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Ionizing radiation-induced circulatory and metabolic diseases

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Abstract

Risks to health are the prime consideration in all human situations of ionizing radiation exposure and therefore of relevance to radiation protection in all occupational, medical, and public exposure situations. Over the past few decades, advances in therapeutic strategies have led to significant improvements in cancer survival rates. However, a wide range of long-term complications have been reported in cancer survivors, in particular circulatory diseases and their major risk factors, metabolic diseases. However, at lower levels of exposure, the evidence is less clear. Under real-life exposure scenarios, including radiotherapy, radiation effects in the whole organism will be determined mainly by the response of normal tissues receiving relatively low doses, and will be mediated and moderated by systemic effects. Therefore, there is an urgent need for further research on the impact of low-dose radiation. In this article, we review radiation-associated risks of circulatory and metabolic diseases, addressing epidemiological, biological, risk modelling, and

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Declaration of interests

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systems biology aspects, highlight the gaps in knowledge and discuss future directions to address these gaps.

Keywords

ionizing radiation; circulatory disease; heart; endothelial; metabolic syndrome; radiotherapy; systems biology

1. Introduction

The general goal of this review is to have a comprehensive quantitative and mechanistic understanding of all radiogenic health effects, especially at low doses. Dose limits in radiation protection are based on knowledge of radiation cancer risk derived from epidemiological studies and assumed risk of heritable effects in humans (ICRP 2007). Epidemiologically-derived health risk estimates are limited in power below 100 mSv; depending on the cancer type, the applied models for risk inference can be linear or linear quadratic. However, for risk management purposes, it is a linear non-threshold (LNT) model that is applied, justified on the basis of a biologically plausible argument that relates direct damage to nuclear DNA to mutations in specific genes that drive carcinogenesis.

In addition to cancer risks, there is increasing evidence for risk of non-cancer conditions, notably circulatory disease, cataracts and neurological effects in response to low and moderate radiation doses. Defining the risks of non-cancer diseases at low and moderate dose levels would be important for protection of people and the system of radiation protection. The identification of such risks at low doses could lead to reconsideration of radiation detriment calculations, tissue weighting factors, dose limits, and reference levels. Furthermore, there might also be a need to consider additional protection measures.

In the context of the Multidisciplinary European Low Dose Initiative (MELODI), low doses and/or low dose rates refer to a range of acute and/or protracted exposures of ionizing radiation (IR) that are typical of those encountered in the workplace, the environment and in diagnostic and therapeutic medicine. Doses below 100 mSv (100 mGy for X-rays and gamma rays) are considered low. Moderate doses, typically in the order of 100–1000 mSv, refer to doses that may be encountered by normal tissues in interventional radiology, radiotherapy (RT) or in nuclear or radiological accidents. Doses above 1000 mSv are considered high and may cause symptoms of acute radiation sickness when received as a total body exposure during a short period of time. Low dose rates were defined by the United Nations Scientific Committee on Effects of Atomic Radiation (UNSCEAR) as dose rates smaller than 0.1 mGy/min averaged over an hour or smaller than or equal to 6 mGy/h averaged over a few hours, consistent with the BEIR VII report (BEIR 2006) and others, as reviewed recently (Ruhm et al. 2015). In the radiation protection context, annual dose rates below 100 mSv may be considered low.

The aim of the current paper is to review the state-of-the-art of radiation-induced circulatory and metabolic diseases, present research gaps and recommend research strategies. The review is based on presentations and discussions during the workshop on “Non-cancer

effects of ionizing radiation" which took place in Sitges, Spain, in April 2019. The workshop was organized by MELODI together with CONCERT, European Joint Programme for the Integration of Radiation Protection Research. The participants discussed clinical and epidemiological studies, experimental models, mechanistic approaches, and dosimetric aspects, judging the quality and quantity of information available. A wide range of long-term complications have been reported among cancer survivors treated by RT, in particular cardiovascular diseases (CVD) and metabolic diseases that are major risk factors for circulatory diseases. Here, we focus on the question of low-dose effects and consider potential mechanisms of radiation action. The objective of the Sitges workshop was to provide input for the European roadmap for research in these areas, summarizing the research needs, giving recommendations on research needed, required resources anticipated and the expected timespan for studies that could be expected to yield considerable progress in this area. Furthermore, potential implications for the system of radiation protection were discussed. As for the resources required and timespan needed, a joint roadmap was developed by MELODI in collaboration with other European radiation protection research associations after the Sitges workshop (CONCERT et al. 2020).

2. Radiation-associated circulatory effects, overview of the epidemiology and the role of lifestyle factors

The risks of radiation-associated circulatory disease have been observed in therapeutically- or diagnostically-exposed cohorts even at low doses. Similarly, occupationally- and environmentally-exposed groups and the Life Span Study (LSS) and related Adult Health Study (AHS) of Japanese atomic bomb survivors show increased circulatory risk. Ischaemic heart disease and cerebrovascular disease are mostly caused by atherosclerosis and may lead to acute myocardial infarction and stroke. In the following section, the attention will be concentrated on studies with high quality individual organ dosimetry, based on the previous systematic reviews (Little et al. 2012a; Little et al. 2008), which have been updated for the present paper, based in part on updates, but also on previously reported (non-systematic) reviews of the moderate/low-dose literature (Little 2013; Little and Lipshultz 2015); similar to a recent review (Little 2016) the organ or tissue dose range that is to be considered is not constrained.

2.1 Therapeutically exposed groups

Recent studies have suggested radiation-associated excess morbidity and mortality in groups of childhood cancer survivors (Table S1) (El-Fayech et al. 2017; Haddy et al. 2016; Mulrooney et al. 2009; Tukenova et al. 2010a). The RT organ dosimetry is of variable quality, but higher in the French childhood cancer cohort (El-Fayech et al. 2017; Haddy et al. 2016; Tukenova et al. 2010b), in that it is fully individualized, based on Monte Carlo reconstructions derived from individual treatment records (Diallo et al. 1996; Shamsaldin et al. 1998). The US study adjusted for tobacco use (Mulrooney et al. 2009), and although data on smoking and body mass index was available in some studies (El-Fayech et al. 2017; Haddy et al. 2016), adjustment for these did not materially alter results. In addition, none of these four studies corrected for known risk factors for circulatory disease. There have been a number of studies of circulatory disease in Hodgkin lymphoma (HL) patients, (Cutter et

al. 2015; Hahn et al. 2017; Maraldo et al. 2015; van Nimwegen et al. 2017; van Nimwegen et al. 2016), as well as studies focusing on circulatory disease in lung cancer (Dess et al. 2017; Wang et al. 2017a; Wang et al. 2017b) and breast cancer patients (Darby et al. 2013; Jacobse et al. 2019), doses in both of which tend to be lower than in the HL patients. Most of these studies suggest modest but generally highly significant radiation-associated excess risk (Table S1).

Doses in the US peptic ulcer patients (Little et al. 2012b) were generally lower than in any of the cancer studies and documented significant excess mortality risks for all circulatory disease and ischaemic heart disease (IHD) and indications of excess risk for cerebrovascular disease (CeVD). Doses to a number of different target tissues, specifically heart, thyroid, kidney, pancreas, and brain, were used to assess radiation effects. Using thyroid dose (a surrogate for dose to the carotid artery) for CeVD and heart dose for other circulatory disease endpoints resulted in significant heterogeneity of risk between endpoints, which was not the case when heart dose was used throughout (Little et al. 2012b). Using brain or thyroid dose resulted in somewhat higher risks for CeVD, the risk being particularly high for brain dose. As noted by Little et al., “one limitation of the study is that the radiation dosimetry, although of high quality in many respects, fails to account for variability in patient anatomy, e.g., the heart size/shape/position and its relation to the diaphragm and stomach” (Little et al. 2012b).

Many of these studies have a rich set of lifestyle and environmental risk factors, including many of the known risk factors for circulatory disease, in particular the childhood cancer studies (El-Fayech et al. 2017; Haddy et al. 2016; Mulrooney et al. 2009), the Netherlands HL studies (Cutter et al. 2015; van Nimwegen et al. 2017; van Nimwegen et al. 2016), the Nordic breast cancer study (Darby et al. 2013) and the US peptic ulcer study (Little et al. 2012b), and adjustment for these did not materially alter results.

The risks suggested by these studies are generally consistent with each other, and with those in the diagnostically and other, lower-dose, studies; a possible exception is the French-UK study (Tukenova et al. 2010b), where risk is much higher than for many of the other studies considered. The discrepancy with other studies (e.g., of adult exposure) may reflect the younger exposure age or younger age at follow-up in this group, although this would not explain the discrepancy with risks in the US childhood-cancer survivor study (Mulrooney et al. 2009). Excess relative risk (ERR) of circulatory disease in the Japanese LSS cohort is significantly modified by attained age (Little et al. 2012a; Shimizu et al. 2010). The fact that the ERR in relation to cumulative heart dose or in relation to equivalent doses delivered in 2-Gy fractions (EQD2) in the Nordic breast cancer study (Darby et al. 2013) agrees well with those in many other radiation-exposed groups (Little 2016), suggests that either of these measures (cumulative heart dose, EQD2 heart dose) may be relevant for this outcome (IHD) (Little et al. 2013). The fact that risks evaluated using brain dose for CeVD in the US peptic ulcer study yielded much higher risks than those observed using heart or thyroid dose, or in the LSS (Little et al. 2012a; Shimizu et al. 2010), in which doses are more or less uniform whole body, suggests that, assuming the risks in the two cohorts are to be consistent, brain may not be the most relevant organ for CeVD.

2.2 Diagnostically exposed groups

The two major studies of circulatory disease mortality in relation to medical diagnostic exposure are both of groups that received repeated fluoroscopic doses as part of the lung collapse treatment for tuberculosis (TB), in Canada (Zablotska et al. 2014) and in Massachusetts (Little et al. 2016). A pooled analysis of the two datasets has recently appeared (Table A1) (Tran et al. 2017). Although there is no dose-response overall in the pooled data, if analysis is restricted to persons with < 0.5 Gy, the dose response trends (ERR/Gy) for all circulatory disease and IHD become much steeper, and statistically significant. This observation is consistent with the findings from a recent meta-analysis (Little 2016) and also from findings in the LSS discussed below. In both cohorts there is limited medical and lifestyle information. This is more extensive in the Massachusetts data, and includes smoking and alcohol consumption, thoracoplasty, and pneumolobectomy; some of these variables were included in baseline models for certain disease endpoints (Little et al. 2016).

2.3 Non-medically exposed groups

2.3.1 Japanese atomic bomb survivors—Excess radiation-associated mortality from heart disease and stroke has been observed in the LSS cohort (Shimizu et al. 2010; Takahashi et al. 2017), also for stroke among those exposed in early childhood (Tatsukawa et al. 2008). In the latest follow-up of the Adult Health Study (AHS), a subset of the LSS cohort subject to biennial clinical examinations showed no radiation-associated excess risks of hypertension or myocardial infarction morbidity (Table S2) (Yamada et al. 2004). Analysis within the AHS of those exposed in early childhood showed a significantly increased incidence of non-fatal stroke or myocardial infarction, although there was no excess risk among those exposed in utero for whom the average exposures were much lower (Tatsukawa et al. 2008). Recent analysis of the Japanese LSS data taking account of dose measurement error suggested downward curvature in the dose response for all circulatory disease, so that the ERR/Gy is higher at lower doses (Little et al. 2020).

2.3.2 Occupationally exposed groups—The International Agency for Research on Cancer 15-country study of radiation workers found increasing dose-related trends for mortality from all circulatory diseases and CeVD, and decreasing trends for IHD, heart failure, deep vein thrombosis, and pulmonary embolism (Vrijheid et al. 2007), although none of these trends was statistically significant. Further follow-up of the UK, US and French cohorts from this dataset has been recently published. This study suggests significant radiation-associated increases in risk for all circulatory disease, IHD and CeVD, with significant downward curvature in the dose response for CeVD, but no curvature for the other endpoints (Table S2) (Gillies et al. 2017). It would appear from the results of the component workforces that make up this study that the significant trends are largely driven by those in the UK (Azizova et al. 2018; McGeoghegan et al. 2008; Muirhead et al. 2009), the trends in the US and French data being generally null (Leuraud et al. 2017; Schubauer-Berigan et al. 2015); however, there are only borderline significant indications of variation by country (Gillies et al. 2017).

Radiation-associated excess circulatory disease, IHD and CeVD morbidity were observed in Chernobyl recovery workers, although morbidity from hypertensive heart disease and other heart disease was not increased (Ivanov et al. 2006; Kashcheev et al. 2017; Kashcheev et al. 2016). The analysis of circulatory disease mortality in this cohort was based only on comparison with external circulatory disease rates, via use of standardized mortality ratios (Ivanov et al. 2001). As such, this analysis almost certainly yields biased estimates of risk, as the general Russian population is very likely not representative of the Chernobyl recovery workers, because of generally observed healthy-worker selection effects (Bell and Coleman 1987; Doll et al. 1965).

For IHD and CeVD in the Mayak workers there was a highly statistically significant trend with dose for morbidity, but the trend of IHD and CeVD mortality was less clear, and generally not statistically significant. There have been a number of analyses of the Mayak worker cohort in the last few years (Azizova et al. 2018; Azizova et al. 2015a; Azizova et al. 2015b; Azizova et al. 2014; Moseeva et al. 2014; Simonetto et al. 2014; Simonetto et al. 2015), based on a similar underlying dataset, but with slight variations in disease endpoints, year of follow-up and dosimetry system. The study is unusual in that doses to certain internal organs, especially the lung and liver, were dominated by doses from internally deposited radionuclides, especially plutonium. Doses in this study are among the highest for the occupationally-exposed groups considered in this section, and arguably more comparable with at least the medical-diagnostic or even the RT-exposed groups considered above: average total body doses for external γ rays were 0.5 to 0.6 Gy. However, unlike the partial-body doses received from RT, or even those in the tuberculosis fluoroscopy cohorts, the external whole-body doses received by the Mayak workers generally accumulated over a long time with an average dose rate of <5 mGy/hour, so must it be considered a low dose-rate exposure (Wakeford and Tawn 2010).

2.3.3 Environmentally exposed groups—A study of a cohort of environmentally exposed individuals in the Southern Ural Mountains reported a statistically significant or borderline significant increase (depending on the latent period used) of both all circulatory disease mortality and IHD mortality (Table S2) (Krestinina et al. 2013).

Circulatory disease mortality was studied in a Kazakhstan group exposed to fallout from nuclear weapons tests at the Semipalatinsk site (Grosche et al. 2011). No excess circulatory disease risk was reported in the group of exposed settlements, although if exposed and unexposed settlements were analysed together, the excess risks were highly statistically significant and implausibly large. The dosimetry in this cohort is problematic because it is based on assessments of residence, estimates of time spent outdoors, and diet, all of which were collected by interviews more than 30 years after the bomb tests. As such, the results of this study may be less informative than others considered here.

2.4 Lifestyle factors as targets for intervention

The lifestyle factors are major contributors to circulatory diseases illustrated by an example from North Karelia, eastern province in Finland. The extremely high cardiovascular mortality caused great concern among the local population. In response, the North Karelia

project was launched in 1972 to carry out a comprehensive community-based prevention program, as reviewed recently (Vartiainen 2018). The main aim to reduce the high serum cholesterol, blood pressure and smoking levels with lifestyle changes and improved drug treatment, especially for hypertension, was successful. Coronary mortality reduced in the middle-age population by 84% from 1972 to 2014. About 2/3 of the mortality decline was explained by risk factor changes and 1/3 by improvement of new treatments developed since 1980s. This example illustrates how important it is to collect information on lifestyle factors in any radiation epidemiological studies addressing risk of circulatory diseases.

2.5 Genetic susceptibility to circulatory diseases

Identifying genetic predisposition to circulatory disease could help understanding the disease process and thereby feed into the research strategies investigating the role of radiation in the pathogenesis. Genome-wide association studies (GWAS) have identified over 200 genome-wide significant and suggestive risk loci that modulate the risk of coronary artery disease (CAD) (Nikpay et al. 2015). Several of the genes implicated to date in large-scale analyses of CAD susceptibility encode proteins with a known role in the biology of circulating risk factors for CAD, notably lipid levels and the metabolism of lipoproteins; others relate to additional atherosclerosis risk factors, such as genes implicated in systemic inflammation and in hypertension. Interestingly, genes involved in DNA damage response pathways do not show up in these GWAS studies. Almost all risk variants identified by GWAS are commonly found in the European population, and average European carries tens of these risk alleles (Kessler et al. 2016). However, most CAD-associated single nucleotide polymorphisms (SNPs) are located in non-coding regions of the genome and do not have known biological roles (Kovacic and Bakran 2012). This suggests that these variants are more likely to affect gene regulation rather than protein structure.

So far, there is lack of GWAS studies looking for loci predisposing to circulatory disease among radiation-exposed populations. Circulatory disease is considered as a late-appearing tissue reaction, having a latency of up to decades after the radiation exposure (ICRP 2012). GWAS studies among patients treated with RT have looked for loci associated with the development of toxicity in normal tissues in the months or few years following RT, focusing on tissue toxicity endpoints that are typical for the affected area and causing functional impairment. As reviewed recently, RT for breast or lung cancer inevitably leads to the exposure of the heart and major blood vessels in the chest and neck area (Rosenstein 2017). In the radiogenomics studies on breast cancer, associations with adverse toxic outcomes have been reported for SNPs related to the *Tgfb1* gene (a multipotent growth factor affecting cell differentiation, proliferation, apoptosis and matrix production) or the *Tnfa* (a cell signalling cytokine involved in systemic inflammation), as well as genes whose products are involved with responses to oxidative stress. Furthermore, a SNP in *Xrcc1* that plays a role in base excision repair of oxidative damage produced by radiation was found to be associated with risk for skin toxicities. Toxicities related to the RT of the lung have revealed associations with heat shock proteins, e.g. HSP27, that increase cellular resistance to heat shock, oxidative stress and inflammatory mediators. Inflammation and oxidative stress are among the mechanisms implicated in the development of circulatory disease after radiation

exposure, with inflammation emerging from GWAS studies as a common factor associated with circulatory diseases and tissue toxicities with or without radiation exposure.

There is increasing but still limited experimental evidence for genetic susceptibility to radiation-induced circulatory disease in mouse models (Foray et al. 2016). Irradiation accelerated the development of atherosclerotic lesions in apolipoprotein E deficient ($ApoE^{-/-}$) mice (Stewart et al. 2006) which may have implications for atherosclerosis-prone individuals. Accumulation of p53 was required for the transition from cardiac hypertrophy to heart failure (Sano et al. 2007) and p53 deficiency in endothelial cells caused myocardial injury and heart failure after irradiation (Lee et al. 2012). $ApoE^{-/-}$ $p53^{+/-}$ mice showed the accelerated progression of spontaneous and radiation-induced atherosclerosis compared with $ApoE^{-/-}$ $p53^{+/+}$ (Mitchel et al. 2013). Mice lacking p21 were predisposed to radiation-induced myocardial injury (Lee et al. 2012). Deficiency of Wip1 phosphatase, a negative regulator of the protein kinase ataxia-telangiectasia mutated (ATM) signalling, prevented atherosclerosis (Le Guezennec et al. 2012) but deficiency of ATM accelerated atherosclerosis in $ApoE^{-/-}$ mice (Schneider et al. 2006). These suggest that ATM, p53, and p21 may play a protective role in atherogenesis.

3. Radiation-associated circulatory effects, overview of the biology

High doses of IR increase the risk of CVD, with damage to coronary arteries (atherosclerosis) and microvascular insufficiency frequently observed after high-dose irradiation (Adams et al. 2003; Demirci et al. 2009; Tapio 2016). Endothelial cells (EC), a monolayer forming the inner coating of all vasculature, play an important role in these pathologies. EC form a barrier between blood and the sub-endothelial matrix and modulate blood clotting, vascular tone, and immune and inflammatory response (Luscher et al. 1990; Marsden et al. 1991). High-dose IR induces endothelial dysfunction that is characterized by pro-inflammatory and pro-fibrotic state with premature endothelial senescence, increased oxidative stress, reduced levels of nitric oxide (NO), and enhanced adhesiveness based on high expression of selectins, integrins, and other cellular adhesion molecules such as VCAM, ICAM, and PECAM (Azimzadeh et al. 2015; Philipp et al. 2017; Sievert et al. 2015; Yentrapalli et al. 2013a; Yentrapalli et al. 2013b). Although much less is known about the possible adverse effects of low-dose IR, some recent data suggest that biological mechanisms may differ depending on the dose in a nonlinear manner (Averbeck et al. 2018).

3.1 Cellular studies

Increased adhesion and leukocyte migration through the endothelium is the first step in atherosclerosis. Using human coronary artery endothelial cell line (HCAEC) as a model, increased adhesion of monocytes and release of pro-inflammatory cytokines (Interleukin-6 and IL-8) was observed at the dose of 2 Gy X-rays (Baselet et al. 2017a). This effect became significant seven days after the exposure. However, when cells were exposed to iron ions (2 Gy, 170 keV/μm) a decreased adhesion of monocytes and no effect on the release of pro-inflammatory cytokines was observed (Baselet et al. 2017a). Both X-rays and iron ions resulted in a marked decline of cell numbers in the confluent EC monolayer.

The radiation exposure of human umbilical vein endothelial cells (HUVEC) to single doses of X-rays (≥2 Gy) and carbon ions (≥0.1 Gy) resulted in significantly increased expression of ICAM-1 protein, which was partially mediated by TGF-beta1 (Kiyohara et al. 2011). Even lower X-ray doses have shown similar effects, and exposure to single X-ray doses of 0.125, 0.25 and 0.5 Gy or fractionated doses of 2 x 0.125 Gy and 2 x 0.25 Gy, with 24-hour interfraction interval, resulted in significantly increased ICAM-1 protein expression and enhanced adhesion of peripheral blood mononuclear cells (PBMC) 18 hours post-irradiation (Cervelli et al. 2014). A simultaneous enhancement of intracellular reactive oxygen species (ROS) generation and activation of NF-κB via p65 phosphorylation was observed. These doses neither triggered apoptosis nor had any effect on viability. This study suggests that even fractionated low-dose radiation may accelerate chronic vascular inflammation preceding the atherosclerotic process.

However, if the EC are in an inflammatory state at the time of radiation exposure, low-dose irradiation is known to have an anti-inflammatory effect. This low-dose effect is being used in the X-irradiation therapy that has been clinically applied for several decades especially in Germany in the treatment of non-malignant inflammatory and degenerative diseases (Ott et al. 2014; Seegenschmiedt et al. 2004). To further clarify this mechanism, the endothelial cell line EA.hy926 was grown to confluence, stimulated using TNF-α to induce a pro-inflammatory state and irradiated 4 hours later using X-ray doses between 0 and 1 Gy (Large et al. 2015; Large et al. 2014). The adhesion of PBMC showed a nonlinear significant reduction at 0.5 Gy, returning to elevated levels at higher doses. This reduction coincided with a decreased expression and activity of oxidative stress proteins glutathione peroxidase, superoxide dismutase 1, and nuclear factor erythroid 2–related factor 2 (Nrf2) suggesting an enhanced ROS production at 0.5 Gy. Indeed, scavenging of ROS by N-acetyl-L-cysteine or activation of Nrf2 by its activator molecule AI-1 significantly restored adhesion of PBMC to EC at the dose of 0.5 Gy. A similar effect was seen with primary human dermal microvascular EC (Large et al. 2015), implying an anti-inflammatory effect at doses around 0.5 Gy.

In addition to increased adhesion and production of ROS in EC, the reduction of NO, responsible for the maintenance of basal vasodilator tone, is a hallmark of EC dysfunction (Sandoo et al. 2010). An immediate (1 day) radiation-induced decline in the activity of endothelial NO synthase was followed by a late (14 days) reduction on the level of NO for a dose as low as 0.5 Gy (X-rays) in HCAEC (Azimzadeh et al. 2017b). The late reduction of NO coincided with the reduced expression of the antioxidant protein glutathione S-transferase omega-1 and increased levels of oxidized proteins, suggesting that increased production of ROS was coupled to reduced levels of NO. Downregulation of proteasome activity, increased protein ubiquitination and enhanced expression of senescence markers $p16^{INK4a}$ and $p21^{WAF1}$ was also observed 14 days post-irradiation (Azimzadeh et al. 2017b). Furthermore, the phosphorylation of RhoGDI, a modulator of rho family G proteins, was reduced 24 hours after irradiation, thus leading to the induction of RhoA signalling.

A rapid activation of the RhoA pathway was also seen in EA.hy926 cells for doses as low as 0.2 Gy (Co-60 gamma rays). Activated RhoA signalling is known to result in increased cell adhesion and permeability (Beckers et al. 2010; Wojciak-Stothard and Ridley

2002). Previous data further suggest that RhoA activation by inflammatory cytokines and agonists of G-protein-coupled receptors triggers vascular disease (Seasholtz and Brown 2004). Indeed, Rho kinase inhibitors have been shown to have therapeutic potential in prevention and treatment of CVD (Shimokawa and Takeshita 2005).

Transcriptomic profiling of HCAEC revealed an immediate induction of pro-inflammatory genes 24 hours after exposing the cells to 0.5 Gy or 2.0 Gy X-rays (Baselet et al. 2017b). Furthermore, these cells showed increased secretion of pro-inflammatory cytokines IL-6 and chemokine CCL2 between days 2 and 7 post-irradiation. This pro-inflammatory phenotype was not observed at 0.05 Gy or 0.1 Gy. In contrast, senescence-associated β-galactosidase activity was enhanced at all doses implying that premature senescence may occur even at low doses.

In agreement with these data, non-irradiated HCAEC treated with the secretome of irradiated cells using 10 Gy X-rays showed significantly increased expression of $p21^{Waf1}$ (Philipp et al. 2017). In addition, these non-irradiated, but secretome-treated bystander cells showed enhanced levels of ICAM-1, STAT1, and p38 suggesting a pro-inflammatory phenotype.

Chronic low-dose-rate radiation of HUVEC also triggered premature endothelial senescence observed by increased senescence-associated β-galactosidase staining (Yentrapalli et al. 2013a; Yentrapalli et al. 2013b). Senescent cells expressed low levels of RhoGDI, high levels of $p21^{Waf1}$ and showed inhibition of the P13K/Akt pathway.

3.2 Animal studies

Data from animal models using high-dose IR are in agreement with some of the human data from cancer therapy patients highlighting acceleration of atherosclerotic plaque formation and predisposition to an inflammatory, thrombotic plaque phenotype (Cottin et al. 2001; Hoving et al. 2008; Pakala et al. 2003; Raghunathan et al. 2017; Stewart et al. 2006; Stewart et al. 2010). Some human studies such as those in *Tinea capitis* cohorts with relatively low cardiac radiation doses also show increased CVD risk (Boaventura et al. 2018; Shai et al. 2009). Many animal studies have used mice that are genetically predisposed to atherosclerosis such as the $ApoE^{-/-}$ mouse.

The few low-dose studies existing at the moment emphasize the role of dose rate in the atherosclerotic plaque formation. Mitchel et al. exposed $ApoE^{-/-}$ mice to total body Co-60 gamma doses of 0.025, 0.05. 0.10 or 0.50 Gy, either at low dose rate (1.0 mGy/min) or at high dose rate (about 0.15 Gy/min) at an early (2 months of age) or late (8 months of age) stage of atherogenesis (Mitchel et al. 2011). If the irradiation was given early at a low dose rate and at the lowest doses examined (25 or 50 mGy), the lesion frequency was reduced in animals 3 months after the exposure, and this effect persisted until 6 months after the exposure. Similarly at the high dose rate, the lowest doses used (25–50 mGy) tended to be the most effective at reducing both lesion frequency and size. However, the lesion severity and pro-inflammatory status as well as the total serum cholesterol levels were increased at all doses. If the irradiation was given late at a low dose rate, a small inhibitory effect on the progression of lesion severity was seen but the deceleration was only significant at 0.025

Gy. Furthermore, a dose-dependent decrease in total serum cholesterol was observed. No persistent significant changes were seen at the high dose rate.

A similar study comparing the effect of low and high dose rates on the atherosclerotic progress in ApoE$^{-/-}$ mice with cumulative doses of 0.3 Gy or 6.0 Gy showed that at high-dose-rate irradiation the number of plaques was significantly increased at 6.0 Gy but not at 0.3 Gy (Mancuso et al. 2015). The plaques developed principally in the aortic arch. Using the low-dose-rate irradiation (1 or 20 mGy/day), both doses increased markedly the plaque area although the number of plaques decreased. Plaques were observed both in the aortic arch and in the descending thoracic aorta.

Since the dose rate seems to play an important role in the atherosclerotic outcome, Ebrahimian et al. investigated the effect of very low-dose-rate radiation (12 or 28 μGy/h) on the plaque formation in ApoE$^{-/-}$ mice that were exposed chronically for 8 months (Ebrahimian et al. 2018). The cumulative doses were around 67 mGy and 157 mGy, respectively. Exposure at 12 μGy/h had no significant effect on the parameters tested, but that at 28 μGy/h resulted in an increase in anti-inflammatory cytokine production (IL-4, IL-10, IL-13, IL-18) and in antioxidative gene expression (*Cat*, *Ctat1*, *Sod1*, *Sod2*). Furthermore, it reduced the plaque size and increased the plaque stability.

Although anti-inflammatory and hormetic effects of low doses have been observed in cellular and animal studies their role in the context of radiation protection is not yet known. The fact that low-dose RT has been successfully used for benign degenerative inflammatory disorders for decades (Ott et al. 2019) is out of the scope of this review but emphasizes the need for more research on the low-dose area.

4. Biologically-based models for the radiation risk of cardiovascular events

IHD and CeVD are mostly caused by atherosclerosis and may lead to acute myocardial infarction and stroke. Classical risk factors of atherosclerosis comprise smoking, high blood pressure, dyslipidemia, obesity and diabetes. The pathobiological mechanisms of radiation on the circulatory system have been reviewed recently (Baselet et al. 2016; Tapio 2016). Hughson et al. have presented an overview of the pathological processes targeted by radiation at different levels of biological organization from the molecular and cellular to the organ level (Hughson et al. 2018). In general, radiation exposure can initiate or accelerate many pathogenic processes that may increase incidence of myocardial infarction and stroke. RT significantly enhances the risk for these events by about 7% per Gy in breast cancer patients (Darby et al. 2013). These data were later confirmed results with the suggestion that the volume of the left ventricle receiving 5 Gy was the most important prognostic dose-volume parameter (van den Bogaard et al. 2017).

Atherosclerotic changes of the vasculature may be the main drivers for the risk of myocardial infarction and stroke in response to RT. These changes and the impact of radiation on the vascular system can be measured with imaging procedures such as computed tomography (CT) scans and ultrasonography. Thickness of the carotid intima

media (CIMT) increased by about 0.1 mm in astronauts after long space flights and in head and neck cancer patients after RT (Arbeille et al. 2016; Wilbers et al. 2014). CIMT is a moderate predictor of risk for myocardial infarction and stroke using a linear response in Cox regression models of proportional hazards (Lorenz et al. 2007). Myocardial infarction and stroke are caused by ruptures of arterial walls which have become unstable under the influence of atherosclerotic plaques (Libby and Theroux 2005). Wall rupture is a critical phenomenon characterised by a sudden transition brought about by continuously deteriorating stability. Simonetto et al. (2020) suggested that an age-adequate CIMT in a healthy person does not pose an additional risk for myocardial infarction or stroke and observed a strong nonlinear risk response for a positive deviation from the age-adequate value (Simonetto et al. 2020a). As a consequence, radiation risk cannot be characterized by the same coefficient for all exposed individuals, but rather strongly depends on the stage of atherosclerotic progression. For healthy individuals, radiation exposure might not pose an additional risk for myocardial infarction or stoke, whereas exposure for individuals with vasculature showing an advanced atherosclerotic state carry a high risk. In view of these findings the risk coefficient of 7% per Gy should be considered as an average value.

Biologically-based models for the risk of myocardial infarction and stroke must address the emergence of atherosclerosis in the vasculature in space and time. However, such risk models are currently not available. In the EU-funded MEDIRAD project a mechanistic prediction model for the risk of myocardial infarction and stroke in breast cancer patients receiving RT is under development (http://www.medirad-project.eu/). Since wall rupture is the key event in the causal chain which builds up the risk for myocardial infarction or stroke, a good conceptual model should address this chain in an adequate form. The chain involves the development of atherosclerosis from fatty streaks via fibrous plaques to complicated lesions that eventually cause a rupture.

To model the dynamics of atherosclerosis, Simonetto et al. have constructed a Markov Chain Monte Carlo code with continuous state space representing the coronary artery intimal surface area that is burdened with atherosclerotic lesions of increasing severity (Figure 1) (Simonetto et al. 2020b). Myocardial infarction rates are assumed to be proportional to the area of most complicated lesions which appear at the end of the chain. The model is fitted simultaneously to infarction incidence rates observed in the German KORA registry (Kuch et al. 2008), and to the age-dependent prevalence and spatial extent of atherosclerotic lesions in the PDAY study (PDAY 1993). To allow for nonlinear transition rates and to consider at the same time randomness and inter-individual heterogeneity, the model applies extensive simulations of the state space. The model provides biological explanation for pertinent features of the incidence curve. For women, the significant age-dependence of model parameters around the age of menopause qualitatively reproduces the known vascular effects of female sex hormones. For men, the incidence curve flattens at old age. According to the model, flattening is explained by a) saturation of the atherogenic process and b) removal from individuals at high risk from the cohort (frailty). Importantly, the model offers an interface to derive its parameters from imaging data that is routinely taken in the form of CT scans before and after RT. Hence, the individual atherosclerotic state of a patient can be projected into a biologically-based model. Compared to the one-size-fits-all approach of

applying a single risk coefficient to every patient, this approach would offer a step forward to a more personalized projection of CVD risks after RT.

5. Radiation-associated metabolic effects

Metabolic syndrome (MS) is a pathologic condition characterised by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia (Alberti et al. 2009). It is one of the leading causes of death (Saklayen 2018) and strongly associated with increased risk for CVD, type 2 diabetes, and other disabilities (Tune et al. 2017). MS shares many features with the known consequences of high-dose IR, both showing pro-inflammatory, pro-thrombotic phenotype and elevated levels of oxidative stress (Azzam et al. 2012b; Kajimoto and Kaneto 2004; Pickup 2004; Spahis et al. 2017). Discrimination between MS-related and radiation-related atherogenicity or the causal relation between radiation exposure and development of MS represent therefore major challenges.

High concentrations of triglycerides in combination with low concentrations of HDL-C are important factors for MS-related atherogenicity. Atherogenic index of plasma (AIP), defined as the logarithm of the ratio between the triglyceride concentration and the high-density lipoprotein cholesterol (HDL-C) (Dobiásová and Frohlich 2001) is a promising tool to estimate the level of MS-related atherogenicity. AIP has been successfully used in cohorts of children, healthy adults, pre- and postmenopausal women, patients with hypertension, type 2 diabetes, dyslipidemia and patients with positive or negative angiography findings (Dobiásová 2004; Guo et al. 2020). MS-related risk factors include large waist circumference, and increased levels of HDL-C, triglycerides, fasting glucose and blood pressure (Alberti et al. 2009; Assmann et al. 2007). Other factors related to MS are age, sex, family history, physical inactivity, atherogenic diet, and also the traditional plasma lipid ratios (Manninen et al. 1992).

Recently, data have been accruing suggesting high-dose IR as a causal factor for MS. In particular, a wide range of long-term complications including CVD and MS have been reported in cancer survivors (Diller et al. 2009; Oeffinger et al. 2006; Phillips et al. 2015), with cancer treatments playing a pivotal role in this context (Carver et al. 2007; Oeffinger et al. 2006; Phillips et al. 2015). In particular, RT that is received by over 40% of cancer patients, in the form of targeted or total body irradiation (TBI) (Baskar et al. 2012), significantly increases the risk for endocrine and metabolic diseases up to decades after exposure (Baker et al. 2013; Geenen et al. 2010; Oeffinger et al. 2009). Such metabolic complications, ranging from obesity to insulin resistance, further predispose exposed survivors to CVD and dramatically affect their health trajectory (Baker et al. 2013; Geenen et al. 2010; Oeffinger et al. 2009). In light of the constant increase in the number cancer survivors, there is an urgent need to better understand the link between the use of RT and the development of MS to identify individuals at risk of CVD and guide preventive and therapeutic strategies. As there is paucity of information available regarding the impact of low dose irradiation in the context of cancer, the currently available knowledge obtained from high dose studies will be reviewed here.

5.1 Cranial RT, endocrine disturbances and body composition

Although cranial RT (CRT) is not as commonly used as it once was in the treatment of childhood malignancies, the increase in survival rates for childhood cancer has led to the emergence of a constantly growing population at risk of metabolic diseases (Darzy et al. 2009; Follin et al. 2014). Some of the complications reported in that population include growth hormone (GH) and adrenal insufficiency (Follin et al. 2014), impaired leptin metabolism (Brennan et al. 1999), altered body composition or increased obesity (Baker et al. 2013; Garmey et al. 2008), and insulin resistance or diabetes (Baker et al. 2013; Oeffinger et al. 2009). Several reports have identified an increase in body mass index (BMI) in cancer survivors treated with CRT (Garmey et al. 2008; Meacham et al. 2010; Oeffinger et al. 2009). Body composition, and in particular adiposity, fall under the influence of hormonal factors, including GH and the appetite-regulating hormone leptin. GH deficiency (GHD) has been frequently reported following CRT for childhood cancer (Brennan et al. 1999), leading to increased adiposity, with GH supplementation normalizing adiposity (Bulow et al. 2004). Such hormonal or body composition changes have long been established as risk factors of insulin resistance. Thus, several large cohorts of cancer survivors have identified CRT as a contributor to the development of insulin resistance (Baker et al. 2013; Oeffinger et al. 2009). However, conflicting observations have also been reported with some studies failing to link GHD or leptin disturbances with increased BMI or insulin resistance (Papadia et al. 2007). Such discrepancy could stem from the various radiation doses used in the course of treatment, with reports observing that only higher doses of radiation (usually above 20 Gy) resulted in increased BMI (Craig et al. 1999; Meacham et al. 2005; Oeffinger et al. 2003). The risk of CRT-induced metabolic complications is also dependent on the age at treatment, as children receiving CRT at a younger age are at a higher risk of obesity (Garmey et al. 2008) or gender-dependent, with female survivors showing higher risks of obesity than males (Craig et al. 1999; Garmey et al. 2008; Oeffinger et al. 2009).

5.2 Metabolic complications following total body or abdominal irradiation

Similarly to CRT, TBI and abdominal irradiation have been widely associated with changes in body composition, altered lipid profile (Amorim et al. 2020; Neville et al. 2006; Oeffinger et al. 2009; van Waas et al. 2012) and the development of insulin resistance in childhood cancer survivors (Daniel et al. 2018; Meacham et al. 2009; Neville et al. 2006; Oeffinger et al. 2009), with some studies identifying TBI as exerting a stronger effect than CRT or abdominal irradiation (Meacham et al. 2010). Similar to CRT, GH deficiency (Galletto et al. 2014), altered body composition, including fat distribution, and impaired pancreatic function have been observed in response to TBI (Amorim et al. 2020; Wei et al. 2015a; Wei et al. 2015b) or abdominal irradiation (Cicognani et al. 1997; de Vathaire et al. 2012; Neville et al. 2006; Oeffinger and Sklar 2012; Teinturier et al. 1995; van Waas et al. 2012). Increased systemic levels of triglycerides, low density lipoprotein cholesterol and free fatty acids up to decades post-irradiation (Daniel et al. 2018; Amorim et al. 2020), suggestive of impaired lipid metabolism, could indicate long-term damage to the liver, but also potentially to the adipose tissue which has shown a particular sensitivity to radiation exposure (Nylander et al. 2016; Poglio et al. 2009). In addition, the persistence of elevated glucose or insulin levels (Daniel et al. 2018; Meacham et al. 2009; Neville et al. 2006; Amorim et al. 2020)

is suggestive of long-lasting alterations affecting the pancreas (van Waas et al. 2012), the liver, the adipose tissue or the skeletal muscle considering their anatomical position and their critical role in the regulation of glucose metabolism (Saltiel and Kahn 2001), although clinical data is still lacking to clearly establish the presence of such damage.

Thus, mouse models have been used to investigate the molecular mechanisms underlying radiation-induced metabolic changes. Mice exposed to 6 Gy TBI developed long-lasting perturbations in skeletal muscles metabolism, adipocytes and pancreatic functions, mediated by epigenetic changes, resulting in altered whole body metabolism and insulin resistance (Amorim et al. 2020; Nylander et al. 2016). Such perturbations led to a dramatic remodelling of the systemic lipidomic signature in mice, consistent with the signature observed in long-term childhood cancer survivors (CCS) more than 10 years after TBI (Amorim et al. 2020). In the same population, a remodelling of the T-cell epigenome was associated with increased T-cell activation and increased production of pro-inflammatory cytokines (Daniel et al. 2018). These immune changes were associated with systemic inflammation and insulin resistance, mimicking what has been previously described in the context of diabetes (Shoelson et al. 2006). These observations suggest that skeletal muscle and the immune system could play a role in the development of radiation-induced metabolic complications in exposed populations.

In BALB/c mice, low-dose TBI (0.1 Gy X-rays) induced a metabolic shift from oxidative phosphorylation to aerobic glycolysis in the small intestine, resulting in increased radiation resistance (Lall et al. 2014). This metabolic shift, also observed in human lymphocytes and fibroblasts, highlighted the upregulation of genes encoding glucose transporters and enzymes of glycolysis and the oxidative pentose phosphate pathway, concomitant with downregulation of mitochondrial genes, with corresponding alterations in metabolic flux through these pathways (Lall et al. 2014). This phenomenon was ROS-dependent and occurred *in vitro* only under physiological oxygen concentration (5% O_2).

5.3 Radiation-induced changes in cardiac metabolism

Heart muscle needs continuously high levels of energy due to its lifelong contracting function. The energy is mainly produced as ATP in the respiratory chain of cardiac mitochondria (Lopaschuk 2017). Fatty acids are the heart's main source of fuel, although it can also derive energy from glucose, lactate, pyruvate or ketone bodies (Grynberg and Demaison 1996). In the normal heart, there is a great flexibility to switch from one source to another depending on the energy demand. However, the cardiac ATP store is limited and can support only a few cardiac cycles (Grynberg and Demaison 1996).

The first indications that IR may affect the cardiac energy metabolism came from studies using mice locally irradiated to the heart (Azimzadeh et al. 2013; Barjaktarovic et al. 2011; Barjaktarovic et al. 2013). A high dose of 16 Gy (X-rays) resulted in a decline in cardiac mitochondrial number, destruction of the cristae structure and decreased expression of the mitochondrial transcription factor TFAM (Azimzadeh et al. 2013). Furthermore, a deactivation (phosphorylation) of peroxisome proliferator-activated receptor alpha (PPAR alpha), the main regulator of the lipid metabolism in the heart, and a slight but significant increase of serum glucose and oxidised LDL was shown 16 weeks after local heart

irradiation (Azimzadeh et al. 2015; Azimzadeh et al. 2013). The X-ray dose of 2 Gy, but not 0.2 Gy, resulted in a rapid (4 weeks) but persistent (40 weeks) reduction in the succinate-driven respiration in mitochondria isolated from irradiated mouse hearts (Barjaktarovic et al. 2011; Barjaktarovic et al. 2013).

Using the Gottingen minipig model, Kenchegowda et al. showed radiation-associated insulin like growth factor-1 (IGF-1)-dependent inhibition of the anti-inflammatory, anti-oxidant insulin signal transduction pathway (IRS/PI3K/Akt) and induction of the pro-inflammatory mitogen-activated protein kinase (MAPK) pathway (Kenchegowda et al. 2018). Selective IGF-1 resistance was associated with an amplification of reactive oxygen species-induced damage, inflammation and endothelial dysfunction.

A dose-dependent increase in IHD incidence and mortality has been shown in the Mayak workers chronically exposed to external gamma rays (Azizova et al. 2010; Azizova et al. 2012). A *post mortem* proteomics analysis was carried out using cardiac left ventricle samples from three dose groups (<100 mGy, 100–500 mGy, and >500 mGy) compared to non-exposed control group (Azimzadeh et al. 2017a). All workers and the participants of the control group were diagnosed with IHD, which was the cause of death. A dose-dependent down-regulation of glycolytic and mitochondrial proteins and inactivation of PPAR-alpha was shown in the two highest dose groups (Azimzadeh et al. 2017a; Papiez et al. 2018) suggesting an impairment in both lipid and carbohydrate utilization. This observation may represent an exceptional pathological scenario not similar to that of a failing heart (Ingwall 2009; Neubauer 2007). It suggests little flexibility in metabolic switching between lipids and carbohydrates for energy production and indicates a slow but progressive depletion of ATP, possibly leading to impairment of the contractile function (Azimzadeh and Tapio 2017).

6. Systems biology in the present and future circulatory and metabolic studies: an outlook

According to the current understanding, one of the major determinants of biological response to IR is the induction of damage to DNA, proteins, and lipids which initiates further responses of the cells or tissues and to a great extent determines the systemic nature of radiation effects (Formenti and Demaria 2009; Ji et al. 2019; Mavragani et al. 2019). The magnitude of the initial damage is very important not only in the area of radiation protection, but is of major concern in different areas of biology, with implications to human pathophysiology (Ermolaeva and Schumacher 2014; Martin et al. 2011).

For the biological response, communications of DNA damage response (DDR) with the immune system play an important role at multiple levels. DDR, induced especially in the case of complex DNA damage in healthy tissue, may be instrumental in the initiation of various chronic and late effects involving inflammatory and immune responses and usually through the mediation of oxidative stress (Pouget et al. 2018). In other words, the initial cellular damage usually results in a cascade of events involving the release of ROS (Azzam et al. 2012a) and damage-associated molecular patterns (DAMPs) which are recognized by Toll-like receptors (TLRs), even at low doses (0.05 and 0.1 Gy) (El-Saghire et al. 2013). Bioinformatics work has shown a close association and crosstalk between radiation response

and immune system components (Georgakilas et al. 2015), as well as those of DDR and innate immune system (Pateras et al. 2015).

Exposure conditions (e.g., partial body/total body, dose and dose rate, fractionation, acute or chronic, radiation quality) might affect the immune system to different degrees. The idea of the pivotal, but also complicated involvement of the immune system in the organism's reaction to whole-body or partial-body irradiation is also supported by different studies as reviewed recently (Diegeler and Hellweg 2017). Nevertheless, complex DNA damage is currently accepted as the main instigator of unrepaired or misrepaired lesions. The low dose effects can be partially attributed to these complex DNA lesions that may arise from one double strand break (DSB) if several other non-DSB lesions or even single strand breaks are expected in the vicinity. As shown in some studies, these complex non-DSB DNA lesions can be converted into DSBs during the repair process (Mavragani et al. 2019). Furthermore, DNA damage after low radiation doses may escape cellular surveillance and repair and progress to a mutagenic catastrophic event at later stages especially when replication or mitosis is initiated (Lobrich et al. 2005).

Radiation exposure can affect different levels of cellular organization and communications between DNA and proteins or between proteins and lipids, a process similar to that observed in the induction of oxidative stress and oxidative damage. This suggests the use of more integrative biology approaches like omics: transcriptomics, proteomics (Fedorova et al. 2015).

Although many radiation studies on the plethora of biological and especially non-cancer effects refer to moderate-to-high doses like those applied in RT (Rodriguez-Ruiz et al. 2018) or space travel (Beheshti et al. 2019), low doses are always implicated in the real-life scenarios (Hammi et al. 2020). In RT, doses at surrounding normal tissues can be below 0.1 Gy. Therefore, radiation effects in the whole organism after an acute or chronic radiation exposure will be determined mainly by the relatively low doses at normal tissues and systemic effects mediated by the immune system (Mavragani et al. 2016).

As mentioned earlier, cardiac and metabolic effects of low-dose IR have been studied under various biological models from cells to mice and humans (Azzam et al. 2011; Baselet et al. 2016; Beheshti et al. 2019; Hughson et al. 2017; Yan et al. 2014) and particularly highlighted in the recent NASA Twins study (Garrett-Bakelman et al. 2019). Most epidemiological studies agree that inflammatory and immune response networks play a central role in the biological response (Baselet et al. 2016). Recent studies suggest that the nucleotide-binding domain and leucine-rich-repeat-containing family pyrin 3 (NLRP3) inflammasome plays a pivotal role in radiation-induced cardiovascular injury (Huang et al. 2020). Omics studies performing transcriptome profiling in the left ventricular murine cardiomyocytes isolated from mice exposed to 0.9 Gy, 1 GeV proton (^{1}H) and 0.15 Gy, 1 GeV/nucleon iron (^{56}Fe) over 28 days after exposure have categorized some major differentially expressed genes (DEGs) belonging to cell cycle, oxidative responses, inflammation and transcriptional regulation functional groups (Coleman et al. 2015). Recent metabolomics analysis in female mice receiving local heart irradiation with 6 MV photons at 0.2 and 2 Gy induced changes in energy metabolism, fatty acid beta-oxidation, oxidative

stress and cellular damage. This study suggests that metabolomics may be an applicable and sensitive tool even in future human studies investigating cardiac response to radiation (Gramatyka et al. 2020).

7. Concluding remarks

This review provides strong evidence in support of a causal association between acute high-dose and chronic low-dose radiation exposure and most types of circulatory disease, in particular IHD and CeVD. These findings confirm the results of previous systematic reviews and meta-analysis of moderate and low-dose groups (Little 2016; Little et al. 2012a). The association is less certain for other circulatory diseases given the only marginal level of statistical significance and the highly significant inter-study heterogeneity of risks in studies of this endpoint (Little 2016). A previous meta-analysis suggested that if the association between low-level radiation exposure and the risk of circulatory disease reflects an underlying causal relationship, linear in dose, then the overall excess risk of mortality after exposure to low doses or low dose-rates of radiation may be about twice that currently assumed (Little et al. 2012a). Since the risks that are derived here using a somewhat larger body of data are consistent with those, the implications for low-dose radiation risk are unaltered. Nevertheless, the possible mechanisms for risk at low doses and low dose rates are, in contrast to the situation at higher doses and dose rates, relatively little understood. There is an urgent need for further research in this area (Kreuzer et al. 2015).

The biological data are supporting the epidemiological data indicating that even low-dose IR, if given to EC or vasculature in a normal non-inflammatory state, results in a pro-atherogenic outcome in the form of increased adhesiveness, inflammation, and premature senescence. Furthermore, adverse metabolic consequences can be seen in the heart muscle even below 0.5 Gy. In contrast, if the cells or vasculature are in inflammatory state low doses of IR may function in an anti-inflammatory manner.

As in the epidemiology, the knowledge of possible cellular and molecular mechanisms and relationships between radiation exposure and consequent circulatory and metabolic effects is still scarce. Especially, the years of latency between radiation exposure and the appearance of clinically relevant symptoms and the complexity of the clinically relevant endpoints make it difficult to identify those early cellular and molecular changes that are involved in the development of relevant late effects. This is partly due to the lack of good animal models for the human situation. At the moment, almost all animal data of the low-dose IR come from the $ApoE^{-/-}$ mouse studies. Furthermore, radiation exposure in connection with other risk factors is of additional importance. Other risk factors such as MS, associated with obesity or diabetes, can either precede or occur during or after the radiation exposure. Since recent data indicate that especially high-dose IR can be a causal factor for both CVD and MS it is relevant to investigate the molecular mechanisms that play a role in the aetiology of these different scenarios.

Recent data strongly suggest an association between radiation and the development of metabolic complications in cancer survivors exposed to high localized RT dose or TBI. Although the leading mechanisms are yet to be fully uncovered, persisting endocrine

changes, functional alterations affecting the pancreas, the adipose tissue, the liver or skeletal muscles, and long-lasting immune impairments could all play a role. If total body irradiation seems to exert the strongest effect on the development of metabolic diseases, CRT and abdominal irradiation can also affect metabolic functions. There is currently no evidence on causal association between low doses and metabolic changes in human, only in animal models, but in occupational settings moderate doses (100 – 500 mGy) at low dose rate are able to alter the energy preferences in the cardiac muscle.

In the face of a constantly growing population diagnostically, environmentally or occupationally exposed to low-dose radiation, there is an urgent need to better identify and monitor individuals at risk of circulatory or metabolic complications. Especially low doses may contribute to the systemic normal tissue damage in all these populations. Therefore, low-dose studies are the basis for prevention and amelioration of adverse late effects providing a deeper understanding of the long-lasting impact of radiation on circulatory and metabolic functions and the underlying mechanisms.

8. Recommendations for future research

MELODI developed several recommendations for the way forward in research on radiation-induced circulatory and metabolic diseases. The two main recommendations for future research were (i) to continue to follow large adult cohort studies (Japanese atomic bomb survivors, worker and clinical studies) as well as paediatric cohorts (e.g. *Tinea capitis*, CT) and (ii) and to collect more biological samples in order to better understand the radiation impact on the disease process. Furthermore, identifying new existing suitable cohorts with a good statistical power will be important in the future. A precise dosimetric assessment in epidemiological studies is necessary and should include information on dose and dose rate, fractionation, and part of body or organ exposed, in particular in the case of sensitive structures such as heart, liver or carotid arteries. In the follow-up studies, information about morbidity and mortality, a clear diagnosis and definition of heart disease and related diseases such as MS or diabetes, but also heart function and echocardiology are relevant. In particular, patient and occupationally exposed cohorts may be ideal due to reliable information on dosimetry and diagnoses, but also presenting a possibility to access biosamples. In the short term, the highest potential to advance understanding in radiation-induced circulatory and metabolic diseases is expected from studies at near-field and/or out-of-field therapeutic doses. In the long term, basic and clinical research addressing CVD and metabolic diseases at progressively lower doses is warranted.

A general weakness of the current low-dose studies involving circulatory and metabolic disease is the lack of information on lifestyle factors, in particular those having an impact on the pathogenesis such as smoking, alcohol consumption, diet, obesity, physical activity, and genetic background. A range of biological samples (blood, urine, saliva, fecal samples) can be informative to fill this gap, elucidating radiation-associated changes in the metabolic (fasting glucose, cholesterol, AIP or other plasma lipid ratios), inflammatory (acute phase proteins, cytokines, chemokines), or cardiovascular status (e.g. cardiac troponin, C-reactive protein, B-type natriuretic peptide). For that matter, imaging data, biopsies and even autopsies represent good sources of information.

It is obvious that also mechanisms other than the classical DDR pathways are involved in the radiation-induced circulatory and metabolic responses. This calls for a new insight on potential mechanisms and effect of modulating factors, such as inflammatory, stress and immune responses, and lifestyle factors (Table 1). Disease relevant cell types, such as EC, macrophages and smooth muscle cells of the vessel wall, hepatocytes and adipocytes should be used for hypothesis-driven studies addressing possible mechanisms, looking at, but not limited to, epigenetics, accelerated aging, mitochondrial dysfunction, oxidative stress, and (other) links between metabolic and circulatory diseases.

Adverse outcome pathways of low-dose-related CVD and MS should be further investigated (Figure 2) (OECD 2013). Advances in medical imaging and automatic image analysis will significantly improve the quantitative assessment of progressing atherosclerosis in the vascular system. Integrating these imaging data with epidemiological cohorts of incidence for CVD provides opportunities for the development and testing of biologically-based risk models that make use of the actual pathologic state for more accurate personalized risk projection.

Macromolecular interactions:

The left column illustrates the initiating events, the deposition of energy in tissue, whereby highly reactive radicals are formed and most of them are quickly removed by chemical repair. Some radicals react with cellular macromolecules, either directly with DNA (4% of energy deposition), proteins, and lipids (16% of energy deposition) or indirectly via radiolysis of water (80% of energy deposition). The physical attributes of the radiation (radiation quality) and dose delivery (e.g. high or low single dose or fractionated/protracted exposure) modulate the responses.

Cell and tissue level effects:

Unrepaired or misrepaired damage to cellular macromolecules leads to damage response signalling and bystander effects mediated by reactive oxygen species (ROS), miRNAs, cytokines and other small molecules. At the cellular level, damage manifests as apoptosis, cellular senescence, and inflammatory phenotype creating continuous oxidative stress. Damage response signalling and bystander effects expand the physiological change from single cells to a population of cells and tissues. Note that mutations caused by misrepaired DNA damage are not shown in this scheme, although they are major drivers for stochastic effects (cancer, germline instability). Such clonal expansion of cells carrying specific mutations is not known to take place in the development of circulatory or metabolic diseases.

Organ and organ system level:

The cellular and tissue level effects can lead to a variety of tissue reactions impairing organ functions within weeks (early toxicity/tissue reactions), months or years (late toxicity/tissue reactions). Both the dose and the dose rate impact the presentation and severity of the tissue reaction or toxicity. Typical phenomena and mechanisms underlying tissue reactions include inflammation, oxidative stress, immunological effects, epigenetic changes, and accelerated

aging of cells and tissues. Such adverse pathways contribute to endothelial dysfunction and metabolic changes that lead to adverse circulatory and metabolic outcomes.

Adverse health outcome:

Circulatory disease and metabolic disease represent the main complications appearing after a long latency period of years or even decades. The length of the latency period depends on the dose, high doses leading to an earlier onset of the tissue reaction. Note that circulatory and metabolic diseases are interrelated, metabolic disease being a major risk factor for circulatory disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Ionizing radiation causes adverse circulatory and metabolic health effects at high doses
- Strong epidemiological evidence supports of a causal association between chronic low-dose radiation exposure and most types of circulatory disease
- The impact of low-dose radiation may be modulated by lifestyle factors and inflammatory, stress and immune responses but more research is needed

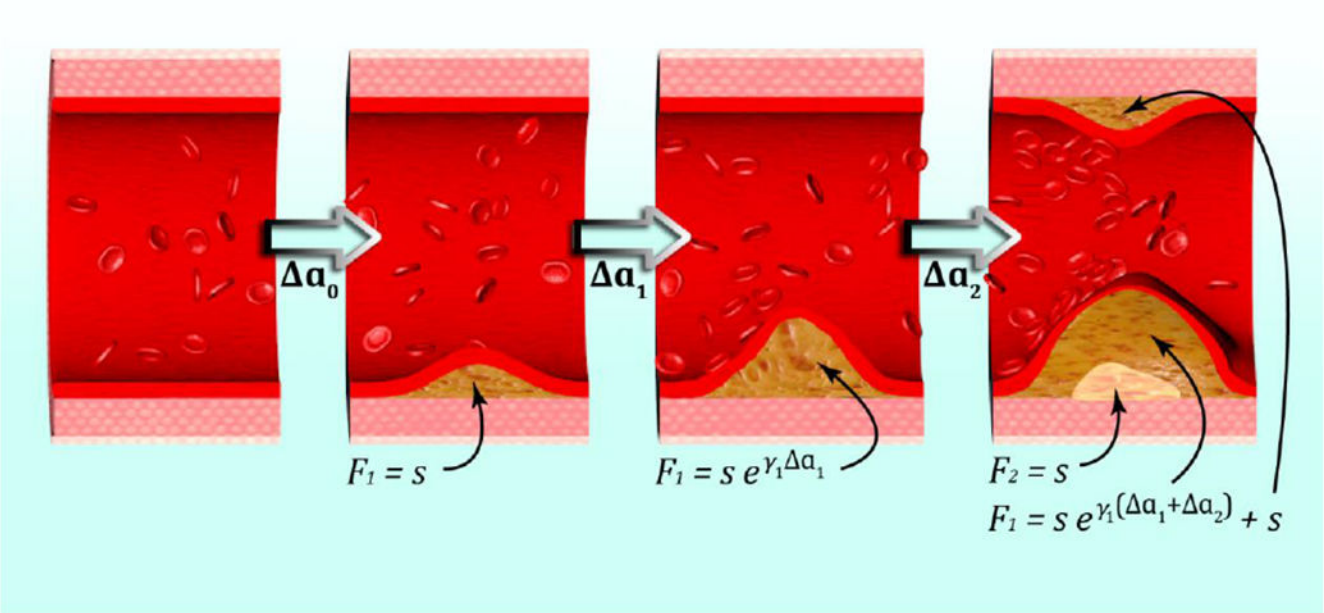

Figure 1. A model of early plaque development.

A first fatty streak appears after time Δa_0 with area $F_1 = s$. Subsequently it expands with growth rate γ_1. At the last depicted time point, part of the fatty streak has become a fibrous plaque, with area $F_2 = s$. The intimal surface area involved with fatty streaks (and more advanced lesions), F1, results from further growth of the first fatty streak and from the origin of a second fatty streak (Simonetto et al. 2020b).

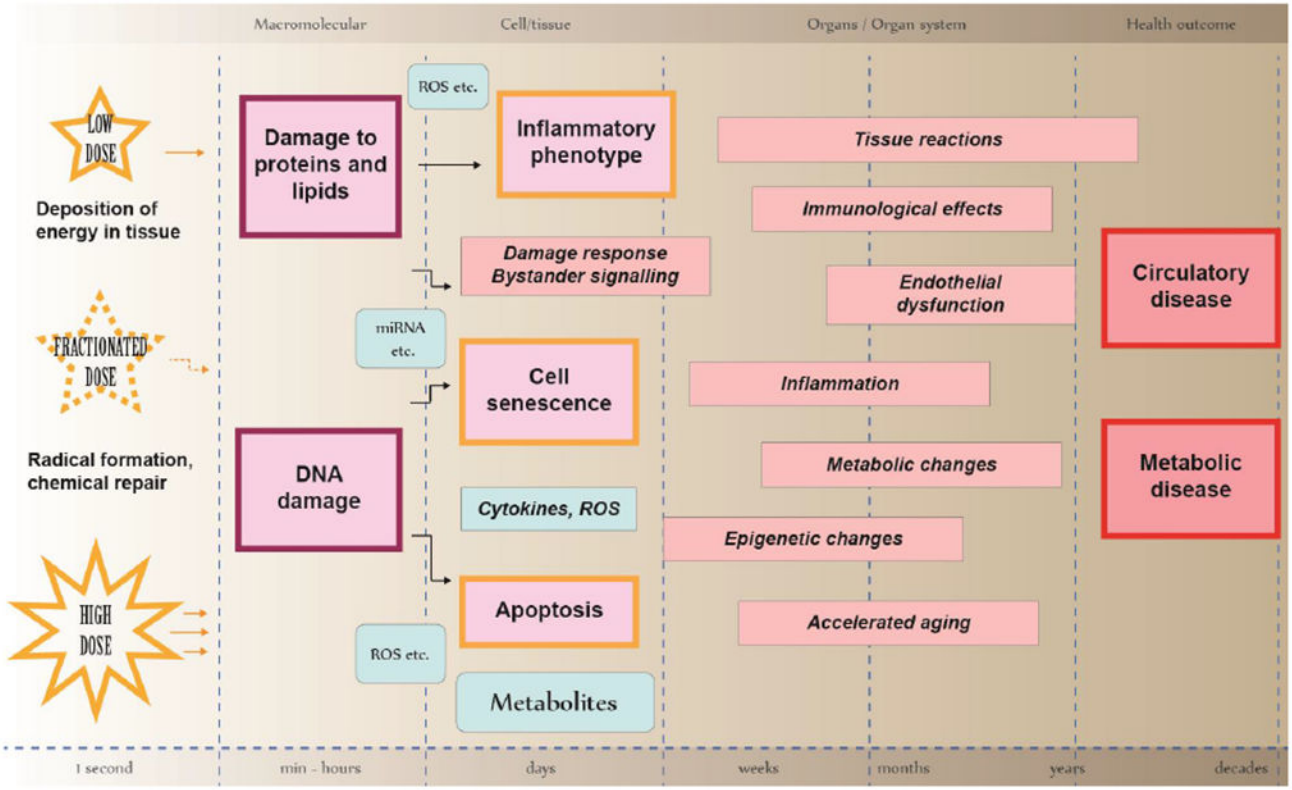

Figure 2.

Schematic representation of the components, interrelations and timing of a network of adverse outcome pathways and key events contributing to the development of adverse health outcome: circulatory and metabolic diseases.

Table 1.

Adverse Outcome Pathways (AOP) leading to long-term health consequences.

Level of organisation	AOP				
Macromolecular (seconds, hours, days)	Deposition of energy to tissue				
	DNA Damage			Damage to other cellular components (RNA, proteins and lipids)	
	DNA mutation	Misrepair	Apoptosis	Biochemical response to damage	
	Mutations in critical genes	Chromosomal aberrations Complex damage	Damage reponse	Induction of oxidative stress	Cytokines reponding to damage
Cell/tissue (days, weeks)	Oncogene activation	Altered signalling, bystander effects		Senescence	Epigenetic changes
	Tumour suppressor gene inactivation	Increased proliferation	Genomic instability	Oxidative damage	Inflammation
Organ/Organ system (months, years)	Clonal expansion Hyperproliferation Genomic instability	Altered physiology	Systemic effects	Immunological effects	Endothelial dysfunction
	Tumour	Tumour microenvironment	Dyslipidemia Insulin resistance	Circulatory disease	Atherosclerosis
Health outcome (years, decades)	Cancer Metastasis		Metabolic syndrome	Mortality	Heart attack

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