

Risks and Mechanisms of radiation-induced cardiovascular and cerebrovascular disease

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Epidemiological studies have shown a clear association between high therapeutic doses of thoracic irradiation and increased risks of cardiovascular disease in long-term cancer survivors, although these effects may take decades to manifest. Survivors of Hodgkin's lymphoma and childhood cancers, for example, have 2 to >7-fold increased risks for cardiac deaths after total tumour doses of 30-40 Gy, given in 2-Gy fractions. Increased cardiac morbidity and mortality has also been widely reported after irradiation for breast cancer. Only a small part of the heart is in the treatment field and the risks are consequently lower than for Hodgkin's lymphoma survivors (RR 1.1-1.4). Some studies also show increased risks after much lower total body radiation exposures. A-bomb survivors, for example have estimated excess risks of death from heart disease and cerebrovascular disease of 14% per Gy and 9% per Gy, respectively. Other large cohorts exposed to cardiac or brain doses < 2 Gy have also been analysed and some, but not all, demonstrated increased risks related to radiation exposure dose. The clearest indications of increased risk are for populations exposed to doses >0.5 Gy and there is a great deal of uncertainty associated with risk estimates at lower doses. The mechanisms whereby these effects occur are, however, poorly understood. Experimental studies can help to unravel some of these mechanisms and may identify suitable strategies for managing these risks. Experimental studies show that doses of ≥ 2 Gy induce the expression of inflammatory and thrombotic molecules in endothelial cells. In the heart this causes progressive loss of capillaries and eventually leads to reduced perfusion, myocardial cell death and fibrosis. The animal data are supported by clinical studies demonstrating regional perfusion defects in non-symptomatic breast cancer patients 6 months after radiotherapy. In large arteries, radiation (≥ 2 Gy) initiates atherosclerosis and predisposes to the formation of unstable lesions, which are prone to rupture and may cause a fatal heart attack or stroke. After doses < 2Gy, it seems likely that other mechanisms are responsible for cardiovascular effects. Persistent increases in pro-inflammatory cytokines and long-term impairment of T-cell-mediated immunity may well be involved. Monocyte killing and increased levels of chemoattractant proteins may also play a role in initiation and progression of atherosclerosis.