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Low Dose Radiation Exposure and Cardiovascular Diseases: A Review

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Abstract

The International Commission on Radiological Protection (ICRP) states that particular attention should be paid to radiation effects on the cardiovascular system because of recent published observations of their effects occurring at lower doses than previously reported (ICRP, 2007 and 2012). The review was based on scientific articles available in open literature and major reviews by organizations, in particular ICRP118. In this review, we describe the low-dose ionizing radiation effects, the causes of cardiovascular diseases (CVDs), the relationship between low-dose ionizing radiation and CVDs, and the importance of elucidating the relationship between low-dose ionizing radiation and CVD.

INTRODUCTION

The International Commission on Radiological Protection (ICRP) states that particular attention should be paid to radiation effects in the cardiovascular system because of recent published observations of their effects occurring at lower doses than previously reported (ICRP, 2007 and 2012). Our experimental study showed that repeated low-dose radiations promote abdominal aortic atherosclerosis in mice (unpublished data). Based on these informations, the relationship between low-dose radiation exposure and cardiovascular diseases (CVDs) was investigated in this review.

Low-Dose Ionizing Radiation Effect

Low-level radiations include low-dose and low-dose-rate-ionizing radiations, low linear-energy-transfer (LET) radiation (dose less than 0.2 Gy) or high LET radiation (dose less than 0.05 Gy), and dose rate less than 0.05/Gy/min. Studies on low-dose radiation remain inconclusive. Two opposing points of view are present in low-dose radiation: radiation hormesis and linear non-threshold (LNT) theory. In 1991, the US Department of Energy reported that workers with lifetime work doses of > 5 mSv had 24% lower full-fatality rates than non-nuclear workers, thereby confirming radiation hormesis. In 2006, an epidemiological study of high-background-radiation areas in Yangjiang (China) showed that adaptive responses, such as DNA repair, waste removal, apoptosis, and immune responses, occurred when the underlying level of damage expanded or spread to biological tissues [1]. Current radiation protection regulatory limits are based on the LNT theory using health data from atomic bomb survivors. Studies in recent years have sparked debate about the validity of the theory, especially at low doses [2]. The LNT model was recommended by the ICRP from a radiation protection point of view. This model states that the probabilities of inducing cancer and hereditary effects increase with dose linearly. Consequently, radiation exposure must be reasonable and have adequate protections standard in place to keep the exposure below dose limits. The LNT model shows satisfactory evidence at high doses; however for low doses, a linear fashion has less scientific evidence. Applications of the LNT model and radiation hormesis have an important effect on radiation protection and general human health [3].

Causes of Cardiovascular Diseases

CVD is the leading cause of death and disability in elderly people. Major modifiable risk factors for CVD include smoking, physical inactivity, hypertension, hyperlipidemia, diabetes, and obesity. Constitutional non-modifiable risk factors are age, gender, ethnicity, and family history. The Canadian Heart Health Survey in 1999 has revealed that smoking and stress are the main causes of heart disease, accounting for the largest proportion of patients (41% and 44%, respectively), whereas hypertension accounted for only 16% [4]. According to the exposure distribution estimated by the China Health and Nutrition Survey in 2009, the population attributable risk for CVD events was 47.3% for hypertension, 23.2% for physical inactivity, 18.5% for smoking, 13.5% for high BMI, 13.0% for high LDL cholesterol, 11.8% for hyperglycemia, 11.1% for low intake of fruits and vegetables, 7.1% for high sodium intake, and 3.5% for low polyunsaturated fatty acid intake; moreover, these values for the 2002 survey were 78.0%, 18.8%, 20.9%, 21.9%, 8.2%, 16.1%, 12.0%, 20.3%, and 2.0%, respectively [5]. Most studies on adults and elderly showed that aging increases the chance of obtaining CVD. Age is the most common non-modifiable risk factor,

and diabetes, hyperlipidemia, and hypertension are highly common modifiable risk factors for CVD [6]. Moreover, race is a non-modifiable risk factor for CVD. According to the British Heart Foundation, different ethnic groups have their own culture and traditions [7]. A recent systematic review found the relative risk (RR) of early CVD. Family history can increase CVD events by more than 70%. In addition, family history of ischemic stroke can increase CVD risk in men by 89% [8]. Other factors, such as diet, lifestyle, and metabolic risk factors for chronic diseases, also lead to high CVD morbidity and mortality.

Relationship between Low-Dose Ionizing Radiation and Cardiovascular Diseases

In the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), cardiovascular data were recently updated up to the end of 2000, and estimated relative risk (ERR) of ischemic heart disease was 0.41 Gy^{-1} [9].

Atomic Bomb Survivors

Low-dose radiation increases risk for CVD; this finding was first observed from non-cancer disease data of the Life Span Study (LSS), which investigated Japanese atomic bomb survivors that were exposed to radiation doses < 5 Gy [10, 11]. 60 percent of non-cancer patients dying with circulatory disease [11].Most studies on low-dose radiation were associated with increased CVD, including heart disease, high blood pressure, rheumatic heart disease, and heart failure [11]. Moreover, a dose–response relationship was found in a study of 288 incident cases of myocardial infarction in the clinical (Adult Health Study) subset of the LSS cohort, and RR at 1 Gy was estimated to be 1.17 (95% CI 1.01–1.36) [12].

Occupational Exposures

Mineral studies in Newfoundland and Canada have shown a correlation between coronary heart disease and radon exposure [13, 14]. RR of coronary heart disease mortality increased with cumulative radon exposure dose, but the trend test was borderline (P = 0.09). In a large cohort study of 59,000 miners working in a uranium mine in Wismut (Germany) from 1946 to 1989, 5,417 deaths from circulatory diseases (3,719 cases of heart disease, 1,297 cases of cerebrovascular disease) were followed up to the end of 1998 [14]. The pooled analysis involved approximately 42,000 employees with external and internal radiation exposures at British Nuclear Fuels plc; furthermore, a significant dose–response relationship was observed for mortality from circulatory disease (ERR/Sv = 0.65, 90% CI 0.36–0.98) and ischemic heart disease (ERR/Sv = 0.70, 90% CI 0.33–1.11) [15]. Notably, among US radiological technologists, early workers have increased cardiovascular and cerebrovascular mortalities [16].

Medical Exposures

A dose–response relationship was observed between coronary heart disease and radiation doses [17]. Increasing cardiac morbidity and mortality and risk of CVDs have been widely found after radiation therapy (RT), especially beam RT, for breast cancer, lung cancer, esophageal cancer, and even peptic ulcer [18-21]. General risk factors for CVDs, such as hypertension, diabetes, hypercholesterolemia, obesity, and smoking, probably also increase the risk of CVDs in patients treated with radiotherapy indirectly; for example, irradiation of the left kidney during para-aortic and spleen radiotherapy can result in hypertension [22-26]. The estimated ERR/Gy of cardiovascular morbidity as a whole is 0.10 (95% CI 0.07–0.13) and that of mortality is 0.08 (95% CI 0.04–0.12). Not all circulatory disease cases are lethal; however, they have a high corresponding percentage of morbidity. Based on the hypothesis, a radiation of approximately 0.5 Gy may induce circulatory disease at approximately 1% of the exposed population [11].

Molecular Mechanisms

The main mechanisms of low-dose radiation-induced cardiac damage are inflammatory processes [11]. Many inflammatory markers (C-reactive protein, IL-6, and sialic acid) are increased significantly at a dose-related fashion [27, 28]. The data of health examination showed radiation can induce calcification of aortic arch, a rise in systolic and diastolic blood pressure [29] and serum cholesterol levels [30], and has dose effect relation to some extent[31]. Whole-body doses of rats from 0.1–0.6 Gy inhibited leukocyte adhesion to endothelial cells [32], and doses from 0.025–0.05 Gy manifested protective effects on the development of atherosclerosis in ApoE knockout mice, especially at low dose rates [33]. It suggested that an non-liner dose-response relationship existed between radiation and atherosclerosis, that is also to say a protective effect on cardiovascular in very-low-dose occupational exposures (0.02 Sv), but detrimental effects in higher doses (0.2 Sv) in epidemiological researches [34]. After low-dose radiation, the earliest morphological changes in the irradiated heart were lymphocyte adhesion and extravasation, thereby causing changes in the function of capillary endothelial cells and leading to thrombosis, microvascular obstruction, and decreased capillary density, accompanied by loss of endothelial cell markers of alkaline phosphatase [35-37]. Increased proliferation ability of the remaining capillary endothelial cells is not sufficient to maintain proper microvascular function and therefore led to ischemia, myocardial cell death, and fibrosis [38]. Radiation-induced genomic instability [39], monocyte killing, and increased levels of monocyte chemo-attractant protein 1 have been presumed to be associated with low-dose post-atherosclerosis initiation and progression [40].

CONCLUSIONS

From atomic bomb survivors, occupational exposures, medical exposures, and accidental exposures, the relationship between low-dose radiation and CVDs was investigated, and the molecular mechanisms were summarized. Data from the LSS cohort of Japanese atomic bomb survivors indicated that the mortality rate of circulatory disease is high. The dose–effect threshold of heart disease is 0 Gy, signifying no threshold. Patients exposed to 1–2 Gy radiotherapy had increased risks of CVD; however, this risk becomes notable 10–20 years after exposure. The risk of CVD in accidental or occupational total-body exposure is high; however, due to carious confounding factors, the correlation between radiation and CVD cannot be concluded. The dose–effect model below 0.5 Gy is uncertain. The microvascular damage of myocardium

is main cause of Radiation-induced heart disease, generally lead to focal myocardial degeneration, fibrosis, and accelerated atherosclerosis in major blood vessels. Occupational and medical exposures account for the largest proportions in the low-dose population. Repeated radiological diagnostic examinations induce significant radiation exposure and their use increase every year. On the other hand, in 2006, the per capita dose from medical exposure (not including dental imaging or radiotherapy) in the USA was approximately 0.003 Sv. The main radiation sources were computed tomography scans, angiography, and vascular interventions. The average lifetime dose was estimated to be 20 Sv in radiologists between 1897 and 1920, 3.8 Sv between 1921 and 1935, 1.25 Sv between 1936 and 1954, and 0.1 Sv between 1955 and 1979 [41-43]. Statins (usually used to treat heart disease) and glutamine supplementation have therapeutic effects; however, no remission agents are known to slow radiation-induced CVD. Fortunately, ongoing laboratory studies are further exploring the efficacy of stem cell transplantation or stem cell products. Therefore, the relationship between low-dose ionizing radiation and CVD needs to be elucidated.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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