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# Radiation and circulatory disease

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ABSTRACT

Exposure to therapeutic doses of ionizing radiation is associated with damage to the heart and coronary arteries. However, only recently have studies with high-quality individual dosimetry data allowed this risk to be quantified while also adjusting for concomitant chemotherapy, and medical and lifestyle risk factors. At lower levels of exposure the evidence is less clear. In this article I review radiation-associated risks of circulatory disease in groups treated with radiotherapy for malignant and non-malignant disease, and in occupationally- or environmentally-exposed groups receiving rather lower levels of radiation dose, also for medical diagnostic purposes.

Results of a meta-analysis suggest that excess relative risks per unit dose for various types of heart disease do not exhibit statistically significant ($p > 0.2$) heterogeneity between studies. Although there are no marked discrepancies between risks derived from the high-dose therapeutic and medical diagnostic studies and from the moderate/low dose occupational and environmental studies, at least for ischemic heart disease and stroke there are indications of larger risks per unit dose for lower dose rate and fractionated exposures. Risks for stroke and other types of circulatory disease are significantly more variable ($p < 0.0001$), possibly resulting from confounding and effect-modification by well known (but unobserved) risk factors. Adjustment for any of mean dose, dose fractionation or age at exposure results in the residual heterogeneity for cerebrovascular disease becoming non-significant. The review provides strong evidence in support of a causal association between both low and high dose radiation exposure and most types of circulatory disease.

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## 1. Introduction

Circulatory disease, which is customarily defined as those causes of mortality and morbidity with International Classification of Diseases 10th revision (ICD10) codes I00-I99 (or equivalently the International Classification of Diseases 8th or 9th revision (ICD8, ICD9) codes 390–459), is the leading cause of death in the developed world [1,2] There are many types of circulatory disease [3]; the main types are listed in Table 1. Circulatory disease accounts for 30.8% of the 2.6 million deaths in the USA in 2014, of which the two leading components are ischemic heart disease (IHD), accounting for 23.4%, and stroke accounting for 5.1%, of all deaths [2]; worldwide IHD and stroke rank first and third in years of life lost [4]. Consistently identified independent risk factors include cigarette smoking, diabetes, high blood pressure, obesity, increased total and low-density-lipoprotein (LDL) cholesterol, or decreased high-density-lipoprotein (HDL) cholesterol [5]. Of emerging importance are certain maternal reproductive factors [6,7]. Circulatory disease has also been shown to aggregate in families, so that children of parents with cardiovascular disease are more likely to develop it themselves. Relative risk (RR) for coronary heart disease in first-degree relatives has been reported to range from 2 to 12 times higher than that of the general population [8–11]. Advances in genetic epidemiology over the past few years have helped to identify several genetic polymorphisms that increase or decrease an individual's chance of developing circulatory disease [12,13]. Such genetic polymorphisms have so far been associated with small effects on cardiovascular risk.

*Abbreviations:* AHS, Adult Health Study; CAD, coronary artery disease; CeVD, cerebrovascular disease; CT, chemotherapeutic/chemotherapy; CI, confidence intervals; EQD2, equivalent dose in 2 Gy fractions; ERR, excess relative risk; GP, general practitioner; Gy, gray; HDL, high density lipoprotein; HL, Hodgkin's lymphoma; ICD10, International Classification of Diseases 10th revision; ICD8, International Classification of Diseases 8th revision; ICD9, International Classification of Diseases 9th revision; ICRP, International Commission on Radiological Protection; IHD, ischemic heart disease; LDL, low density lipoprotein; MWDS, Mayak Worker Dosimetry System; OR, odds ratio; PA, Production Association; PTH, parathyroid hormone; REML, restricted maximum likelihood; RR, relative risk; RT, radiotherapeutic/radiotherapy; Sv, sievert; TB, tuberculosis.

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**Table 1**
Major types of circulatory disease.

| Disease endpoint | International Classification of Diseases 10th revision (ICD10) coding | Description |
|---|---|---|
| Arteriosclerosis | I25.0, I25.1, I70 | Arteriosclerosis is characterized by a thickening, hardening and loss of elasticity of the walls of arteries. This process gradually restricts the blood flow to organs and tissues. and comprises three main types, (a) Monckeberg (medial calcific) sclerosis, (b) arteriolosclerosis, and (c) atherosclerosis. Monckeberg sclerosis is caused by calcium build-up in the arterial walls, and results in them becoming stiffer, and is often asymptomatic. Arteriolosclerosis is the process of artery thickening and hardening in the small arteries and arterioles. Hyaline arteriolosclerosis results from (a) lumenal protein leakage into and build-up in the arterial walls, resulting in thickening and stiffening of the arterial wall and reduced blood flow through the lumen or (b) diabetes, which causes high levels of blood sugar that directly damages the endothelial cell layer, likely via alterations in carbohydrate and fat metabolism, resulting in damage to the basement membrane of the blood vessels. Hyperplastic arteriolosclerosis results from extreme hypertension and compensatory thickening, via build up of smooth-muscle cells in the arterial wall. In contrast, atherosclerosis is caused by build-up of cholesterol-rich atheromatous plaques in the tunica intima (the part of the arterial wall immediately behind the endothelial cell layer) and is a disease of the large arteries (e.g., coronary, carotid). Plaque build-up and rupture, which results in clotting of the blood at the site of rupture, reduces blood-flow in the affected arteries. If blood flow to the kidneys is reduced for whatever reason (whether due to atherosclerosis or arteriolosclerosis), the kidney interprets this as low blood pressure and activates the renin-angiotensin-aldosterone system, raising blood volume and so blood pressure, causing hypertension (high blood pressure). When arteriolosclerosis leads to chronically reduced blood flow to the kidney arteriolonephrosclerosis is produced, which if untreated can lead to chronic renal failure. Atherosclerosis is also caused by hypertension, as well as by smoking, by elevated levels of low density lipoprotein (LDL) cholesterol, or by reduced levels of high density lipoprotein (HDL) cholesterol. The weakening of the arterial wall that results from atherosclerosis can lead to aneurysms in many parts of the body, in particular the intestine (e.g., abdominal aortic aneurysms). The term arteriosclerosis is sometimes (incorrectly) used interchangeably with the term atherosclerosis. Arteriosclerosis is mostly subsumed within IHD, but a substantial component (atherosclerosis, ICD10 I70) is independent of that. It is a relatively common type of cardiovascular disease, and the substantial part subsumed within IHD accounts for about a third of all IHD deaths, so about 4% of all deaths in the UK [104,105]. |
| Cardiac valve diseases | I05–I09, I34–I39 | This rubric includes a variety of abnormalities to one or more of the heart valves (tricuspid, pulmonary, mitral, and aortic valves). Problems in all four valves are typically of three types (a) regurgitation or backflow – when the valve doesn't close properly (b) stenosis – when the valve flaps stiffen or fuse and (c) atresia – when a valve lacks an opening for blood to flow through. Cardiac valve disease can be congenital, but can also be acquired over the course of life. This is a less common type of circulatory disease mortality, and accounts for about 0.6% of all deaths in the UK [104,105]. |
| Cardiac arrythmias | I47–I49 | Cardiac arrhythmia, also known as cardiac dysrhythmia or irregular heartbeat, is a group of conditions in which the heartbeat is irregular, too fast, or too slow. This is a less common type of circulatory disease mortality, and accounts for about 0.6% of all deaths in the UK [104,105]. A heart rate that is too fast – above 100 beats per minute in adults – is called tachycardia and a heart rate that is too slow – below 60 beats per minute – is termed bradycardia. Many types of arrhythmia have no symptoms. When symptoms are present these may include palpitations or feeling a pause between heartbeats. More seriously there may be lightheadedness, fainting, shortness of breath, or angina. While most types of arrhythmia are not serious, some predispose a person to complications such as stroke or heart failure. Others may result in cardiac arrest. There are four main types of arrhythmia: (a) extra beats, (b) supraventricular tachycardias, (c) ventricular arrhythmias, and (d) bradyarrhythmias. Extra beats include premature atrial contractions and premature ventricular contractions. Supraventricular tachycardias include atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia. Ventricular arrhythmias include ventricular fibrillation and ventricular tachycardia. Arrhythmias are due to problems with the electrical conduction system of the heart. Arrhythmias may occur in children; however, the normal range for the heart rate is different and depends on age. |
| Cardiomyopathy | I25.5, I42–I43 | Cardiomyopathy is characterized by the heart muscle becoming enlarged, thick, or rigid. In rare cases, the muscle tissue in the heart is replaced with scar tissue. This is a less common type of circulatory disease mortality, and accounts for about 0.3% of all deaths in the UK [104,105]. As cardiomyopathy worsens, the heart becomes weaker, and less able to pump blood through the body and maintain a normal electrical rhythm. This can lead to heart failure or irregular heartbeats called arrhythmias. In turn, heart failure can cause fluid to build up in the lungs, ankles, feet, legs, or abdomen. The weakening of the heart also can cause other complications, such as heart valve problems. The four main types of cardiomyopathy are (a) hypertrophic cardiomyopathy, (b) dilated cardiomyopathy, (c) restrictive cardiomyopathy, and (d) arrhythmogenic right ventricular dysplasia. Cardiomyopathy can be congenital or acquired over the course of life. |
| Cerebrovascular disease (CeVD) | I60–I69 | CeVD, commonly termed stroke, arises because of problems with the circulation of blood in the blood vessels of the brain. This is the second most common type of circulatory disease mortality, and accounts for about 7% of all deaths in the UK [104,105]. A blockage with effects lasting less than 24 h is referred to as a transient ischemic attack (TIA). Loss of blood and oxygen to areas of the brain can lead to cell death and consequently permanent brain dysfunction. Two major forms of stroke are recognised (a) ischemic stroke, caused by narrowing of blood vessels, and (b) hemorrhagic stroke, cause by bursting of a blood vessel in the brain. Ischemic stroke is divided into those caused (a) by blockage due to blood clots forming locally (thrombotic stroke) or (b) fragments from distant clots lodging in the brain vasculature (embolic stroke). |
| Hypertensive disease | I10–I15 | Hypertension (high blood pressure) has a number of adverse effects on the circulatory system; in particular, as the heart pumps against this pressure, it must work harder, causing the heart muscle to thicken, and eventually heart failure may develop. This is a less common type of circulatory disease mortality, and accounts for about 0.7% of all deaths in the UK [104,105]. With increasing blood pressure risk of hemorrhagic stroke increases. The major types of hypertensive disease include (a) hypertensive heart disease, (b) hypertensive chronic kidney disease, and (c) hypertensive heart and chronic kidney disease. Hypertension also results in damage to and thickening of the arterial walls, resulting in |