear dose threshold for heart disease, but that for stroke was 0.5 Gy.

Multi-model statistical inference has several potential advantages for analysing data with nonlinear relationships. Multi-model inference requires three steps.

1. Alternative statistical models to be included are selected heuristically.
2. Statistical goodness-of-fit weights are determined for each model.
3. Using those weights, the probability density functions of, for example, the ERR at a given age at exposure and age attained, are sampled from the individual models.

In the central region of the distributions of the variables, results are not often affected by the choice of statistical model, but data on the tails of the distributions may give substantially different results in some models. Multi-model inference can better characterise both the centre and the tails of the distribution, so the composite multi-model may be more informative for non-uniform risk coefficients across the whole range of variables (as, for example, dose or age). The uncertainty bounds from multi-model inference are often larger than those of single models, especially in the tails of the distributions of predictor variables, because they include model uncertainty.

Schollnberger and colleagues [29] applied multi-model inference to earlier LSS CVD data on the mortality from cerebrovascular diseases (here designated as CBVD) and from other cardiovascular diseases, noted here as ‘heart diseases’ [29]. To minimise a possible healthy survivor effect on the dose–response, only data after 1967 were used. For CBVD, different dose–response patterns were found below and above 0.6 Gy. In the lower dose range, the response was weak, and the ERR was lower than that of a linear no-threshold (LNT) model by a factor of about three. Between 0.6 and 1.0 Gy, the response was stronger than in the LNT model and was independent of age attained and age at exposure. This step regarding the dose–response suggests only a weak mechanism for excess CBVD mortality below several hundred milligray, whereas effects become stronger at higher doses. For heart diseases, the composite model resembled a linear–quadratic model. At several hundred milligray, the ERR dose–response was weaker than in the LNT model by a factor of about two. The ERR decreased with age at exposure.

In summary, multi-model inference is relatively independent of the assumptions made by individual models, provides a more realistic estimate of uncertainties and can yield a more informative analysis of dose, time, age and other effects.

Presentation 4. Dose–response considerations in radiation-related cardiovascular disease

Dr Nobuhiko Ban, Tokyo Healthcare University, Tokyo, Japan

Cardiovascular disease is thought to arise from injury to populations of cells and is thus regarded as a tissue reaction with a dose threshold, rather than a non-threshold stochastic effect arising from alteration of a single cell. However, the atomic bomb study and some other epidemiological studies suggest a significant increase in CVD risk at doses below 1 Gy, indicating the possibility of a dose–response without a threshold. This apparent contradiction...
may be explained by the nature of CVD as a lifestyle-related disease that is associated with various risk factors and that has a high prevalence among adults. Although radiation is one of the risk factors for onset of CVD, other lifestyle-related factors may have dominant effects when the radiation dose is not high. Consequently, the radiation dose–response relationship at low-to-medium doses will be distorted in the presence of other risk factors.

The radiation relationship can be described mathematically as a logistic function with a typical S-shaped dose–response curve for tissue reactions. When a random variable is added to account for the effects of other risk factors, the slope of the curve becomes shallower and the threshold diminishes. Thus, the shape of the radiation dose–response curve would tend to be linearised by other risk factors, even if these factors did not confound the relationship with radiation dose, and will be more similar to models of stochastic effects when the frequency of other risk factors is high, making the determination of a threshold value very uncertain.

3. Session II. Clinical research on radiation and cardiovascular disease

Chair, Dr Fiona Stewart, The Netherlands Cancer Institute, Amsterdam, Netherlands

Presentation 5. Cardiomyopathy after radiation exposure in survivors of childhood cancer

Dr Steven E Lipshultz, Department of Pediatrics, Leonard M Miller School of Medicine, University of Miami, USA

Studies of radiation-induced cardiomyopathy provide insights into the basic mechanisms of its pathology. The course of paediatric cardiomyopathy is usually progressive, so timely, frequent surveillance and early diagnosis of children who are at risk for ventricular dysfunction is needed to change the disease course using targeted strategies.

Long-term follow-up of children who have had cancer radiotherapy reveals an increasing cumulative incidence of chronic health conditions [30, 31], including cardiotoxicities, such as congestive heart failure, myocardial infarction, pericardial disease and valvular disease [32] that can be pervasive, persistent and progressive but that go undiagnosed before advanced disease becomes clinically apparent. Cardiovascular mortality is also increased after radiotherapy during childhood: 30 years after therapeutic exposures for childhood cancer, 1 in 9 survivors experiences severe heart disease [33]. Cumulative radiotherapeutic dose, younger age at exposure and concomitant treatment with other cardiotoxic therapies are risk factors for late radiation-associated cardiotoxicity [34].

Cardiotoxicity is probably caused by the interaction of genetic, environmental and temporal factors. Radiotherapy increases ventricular diastolic dysfunction, leading to a restrictive cardiomyopathy and heart failure, but it is also associated with accelerated atherosclerosis, progressive valvular heart disease leading to endocarditis, intracardiac conduction defects leading to sudden death, coronary artery disease leading to myocardial infarction and decreases in quality of life and physical functioning [5, 35, 36]. Persistent mitochondrial damage after radiotherapy, seen as copy number mutations, may be related to subsequent cardiotoxicity [37]. Cranial irradiation is associated with increased adiposity, growth hormone deficiency and reduced left ventricular mass and dimension [38–41].

Cardiac monitoring may allow heart failure to be delayed and quality of life to be improved [42]. Several predictive markers have been established, including IL-6, TNF-α, hsCRP, cystatin-C, protein ST2, NT-proBNP, galectin-3 and selected matrix metalloproteinases. Validated biomarkers for cardiac damage, heart dysfunction and cardio-renal interactions also need to be identified. Strong evidence highlights the need to identify risk factors and high-risk populations to determine targeted preventive and therapeutic strategies to minimise cardiotoxicities.
Presentation 6. Overview of cardiovascular disease investigations in the adult health study (AHS)
Dr Ikuno Takahashi, Department of Clinical Studies, RERF

Since 1958 the AHS has conducted biennial medical examinations and laboratory tests of a fixed cohort of about 20,000 LSS high-dose and matched low-dose survivors. Extensive observations have documented specific clinical or biological manifestations of radiation-induced late effects.

In terms of radiation-associated CVD, an AHS cohort study from 1968 to 1998 found a quadratic dose–response relationship for non-fatal myocardial infarction for people exposed before 40 years of age, indicating risk primarily at higher doses, but no significant dose–response for non-fatal stroke morbidity [16]. However, a recent study of the incidence of stroke during 1980–2003 found a statistically significant association for radiation exposure and haemorrhagic stroke, but not for ischaemic stroke [17].

Several current and planned investigations are studying the types, degree and causes of radiation-associated CVD risks in the AHS. A planned study of heart disease incidence will use consistent diagnostic criteria to study disease subtypes. Because the LSS study found that radiation exposure was associated with hypertensive heart disease, rheumatic or valvular heart disease and heart failure, these conditions will be examined in more detail in the AHS. An echocardiographic assessment is planned to document preclinical heart failure and valvular damage. Data on several biomarkers of circulatory disease are also being obtained, as are data on biological risk factors for CVD, such as metabolic disorders [43, 44], hypertension [45], kidney dysfunction [46], liver disorders, arteriosclerosis and microvascular changes.

Presentation 7. Biological mechanisms of radiation-induced cardiovascular disease
Dr Fiona Stewart, The Netherlands Cancer Institute, Amsterdam, Netherlands

The mechanisms of the effects of radiation on CVD are not fully understood. The mechanisms involved after high doses to the heart are probably different from those involved after low total body exposures, which result in different cardiac pathologies. For example, coronary artery atherosclerosis and myocardial infarct typically follow high-dose irradiation, as opposed to microvascular damage and fibrosis, which lead to congestive heart failure at lower doses. Experimental studies show that doses of 2 Gy or more induce the expression of inflammatory and thrombotic molecules in endothelial cells [47], which causes progressive loss of capillaries and reduced angiogenic responses [48, 49] and eventually leads to reduced perfusion [50], cell death and fibrosis [48, 49]. The results of animal studies are supported by those of clinical studies, which have found regional perfusion defects in non-symptomatic breast cancer patients 6 months after radiotherapy [50]. Local irradiation of large arteries with doses greater than 2 Gy, in combination with elevated cholesterol concentrations, initiates and accelerates the development of atherosclerosis. Local irradiation also favours the formation of unstable lesions, which are prone to rupture and may cause a fatal heart attack or stroke [51]. By contrast, experimental evidence indicates that local inflammatory processes and atherosclerosis may even be inhibited by doses under 0.5 Gy [52].

It therefore seems likely that mechanisms other than atherosclerosis are responsible for any increased risk of cardiovascular damage after low-dose TBI [6]. Systemic increases in pro-inflammatory cytokines and long-term impairment of T-cell-mediated immunity (T-cell senescence) [53] may be involved. Some evidence suggests that low-dose cardiovascular effects are, at least partly, secondary to increased serum cholesterol concentrations [49, 52], hypertension and renal damage [45, 49]. Such systemic effects are not seen after local thoracic irradiation, even after high doses.
4. Session III. Animal models for radiation and cardiovascular disease research

Chair, Dr Norio Takahashi, Consultant, RERF

Presentation 8. Genetic analysis of stroke-prone spontaneously hypertensive rats

Dr Toru Nabika, Department of Functional Pathology, Shimane University School of Medicine

Radiation exposure may cause several somatic mutations, which could result in deterministic effects on CVD, although the mechanisms are not clear: general cell senescence [54], depletion of stem (or progenitor) cells [55, 56] and mitochondrial DNA dysfunction [57] in many cells may be involved in radiation-associated CVD. Radiation also seems to disrupt the balance of signalling-molecule (e.g. cytokine) expression for an extended time, perhaps reflecting a cascade of effects that prevent a return to normal homoeostasis. Transient radiation injury may also induce permanent arteriosclerosis or reduce vascular beds, which could impose a long-term burden on the circulatory system in the heart and brain.

The importance of experimental research was illustrated by the stroke-prone spontaneously hypertensive rat (SHRSP) model for exploring the mechanisms of CVD. This model is thought to be an excellent model of cerebrovascular diseases caused by severe hypertension and arteriosclerosis because the overall vascular changes in the brain and other organs are consistent with those seen in malignant hypertension, so it may be a useful model for investigating radiation-associated CVD.

To clarify the genetic mechanisms of susceptibility to stroke in the SHRSP rat, a quantitative trait locus (QTL) analysis was performed, and two major QTLs for stroke latency under salt loading were identified on chromosomes (chr) 1 and 18, respectively. Results from six reciprocal single and double congenic rats for these QTLs showed that substituting the SHRSP-fragment for the SHR-fragment at the chr-1 and -18 QTLs increased the relative risk for stroke 8.8- and 5.2-fold, respectively, with a combined 10-fold effect on stroke risk. They also had a clear effect on salt-dependent blood pressure, which suggests a QTL-regulated link between blood pressure and susceptibility to stroke. These double congenic strains thus may provide a good experimental system for exploring radiation-associated CVD.

Presentation 9. An animal model of radiation and cardiovascular disease at the RERF

Dr Yasuharu Niwa, Department of Radiobiology/Molecular Epidemiology, RERF, and Dr Norio Takahashi, Consultant, RERF.

Findings from the LSS, AHS and radiotherapy studies indicate that radiation may be associated with an increased risk of hypertension, possibly leading to hypertensive heart disease and stroke [1–5, 15–18, 45, 58, 59], though results of studies of low-dose occupational and environmental exposures have been inconsistent [9–11, 60]. To provide experimental verification, a study using acutely irradiated SHRSP rats is assessing whether the risk of stroke is dose-related. The study is using lifespan shortening, morphological and pathological examinations of autopsy tissues and measurements of selected blood biomarkers to identify radiation-related CVD phenotypes. The study also will provide data regarding mechanisms of radiation-related stroke that might be useful to guide human studies.

Male SHRSP rats were irradiated by gamma rays at dose levels of 1, 2 and 4 Gy, with sham-unirradiated control rats. Preliminary results indicate that the life span of irradiated rats is significantly shorter than that of unirradiated rats and that perivascular changes in the organs (brain, heart and kidney) of the irradiated rats were more severe than those observed in the organs of the control rats. Given the positive results found even at 1 Gy, a similar but larger study is now being conducted at doses of 0.25, 0.5, 0.75 and 1 Gy. Again, life
spans and morphological and pathological phenotype changes will be determined. About 30 candidate biomarkers for CVD effects will be assessed, paralleling those investigated in our AHS radiation studies. The study may help confirm radiation effects at low-to-moderate doses and provide mechanistic clues for further examination in human studies.

5. Session IV. Group discussion

Chairs, Dr Roy Shore, Chief of Research, RERF, and Dr Masazumi Akahoshi, Department of Clinical Studies, RERF

Future directions for CVD research by RERF were discussed in this session, and the recommendations are summarised here.

- More detailed analysis of subtype-specific CVD mortality and its incidence in the life span study and the adult health study is needed. The diversity of heart disease subtypes may complicate estimation of the effect of radiation, so subtype-specific analyses are needed that consider the shape of the dose–response and possible confounding factors, and use uniform, reliable diagnostic criteria and measurement methodologies. The temporal changes in CVD risk patterns should also be examined.
- Potential biomarkers should be measured in stored biological samples, and advanced cardiac imaging tests should be conducted. Leading investigators should be consulted regarding optimal CVD biomarkers to best use the stored samples.
- Introduce new, robust statistical methods and collaborate with outside researchers to complement the standard methods employed in the epidemiological analyses.
- Experimental data suggest that effects of low-dose TBI may cause different pathological changes (microvascular damage and altered metabolism) than high doses limited to the heart. Thus, studies of risk and mechanisms in animal models, especially at lower doses, are encouraged. Obtaining clinical measurements of renal function, plaque instability, microvascular damage and fibrosis in the AHS will also be valuable.
- The joint roles of radiation and other CVD risk factors should be evaluated to determine whether other risk factors modify risk (effect modifiers) or serve as intermediate variables in causal pathways from radiation to CVD.
- Susceptible subpopulations (candidates: children and subgroups identified by genetic profiles) should be identified and examined for radiation effects.
- Baseline rates for various subtypes of CVD have differed substantially between Japanese and Western populations, so studies of methods of risk extrapolation are needed.

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