Strahlenschutzkommission

Geschäftsstelle der
Strahlenschutzkommission
Postfach 12 06 29
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Cardiovascular diseases following admissible levels of occupational radiation exposure

Statement and scientific background
by the Commission on Radiological Protection

Adopted at the 256th meeting of the Commission on Radiological Protection on 19 and 20 April 2012

The German original of this English translation was published in 2015 by the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety under the title:

Herz-Kreislauferkrankungen nach zulässigen beruflichen Strahlenexpositionen

Stellungnahme der Strahlenschutzkommission mit wissenschaftlicher Begründung

This translation is for informational purposes only, and is not a substitute for the official recommendation. The original version of the recommendation, published on www.ssk.de, is the only definitive and official version.

Introduction

It is a long-known fact that radiation treatment against breast cancer can lead to cardiovascular diseases due to high radiation doses to the heart. Recent studies have confirmed this. For a long time it was assumed that these diseases were the result of damage to a large number of cells and that the effect is deterministic. For this effect, a threshold dose of 2 Gy was assumed, meaning it was assumed that a dose of less than 2 Gy would not cause cardiovascular diseases.

Over the past 10 years, however, evidence increasingly suggested that lower doses cause additional cardiovascular diseases among the survivors of the atomic bombs in Hiroshima and Nagasaki. Subsequent epidemiological studies on occupational and environmental exposure gave no clear indication of cardiovascular risks following exposure to a dose of several hundred milligray. Generally, however, evidence suggested an increased risk.

In 2012, two assessments of cardiovascular risk following radiation exposure of several hundred milligray were published. ICRP calculated that 1 % of persons exposed developed an additional cardiovascular disease following an exposure of 500 mGy, while underlining the great uncertainties of this assessment. Against this background, the risk of cardiovascular diseases due to radiation is far lower than the risk of cancer. In contrast, a large group of renowned experts published calculations the same year, according to which the risk of cardiovascular diseases following exposure to a dose of 100 mGy is similar to or even higher than the risk of cancer.

Pursuant to the Radiation Protection Ordinance the critical lifetime dose for occupational radiation exposure is 400 mGy. The risk of cardiovascular diseases may therefore be significant for assessing this threshold. The Federal Ministry for the Environment, Nature Conservation and Nuclear Safety (BMU) asked the Commission on Radiological Protection for a statement. The Commission on Radiological Protection established a working group to fulfil this task. The members of this working group are:

- Prof. Dr Guido Hildebrandt, Universitätsklinikum Rostock
- Dr. Peter Jacob, Helmholtz Zentrum München
- Prof. Dr Christa Meisinger, Klinikum Augsburg, MONICA/KORA Herzinfarktregister and Helmholtz Zentrum München
- PD Dr Susanne Schultz-Hector, Else Kröner-Fresenius-Stiftung, Bad Homburg
- Prof. Dr Brigitte Stöver, formerly Charité Berlin
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Bonn, March 2015

Prof. Dr Wolfgang-U. Müller
Chair of the
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Dr Peter Jacob
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Contents

1 Introduction

High doses of ionising radiation increase the risk of cardiovascular diseases. New studies indicate higher rates of illness following exposure to lower doses than had previously been assumed. In response, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety issued the Commission on Radiological Protection with a consulting contract on 13th June 2008, requesting a statement on *The impact of radiation within the scope of occupational radiation exposure*. The Commission on Radiological Protection waited for the results of two major European projects investigating a possible correlation between low dose radiation exposure and the occurrence of cardiovascular diseases – CARDIORISK and NOTE – before conducting its own initial analysis.

Within the context of occupational radiation exposure, both the limits applied to annual radiation exposure and the restriction of the dose accumulated over an entire working life play a significant role. Pursuant to § 56 of the Radiation Protection Ordinance, *"the limit for the sum of the effective doses of occupationally exposed persons determined in all calendar years … shall be 400 millisieverts."* This statement therefore analyses the possible risk of cardiovascular disease resulting from long-term radiation exposures to an effective dose of several hundred millisieverts.

The number of persons occupationally exposed to radiation levels that exceed the dose limit for an entire working life is low. By the end of 2009, of some 1,134,323 persons recorded in the German Radiation Protection Register, only 112 individuals charted sum doses in excess of 400 mSv. A dose value over 200 mSv was found to apply to 1,029 persons.

This statement refers solely to the risk of cardiovascular diseases following exposure to low LET radiation (especially X-rays and gamma radiation) within the range of a few hundred milligray. Risks posed by neutron radiation or by incorporated alpha emitters (e. g. radon and its decay products) are not addressed by this statement.

The risk observations included in this statement are based on the absorbed dose measurand, which, in contrast to the effective dose used in radiation protection, does not contain any weighting factors for different types of radiation or specific bodily organs. For the low LET radiation under examination in this instance, the numerical values – whether they relate to effective doses quoted for homogeneous total body irradiation or to organ doses – are identical to the commensurate absorbed dose averages.

Internationally the definition of a low absorbed dose is applied to doses below 100 mGy. This statement describes absorbed doses in excess of 1,000 mGy as high, and mid-range doses as moderate. An absorbed dose of 400 mGy caused by low LET radiation is at the lower end of the moderate dose range.

The term *cardiovascular disease* refers in the broadest sense to all diseases associated with the heart and the circulatory system, logged under ICD10 I00-I99 in the WHO International Classification of Diseases. The term cardiovascular diseases is synonymous with heart and circulatory diseases. In Germany, cardiovascular diseases are the leading cause of death. The most common sub-groups which have been subject to the most research are

- ischaemic heart diseases (ICD10 I20-I25) and
- cerebrovascular diseases (ICD10 I60-I69).

In addition to the category of cardiovascular disease as a whole, this statement particularly addresses these two groups.

The mechanisms which lead to the occurrence of radiation-induced cardiovascular diseases remain largely unexplained. Epidemiological studies into the risks of cardiovascular diseases

following exposure to low and moderate doses of radiation have been conducted on the atomic bomb survivors of Hiroshima and Nagasaki, on the employees of the Mayak plutonium production plants in the South Urals, and on other occupationally exposed individuals.

In a statement dated 21 April 2001, the ICRP indicates that the threshold for the induction of cardiovascular diseases could be as low as 500 mGy. In the process, the ICRP defines the threshold as the dose value below which, in addition to the spontaneous rate, the observed disease occurs among less than one percent of the exposed individuals. This current recommendation emphasises the importance of analysing existing studies, also with respect to the type of dose-response relationship within the moderate dose range.

2 Cardiovascular diseases in Germany – a descriptive epidemiology

In its broadest sense, the term *cardiovascular disease* covers all diseases relating to the heart and the circulatory system. According to the Federal Statistical Office, in 2008 42 % of deaths in Germany were attributable to cardiovascular diseases; the age-standardised cardiovascular mortality rate was approx. 434 cases per 100,000.

Ischaemic heart diseases accounted for approx. 17 % of deaths in the case of men and 15 % of deaths in the case of women; 6 % of men and 9 % of women died from cerebrovascular diseases.

Although data on cardiovascular mortality can be derived from the cause of death statistics issued by the Federal Statistical Office, no figures exist in Germany on the prevalence and incidence of cardiovascular diseases. Both the Augsburg myocardial infarction registry and the Ludwigshafen stroke registry, however, collect population-based data, thus enabling estimates about the incidence and prevalence of these two diseases to be made on a nationwide scale.

Acute myocardial infarction occupies a dominant position within the ischaemic heart diseases group. In the case of men and women alike, the frequency of heart attacks increases with advancing age. Most infarctions occur among men and women aged over 85. In 2008, out of a total female population in Germany of approx. 42 million, 104,000 women suffered an acute myocardial infarction; among the 40-million strong male population, this figure was 145,000.

Stroke is the most common cerebrovascular disease. During 2006 and 2007, the age-adjusted figure for new cases per 100,000 person-years was 146. Stroke occurrence demonstrates a pronounced dependency on age: from an incidence rate of just 9 per 100,000 person-years for men and women in the 25-34 age group, there is an increase to 1,672 per 100,000 person-years among the over-85s. Overall, more than 70 % of all strokes are seen to occur within the over-65s group.

Bearing in mind the demographic shift currently taking place in Germany, it can be expected that there will be a considerable increase in the number of heart attack and stroke patients in the coming years.

3 Cardiovascular disease pathogenesis

Numerous potentially modifiable risk factors are responsible for the occurrence of cardiovascular diseases. The conventional risk factors are smoking, hyperlipidaemia,

hypertension and diabetes mellitus; other major risk factors are obesity/adiposity and physical inactivity. When it comes to the development of cardiovascular diseases, risk factors viewed in isolation are less significant than the sum total of age, gender and modifiable factors. Most people who suffer from cardiovascular diseases demonstrate various risk factors that interact with each other, accumulating to produce an overall risk.

Atherosclerotic plaques occur as a result of local and systemic factors. When combined with heightened blood lipid levels (especially LDL), localised blood flow turbulence, responsible for the typical distribution patterns of atherosclerotic plaques, triggers local inflammation in the vascular wall. Accompanied by a cascade of inflammatory signals, the key phases in the development of a typical human atherosclerotic plaque are monocyte infiltration of the vascular wall, metamorphosis into macrophages and then foam cells, lipid deposits and the migration and activation of smooth muscle cells. Despite intensive experimental research, no animal model has yet managed to exactly reproduce this sequence.

In clinical terms, atherosclerotic plaques often remain asymptomatic for extended periods – frequently this can mean years. Only when the plaque become instable, leading in turn to a rupture of its capsule and direct contact between its content and the blood to form a thrombus, do the clinical symptoms of vascular occlusion become apparent.

The clinical symptoms of a heart attack or stroke are triggered by local hypoxia, i. e. by a lack of tissue perfusion in the terminal vessels. Only recently available imaging techniques have made it possible to present and quantify aspects such as myocardial perfusion, drawing attention to the notably amplifying impact of capillary perfusion disorders on the overall character of ischaemic heart diseases. A proper assessment of the role of such disorders and an understanding as to how they occur still remains to be established. Since chronically progressive microcirculatory disorders are a well-known – if for the most part little understood – consequence of therapeutic radiation doses, it is impossible to rule out a direct impact of radiation on the capillary bed, even at doses below 500 mGy.

4 Radiation exposure mechanisms with a potential impact on cardiovascular disease pathogenesis

At many stages the pathogenesis of an infarction or stroke offers potential points of interaction with radiation effects observed in vitro, making it conceivable that radiation may have either a triggering or accelerating effect. Nevertheless, little is still known about the fundamental biological mechanisms relating to low dose radiation exposure and what impact these may have on cardiovascular diseases. It is, however, probable that radiation-induced inflammatory processes play a considerable role in the development of atherosclerosis.

Owing to the multi-factor pathogenesis of atherosclerotic change which extends over decades, the high “spontaneous” frequency in the population, and the independence of the clinical and morphological phenotype from the nature of the trigger, there is a need for mechanistic studies to quantify the risks posed by radiation. The chronic nature of pathogenesis means that, at best, in vitro cell cultures can only offer hints relating to isolated individual processes. Experimental animal models are an important resource for findings, even though they merely provide a limited approximation of the situation in humans, not to mention being extremely expensive and time-consuming owing to the number of key variables (e. g. dose, dose rate, observation time, and genetic risk background) involved.

The EU CARDIORISK project set out to investigate the effect of low, moderate and high radiation doses on mice following local cardiac exposure. Although there appeared to be no

impact on cardiac function within the relevant dose range, molecular changes in the cardiac mitochondria could still be traced four weeks after exposure to 200 mGy. No additional data exist, however, to prove a causal link between these changes and cardiovascular disease following exposure to doses below 500 mGy.

To date only one experimental project has analysed the cardiovascular effects of full body exposure within the relevant dose range. The EU NOTE project exposed ApoE-/- mice, genetically predisposed to atherosclerosis, to doses ranging between 25 mGy and 500 mGy. After three and six months respectively, histological examinations of the ascending aorta were conducted to detect any atherosclerotic changes, including the analysis of a wide range of inflammation markers. The results failed to produce a uniform picture; nor was it possible to rule out the inhibition of atherosclerotic progression, especially in the case of dose groups below 100 mGy. A comparison of different dose rates partially revealed contrary effects, indicating the likelihood that a number of biological mechanisms are in a position to influence disease progression modulation.

When interpreting these results, it is crucial to take into account that to date only the effects of a single exposure have been analysed. The impact of repeated exposures or chronic exposure at low dose rates remains to be investigated; the available results compellingly need to be confirmed using an alternative atherosclerosis model.

5 Epidemiological studies into radiation risk

A growing number of epidemiological studies into radiation are supplying data on the risk of cardiovascular disease as a result of exposure to low and moderate doses of ionising radiation.

The data of the atomic bomb survivors of Hiroshima and Nagasaki (Life Span Study, LSS) are a fundamental basis when assessing the risk of cardiovascular diseases following exposure to moderate doses of radiation. Epidemiological observations made on Mayak workers are also increasing in significance. In the case of both cohorts, data have not only been collected on radiation exposure, but also on additional significant risk factors associated with cardiovascular disease, such as smoking, alcohol consumption, or obesity. Other key studies include the British Nuclear Fuels (BNFL) workforce, those individuals entered in the UK radiation registry, the Chernobyl accident relief workers, the Wismut miners, and the 15-country study on nuclear industry workers.

Any generalisation of the results produced by these individual studies into longer term radiation exposure must, if at all, be approached with caution: the findings, for instance, on partial groups revealed inhomogeneity (BNFL workforce, Chernobyl accident relief workers), and there were contradictory outcomes for mortality and incidence (cerebrovascular diseases among Mayak workers). Nevertheless, viewed in their entirety, the studies do supply a few conclusions concerning the risk of cardiovascular disease following exposure to moderate doses of radiation.

Overall, the existing epidemiological studies into longer term exposure to moderate doses of low LET radiation point to a risk of increased cardiovascular disease frequency. The studies provide no indication that this risk is any different to the risk of those atomic bomb survivors who were acutely exposed to a comparable dose. Huge uncertainty however still exists as to the degree of risk.

The literature supplies analyses of epidemiological data with a linear dose-response relationship. In the case of cardiovascular diseases, these produced excess relative risk (ERR)

values per dose of 0.1 Gy^{-1}. Similar risk values have also been estimated for the ischaemic heart disease and cerebrovascular diseases sub-groups.

There is conflicting evidence concerning whether a threshold exists for the dose-response relationship within the few hundred milligray range, or whether the ERR in this dose range is considerably lower than the value obtained by using a linear dose-response relationship (see existing epidemiological studies). An analysis of LSS data using the multi-model method revealed that the ERR for cardiovascular diseases at a level of 400 mGy is approximately three times lower than the result of the linear dose-response relationship analysis. This means that the ERR for cardiovascular diseases at 400 mGy is a whole order of magnitude smaller than the ERR for cancer. Since the spontaneous risks associated with cardiovascular diseases are higher than those relating to cancer, there is less difference between their relevant excess absolute risks than between their excess relative risks.

6 Conclusion and assessment

Cardiovascular diseases are one of the most common causes of death worldwide. In Germany, 42% of all deaths that occurred in 2008 could be attributed to cardiovascular diseases, thus the principal causal group. The leading causes of death in this respect were ischaemic heart diseases and cerebrovascular diseases.

Cardiovascular diseases are often caused by atherosclerosis, which is associated with genetic predisposition (e. g. hypercholesterolaemia), environmental factors, lifestyle factors (e. g. smoking) or other underlying diseases (metabolic syndrome, diabetes or renal disease). In addition to a narrowing of the afferent arteries, it is the lack of blood supply (ischaemia or infarction), as well as structural or functional deficiencies of the capillary network supplying the organ in question, which in part plays a major role in the clinical manifestation of the disease.

Little is known about the fundamental biological mechanisms relating to low or moderate dose radiation exposure and what impact these may have on cardiovascular diseases. Despite intensive experimental research, no animal model has yet managed to exactly reproduce this sequence. Only one experimental project has sought to address the impact of low and moderate doses of ionising radiation on atherosclerotic progression using an animal model. In this study, all the dose-response relationships examined were non-linear and, as a general rule, following exposure to low doses and a relatively low dose rate, protective – both in the early and late stages of the disease. By contrast, both protective and adverse responses were observed in the early stages of the disease following exposure to a higher dose rate.

An increasing number of epidemiological studies point to a risk of increased cardiovascular disease frequency following exposure to moderate doses of low LET radiation. The studies provide no indication that this risk is any different to the risk of those atomic bomb survivors who were acutely exposed to a comparable dose. Huge uncertainty however still exists as to the degree of risk.

Analyses of existing studies with a linear dose-response relationship have produced ERR values per dose of 0.1 Gy^{-1}. Conflicting evidence exists – with relation to both acute and longer lasting exposure – as to whether the ERR for a few hundred milligray is considerably lower than findings using a linear dose-response relationship (see existing epidemiological studies) indicate. This also applies to whether a threshold exists within the few hundred milligray range.

There remains huge uncertainty about potential cardiovascular risks following exposure to an absorbed dose of radiation of a few hundred milligray. Nevertheless the above observations do allow an initial comparison of the mortality risks associated with cardiovascular diseases and cancer following exposure to a dose commensurate with the dose limit for an entire working life. Thus, the absolute risk of developing cardiovascular diseases following exposure to a dose of a few hundred milligray may be lower, but still of potentially the same order of magnitude as the corresponding risk of cancer. The existence of a threshold in the cardiovascular diseases dose-response relationship within the few hundred milligray range cannot however be ruled out.

Although it remains possible that there is a total absence of risk, due consideration needs to be given in the drafting of statutory regulations – by way of precaution and in view of existing scientific uncertainty – to the potential for increase in cardiovascular diseases risk following exposure to radiation doses of a few hundred milligray.

Further epidemiological, experimental radio-biological and mechanistic modelling studies are needed to assess the dose-response progression for cardiovascular diseases following exposure to low and moderate doses of radiation.

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Scientific background for the statement
by the Commission on Radiological Protection

Adopted at the 256th meeting of the Commission on Radiological Protection on 19 and 20 April 2012

CONTENTS

1 Introduction

This scientific grounds provide a summary of the scientific basis for the SSK statement on cardiovascular diseases following exposure to radiation commensurate with the occupational dose limit prescribed for an entire working life pursuant to § 56 of the Radiation Protection Ordinance. The term cardiovascular diseases includes ischaemic heart diseases (code I20-I25 in chapter IX of the *International Statistical Classification of Diseases and Related Health Problems* (ICD) issued by the WHO, 10th revision) and cerebrovascular diseases (code I60-I69).

The statement refers solely to the risk of cardiovascular diseases following exposure to low LET radiation (especially X-rays and gamma radiation) within the few hundred milligray range. Risks posed by neutron radiation or by incorporated alpha emitters (e. g. radon and its decay products) are not addressed by this statement.

The risk observations included in the statement are based on the absorbed dose measurand, which, in contrast to the effective dose used in radiation protection, does not contain any weighting factors for different types of radiation or specific bodily organs. For the low LET radiation under examination in this instance, the numerical values – whether they relate to effective doses quoted for homogeneous total body irradiation or to organ doses – are identical to the commensurate absorbed dose averages.

In October 2010 the *Advisory Group on Ionising Radiation* of the *Health Protection Association (AGIR)* published a detailed report on the risk of cardiovascular diseases following exposure to radiation. This report may be regarded as a supplementary source of information to the scientific grounds here presented. Both reports share major areas of common ground in their assessment of the facts available. This scientific grounds do, however, also take into account studies published since the completion of the AGIR report.

The grounds are split into the following chapters:

– Cardiovascular diseases in Germany – a descriptive epidemiology

– Cardiovascular disease pathogenesis

– Radiation exposure mechanisms with a potential impact on cardiovascular disease pathogenesis

– Epidemiological studies into cardiovascular diseases following exposure to low or moderate doses of radiation (absorbed dose <1 Gy).

2 Cardiovascular diseases in Germany – a descriptive epidemiology

2.1 Introduction

Cardiovascular diseases are one of the most common causes of death worldwide (WHO 2007). A comparison within Germany reveals considerable discrepancies in overall mortality between the 16 federal states. In 2008, Saxony Anhalt had the highest mortality rate, with 865.3 deaths per 100,000; Baden-Württemberg with 689.6 deaths per 100,000 the lowest. These differences can mainly be attributed to mortality fluctuations related to cardiovascular diseases. The causes for these regional differences in cardiovascular mortality still need to be established. The principal possible causes are the conventional risk factors, not to mention demographic, social, behavioural and even medical care-related factors; in addition there are

also potential environmental and genetic factors. Differences in the way death certificates are filled out or in the coding of causes of death may also be of significance.

2.2 Significance of cardiovascular diseases

In Germany, circulatory diseases account for approximately half of all hospital admissions and days off work. Moreover, in 2008, cardiovascular diseases was the main category of death among men and women in Germany; the leading causes were ischaemic heart diseases and cerebrovascular diseases (cause of death statistics, Statistisches Bundesamt 2008).

Compared with other European countries, Germany occupies the mid-field as far as mortality resulting from coronary heart disease and/or cerebrovascular diseases respectively is concerned. The countries of Eastern Europe top the mortality statistics, while the Mediterranean countries have the lowest mortality rates (Levi et al. 2002).

Since 1975, the mortality rates for cardiovascular diseases in most countries have sunk by 24–28 %. Approximately 45 % of this reduction can be attributed to improved treatment; the remaining 55 % is regarded as being due to a reduction in the cardiovascular risk factors (Hennekens 2003). In recent decades, Germany too has seen a marked reduction in mortality rates: between 1980 and 2008, the mortality rate among women dropped from 803.9/100,000 to 345.6/100,000, while among the men there was a reduction from 628.1/100,000 to 249.6/100,000 (standard population "Germany 1987"; Statistisches Bundesamt). Age-specific mortality has also decreased; owing, however, to the ageing nature of the population, the absolute number of individuals with cardiovascular diseases is set to increase (Löwel and Meisinger 2006). This means that cardiovascular diseases will remain *the* disease in the 21st century, heading the disease table in terms of frequency and cause of death statistics – in both industrialised countries and emerging economies (Murray et al.1994).

2.3 Cardiovascular disease frequency

The frequency with which cardiovascular diseases occurs in a population is described using the two morbidity terms *prevalence* and *incidence*. Prevalence refers to the number of cases of a particular disease in a defined population at a specific point in time. Incidence measures new cases of a particular disease within a defined population during a specific period of time (generally one year).

2.3.1 Cardiovascular diseases in general

In its broadest sense, the term cardiovascular diseases covers all diseases relating to the heart and the circulatory system; it is also however generally used to refer to sub-groups within the category, specifically ischaemic heart diseases and cerebrovascular diseases. The term cardiovascular diseases covers all diseases listed in chapter IX of the *International Statistical Classification of Diseases and Related Health Problems* (ICD) issued by the WHO (Appendix, Table 1). The epidemiological significance of cardiovascular diseases is primarily a result of its frequent appearance in the cause of death statistics. Data on mortality according to the ICD system can be obtained from the cause of death statistics issued by the Statistisches Bundesamt (cause of death statistics, Statistisches Bundesamt 2008).

Although the level of cardiovascular diseases as a percentage of overall mortality has decreased in recent years, cardiovascular diseases still constituted the main cause of death in Germany in 2008; 356,729 individuals died as result, i.e. practically every second death in a total of 844,439 (42.2 %). In total 37.3 % of the men and 46.6 % of the women who died did so as a result of cardiovascular diseases, whereby more than 90% of those affected were aged 65 and over. According to the Statistisches Bundesamt, cardiovascular mortality in Germany

during 2008 was 434.4 per 100,000; in comparison, cardiovascular mortality in 1998 was 501.5 per 100,000 (Statistisches Bundesamt 2008).

Between 1998 and 2008, cardiovascular mortality among men and women saw a decrease throughout all age groups; the reduction was more pronounced among men than among women – especially in the oldest age groups.

Figure 2.1 shows the cardiovascular mortality per 100,000 for men and women in the different age groups in 2008 (source: cause of death statistics, Statistisches Bundesamt 2008). In the case of both men and women, cardiovascular mortality increases with age. The most cases of death per 100,000 attributable to cardiovascular diseases occur among men and women over 90. For all age groups, mortality among men remains higher than that among women – except in the over-ninety age group.

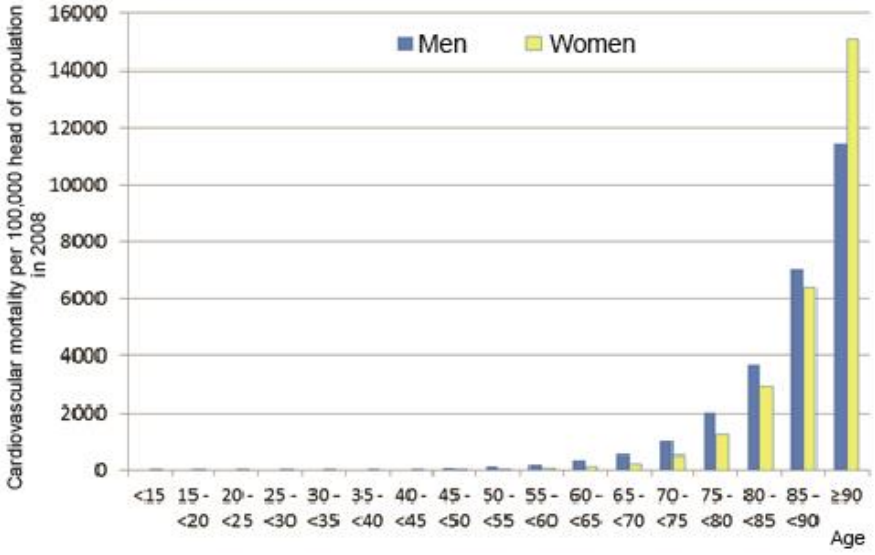

Fig. 2.1: Age and gender-specific cardiovascular mortality per 100,000 head of population in 2008.
(Source: cause of death statistics, Statistisches Bundesamt 2008.)

No data exist for Germany on the prevalence or incidence of cardiovascular diseases in toto or of individual sub-groups. The Augsburg myocardial infarction registry and the Ludwigshafen stroke registry respectively collect population-based data, thus enabling estimates about the incidence and prevalence of these two diseases to be made on a nationwide scale.

2.3.2 Ischaemic heart diseases, coronary heart disease (CHD)

According to information issued by the World Health Organisation (WHO), coronary heart disease is the most common cause of death; in 2002 approximately 7.2 million individuals worldwide died from this disease (WHO 2002). According to the Statistisches Bundesamt, approx. 17 % of deaths among men and 15 % of deaths among women in Germany in 2008 were attributable to an ischaemic heart disease (Statistisches Bundesamt 2008). Although the mortality rates for coronary heart disease are in decline, especially in industrialised Western countries (Hunink et al. 1997), current demographic shifts are nevertheless associated with increased life expectancy and, by extension, with improved survival rates, meaning that in future many people will live considerably longer with the disease (Löwel and Meisinger 2006).

Acute myocardial infarction is a key complication of ischaemic heart diseases. Since 1985, the population-based MONICA/KORA cardiac infarction registry for the Augsburg region has been providing annual data on German cardiac infarction morbidity – one of the most common and acutely life-threatening complications of CHD – per 100,000 aged between 25 and 74 (www.gbe-bund.de).

In the case of men and women alike, the frequency of heart attacks increases with advancing age. Most infarctions per 100,000 occur among men and women aged over 85. In 2008, out of a total female population in Germany of approx. 42 million and a 40-million strong male population, 249,000 individuals (145,000 men and 104,000 women) suffered an acute coronary event. Of these, 2/3 of the heart attacks among men occurred below the age of 75, with 2/3 of the heart attacks among women occurring over the age of 75.

As the data from the Augsburg cardiac infarction registry reveal, the age-standardised rate of cardiac infarction among men aged 25-74 was 248 per 100,000 (95% CI 227–269); in the case of women the rate was 84 per 100,000 (95% CI 72-96).

In the case of both genders, the age-specific lifetime prevalences increase with advancing age. While the occurrence of infarctions among men and women aged 18-30 plays no significant role, the rate of cases of post-myocardial infarction rises threefold among men aged between 30 and 60. The prevalence for 70-79 year-old men is 14.6 %. Allowing for a delay of approximate 10 years, the lifetime prevalence among women approximately matches the level of male prevalence (Wiesner et al. 1999a).

2.3.3 Cerebrovascular diseases

Six percent of men and 9 % of women who died in Germany in 2008 did so as a result of cerebrovascular disease (Statistisches Bundesamt 2008). Stroke is the most common cerebrovascular disease and the third most common cause of death in Germany.

By referring to the Ludwigshafen stroke registry it is possible to estimate the incidence of clinically manifest strokes. During 2006 and 2007 the annual number of new cases per 100,000 person-years (age-adjusted to the European population) was a total of 146 (95% CI 135–157). The age-adjusted incident rate for men was 163 cases per 100,000 (95% CI 146–181) and for women 129 cases per 100,000 person-years (95% CI 115–143) (Palm et al. 2010).

Stroke occurrence demonstrates a pronounced dependency on age: from an incidence rate of just 9 per 100,000 person-years for the 25-34 age group, there is an increase to 1,672 per 100,000 person-years among the over-85s. Overall, more than 70 % of all strokes are seen to occur among the over-65s (Palm et al. 2010).

No reliable information on stroke prevalence derived from primary data exists for Germany. Generally, population-related surveys only record those strokes with milder or more favourable outcomes. Despite this limited coverage and based on the data supplied by the 1998 Federal Health Survey (RKI 1998) on the resident population of Germany aged between 30 and 80, the absolute extrapolated number of individuals who had suffered a stroke was approximately 945,000.

The overall lifetime prevalence (sickness rate of persons who had suffered a stroke at some time in their life) among 18-79 year-olds was 1.55 % for men and 1.73 % for women. There are no significant differences in morbidity between men and women; the prevalence among the female population is 1,730 per 100,000 and 1,530 per 100,000 among the male population. The age-specific prevalence jumps dramatically for women over the age of 60 and for men

once they turn 50. The highest prevalences are found in the 70-<80 age group: 8.4 % for men and 7.5 % for women (Wiesner et al. 1999b).

2.4 Cardiovascular disease risk factors

According to a general categorisation (Grundy et al. 1999), some aspects of which need to be considered in the light of more recent research results, cardiovascular risk factors may be subdivided into independent key risk factors and additional predispositional or other "conditional" risk factors. Predispositional factors are those which increase the level of risk when they co-exist with any of the key risk factors. Other risk factors are those associated with an increased cardiovascular risk, despite the fact that their causal, independent, and quantitative share remains unclear (Table 2.1).

Tab. 2.1: General categorisation of cardiovascular risk factors (Grundy et al. 1999)

Key risk factors	**Predispositional risk factors**	**Other risk factors**
Advanced age	Obesity	Heightened triglycerides
Male	Truncal obesity	Small LDL particles
High blood pressure	Physical inactivity	Heightened homocystein
Smoking	Hereditary factors (e. g. heart attacks suffered by first-degree relatives)	Heightened lipoprotein (a)
Diabetes mellitus	Ethnic background (e. g. South Asian origin)	Prothrombotic factors, e. g. fibrinogen
Low HDL cholesterol Heightened overall and LDL cholesterol	Psychosocial factors (e. g. social isolation, stress in the workplace)	Inflammation parameters, e. g. C-reactive protein
High alcohol consumption		

The male gender, hereditary aspects, or a person's age are factors that cannot be influenced. Following recognition of the significance of hereditary factors, recent years have seen further differentiation, especially relating to genetic predisposition. Direct links have been established between various genotypes and cardiovascular diseases (Nordlie et al. 2005). Of particular interest within this context is the interplay of genetic predisposition and environmental influences.

Numerous potentially modifiable risk factors are responsible for the occurrence of cardiovascular diseases. The "conventional risk factors" are smoking, hyperlipidaemia, hypertension and diabetes mellitus; other major modifiable risk factors are being overweight/obese and physical inactivity. The following addresses these risk factors in more detail.

2.4.1 Smoking

The consumption of tobacco is one of the major avoidable risk factors relating to cardiovascular diseases. The 2004 Health Survey supplied current figures on tobacco consumption in Germany (Lampert 2007). On the basis of these data, 36.5 % of men and 27 % of women aged over 17 in Germany currently smoke. A total of 10.2% of men and 4.7% of women smoke more than 20 cigarettes a day and are therefore classified as "heavy smokers". The prevalence of smoking is highest among young adults; from the age of 60, prevalence drops dramatically. Taking earlier health surveys into account, it is possible to observe trends in the consumption of tobacco among 25-69 year-old men and women over the

last 20 years: from the mid-eighties to 2004, the percentage of male smokers dropped from 41.6 % to 37.4 %; in the case of women, however, an increase from 26.7 % to 29.6 % occurred (Lampert 2007).

2.4.2 Excessive alcohol consumption

According to the results of observation studies, moderate consumption of alcohol is associated with a lower rather than a heightened cardiovascular risk (Di Castelnuovo 2002). In Germany, moderate alcohol consumption is given as 40 g for men and 20 g for women. If daily alcohol consumption exceeds these levels, the consumption of alcohol is said to be high (Singer 2002). Principally it is the antioxidant effects, the increase of HDL cholesterol, not to mention antithrombotic and vasodilatory effects which are quoted in favour of moderate alcohol consumption and its protective effect on the vascular system (Flesch 1998). As studies show, however, higher levels of alcohol consumption increase the overall risk of cardiovascular disease (Malyutina 2002, Leon 2009). As revealed by data from Russia, people who regularly consume large quantities of alcohol are twice as likely to die of cardiovascular diseases (Malyutina 2001).

2.4.3 Dyslipidemia

An increased concentration of cholesterol and/or triglycerides is a major risk factor in atherosclerosis and thus also for cardiovascular diseases. The risk of becoming ill increases as the blood lipid level rises, especially the level of LDL cholesterol.

Hypercholesterolaemia is a marked increase in the level of total blood cholesterol (made up of both LDL cholesterol and HDL cholesterol). In recent years, the risk assessment limit for total cholesterol has been adjusted downwards considerably. A value below 200 mg/100 ml is currently regarded as the level to aim for. As data from the 1998 federal health survey (RKI 1998) reveal, 61.5 % of women and 70.1 % of men aged between 30 and 39 already demonstrate cholesterol levels that are ≥200 mg/100 ml. A total cholesterol value of ≥200 mg/100 ml is most often encountered among the 60–69s. At this age, 86.9 % of men and 94.2 % of women have a heightened total cholesterol level (Thefeld 2000). Although younger women generally demonstrate lower prevalence than men, post-menopause they outstrip male prevalence dramatically.

2.4.4 High blood pressure (hypertension)

High blood pressure is one of the key risk factors associated with the genesis of cardiovascular diseases and reduced life expectancy. High blood pressure is said to exist if the resting systolic blood pressure value is ≥140 mmHg and/or the diastolic blood pressure value is ≥90 mmHg.

Factors which favour the emergence of high blood pressure are: hereditary factors, being overweight, poor diet, nicotine, alcohol, lack of exercise, stress. The 1998 federal health survey (RKI 1998) revealed that a large percentage of persons aged 18-79 had blood pressure values of ≥140/90 mmHg (48 % of men, 39 % of women). For both genders, the prevalence of arterial hypertension increases with advancing age. Among the 70-79s, 72.9 % of men and 73.5 % of women are affected by high blood pressure (Thefeld 2000). Within Germany there are considerable regional differences when it comes to hypertension prevalence.

A recent study revealed that in Western Pomerania and southern Germany, the prevalence of arterial hypertension is higher among men than among women. Specifically, the difference in regional prevalence among 25-74 year-old males, an average of 60.1 % (95% CI 57.9–62.3%) in Mecklenburg-Western Pomerania and 41.4 % (95% CI 39.1–43.1%) in southern Germany,

is greater than among the female populations of these regions – 38.5 % (95% CI 36.6–40.4%) and 28.6 % (95% CI 26.9–30.3%) respectively. Furthermore the study also showed that in both regions approximately 45 % of the men and 30 % of the women were unaware of their high blood pressure (Meisinger et al. 2006).

2.4.5 Diabetes mellitus

In recent years it has become apparent that patients who suffer from diabetes or have pre-diabetic metabolic syndrome are at particular risk of developing atherosclerotic diseases (Hu et al. 2002; Isomaa et al. 2001). Moreover, the post-cardiac infarction prognosis for diabetics is much worse than for those who do not suffer from diabetes. Based on data supplied by a Finnish prospective study, it had been assumed that the cardiovascular risk for diabetics without recognisable signs of cardiovascular diseases would be the same as for non-diabetics following a cardiac infarction (Haffner et al. 1998). According to data held by the MONICA/KORA cardiac infarction registry in Augsburg the incidence of myocardial infarction among men with diabetes mellitus is 3.7 times higher, and among women 5.9 times higher than among non-diabetics (Löwel et al. 1999).

Currently between five and six million people in Germany receive treatment for diabetes. Many cases, however, have yet to be diagnosed and receive medical treatment. KORA S4 (1999-2001) was the first study to conduct an investigation into the frequency of diabetes using an oral glucose tolerance test. The results of KORA S4 revealed a prevalence of undiagnosed diabetes among the 55-74 age group of 8.2 %, approximately as high as the frequency of diagnosed cases. At 2.2 %, the prevalence of undiagnosed diabetes mellitus among 35-59 year-olds was practically as high as the percentage of diagnosed diabetes (2.4 %); in addition 11 % were suffering from pre-diabetes. The new occurrence of Type 2 diabetes (55-74 year-olds) was recorded by the KORA S4/F4 cohort study. Within 7 years 10.5 % of participants developed Type 2 diabetes; among these twice as many men were affected as women. The age-group specific incidence rate (55-74 year-olds) was 1,550 per 100,000 person-years; the result for 55-74 year-old males was 2,020 per 100,000 person-years (women: 1,130 per 100,000 person-years). This is equivalent to approx. 270,000 new cases per year (Rathmann et al. 2003, Rathmann et al. 2009, Meisinger et al. 2010).

2.4.6 Being overweight or obese

To distinguish being overweight from obesity (adiposity), people with a body mass index (BMI) below 25 kg/m² are classed as normal, from 25 up to 30 kg/m² as overweight (pre-adipose), and above 30 kg/m² as obese (WHO 1997). In recent decades the percentage of people who are overweight or obese has increased dramatically, taking on global epidemic proportions. It is estimated that this rate is likely to increase by a further 50 % by 2015, with the number of overweight people worldwide thus exceeding 1.5 billion (WHO 1997). Over the last 20 years, the percentage of people who are overweight and obese has been slowly and surely increasing (Mensink et al. 2005): federal health surveys conducted in 1998 and 2003 revealed an obesity prevalence of approximately 20 %.

Obesity is associated with a high prevalence of pathological sequelae and a general increase in mortality rate (Hauner 1996). High blood pressure, one of the key risk factors associated with cardiovascular diseases and thus with mortality, is one of the most common complications of being overweight. Studies show that arterial hypertension is four times more likely to occur among the overweight than among people with a normal body weight (Sharma et al. 1999).

In all, some 22 % of 25-74 year-old men and 23 % of women are obese, and approximately half of men and a third of women in the same age range are overweight. With advancing age

the percentage share of those who are either overweight or obese increases dramatically. In observing the distribution of both conditions among the different age groups, it becomes apparent that a larger proportion of men of all ages are overweight than women (Meisinger et al. 2007). As data from the 1998 federal health survey reveal, some 8 % of men and 9 % of women aged 20-29 are obese, while 42 % and 26 % respectively are overweight. Among the 60–69s, the prevalence of obesity among women is approximately 35 % and among men approximately 28 %; some 78 % of women and 82 % of men in this age group are overweight (Thefeld 2000).

2.4.7 Physical inactivity

A lack of exercise has been confirmed by various studies as a risk factor in the development of cardiovascular diseases as well as for heightened cardiovascular mortality. Physical inactivity promotes all the conventional cardiovascular risk factors, and thus by extension influences the cardiovascular system in this direction. Regular physical activity prevents hypertension from developing, has a positive influence on the sugar metabolism, leads to weight loss when combined with a low-fat diet, and has a positive impact on the cholesterol metabolism (Lengfelder 2001).

Data on the distribution of sport and physical activity among the German population was collated during a telephone health survey conducted in 2003. In the process, questions relating specifically to sporting activity were considered. The survey revealed dramatic discrepancies with regard to age and gender. Among men, participation in regular sport of two and more hours per week reduces steadily with increasing age (from approx. 52 % among 20-29 year-olds to less than 30 % among the 70s to 79s). In the case of women, the number of people who regularly engage in more than 2 hours of sporting activity a week is lower across the board: with increasing age, the percentage sinks from approx. 40 % among those aged 20-29 to approx. 22 % of the 70-79s (RKI 2003 telephone survey).

2.4.8 Accumulation of cardiovascular risk factors

When it comes to the development of cardiovascular diseases, risk factors viewed in isolation are less significant than the sum total of age, gender, and modifiable factors, such as metabolic disorder, hypertension, obesity, smoking and a lack of exercise. Most people who suffer from cardiovascular diseases demonstrate various risk factors that interact with each other, accumulating to produce an overall risk (Keil et al. 2005).

According to data supplied by the 1998 federal health survey (RKI 1998), about one third of all 18-79 year-olds are not subject to any of the risk factors – smoking on a daily basis, hypercholesterolaemia (>250 mg/100 ml), obesity (BMI ≥30 kg/m²) or hypertension (systolic ≥160 mmHg and/or diastolic ≥100 mmHg). Some 40 % of men and women are subject to one of these risk factors, approx. 20 % to two factors, and 5 % of men and 6 % of women respectively are subject to three risk factors simultaneously. The risk factor frequency increases for both genders with advancing age (Thefeld 2000).

2.4.9 Biomarkers for estimating cardiovascular risk

In recent years, biomarkers have been identified which are associated with a heightened cardiovascular risk. Their causal role and their independent and quantitative contribution to the pathogenesis of cardiovascular diseases are not as well documented as that of conventional risk factors. A series of large-scale epidemiological studies, for instance, revealed that the inflammation marker C-reactive protein (CRP) is an independent predictor of a cardiovascular event among healthy test participants, as well as being a risk marker following an acute cardiac event (Koenig et al. 1999; Ridker 2003). CRP represents one of a

number of new inflammation markers (e. g. serum amyloid A) that – independent of their lipid profile – are associated with future cardiovascular events. Moreover, studies have also revealed lipid-associated markers, such as oxidised LDL (Ox-LDL), and even haemostasis/thrombosis markers (e. g. fibrinogen) to be risk markers associated with a heightened cardiovascular risk. Finally there is a whole range of additional markers with strong forecast reliability relating to the occurrence of cardiovascular diseases (e. g. homocystein, cystatin C). Although prospective studies have shown these markers to correlate statistically with a heightened risk, their practical application in individual cases remains controversial (Pearson et al. 2003). The various guidelines, at least, have yet to recommend their routine use.

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3 Cardiovascular disease pathogenesis

3.1 Introduction

Of the many classifications of cardiovascular diseases, this section only examines those for which experimental, clinical or epidemiological indications exist that point to an association with radiation exposure in general, i.e. including doses >2 Gy. On the one hand this means atherosclerosis and on the other microvascular perfusion disorders. Until a clear conclusion is reached as to which clinical diagnoses are directly linked to exposure <2 Gy, any answers concerning their pathogenesis, with specific reference to dose-response relationships, will be beset with methodological problems.

The following section begins by specifying those information sources suited to deriving hypotheses about diagnoses relevant to cardiovascular radiation impact (3.2). There is then a brief description of the pathogenesis of atherosclerosis and microvascular perfusion disorders respectively (3.3).

3.2 Information sources relating to cardiovascular diseases potentially induced by radiation

3.2.1 Epidemiology

One major source when producing hypotheses on the impact of radiation are those epidemiological data that demonstrate a statistical association between radiation exposure and individual diagnoses. These data are responsible for the current interest in the cardiovascular impact of radiation and are referred to in detail later on (Chapter 5). As far as a precise definition of relevant clinical diagnoses or pathogenetic aspects is concerned, however, epidemiological data are only of limited use: they are frequently based on cause of death statistics, i.e. death certificates, which in diagnostic terms are often inaccurate. Incidence data are generally better suited than cause of death statistics when it comes to assessing the link between radiation exposure and cardiovascular diseases. Diagnoses such as “cardiac death”, as well as “cardiac infarction”, “coronary heart disease”, “stroke” or “peripheral atherosclerosis” are also, however, widespread among the general population, are notoriously dependent on multiple factors, and – in terms of their individual trigger mechanism – are non-specific with regard to clinical presentation. It is therefore not generally possible in specific

cases to trace a connection back to prior exposure. Only in a handful of instances, where isolated atherosclerotic lesions occur in atypical vascular sections that can be clearly linked to a radiation dose administered during prior treatment, it is at least possible to speculate about a connection. One specific example following radiation treatment for breast cancer (Russel 2009) are atherosclerotic changes to the internal thoracic artery, since the latter descends in a completely straight line and demonstrates no "spontaneous" atherosclerosis.

3.2.2 Experimental animal models

Animal experiments are used to reproduce clinically relevant symptoms, whether by means of targeted intervention and/or genetic manipulation, which are then analysed in detail as they develop. Insofar as specific hypotheses relating to relevant illnesses or mechanisms exist, animal models are the main instrument available for analysing their pathogenesis, the dose-response relationships of individual mechanisms, the overall volume-response relationship, and any interaction with other factors or underlying medical conditions. Numerous well characterised experimental animal models, not to mention the rapid growth in recent years in the number of possible functional, imaging, histopathological or molecular biological methods of analysis, support a whole range of promising approaches (see Chapter 4). Nevertheless, despite intensive experimental research, the exact replication of the development of human cardiovascular diseases using an animal model has yet to be achieved.

3.2.3 In vitro models

Owing to the proliferation behaviour of cells in vitro, simple cell culture models have proven to be very useful models for quick-growing malignant tumours. Simple mono-culture systems are not, however, suited to simulating and analysing the impact of radiation on normal tissue, which demonstrates an extremely low turnover of cells in vivo, and in which it can take decades for the consequences of radiation to produce any clinical symptoms. Even in instances where a specific hypothesis relating to individual molecular interactions is to be analysed, it is to be assumed that by increasing cell turnover to 100x its normal physiological rate, the entire phenotypical range of the various cells will alter. Even complex co-culture models, designed for instance to induce differentiation among and inhibit the proliferation of capillary endothelial cells, are only of significance within the context of very specific experimental hypotheses. A detailed discussion on the cell culture models available can be found in the UK Health Protection Agency "Circulatory Disease Risk" report issued in 2010 (HPA 2010).

3.2.4 Theoretical radiobiological considerations

The comprehensive experimental and theoretical findings on the connection between cancer and the biological impact of exposure to ionising radiation cannot be applied indiscriminately to cardiovascular diseases. Fundamental radiobiological considerations based on confirmed "textbook theory" (collated by Stewart and Dörr 2009) imply that

- actively dividing cells are primarily responsible for expressing radiation-induced damage
- the speed with which the impact of radiation on tissue manifests itself depends on the proliferation rate of the tissue in question.

Despite the low turnover of endothelial cells, it is the capillary endothelial cells which account for the largest share of the actively dividing cardiac cell population. Accordingly, this has led to the hypothesis that they are the most probable target population of radiation effects on the heart. For radiation doses within the treatment range, this hypothesis has been confirmed on

an experimental basis during numerous studies, and clinically reinforced by observations of associated regional myocardial perfusion disorders.

As far as the peripheral vascular system is concerned, no such clear hypothesis can be derived from the radiobiological principles mentioned above: unlike cardiac muscle cells, the smooth muscles cells of the vascular media, for instance, have not lost their ability to proliferate.

3.3 Pathogenesis of relevant cardiovascular disease types

3.3.1 Ischaemic heart diseases

As coronary heart disease presents an immediate threat to life, its pathogenesis is the best researched and described form of atherosclerotic vascular disease. Since peripheral atherosclerosis (Peripheral Arterial Disease – PAD) shares similar key risk factors, trigger mechanisms and development stages, the details included here about coronary heart disease are intended to serve as an example.

Atherosclerotic plaques were quickly recognised to be the cause of ischaemic cardiovascular disease. In recent decades, their cellular and molecular trigger mechanisms have formed the subject of intensive research the world over. Although this had led to a range of pharmacological intervention options becoming established, not one of them represents a conclusively satisfactory and efficient treatment approach (Thomas 2011) with the attendant expectation of a dramatic reduction in morbidity and mortality.

The recent advent of non-invasive, high-definition imaging procedures has made individual clinical prospective studies possible for the first time. These have revealed that atherosclerotic plaques can attain stability, remaining asymptomatic for many years. As a result, the pathogenesis of a cardiac infarction or stroke is currently divided into two phases:

A Development of the atherosclerotic lesion

B Destabilisation and rupture of the lesion, potentially leading to thrombosis and vascular occlusion and/or cardiac infarction respectively.

The following section addresses the emergence of plaques, infarction triggers, and the possible contribution of microvascular diseases when examining possible interactions with radiation exposure.

A How an atherosclerotic lesion develops

The risk factors associated with atherosclerosis include genetic factors (e. g. hypercholesterolaemia), environmental factors, lifestyle-related factors (e. g. smoking or metabolic disorder), as well as other underlying diseases (diabetes, renal insufficiency).

For the most part, with the exception of renal insufficiency, which demonstrates specific characteristics relating to its progression and the pathogenesis of the atherosclerosis which commonly occurs as a result (Amann et al. 2003), the clinical and histopathological endpoints of atherosclerosis are divorced from the various disease triggers.

Diabetes is another exception, insofar as it is associated with a combined cardiovascular disease (see below).

The body of original scientific literature on the developmental history of atherosclerotic lesions is vast: there are 57,487 entries which deal with “arteriosclerosis pathogenesis”. The following summary therefore refers to more recent overviews published on the subject (Bui et al. 2009, Hansson 2005, Libby 2002, Libby et al. 2011, Lusis 2000).

A healthy arterial vessel wall is made up of three sections (Fig. 3.1a from Libby et al. 2011). The innermost layer, the tunica intima, comprises the endothelium, one side of which is in contact with the blood, the other side with a basement membrane. The human intima also contains – in contrast to most laboratory animals – smooth muscle cells. The second layer is formed by the tunica media which, in the case of the muscular human arteries primarily affected by atherosclerosis, is made up of elastic connective tissue and smooth muscle cells. The outer layer, or tunica adventitia, contains mast cells, nerve endings and supplying capillaries.

A key triggering and pro-inflammatory role in the initiation of atherosclerotic vascular change is played by local shear stress (forces acting parallel to the endothelium as a result of blood flow turbulence at vessel bifurcations). This stress is responsible for the typical distribution pattern of atherosclerotic vascular changes found around vessel bifurcations or other vascular sections that are generally subject to increased turbulence. Increased shear stress alone is also capable of triggering pro-inflammatory chains of signals in endothelial cells (Orr et al. 2005). NFkappa-B activity (Monaco et al. 2004) is responsible for the initial stimulation of pro-inflammatory signals. NFkappa-B (nuclear factor regulating expression of kappa light-chain immunoglobulin) is a transcriptional regulator, which plays a central role in the innate human immune response system, and which stimulates the transcription of a wide range of pro-inflammatory signals. As soon as there is local activation of endothelial cell inflammation within the context of systemic atherogenic conditions, plaque development is triggered as a result of the interaction of circulating LDL with inflammatory signal cascades (Fig. 3.1 b-c):

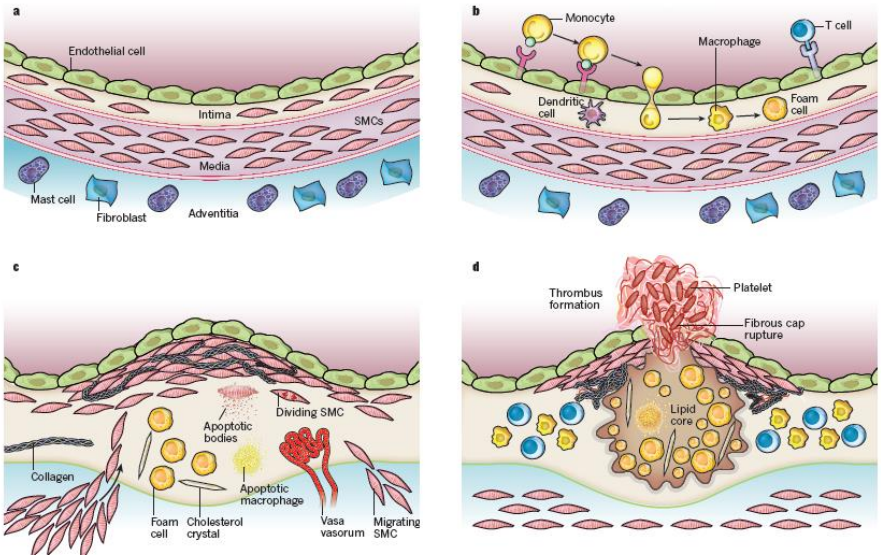

Fig.3.1: Schematic illustration of the healthy vessel wall of a human muscular artery (a), the stage-by-stage development of an atherosclerotic lesion (b and c, see explanation below), and the rupture of the lesion and formation of a thrombus (d).

Figure is used with the kind permission of Macmillan Publishers LTD: Peter Libby et al.: Progress and challenges in translating the biology of atherosclerosis. Nature 473, 317-325, 19 May 2011, doi:10.1038/nature10146, Published online, 18 May 2011 [http://www.nature.com/nature/journal/v473/n7347/abs/nature10146.html] (Libby et al. 2011)

Leucocytes begin adhering to and migrating into the intima. The monocytes which migrate into the intima differentiate into activated macrophages which absorb lipids and then turn into

foam cells, the histological indicator for early stage atherosclerotic lesions (Fig. 3.1b). In the process a whole series of inflammatory signals are released in the intima. During the next stage (Fig. 3.1c) smooth muscle cells migrate from the media to the intima, proliferate, and switch from a dormant and contractile to a proliferating and secreting phenotype. This results in the formation of a lesion core which among other things is characterised by inflammation and foam cells but which is sealed towards the vessel lumen by a layer of smooth muscle cells and a fibrous cap. The lesion can persist in this stage without becoming instable for many years.

B Destabilisation and rupture of the lesion, vascular occlusion resulting from thrombosis

In recent years observations of asymptomatic atherosclerotic plaques demonstrating long-term stability have increasingly focused on the mechanisms of plaque de-stabilisation and the actual triggering of an infarction.

Extra-cellular matrix molecules (such as collagen, elastin, proteoglycans and glycoproteins), which are secreted by the activated smooth muscle cells, play a key role in lesion stability (Finn et al. 2010). If the fibrous cover of the atherosclerotic plaques becomes thinner (<65 µm), however, and no longer contains any smooth muscle cells (Burke et al. 1997, Virmani et al. 2006a), there is a danger of the fibrous cap fissuring or rupturing (Fig. 3.1d).

Other morphological indications of plaque instability are a large necrotic lesion core, increasing signs of inflammation, a measurable change in the geometric proportions of the vessel wall ("vascular remodelling"), increased vasa-vasorum neovascularisation and intra-plaque haemorrhage (Moreno 2010). The transition to instable plaque increases the risk of acute vascular occlusion (Moreno 2010). In the case of patients with clinically asymptomatic proximal coronary artery stenosis, the annual incidence of clinical vascular occlusion is between 4 and 13 % (Moreno 2010). If a fissure or rupture occurs in the fibrous cap, collagen, lipids and inflammation factors enter the bloodstream and a thrombus forms (Fig. 3.1d). The thrombus may either lead to occlusion at that precise point or, following detachment from the vessel wall, cause occlusion in other more peripheral vascular sections.

3.3.2 Peripheral atherosclerosis (Peripheral arterial disease – PAD)

Atherosclerosis should be regarded as a generalised disease affecting the intimae of medium and large-sized arteries, since many of the contributing factors are systemic. Generally, however, clinically relevant vascular stenoses or occlusions occur at certain preferred points of the vascular tree, where an increase in shear stress is present as an additional local trigger (Harloff et al. 2010). Turbulent blood flow particularly occurs at bifurcations; this can be the starting point for endothelial change and – in combination with systemic factors – for atherosclerotic lesions. In addition to the coronary arteries, the carotid bifurcation is a particularly frequent and, owing to the clinical consequences of occlusion (stroke), particularly critical location.

The aorta is also frequently affected by "spontaneous" atherosclerotic changes, though interestingly not in the region of the aortic arch of the ascending intra-thoracic aorta (aorta ascendens (Liu et al. 2009)), but around the bifurcation of the abdominal aorta (aorta abdominalis). Although the risk factors are the same as for atherosclerosis, both the morphology and the developmental history of these lesions would appear to be different (Nordon et al. 2009). The vascular wall construction, not to mention the function of the various sections belonging to the peripheral vascular system, differs immensely. This notwithstanding, the key stages in the development of a carotid artery atherosclerotic lesion are the same as the process described for coronary heart disease (Virmani et al. 2006b).

3.3.3 Myocardial microcirculatory disorders

Microcirculatory disorders, which frequently occur concurrently with macrovascular cardiovascular diseases, are another aspect which has only become the focus of research since imaging techniques made it possible to present myocardial perfusion visually. No definitive conclusion has yet been reached concerning the interaction and relative disease significance of micro and macrovascular circulatory disorders.

Generally speaking, impaired capillary perfusion may lead to insufficient blood supply and myocardial tissue damage, whether in addition to or independently of a reduction in blood supply via the afferent coronary arteries.

In a healthy heart, the capillary network has a high structural and functional reserve as each of the tissue areas supplied by a particular capillary overlap. The functional reserve capacity of healthy individuals, defined as the quotient of maximum myocardial perfusion in relation to perfusion when resting, is approximately 4. This, however, is not the case in patients suffering from ischaemic, inflammatory, or dilated cardiomyopathy, or from high arterial blood pressure (hypertension): in such cases, myocardial microcirculation is revealed to be considerably impaired, both structurally − measured as a reduction in capillary density − and functionally − measured using positron emission topography or Doppler sonography (Karch et al. 2005).

Patient studies show that the extent of an existing microcirculatory disorder is an indicator of individual cardiovascular risk (Rizzoni et al. 2003). In the case of patients with high arterial blood pressure, who suffer from angina pectoris despite showing no anomalies during coronary angiopathy, the reduction in the coronary perfusion reserve is associated with a much higher mortality rate (Marks et al. 2004).

Accordingly, structural or functional disorders relating to myocardial microcirculation are common. They may exacerbate the symptoms of pre-existing coronary heart disease and are also associated, in the absence of atherosclerotic changes to the coronary arteries, with ischaemic heart disease symptoms.

3.3.4 Combined myocardial microcirculatory disorders

Diabetic cardiomyopathy is cited in this instance as one particularly common example of complex cardiomyopathy involving the various components of cardiac tissue. Diabetes and metabolic syndrome are key risk factors in the development of coronary heart disease. Since the early nineteen seventies, scientists have been aware that diabetes is also associated with cardiomyopathy of a functional and structural nature (Fein 1990) which, regardless of atherosclerotic changes to the coronary arteries, occurs with a prevalence of 60 % among sufferers of type II diabetics (Di Bonito et al. 2005).

On the one hand, this leads to structural changes manifesting as interstitial and perivascular fibrosis, an increase in type III collagen, though not of types I or IV (Shimizu et al. 1993), a reduction in capillary density, as well as increased necrosis and apoptosis (Frustaci et al. 2000) of cardiomyocytes (Aneja et al. 2008). At an ultrastructural level, the cardiomyocytes demonstrate a loss of mitochondrial cristae (Dhalla 1998, Bugger and Abel 2008). The functional reserve of the coronary system is therefore compromised even if the coronary arteries remain unaffected by obstructive cardiovascular disease.

Much research is still needed into the pathogenetic mechanism of diabetic cardiomyopathy. Blood glucose concentrations appear to play an immediate role.

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4 Radiation exposure mechanisms with a potential impact on cardiovascular disease pathogenesis

4.1 Introduction

For a long time the heart was regarded as a model radiation-resistant organ. This view was based on the low levels of cell division activity found in the heart, with its post-mitotic myocytes and the extremely slow proliferation of endothelial and connective tissue cells (Lauk and Trott 1990; Schultz-Hector and Trott 2007).

On the one hand, in cases where reactions only occur above a certain threshold dose, unwanted effects following radiation exposure are regarded as deterministic or, as expressed by the current ICRP definition, as "tissue effects/organ reactions" (ICRP 2012). These effects of radiation are generally to be expected as a result of cell destruction, cell ageing, or the apoptosis of either a critical quantity of cells or of a critical cell type. It is relatively certain that such cell-destroying effects are involved in the radiation-induced damage of cardiovascular structures resulting from high doses.

On the other, it is assumed that stochastic effects following both high and low doses of radiation result from persisting changes (including mutations) of individual cells and their clonal expansion. This particularly applies to radiation-induced malignant tumours. In this instance, it is impossible to define a threshold dose below which the absence of any effects, i.e. no tumour-triggering mutations, can be guaranteed.

Currently the potentially existent risk of cardiovascular diseases following exposure to radiation is not taken into account when calculating the detriment due to stochastically induced diseases. In terms of supplying evidence for a causal link between cardiovascular diseases and low doses of radiation exposure, it is to be expected that – taken in isolation – epidemiological studies conducted in the near future will only provide low levels of certainty, if any at all. Additional experimental research into the accompanying mechanisms is therefore crucial when assessing the risk of cardiovascular diseases following exposure to low doses of radiation.

This chapter will begin by addressing the hypothetical mechanisms, then the findings from human studies which currently exist, the results of animal experimental research, and finally the results of in vitro research available to date, as well as their potential and limits in assessing the effects of radiation on the human cardiovascular system.

4.2 Hypothetical mechanisms

The causes of cardiovascular diseases, which may also be triggered or accelerated by radiation, are, as described in detail in Chapter 3, subject to many factors. Experimental and clinical observations suggest similar trigger mechanisms following exposure to high doses of radiation for both the occurrence of atherosclerotic primary lesions and plaque destabilisation, as is the case for spontaneous atherosclerosis. Moreover, exposure to radiation may act not only as an independent risk factor in the incidence of cardiovascular disease, but may also or alternatively influence the conventional, well-established risk factors.

A clear and convincing causal biological link between radiation exposure <500 mGy and cardiovascular diseases has yet to be established. This is aggravated by the fact that atherosclerotic lesions can take decades to develop, their rate of radiation-independent incidence is high, no conclusions can be drawn concerning the occurrence of individual lesions, and that there are currently no biological markers which are able to demonstrate a reliable link between exposure to radiation and cardiovascular diseases.

The potential biological mechanisms described to date for doses below 5 Gy are as follows:

- A monoclonal development of atherosclerotic plaques (mutation theory; Benditt and Benditt 1973; Schwartz and Murry 1998).
- A transformation of smooth muscle cells from dormancy into activated secretion within atherosclerotic pathways (oncogenic activation, LOH and microsatellite instability; Andreassi 2003).
- An inflammation-independent decrease in microvascular perfusion (Marks et al. 2005; Prosnitz et al. 2007). (see Chapter 4.2.3).
- Long-term radiogenic effects on the immune system (Kusunoki et al. 1998; Ross 1999; Hansson 2005). (see Chapter 4.3).
- Inflammation reactions and changes within micro-vessels (inflammatory/micro-vascular theory; Hansson 2005).

4.2.1 Monoclonal development of atherosclerotic plaques (mutation theory)

One of the most controversial hypotheses was proposed by Benditt and Benditt (1973): the idea that human atherosclerotic plaques are monoclonal in origin. As described in detail in Chapter 3.3.1, atherosclerotic plaques are principally made up of vascular smooth muscle cells (SMC), lipids and macrophages.

In their study of female patients, Benditt and Benditt (1973) isolated plaques in various stages of atherosclerotic development and examined them for signs of either homozygosity or heterozygosity relating to the glucose-6-phosphate gene status. Different deposits isolated from the same individual were found to contain the enzyme in either type A or type B form, thus indicating clonogenicity. By contrast, tissue samples taken from healthy vessel media and intima demonstrated a composition concurrent with a heterogeneous origin.

In accordance with the clonal expansion model for malignant tumours, the hypothesis was therefore put forward that atherosclerotic deposits are caused by a trigger mutation in the SMC, probably due to chemical mutagens or viruses, leading to atherosclerotic plaques of monoclonal origin. Since ionising radiation is extremely mutagenic, this would – in theory – explain how even low doses of radiation might cause cardiovascular diseases.

Numerous other studies were unable to confirm these observations, especially those relating to microsatellite instability (Bobik et al. 1999). Moreover, clonogenicity is not synonymous with the transformation of a single cell. Subsequent research has revealed that larger sections of healthy vessel media are monoclonal in origin (Chung et al. 1998). As a result, clonogenicity is far more likely to be attributable to the existence of clones developing in the healthy vessel wall than to mutation. Proof of the hypothesis that DNA damage and cell transformation play a major role, and more specifically that atherosclerotic plaque development is monoclonal in nature, remains unconvincing and therefore unlikely.

4.2.2 Transformation of smooth muscle cells from dormant and contractile SMC to proliferating and secreting SMC

As described in Chapter 3.3.1., the initial inflammation reaction triggered in the intima during the development of an atherosclerotic lesion is followed in the next stage by, among other things, the transformation – under the influence of TGF-ß – of the smooth muscle cells (SMC) found in the vessel wall from a dormant and contractile to a proliferating and secreting phenotype.

Atherosclerotic plaques demonstrate clear indications of chromosomal change and instability. Both microsatellite instability and the loss of heterozygosity (LOH) in atherosclerotic plaques have been variously reported (Hatzistamou et al. 1996; Miniati et al. 2001). As a result, several teams went on to conduct research into the loss of heterozygosity (LOH) in atherosclerotic plaque genes that might conceivably play a major role in the development of cardiovascular diseases (McCaffrey et al. 1997; Grati et al. 2001; Miniati et al. 2001). The high mutation rate of the type II TGF-beta1-receptor gene has also been considered (McCaffrey et al. 1997) as playing a potential role. The occurrence of this mutation in plaques, however, was quickly found to be so rare that no general mechanism for its development could be deduced (Clark et al. 2001). To this day, the quest to specify a particular chromosomal area crucial to the development of atherosclerotic plaques – either causally or as a general marker – has proved unsuccessful, if not impossible. The hypothesis that chromosomal change and chromosomal instability play a major role as potential biological mechanisms in influencing the pathogenesis of atherosclerosis following exposure to radiation remains unconvincing and therefore unlikely.

4.2.3 Inflammation reactions and changes within micro-vessels (inflammatory/micro-vascular theory)

The mechanisms which lead to the occurrence of radiation-induced cardiovascular diseases remain largely unexplained. Past discussions have specifically examined the idea that either DNA damage or cell transformation could play a major role – for which the proof is less than satisfactory. Nevertheless, it does seem likely that inflammation reactions are involved (Schultz-Hector and Trott 2007; Little et al. 2008, 2010; Schultz-Hector and Hildebrandt, 2009; Hildebrandt, 2010). Studies by Stewart et al. (2006) have proven that high doses of radiation lead to the earlier manifestation and increased occurrence of macrophage-rich, inflammatory atherosclerotic changes, and that these show a tendency to haemorrhage within the atherosclerotic plaque, also potentially inducing a decrease in myocardial perfusion.

Vascular intima endothelial cells (see Chapter 3.3.1.) and the cascade of inflammatory mediators are affected by both macrovascular and microvascular radiation effects. It is therefore assumed that the most likely cause of radiation-induced cardiovascular diseases resulting from low doses of radiation is a modulation of the inflammatory response. It is possible that the vascular intima endothelial cells play a crucial role in radiation-induced cardiovascular diseases. Just what effects, however, the endothelium is subject to remain difficult to specify: while in situ measurements can present problems relating to a lack of sensitivity and specificity, research involving cell cultures or animal models can only ever be of limited significance to humans, since such experiments are associated with endothelial cell proliferation rates that differ dramatically from the norm. A considerable number of studies have examined the effect of radiation on endothelial cells in vitro, and a few have been able to corroborate some of their findings in vivo (summary in Schultz-Hector and Trott, 2007).

Finally, it should be reiterated that radiation-induced cardiovascular diseases differ systematically from the conventional deterministic consequences of radiation by virtue of its timeframe (chronically progressive, risk gradually increases over decades), its dose-response relationships (it has not been possible to establish a threshold dose to date), and its trigger mechanism (a quantitative loss of cells is not the decisive mechanism).

4.3 Studies on humans

Changes affecting the abdominal aorta have only been reported in a handful of cases relating to prior radiation treatment. Since these observations refer to relatively high doses of radiation, each case being associated with peculiarities and unique circumstances, no general

indication concerning abdominal aorta radiation sensitivity may be asserted for the purposes of radiation protection.

During a course of curative radiation treatment, doses for the heart and coronary arteries can be extremely high; in the case of M. Hodgkin, for instance, the cumulative dose for defined areas of the heart exceeded 40 Gy (McGale and Darby 2005). A whole range of "tissue effects" (ICRP 2012) have been observed in patients subjected to such high levels of exposure. These result from the deactivation of a large number of cells, accompanied by functional damage to the affected tissue. Such effects include the direct destruction of cardiac structures, with the associated structural and functional consequences generally becoming apparent within a few months and/or years of the therapeutic exposure to radiation. Among these are distinctive diffuse fibroses, especially of the pericardium and myocardium, pericardial adhesions, microvascular damage, and cardiac valve and coronary artery stenoses. Such changes have been confirmed in patients following radiation treatment and also in laboratory animals (Adams et al. 2003).

In the case of M. Hodgkin, impaired cardiac pump performance as well as cardiac valvular abnormalities, both arising specifically as a result of prior radiation treatment administered across large mediastinal areas were noted (Burns et al. 1983; Heidenreich et al. 2005). More recent long-term studies have even found such results to persist after 20 years (Machann et al. 2011).

The latest research shows that, following radiation treatment for breast cancer, regional myocardial function – measured using strain rate imaging – also decreases in accordance with the radiation areas. The existing clinical findings do not, however, reveal whether these results will retain their validity in the long-term, or whether they possess clinical/symptomatic relevance above and beyond an assumed sensitivity to other cardiac burdens (Erven et al. 2011).

The risk of radiation-induced cardiovascular and cerebrovascular diseases increases following a latent period of 10 years, taking an ongoing progressive course. A significant increase has already been observed among cardiac doses amounting to a mere 10 % or less of the generally accepted tolerance doses of 40 Gy - 50 Gy (Schultz-Hector and Trott 2007). In terms of radiation-induced effects, however, the clinical symptoms of coronary heart disease or peripheral atherosclerosis (peripheral arterial disease) are non-specific. It is therefore impossible to assign the symptomatic atherosclerosis of individual cases to radiation exposure rather than to any one of a number of other causes.

Although the mechanisms of radiation-induced cardiovascular and cerebrovascular diseases have yet to be properly understood, there would at least seem to be a correlation between high doses of radiation and macrovascular and microvascular changes respectively.

Macrovascular changes are specifically characterised by a swifter progression of age-related atherosclerosis in the coronary and major arteries. Following breast cancer radiation treatment on the left side, the incidence of coronary stenoses is not only higher than in the case of right breast cancers, but there is also a preferred localisation in the region of the left anterior descending artery, which is necessarily subject to a higher dose than other areas of the heart (Correa et al. 2008). It is striking that not only historical but also current radiation techniques are linked to a significantly enhanced risk of atherosclerosis (Gutt et al. 2008). The observation of atherosclerotic change in the internal thoracic artery following exposure during radiation treatment is impressive, in that this artery, which runs in a straight line without bifurcations, is not affected by "spontaneous" atherosclerosis (Russel et al. 2009).

Microvascular change is characterised specifically by a reduction in capillary vessel density and may lead to consecutive chronic cardiac perfusion disorders and focal degeneration of the myocardium. Following radiation treatment of left-sided breast cancer, focal perfusion deficits of the myocardium were documented using SPECT (single-photon emission computed tomography). The incidence rate increased according to the length of time since the treatment and the size of dose; the localisation of perfusion defects correlated with the dose distribution around the heart (Marks et al. 2005). A prospective study by the same group of researchers showed that these changes also persisted over observation periods lasting 3 and 6 years (Prosnitz et al. 2007).

By contrast, the epidemiological studies which had previously been conducted into the cardiovascular risk of low radiation doses or total body exposure principally referred to symptomatic atherosclerotic change (e. g. stroke or myocardial infarction; see Chapter 5). For the most part it was not possible to chart pathological change, which would have allowed conclusions to be drawn concerning macrovascular change or microvascular perfusion; without the use of sophisticated imaging procedures, pathological change cannot be recorded.

It was therefore assumed that both macrovascular and microvascular change depended on the dose, its distribution, and other risk factors to which the humans or laboratory animals in question had been exposed, with the latent period varying according to dose level. Both forms of cardiovascular change involve the endothelial cells of the vascular intima (see Chapter 3.3) and pro-inflammatory inflammation cascades (Hildebrandt, 2010; Little et al. 2008, 2010; Schultz-Hector and Hildebrandt 2009; Schultz-Hector and Trott 2007;).

The findings of the Life Span Study (LSS) involving survivors of the atomic bombs dropped on Japan formed the epidemiological points of reference for the role of inflammation processes in causing cardiovascular diseases. Many years after exposure occurred, individuals were still found to have slightly, yet nevertheless significantly increased systemic inflammation parameters, featuring heightened interleukin-6 levels (IL 6: 0 Gy: 1.47 pg/ml; 0.005 Gy - 1.5 Gy: 1.53 pg/ml; >1.5 Gy: 1.85 pg/ml), TNF-α, IFN-γ and IL-10 (Hayashi et al. 2003, 2005). Other inflammation markers, such as an increase in the erythrocyte sedimentation rate (ESR) and heightened levels of C-reactive protein, were also discovered in this cohort – once again many years after exposure (Hayashi et al. 2005). Heightened levels of IL-6 were also found in a series of other cohorts (not exposed to radiation) accompanied by increased cardiovascular risk (Ridker et al. 2000; Tzoulaki et al. 2005).

It is moreover possible that other more indirect mechanisms were involved. Owing to the potential significance of infections in the development of cardiovascular diseases, it is possible that immune defects play an indirect role (Ross 1999; Hansson 2005). Studies involving Japanese survivors have revealed that T- and B-cell populations shrink depending on the dose received (≥ 1.5 Gy) (Kusunoki et al. 1998).

Furthermore, these studies of Japanese survivors revealed an increase in parathyroid hormone directly coincident with an increase in radiation dose; this indicates yet another possible indirect mechanism for triggering high blood pressure and cardiovascular diseases (Fujiwara et al. 1994).

A detailed overview and discussion of the potential link between these systemic radiation effects, the development of atherosclerosis and increased cardiovascular morbidity or mortality in the case of atomic bomb survivors can be found in the summary recently published by Hendry et al. (2008). There remains however no indication that these two possible consequences of total body irradiation are causally linked. As a result, no binding statements can be made at present.

4.4 Experimental studies on animals

Whether the types and mechanisms of cardiovascular radiation impact following exposure to doses <1 Gy can be derived from the effects of higher doses is unclear. Based on an experimentally worthwhile working assumption, the following section will, however, begin by examining any existing clinical and experimental findings on changes to morphological and functional parameters relating to the higher dose range. It will then present those animal models suited to research into radiation-induced cardiovascular diseases and conclude by summarising the few animal experiment results which exist on exposure to radiation <1 Gy.

4.4.1 Experimental data on the radiation impact of high radiation doses

4.4.1.1 Atherosclerosis

These days there is much clinical evidence to suggest that the probability of local atherosclerotic change increases following radiation treatment to the thorax (Darby et al. 2010). Wild-type laboratory animals, however, not least owing to their low levels of spontaneous atherosclerosis, fail to provide the degree of sensitivity necessary to enable quantitative research to be conducted into radiation effects in the relevant dose ranges. Although earlier studies used high doses, they did not analyse the coronary arteries in a systematic and quantitative manner.

The non-invasive early detection of atherosclerosis in sub-clinical stages is a necessary requirement of secondary prevention. More recent research has therefore suggested a range of modern methods that might also be potentially suited to longitudinal observation studies following low doses of radiation. These include the CT-based measurement of coronary artery calcium content (Andersen et al. 2010) and peripheral arterial tonometry (Zelcer et al. 2010).

Current systematic experimental research into atherosclerosis following radiation exposure is fully focused on morphological studies involving ApoE-/- mice. On the one hand, morphological research within an experimental context is the simplest and most reliable approach, on the other, the sensitivity of conventional laboratory animals to atherosclerotic change is so low that functional changes are scarcely to be expected, even if a subject is already affected by atherosclerosis. Moreover, the animal model subjected most frequently to research, the ApoE-/- mouse, doesn't develop any coronary stenoses whatsoever, with changes to the ascending aorta appearing instead; in the case of humans, however, the latter does not represent a preferred location for atherosclerosis.

Only recently have Stewart et al. (2006) been able to demonstrate in experimental studies involving ApoE-/- mice and using high, therapeutically effective radiation doses, that the exposure of cardiovascular structures is associated with the accelerated growth and destabilisation of atherosclerotic lesions (see Chapter 3.3.1; Stewart et al. 2006; Hoving et al. 2008), which may potentially lead to myocardial circulatory disorders (Prosnitz et al. 2007). This involved locally irradiating the carotid artery of ApoE-/- mice [1x 14 Gy (Stewart et al. 2006); 1 x 8 Gy, 20 x 2 Gy (Hoving et al. 2008). The authors were able to show that the cholesterol value of irradiated mice was not significantly different to that of a control group of similarly aged mice. Neither was there any rise in systemic inflammatory markers. In comparison with the control group of the same age, however, the mice which were exposed to high doses of local radiation, developed macrophage-rich, inflammatory atherosclerotic changes more rapidly and more extensively, which in turn showed a tendency towards intra-plaque haemorrhaging. These inflammatory plaque changes were not as extensive following an acute radiation dose of 8 Gy as they were after exposure to 14 Gy, which presupposes dose dependency. This study is the first systematic experimental research to prove a causal link

between radiation and atherosclerosis, also indicating that exposure to high doses of radiation can constitute an independent atherosclerosis risk factor.

Another cell type which accumulates in atherosclerotic lesions is the mast cell. One hypothesis is that the gene expression of cathepsins and matrix metalloproteins is increased in the mast cells of lipoprotein receptor-deficient (LDLR-/-) mice owing to the release of the pro-inflammatory cytokines IL-6 and IFNγ (Sun et al. 2007). On the other hand, in comparison to control animals not exposed to radiation, mast cell-deficient rats receiving an acute radiation dose of 18 Gy (250 kV x-ray radiation) demonstrated more pronounced radiation-induced changes, specifically diastolic dysfunction and concentrations of interstitial collagen III; this would appear to indicate that mast cells have a protective function (Boerma et al. 2005).

The findings which exist to date remain insufficient, however; subsequent investigation is required involving radiation exposure to moderate and low doses.

4.4.1.2 Focal perfusion disorders of the myocardium

Clinical observations that exist to date on focal perfusion disorders of the myocardium – both those dependent on dose and time and those of a chronically persistent nature – following local radiation treatment of patients (see Chapter 4.3; Marks et al. 2005; Prosnitz et al. 2007) correspond with animal experiment findings relating to a decrease in capillary density (Lauk 1987; Stewart et al., personal communications) and the focal change that affects the endothelial phenotype. The latter is characterised by a consistent loss of endothelial alkaline phosphatise that has yet to be understood (see Chapter 4.4.1.4).

Until now, research into the impact on perfusion has been limited to that witnessed following exposure to high doses; these effects also need to be studied in the low dose range. Capillary density morphometry post-mortem lacks sensitivity, particularly as far as tracing chronology is concerned. Functional longitudinal studies into myocardial perfusion in laboratory animals following exposure of either the entire heart to radiation or of specific cardiac sections are not yet available. It should nevertheless be possible using modern imaging techniques to conduct such research on rodents as well, extending into the <5 Gy dose ranges that are of interest and potentially including <1 Gy as well.

4.4.1.3 Cardiac pump function limitations

The clinical research into persistent cardiac pump function restriction following exposure to extremely high doses (see Chapter 4.3; Burns et al. 1983; Heidenreich et al. 2005; Machann et al. 2011) corresponds with experimental studies already conducted on laboratory animals. In tests on rats it has been possible to describe a persistent limitation of the left ventricular ejection fraction following extremely high local doses of radiation (20 Gy) administered to the heart, even in the case of (as yet) clinically asymptomatic animals and despite poor optical resolution (Schultz-Hector et al. 1992).

At the same time, both an increase in ß-adrenergic receptors and a decrease in myocardial adrenaline synthesis and myocardial catecholamine levels were noted. Ex vivo tests on explanted, in vitro beating hearts (Langendorff-Herz) have turned out to be more sensitive, possibly because of the lack of compensating positive inotropic influence usually supplied by circulating catecholamines (Wondergem et al. 1991). These days it should be possible to extend these experimental approaches for the relevant dose areas, including the use of sensitised animal models (see below), by applying non-invasive techniques suited to longitudinal studies.

4.4.1.4 Microvascular endothelial cell function limitations

Naturally, when it comes to the functional status of human microvascular endothelial cells, scientists are forced to rely on morphological autopsy findings. Even the earliest research into radiation-induced myocardial change, however, revealed signs of the inflammatory activation of capillary endothelial cells.

Experiments not only confirmed these observations, but also revealed an irreversible, spatial and temporal loss of endothelial alkaline phosphatase reaction associated with myocardial change, which animal models corroborate. Neither the molecular identity and function of the enzyme, nor its role in the development of cardiac radiation effects is clear, even though changes in enzyme activity have also been noted in other microvascular myocardial diseases (Koyama and Taka 2010). Nevertheless, long-term, radiation-induced changes to the phenotype of surviving endothelial cells remains of interest from an action mechanism perspective.

Following acute high dose exposure (14 Gy, 250 kV x-ray radiation) applied to the two major neck arteries (carotid arteries) of ApoE-/- mice, Stewart et al. (2006) observed effects on the endothelial cytoskeleton. Twenty two weeks after exposure to the radiation, atypical swollen endothelial cells were noted in the arteries which had been irradiated. Following fractionated exposure to radiation (20 x 2 Gy, 250 kV x-ray radiation) in the same model, the research team discovered long endothelial strands in the vicinity of an atherosclerotic plaque located close to the carotid bifurcation (Hoving et al. 2008). More recent studies have also revealed significant changes following exposure to radiation doses of 2 Gy (Stewart et al., personal communications).

Furthermore the EU CARDIORISK project (www.cardiorisk.eu) has been investigating analyses into the capacity for survival, migration, and proliferation of in vivo endothelial cells belonging to intact laboratory animals exposed to radiation; its results will be especially relevant to the present analysis.

Observations made on endothelial cells in vitro are of little use when it comes to clarifying the cardiovascular impact of radiation in vivo, since the hundred-fold increase in cell turnover which occurs in vitro and the loss of physiological cell-to-cell and cell-to-matrix contacts leads to a fundamental change in phenotypical characterisation.

4.4.2 Animal models suited to analysing <1 Gy radiation doses

Whether any of the aforementioned functional endpoints are relevant to radiation doses in the low (<100 mGy) and moderate ranges (<1 Gy) remains an open question. In addition, there are additional cardiovascular risk factors which are generally of relevance to the human lifestyle, which need to be taken into account when transferring these findings and applying them to human populations.

For the following reasons, the healthy rodents used in older experiments involving extremely high doses of radiation (>10 Gy) are scarcely suited to an analysis of doses <1 Gy:

- only slight change, which can be functionally compensated, is to be expected in healthy animals; moreover such change occurs relatively infrequently.
- rodents per se demonstrate high cardiovascular resistance.

A systematic comparison of different animal models demonstrating cardiovascular impairment is most likely to supply relevant information relating to the impact of radiation doses of <1 Gy. In the process, new high resolution imaging techniques are becoming increasingly available for use in longitudinal, non-invasive studies (Liu and Rigel 2009; Tsui

and Kraitchman 2009; Golestani et al. 2010). Within this context, genetically modified animal models are of most interest when it comes to analysing and influencing the development of atherosclerotic lesions.

The majority of research has been conducted on C57BL/6 mice, which are more sensitive to atherosclerosis than other inbred strains (Paigen et al. 1990). The ApoE-/- variant of these strains has often been used in cardiac disease research owing to its frequent development of spontaneous arterial lesions. This mutant strain of mice is deficient in the primary LDL receptor ligand (LDL= low density lipoprotein). The laboratory animals are therefore characterised by heightened concentrations of cholesterol plasma (Lutgens et al. 2001). Low density lipoprotein is essential for supplying tissue with cholesterol; in its oxidised form, however, it is associated with the cascade-like onset of pathological development which in turn leads to cardiovascular diseases.

The two genetically modified animal models most often used in current cardiological research are therefore ApoE-/- mice and LDL receptor-deficient mice (LDLR-/-). The clinical relevance of both animal models, however, is considerably diminished by the fact that atherosclerosis tends to occur in the ascending aortic arch – a vascular section with a particularly unique anatomical wall structure owing to its elastic buffer function. The vascular media (see Chapter 3.3.1.1) of such buffer vessels principally consist of elastic fibres (elastic arteries), allowing these vessels close to the heart to ensure that blood flow remains even during both systolic and diastolic phases. In humans these vascular sections are not commonly subject to atherosclerosis. The coronary arteries in both models are scarcely affected (Russell and Proctor 2006; Dougherty et al. 2009).

Mice models referring to diabetes (Matrougui 2010), metabolic syndrome (Kennedy et al. 2010) or hypertension (Mourad and Laville 2006) could also prove particularly relevant to radiobiological experiments, since they are also subject to microvascular change and the potential for interaction with radiation effects is of especial interest.

Genetically uniform inbred strains of rats are available; indeed, their body size makes them more suited to in vivo research than mice. To date, however, few genetically manipulated rat disease models exist. Thanks to the current availability of new rat genetic manipulation methods, this seems likely to change in the near future (Geurts and Moreno 2010). For an overview of currently available cardiovascular disease models, please refer to the relevant literature (Bader 2010).

Diet-induced and spontaneous atherosclerosis in particular is also found among hamsters, rabbits and guinea pigs. The primary disadvantage associated with these species – especially when researching the effect of small doses – is that they are not inbred and therefore demonstrate higher rates of interindividual variability (Singh et al. 2009).

Owing simply to the human anatomical situation, experimental animal models involving pigs get closer to the mark than other animal models and also demonstrate greater cardiovascular sensitivity than rodents. Nevertheless, the interindividual rate of variability remains higher than among inbred rodents. Large groups are needed for the experiments to be conclusive. Bearing in mind, however, the lengthy observation periods required when researching the cardiovascular effects of radiation and the high running costs, it is likely that only a handful of carefully selected experiments would receive financing (Singh et al. 2009). For a comprehensive and detailed discussion, please refer to the 2010 HPA report (HPA 2010).

4.4.3 Experimental data on the radiation impact of radiation doses <1 Gy

Early animal experiments were only designed to measure the cardiovascular impact of high and/or extremely high doses of radiation; they were not intended to investigate atherosclerotic

changes following radiation exposure, i.e. the coronary arteries and peripheral arteries were not systematically examined.

One recent systematic study has managed to prove a causal link between high dose radiation and atherosclerosis, thus also indicating that exposure to high doses of radiation can constitute an independent atherosclerosis risk factor (see Chapter 4.4.1.1). This research using ApoE-/- mice revealed that local exposure to high doses of radiation furthered the development of atherosclerosis and created a predisposition towards inflammatory, thrombotic plaques (Stewart et al. 2006; Hoving et al. 2008). Inflammatory and thrombotic changes to the endothelial cells generally have a major influence on the development of atherosclerotic changes (see Chapter 3.3.1.); moreover, there is also a strong link between instability and possible rupture of the plaque and the clinical symptoms of atherosclerosis (see Chapter 3.3.2).

Little systematic animal experimentation research has been conducted to date into the link between exposure to low (<100 mGy) or moderate (<1 Gy) doses of radiation and atherosclerosis.

The EU CARDIORISK project examined the effect of low and moderate doses of radiation applied locally to the hearts of C57Bl/6 mice on the mitochondrial proteome four weeks following exposure. Despite no apparent impact on cardiac function following exposure to 0.2 Gy, changes were noted in the protein composition, leading to the deduction that both the pyruvate metabolism and cytoskeletal structure proteins were affected. These observations are in line with the results of earlier research, during which an increase in lipid peroxidation and protein oxidation in cardiac tissue was noted 5 and 24 hours after total body irradiation with 3 Gy (Azimzadeh et al. 2011).

These initial results issued by CARDIORISK indicate that either indirect or direct change to the cardiac mitochondria could play a role in the emergence of radiation effects. Nevertheless it is not yet possible at this time to assign the effects observed to either cardiomyocytes or endothelial cells, for instance, while other factors such as temporal or dose dependency or any association with clinically relevant endpoints remain unknown.

Within the context of the integrated NOTE (Non-targeted Effects of Ionising Radiation; http://note-ip.org) project, the reaction, among other things, of macro and microvascular endothelial cells to targeted exposure with low and moderate doses was examined. One particular issue addressed by this project was to test – using the ApoE-/- mouse model – whether total body irradiation with low or moderate doses of radiation affects the progress of atherosclerosis, with specific reference to genetic background and the extent of existing atherosclerotic change at the time of exposure. In addition the project researched whether these effects may also be conveyed by stress and/or inflammation reactions. Within this context the markers IL-6, IL-10, KC, MCP-1, TNFα, IFNγ, TGFß, sICAM-1, sVCAM-1, sE-selectin and fibrinogen were analysed.

Studies were conducted on C57BL/6J mice that were susceptible to developing atherosclerosis (ApoE-/-; see Chapter 4.4.2). Control (0 Gy) mice were handled and transported in the same manner as exposed mice. The laboratory animals were exposed to different radiation doses (0; 0.025; 0.05; 0.1; 0.5 and 2.0 Gy) during the early (8 week old animals) or late stages of disease (8 month old animals). The animals were exposed at either high dose rate (150 mGy/min) or at a low dose rate (1 mGy/min, 100 mGy/day, 5 days per week).

Different experimental parameters were analysed 3 and 6 months following the earlier radiation exposure and 2 and 4 months following the later radiation exposure. An analysis of the chronology of atherosclerosis formation and development using morphological parameters

(aortic luminal surface lesion analysis; localisation, quantity, size/area and development stage of aortic root atherosclerotic plaque; immunohistochemical analysis of cardiac tissue) and chemical laboratory parameters (serum cholesterol, serum lipoprotein profile, cholesterol distribution; cytokines, adhesion molecules and thrombogenic markers in the serum) was conducted (see Fig. 4.1).

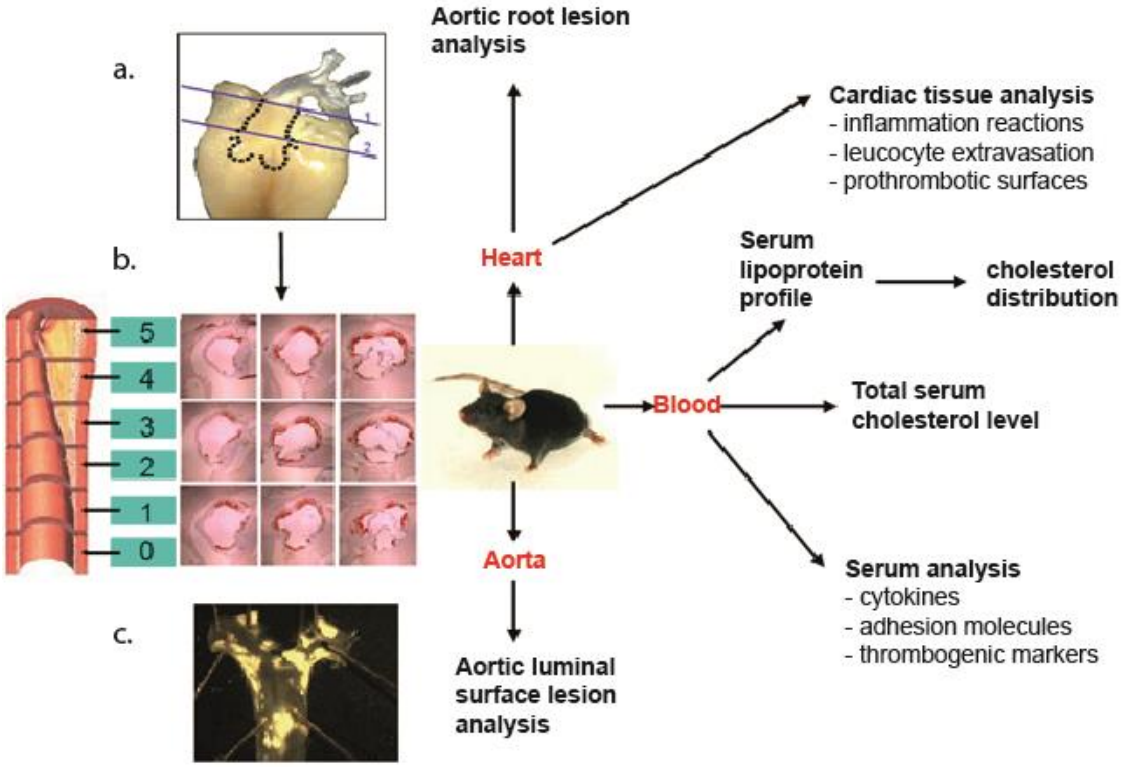

Fig. 4.1: Chronologies and parameters analysed during animal experiments using the ApoE-/-- mouse model, with correlated readings from the same laboratory animals (for example quantity, size and severity of aortic arch atherosclerotic plaques (a. and b.); aortic luminal surface lesion analysis (c.); immunohistochemical analysis of cardiac tissue; serum cholesterol, serum lipoprotein profile, cholesterol distribution).

The findings of these experiments indicate that, depending on dose, dose rate and the developmental stage of atherosclerosis at the time of exposure, the total body irradiation of genetically sensitive laboratory animals with low and moderate doses of radiation would appear to provide potential protection against the atherosclerotic progression parameters under examination (Mitchel et al. 2011). In the case of low doses (25mGy - 50 mGy) in particular, applied at a relatively low dose rate (1 mGy/min) either in the early or late stages of atherosclerosis, the morphological parameters of atherosclerotic progression decreased. Some effects were still traceable months after an acute exposure; others were of a temporary nature. In contrast to exposure to low dose rates, exposure to high dose rates during the early stages of the disease revealed both decreases and increases in morphological atherosclerotic progression parameters, which suggests that low doses and low dose rates have the potential to modulate disease progression via other biological mechanisms, and that the dose rate is a potentially key factor.

These experimental observations are thus in direct contrast to the assumption that the familiar and generally disadvantageous effects of high-dose radiation exposure on atherosclerotic progression must therefore also directly apply to low-dose radiation exposure. Moreover the findings also imply that a linear extrapolation of the known cardiovascular risks from the high-dose into the low-dose range is probably unsuitable (Mitchel et al. 2011).

When interpreting the results, it is important, however, to take into account that this particular experimental research project investigated the effects of acute total body irradiation and that the only experimental study involving animals released to date concentrates on this dose range. The impact of repeated exposure or chronic exposure at low dose rates remains to be investigated; the available results urgently need to be confirmed using an alternative atherosclerosis model.

Although these initial molecular findings following low-dose exposure suggest that changes to molecular signal cascades may be permanently verifiable, it still remains unclear what biological significance such changes are likely to have as far as the influence on cardiovascular diseases following exposure to radiation is concerned.

4.5 In vitro studies

To date very little is known about possible cellular and molecular mechanisms and the relationship between radiation exposure and cardiovascular diseases in general. It is principally possible with the help of in vitro cell models to analyse radiation-induced changes following exposure to low (<100 mGy) and moderate (<1 Gy) doses of radiation using a range of molecular endpoints. The latent period, during which years may pass between radiation exposure and the occurrence of clinically relevant symptoms, not to mention the complexity of the clinically relevant endpoints which have yet to be conclusively specified, however, make it extremely difficult to identify those early cellular and molecular changes which are involved in the development of subsequent relevant sequelae.

There is currently no mechanistic link, though suggested by current epidemiological studies (see Chapter 5), between exposure to low or moderate doses of radiation and the development of cardiovascular diseases. This is partly due to a lack of suitable animal models capable of reflecting the human situation (see Chapter 4.4.2). There are definitely indications, however, that the radiation-induced molecular mechanisms leading to cardiovascular diseases differ fundamentally from the pathology of sporadic forms of the disease. While blood flow turbulence and increased shear stress, which occur for instance at bifurcations, are necessary for the development of spontaneous atherosclerosis, radiation-induced atherosclerosis is apparently also able to occur in their absence (see Chapter 3.3.2). Moreover, Russel et al. (2009) were able to demonstrate that, in comparison with spontaneous atherosclerosis, the composition of those atherosclerotic plaques which occurred following high-dose radiation exposure was different (higher proteoglycan content).

Furthermore, when taken with other risk factors, radiation exposure acquires additional significance as an additional risk factor, which may either emerge right at the beginning of the disease, occur during the course of the disease, or even both (Hoving et al. 2008). That's why it is relevant to examine the molecular mechanisms which play a role in the aetiology of sporadic cardiovascular diseases in general following exposure to radiation as well.

As described in detail in Chapter 3.3.1, the pro-inflammatory endothelial cell signal chains triggered by NFkappa-B (Monaco 2004, Orr 2005), the following adhesion and migration of leucocytes in the vessel wall, and finally the increased release of oxygen radicals by both activated endothelial cells and leucocytes (Teupser et al. 2002), which in turn oxidise the LDL accumulating in the vessel wall to make OxLDL, thus stimulating the endothelial expression of selectin and cytokine adhesion molecules, are all decisive factors in the development of atherosclerotic lesions. As a result, it is assumed that inflammation and the corresponding increase in the production of reactive oxygen species (ROS; e. g. hydrogen peroxide, superoxide and hydroxyl radicals) is involved in practically every stage of spontaneous atherosclerosis, and specifically in its initial stage (Hansson 2005; Ramos et al. 2007; Ross

1999). Moreover there are also signs that detectable DNA damage arising in cases of spontaneous atherosclerosis is more likely to be caused by reactive oxygen species than by direct exogenous effects (Mercer et al. 2007).

In contrast to mutations, oxidative stress thus plays a key role in the entire process of cardiovascular disease initiation and progression. ROS and reactive nitrogen species (RNS) are generated both at the outset of atherosclerosis and in advanced atherosclerosis, particularly by macrophages, but also by smooth muscle cells (SMC) and endothelial cells (EC) (Bennett 2001). Hydrogen peroxide (H_2O_2), a reactive oxygen species, which penetrates the lipid membranes, can inflict damage on multiple cellular components, such as lipids, proteins and DNA (Allan et al. 1988; Eny et al. 2005). ROS can trigger oxidative stress, which is known to promote vascular disease and contribute to endothelial cell dysfunction (Coyle and Kader 2007). While high ROS concentrations inflict direct damage on vessel walls, low ROS concentrations stimulate signal pathway changes and the type of gene expression which may alter vessel function (Wolf 2000). Although the role of ROS in cardiovascular diseases is undisputed, many aspects regarding the origin of ROS and their principally cellular target structures remain unresolved. In the case of most tissues, mitochondrial respiratory chain complexes I and III are the primary cause of ROS effects (Lambert and Brand 2009).

As part of the CARDIORISK project, proteome changes within human endothelial cell lines were analysed in vitro following exposure to 200 mGy, changes which would indicate the potentially radiation-induced modulation of endothelial oxidative stress responses. After 4 and 24 hours, changes to the Ran and RhoA signal pathways were specifically noted; both of these had already been linked to oxidative stress responses in a wide range of experimental situations (Pluder et al. 2011).

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5 Epidemiological studies into radiation risk

5.1 Introduction

Owing to the high frequency of cardiovascular diseases and in addition to the risks associated with high doses of radiation, there remains the important question as to whether and which risks are caused to the cardiovascular system by low and moderate radiation doses. A series of more recent studies have supplied epidemiological findings on this subject which the following will present and discuss. In addition to new research findings on the survivors of Hiroshima and Nagasaki, particular significance is attached to the latest data on employees from the Soviet Mayak facility, as well as to results from other studies conducted on individuals exposed occupationally to radiation.

As well as the issue of increased risk potentially relating directly to radiation exposure, this section particularly focuses on assessing the existing studies with regard to the dose-response relationship in the range below approx. 1 Gy.

Epidemiological research has been successful in pinpointing a whole range of major cardiovascular risk factors. In addition to age and the male gender, these specifically include smoking, heightened cholesterol values, obesity, diabetes, raised alcohol consumption, a lack of physical activity and socioeconomic status. These factors need to be taken into account when assessing whether exposure to ionising radiation has an impact on cardiovascular risk. Please see Chapter 2 for details of the known causes of cardiovascular diseases.

5.2 Methodological aspects

5.2.1 Reviewing the literature

Relevant publications were located by conducting a targeted literature search of the Pubmed database and sifting through the bibliographies of existing studies. Only those studies into humans were selected which were found to contain a combination of the terms “ionising radiation”, “epidemiology”, “cardiovascular” and “risk” or other suitably related terminology. Research relating solely to alpha radiation (e. g. radon) was not included. The literature database search produced 68 hits during a timeframe restricted to the years 2000 - 2010. By reviewing the titles and abstracts, eleven publications on epidemiological primary research, all of which featured epidemiological risk assessments for one or more cardiovascular endpoints, were found to merit presentation in detail. In addition, nine reviews or scientific reports (BEIR, AGIR; UNSCEAR) as well as three studies which gave fewer risk specifics were also included. Two older studies that also featured cardiovascular risk assessments relating to

radiation exposure in the context of medical treatment were identified and selected for inclusion. While in the process of writing the report, the working group discovered four publications from the years 2011 and 2012 which were considered significant to the body of epidemiological evidence; these were therefore incorporated.

In recent years a series of reviews has been published on the cardiovascular risks presented by low doses of radiation (Hoel 2006; Mc Gale and Darby 2008; Little et al. 2010). Moreover the UNSCEAR 2006 report (UNSCEAR 2008) also proved a crucial resource when compiling this summary overview of existing studies on the topic.

The following populations, analysed to date for the purposes of risk observation, are of relevance to the task in hand:

- Survivors of the atomic bombs dropped on Hiroshima and Nagasaki
- Patients undergoing diagnosis and (low-dose) treatment
- Occupationally exposed individuals including Mayak workers
- Individuals exposed following the Chernobyl disaster.

Research into patients with high internal doses (e. g. following applications of Thorotrast) and examinations involving gynaecological tumour patients have not been included in the present study.

5.2.2 Endpoints

When researching the cardiovascular consequences of ionising radiation, the literature makes use of a series of different endpoints. A few studies take a general look at all types of cardiovascular diseases. Frequently all forms of ischaemic heart diseases and/or cerebrovascular diseases respectively are examined together as a group. Other studies use individual diagnostic entities, e. g. cardiac infarction or hypertension, as the target disease to be examined. This endpoint heterogeneity must be taken into account when comparing the studies and their results.

5.2.3 An overview of exposure and dose levels

The radiation to which the persons in these studies were exposed was mainly gamma and x-ray in nature. The doses relating to the health effects observed ranged from cumulative total body doses of some 100 mGy in the case of occupationally exposed nuclear power plant workers, and moderate values for cumulative organ doses, to as much as 2.5 Gy administered in the treatment of ankylosing spondylitis. Moderate cardiovascular organ doses of a similarly high level resulting from diagnostic measures were established in a study of patients with gastric ulcers; slightly lower doses were registered among scoliosis patients owing to frequent radiography procedures.

In the analysis of Mayak workforce data, liver doses were used as a substitute for the unknown heart and vascular doses. Effects attributable to gamma radiation with minor neutron radiation contributions were observed among Mayak workers exposed to levels of a few hundred milligray. Exposure to plutonium was considered relevant even if the liver doses were low.

5.2.4 Risk assessments and the “healthy worker effect”

Research into radiation epidemiology is generally based on dose-related analysis. This involves producing estimates of absolute and/or relative risk per dose, usually using linear regression models. It is customary in radiation epidemiology to give details about the excess

absolute risk (EAR) and the excess relative risk (ERR) per dose, where risks per 1 Gy or 1 Sv and the corresponding confidence intervals of 90 % or 95 % are frequently given as estimates. Details relating to the dose-dependent risk of cardiovascular diseases were lifted from the epidemiological studies selected.

In the studies conducted on individuals exposed occupationally to radiation, it should be remembered that these persons often demonstrate a lower mortality rate than the population at large; the group has been positively selected according to its productivity and its members are often part of a health care programme or are subject to health monitoring on occupational grounds. This so-called "healthy worker effect" (HWE) is often more pronounced in the case of cardiovascular diseases than in the case of cancer, since cardiovascular risk factors and/or existing cardiovascular conditions often play a role when it comes to recruiting employees and/or workers being able to remain in such employment. In the case of dose-related risk assessments which compare, for instance, the varying levels of radiation dose received by different cohort members, the HWE is generally insignificant, since such assessments do not entail comparison with the general population. Other aspects of the HWE, relating to the duration of employment and/or length of exposure, do however need to be taken into account during internal assessments, meaning for instance that statistical corrections need to be conducted for the period that has elapsed since the person's initial employment or for the duration of the follow-up.

5.3 Epidemiological studies

Table 5.1. provides an overview of the studies, subsequently to be described in brief, which are relevant to this section of the report. A tabular summary of key points relating to the overall analysis can be found in tables 5.2 - 5.4.

Tab. 5.1: Overview of epidemiological studies published on the risks of cardiovascular diseases associated with radiation referred to in this report (CVD)

Cohorts	Reference	Key endpoints	No. of members	Absorbed dose (Gy), range	Confounders (excluding gender); comments
Atomic bomb survivors AHS	Yamada (2004)	Incidence: ischaemic heart diseases cerebrovascular diseases	10,339	0.1 (0 - 4) large intestine dose	smoking, alcohol
Atomic bomb survivors AHS	Shimizu (2012)	Mortality: all CVD all heart diseases cerebrovascular diseases	86,611	0.1 (0 - 4) large intestine dose	smoking, alcohol, socioeconomic factors, state of health
BNFL workforce	McGeoghegan (2008)	Mortality: all CVD cerebrovascular diseases ischaemic heart diseases	38,799	0.06 (0 - >0.73)	Modifications acc. to employment variables
Mayak workforce	Azizova (2011)	Incidence and mortality: ischaemic heart diseases:	18,763	M: 0.66 (0 - 2.5) F: 0.52 (0 - 2.0)	smoking, alcohol, hypertension, BMI
Mayak workforce	Azizova (2011a)	Incidence and mortality: Cerebrovascular diseases	18,763	0.66 (0 - 2.5)	smoking, alcohol, hypertension, BMI
Nuclear industry employees (15 countries)	Vrijheid (2007)	Mortality: ischaemic heart diseases cerebrovascular diseases	275,312	0.02 (0 - >0.5)	broad adjustments acc. to socioeconomic status
Semipalatinsk Historical Cohort	Grosche (2011)	Mortality: all CVD ischaemic heart diseases cerebrovascular diseases	19,545	0.09 (not specified)	–

Tab. 5.1: Overview of epidemiological studies published on the risks of cardiovascular diseases associated with radiation referred to in this report (CVD) (cont.)

Cohorts	Reference	Key endpoints	No. of members	**Absorbed dose (Gy), range**	Confounders (excluding gender); comments
Tuberculosis patients	Davis (1989)	Mortality: All CVD	13,385	0.84 (not specified) pulmonary dose	–
Chernobyl accident relief workers	Ivanov (2006)	Incidence: all CVD ischaemic heart diseases cerebrovascular diseases	61,017	0.11 (0 - >0.5)	–
UK Radiation Registry	Muirhead (2009)	Mortality: all CVD coronary heart diseases cerebrovascular diseases	174,541	0.025 (0 - >0.4)	Modifications acc. to employment variables
Uranium miners	Kreuzer (2006)	Mortality: all CVD all heart diseases cerebrovascular diseases	59,001	0.04 (0 - >0.3)	Modifications acc. to employment variables

5.3.1 Data on atomic bomb survivors

Indications that atomic bomb survivors are subject to increased cardiovascular risk have been around for a considerable time. The latest analysis of the LSS cohorts was published in 2010 (Shimizu et al. 2010). Mortality data from the years 1950-2003 relating to 86,611 survivors as well as dose data from the DS 02 were available; there were also additional data for a sub-group of approximately 36,500 individuals relating to other risk and sociodemographic factors taken from a survey conducted in 1978. A linear model approach was used in the analysis, while other models were also checked.

The authors reported a total of 19,054 cardiovascular deaths (ICD9 390-459) during the period under observation, of these 8,463 owing to heart diseases[1], 9,622 owing to cerebrovascular diseases (ICD9 430-438, described by the authors as 'strokes') and 969 owing to other circulatory diseases. Taken together, this produced an excess relative risk (ERR) per dose of 0.11 (95% confidence interval: 0.05; 0.17) Gy^{-1} for all cases of cardiovascular death. The ERR per dose for heart diseases was somewhat higher (0.14; 95% CI: 0.06; 0.23) Gy^{-1}; for cerebrovascular diseases it was slightly lower (0.09; 95% CI: 0.01; 0.17) Gy^{-1}. There was no significant increase in cases of death resulting from other circulatory diseases.

In the range below 0.5 Gy the ERR estimate per dose for heart diseases was 0.2 Gy^{-1}, yet owing to a lack of power was classified as insignificant (95% CI: -0.05; 0.45). Doses below 0.5 Gy gave no indications of a heightened risk of cerebrovascular diseases.

The excess absolute risk (EAR) per dose for all cardiovascular deaths was 5.5 (95% CI: 2.7; 8.4) $(10^4 PY\ Gy)^{-1}$. The EAR per dose for heart diseases, with a value of 3.2 (95% CI: 1.3; 5.2) $(10^4 PY\ Gy)^{-1}$, contributed approx. three fifths of the entire risk, with the EAR for cerebrovascular diseases – at 2.3 (95% CI: 0.4; 4.4) $(10^4 PY\ Gy)^{-1}$ – making up about two fifths. It should be noted that in cohort studies into mortality, the spontaneous mortality rate and thus, by extension, the absolute risk, changes with age and the calendar year.

None of the causes of death under examination revealed any statistically significant indications relating to threshold doses. For strokes, the best threshold dose estimate was 0.5 Gy with a 95% confidence interval ranging from less than 0 Gy to 2 Gy. The best threshold estimate for heart diseases was 0 Gy with an upper limit of the 95% confidence interval being set at 0.5 Gy.

Socioeconomic and life-style related confounders (smoking, alcohol consumption) as well as health aspects were included in the analyses. These however had little or no impact on the results relating to excess relative risk. The authors were keen to emphasise the uncertainty surrounding the progression of the dose-response relationship, especially with reference to strokes. Nevertheless, the new data are considered to be significantly more meaningful than previous analyses (e. g. Preston et al 2003). To sum up, this study confirms a slightly raised, dose-dependent cardiovascular risk, especially with relation to heart diseases among the survivors of Hiroshima and Nagasaki. The case for strokes is less clear.

In the Adult Health Study, another investigation involving atomic bomb survivors, health-related data on an LSS sub-cohort are continually being recorded. Morbidity data is available as a result. The latest publication dated 2004 (Yamada et al. 2004) revealed an insignificant

[1] 3,252 cases of ischaemic heart diseases (ICD9 410-414) were registered. According to the authors, mistakes occurred in the allocation of heart diseases to the individual sub-types such as ischaemic heart diseases. Since the authors regard the results for all types of heart diseases (ICD9 390-398, 402, 404, 410-429) as more reliable, these were the results used in this paper.

increase in ERR per dose for ischaemic heart diseases of 0.05 (95% CI -0.05; 0.16) Gy^{-1}, yet a significantly positive ERR per dose for hypertension and myocardial infarction, with increases between 0.03 Gy^{-1} and 0.17 Gy^{-1}, depending on the analytical method used (linear or quadratic model). The ERR per dose for the 'stroke II' endpoint (ICD9 430, 431, 433, 434, 436) was 0.07 (95% CI: -0.08; 0.24) Gy^{-1}.

5.3.2 Patients – treatment and diagnosis

Several studies, some of them published a while ago, quantify the cardiovascular risk of patients treated with ionising radiation for diseases other than cancer, who in the process received cumulative doses extending into the lower Gray range.

In the United Kingdom, Darby et al. (1987) conducted a study into patients with ankylosing spondylitis. In the context of radiation treatment these had received average cardiac doses of around 2.5 Gy (range 0 - approximate. 17 Gy; exposure of different areas of the heart). They were unable to detect any increased risk of cardiovascular mortality. The ERR per dose calculated by Little et al. (Little et al. 2008) for cardiovascular diseases excluding strokes was 0.01 Gy^{-1}; for strokes the value was -2.43 (95% CI: -4.29; 0.71) Gy^{-1}.

In a cohort study of gastric ulcer patients in the USA, who had either received treatment with x-ray radiation (n=1 859) or some other means (n=1 860) between the years 1936-1965, and whose cases were followed until 1997, there was a pronounced overall increase in the risk of death among the irradiated group compared to population data (comparison of observed and expected cases) (Carr et al. 2005]. During treatment only a small section of the heart (apex approx. 5 %) was located directly in the radiation field; the remaining heart tissue was however exposed to scatter radiation. The authors demonstrated a statistically significant trend, associated with increasing dosage, in the relative risk of coronary heart disease. In the process, there was found to be an approx. 50 % increase in risk for the patient group with the highest average cardiac dose (3.9 Gy). This value was statistically adjusted to take other key influencing factors into account. No increase in risk was detected for cerebrovascular diseases. For this study Little et al. (2008) calculated an ERR per dose for coronary heart disease of 0.11 (95% CI: 0.01; 0.22) Gy^{-1}. Other types of cardiovascular diseases failed to demonstrate a positive dose-response relationship. Considerably higher doses were estimated for the section of the heart located in the path of the beam, meaning that this study cannot be taken as evidence for low and moderate doses.

In a cohort study by Davis et al. (1989), tuberculosis patients who were subjected to repeated x-rays and thus received pulmonary doses averaged over the patient collective of approximate 0.84 Gy (~ approximate cardiac dose, no extra details available on organ exposure) failed to demonstrate an increased risk of cardiovascular diseases. In the cohort of 13,385 tuberculosis patients, the ERR per dose was – 0.11 (95% CI: - 0.20; -0.01) Gy^{-1} (acc. to Little et al. 2008).

5.3.3 Occupationally exposed individuals

The occupationally exposed groups investigated to date have been mostly medical staff, nuclear industry and nuclear weapons production employees (pooled data, workers in UK, Mayak workforce) and uranium miners.

5.3.3.1 Medical staff

Medical staff subject to occupational radiation exposure have formed the subject of numerous cohort studies. Generally these studies demonstrate an extremely limited dosimetry and use substitute measurements in producing their dose estimates.

Hauptmann et al. (2003) reported on the cohort of medical-technical radiology assistants in the USA. Within this major cohort (90,284), signs of increased risk of cardiovascular mortality were found among those cohort members who had started work before 1950, in the days when radiation protection was still in its infancy. For those who began working as radiology assistants before 1940 the risk was 42 % (95% CI: 4; 94%) higher than for those who began their career in 1960 or later.

When compared with non-radiologists, there was no demonstrable increase in the risk of developing cardiovascular diseases among radiologists in the United Kingdom. In the study conducted by Berrington et al. (2001) there was no difference in the risk to radiologists and non-radiologists – even during different historical periods. By contrast, there were signs of increased cancer risk in the early years of the twentieth century, possibly as a result of heightened radiation exposure. Early studies conducted on US radiologists turned up no significant increases in risk, even in the case of cardiovascular mortality (Matanoski et al. 1975).

5.3.3.2 International study on nuclear industry employees

Many of the major nuclear industry employee cohorts were included in the 15-country study conducted by the International Agency for Research on Cancer (IARC). Vrijheid et al. (2007) published cardiovascular mortality results for these cohorts. Socioeconomic data, which were factored into the calculations, were available for 275,312 cohort members. Slight, but by no means significant increases in risk and/or positive dose-response relationships were recorded for several cardiovascular endpoints. The ERR per dose for all types of cardiovascular diseases was 0.09 (95% CI: –0.43; 0.70) Gy^{-1}.

5.3.3.3 UK employees exposed to radiation

A more recent analysis of the British Nuclear Fuels employee cohort (BNFL cohorts; n=64 937) from the United Kingdom for the period 1946-2005 (McGeoghegan et al. 2008) produced a significantly positive ERR per dose for cardiovascular mortality of 0.65 (90% CI: 0.36; 0.98) Gy^{-1}. An ERR per dose of 0.43 (90% CI: -0.10; 1.12) Gy^{-1} was calculated for cerebrovascular mortality. There are difficulties however in interpreting the study owing to the inhomogeneity of the effects in the different dose and employee groups.

The latest analysis of data taken from the UK Radiation Register (Muirhead et al. 2009) also indicates an increased risk of cardiovascular diseases. This study encompassed 174,541 occupationally exposed individuals and featured some data from the BNFL cohort. The ERR per dose calculated for all types of cardiovascular diseases was 0.25 (95% CI: 0.01; 0.54) Gy^{-1}. As a result the risk coefficient is still higher than the LSS data, but remains compatible with the LSS results owing to the confidence interval. The size of the cohort investigated here needs to be emphasised; nevertheless, data on potential confounders was for the most part still lacking.

5.3.3.4 Mayak workforce

The Mayak workforce cohort analysed by Azizova et al. (Azizova et al. 2010a, Azizova et al. 2010b) comprised 12,210 employees, who worked at one of the three main facilities operated by the Mayak Production Association (nuclear power plants, radiochemical plants, plutonium production facility) during the period 1948 to 1958. The data on mortality and incidence of cerebrovascular and cardiovascular diseases comprised the time from the point of initial employment through to the disease diagnosis, the death of the individual and/or the end of the time period in which current information was still available about the worker in question (31 December 2000 at the latest).

The "Doses 2005" dosimetry system for the Mayak employees contains components for calculating the annual organ doses due to both external radiation and incorporated plutonium (Vasilenko et al. 2007). The external dose due to gamma radiation with, in the case of a handful of workers, minor neutron radiation input, was already known for practically all workers (99.9 %). The average dose for men was 0.91 Gy (standard deviation, σ = 0.95 Gy) and for women 0.65 Gy (σ = 0.75 Gy). When calculating the risk posed by external radiation, incorporation levels were corrected to take the effects of plutonium into account. Measurements relating to the concentration of plutonium in urine were available for 30 % of the workforce who had been potentially exposed to plutonium, not to mention biokinetic models based on comprehensive autopsy readings. Among the employees with corresponding urine readings, the average liver dose due to plutonium was 0.40 Gy (σ = 1.15 Gy) for men and 0.81 Gy (σ = 4.60 Gy) for women. For the remaining workers, a system of classification was used, determined according to type, location and duration of employment.

3,751 cases of ischaemic heart diseases were registered among the cohorts, 683 of them being acute myocardial infarctions. For 1,495 employees, ischaemic heart diseases were the cause of death, of these 338 suffered acute myocardial infarctions. Ischaemic heart diseases increased with an increase in the external dose (ERR per dose = 0.11 (95% CI: 0.05; 0.17) Gy^{-1}). Within the 0.5 Gy - 1 Gy dose range, the risk compared with workers exposed to doses below 0.5 Gy was no higher (relative risk of 1.02 (95% CI: 0.92; 1.13)). No significant dose dependencies were noted with relation to ischaemic heart disease mortality; the ERR per dose was 0.07 (95% CI: -0.02; 0.15) Gy^{-1}.

4,418 cases of cerebrovascular diseases were reported within the cohorts, of these 665 were strokes. Cerebrovascular diseases were given as the cause of death for 753 workers, of these 404 workers suffered strokes. The incidence of cerebrovascular diseases increased with an increase in the external dose (ERR per dose = 0.46 (95% CI: 0.36; 0.57) Gy^{-1}, as well as with increased plutonium incorporation (ERR per liver dose = 0.33 (95% CI: 0.17; 0.49) Gy^{-1}. Compared to employees with doses below 0.5 Gy, a relative risk of 1.14 (95% CI: 1.04; 1.25) was observed for workers with external doses in the 0.5 Gy - 1 Gy range. The risk was also increased in higher dose groups. Compared to employees with doses below 0.1 Gy, a relative risk of 1.23 (95% CI: 1.13; 1.35) was observed for workers with liver doses due to plutonium incorporation in the 0.1 Gy - 0.5 Gy range. The risk was also increased in higher dose groups. Adjustments made for risk factors other than radiation (hypertension, smoking, alcohol consumption and obesity) produced no significant changes to the results. The existence of personalised information relating to these factors is one of the strengths of this particular study.

A recent analysis, involving a slightly larger cohort (18,763 individuals) and with a follow-up which concluded at the end of 2005, produced an ERR per dose for ischaemic heart disease incidence of between 0.10 Gy^{-1} and 0.12 Gy^{-1}, depending on the method of analysis used; this value was therefore practically the same as the one from the previous analysis (Azizova et al. 2011a). The incidence in the dose group 0.2 Gy to 0.5 Gy due to external radiation exposure was significantly reduced in comparison with the dose group in the range below 0.2 Gy (RR = 0.90 (95% CI: 0.82; 0.98)).

This enlarged cohort produced an ERR per dose for cerebrovascular disease incidence of between 0.38 Gy^{-1} and 0.43 Gy^{-1}, depending on the method of analysis used; this value was therefore practically the same as the one from the previous analysis (Azizova et al. 2011b). The incidence in the dose group 0.2 Gy to 0.5 Gy due to external radiation exposure was significantly higher than in the dose group in the range below 0.2 Gy (RR = 1.12 (95% CI: 1.04; 1.22)).

In contrast to the data on morbidity rates, the mortality rate data for cerebrovascular diseases revealed in toto no significant dose dependencies, either in the short or long-term follow-up. Analyses of the stroke data produced no significant results, relating to either morbidity or mortality. Owing to low case numbers the statistical power of these sub-studies was limited.

5.3.3.5 Uranium miners

The cardiovascular mortality of German uranium miners recorded in the Wismut study with a follow-up that concluded at the end of 1998 forms the subject of a report by Kreuzer et al. (Kreuzer et al. 2006); in contrast to this first publication, an update featuring a second follow-up to the end of 2003 (Kreuzer et al. 2010) features no data on gamma radiation. The analysis covered 59,001 workers who had been exposed to the alpha emitter radon, long-lived alpha emitters and/or gamma radiation respectively. Of the total number of deaths (5,417) attributable to cardiovascular diseases, 3,719 cases were caused by heart diseases (ICD10: I00-I52) and 1,297 by cerebrovascular diseases. The statistical analyses revealed no increase in risk resulting from exposure to gamma radiation. The ERR per dose for cardiovascular diseases was -0.26 (95% CI: -0.6; 0.009) Gy^{-1}, for heart diseases -0.35 (95% CI: -0.7; 0.009) Gy^{-1} and for cerebrovascular diseases 0.09 (95% CI: -0.6; 0.8) Gy^{-1}.

Lane et al. (2010) recorded the mortality among a cohort of 17,660 Eldorado uranium miners with a follow-up that ended in 1999. With relation to gamma radiation, the ERR per dose for ischaemic heart diseases was 0.15 Gy^{-1}. The ERR per dose for cerebrovascular diseases was – 0.29 Gy^{-1}. Both values were statistically insignificant.

5.3.4 Individuals exposed following the Chernobyl accident

Following the accident at Chernobyl, several hundred thousand individuals – mainly from the military – were deployed in the clean-up. Ivanov et al. researched the incidence rate of cardiovascular diseases in a cohort of 61,017 Russian accident relief workers (Ivanov et al. 2006). At 0.18 (95% CI: -0.03; 0.39) Gy^{-1}, the ERR per dose for all types of cardiovascular diseases did not see a significant statistical increase; for ischaemic heart diseases (ERR per dose = 0.41 Gy^{-1}) and cerebrovascular diseases (ERR per dose = 0.45 Gy^{-1}) sub-groups, however, it was considerably and significantly raised. In this cohort the average doses were relatively low, in the region of 100 mGy, nevertheless the dose estimates are subject to considerable uncertainty. It is possible that confounders played a considerable role in the risk increases observed; however, it was not possible to obtain any data on them. The risk was particularly increased, demonstrated by relatively high doses and dose rates, for those sent into the accident zone early on.

5.3.5 Individuals exposed owing to nuclear weapons testing

In a cohort of 19,545 Kazakh villagers either exposed to nuclear fallout as a result of the nuclear weapons testing programme at Semipalatinsk or whose regions served as control areas, Grosche et al. (2011) did discover a pronounced overall increase in the rate of cardiovascular mortality among those exposed; further analysis revealed, however, that this was clearly attributable to a higher background rate of mortality in the exposed villages. It must be said that no information on additional cardiovascular risk factors was available for the cohort. The ERR per dose calculated for all types of cardiovascular diseases was 0.02 Gy^{-1} (95% CI: -0.32; 0.37). The ERR per dose for ischaemic heart diseases was found to be 0.06 (95% CI: -0.39; 0.52) Gy^{-1}, and for strokes – 0.06 (95% CI: -0.65; 0.54) Gy^{-1}.

5.3.6 Reviews and meta-analyses

UNSCEAR (2006) reported on cardiovascular diseases and other non-cancerous diseases. It made the general observation that far fewer data exist on cardiovascular diseases than on cancer, and that methodological problems, such as the monitoring of confounders, make interpreting the data that are available more difficult. Those studies named in this paper which predate 2005 or thereabouts were included in the UNSCEAR analysis. The committee concluded that the data that predate 2005 are insufficient to prove a causal relationship between ionising radiation and cardiovascular diseases for dose levels below 1 Gy - 2 Gy. Moreover the lack of a plausible biological mechanism was also emphasised.

In a summary Hoel (2006) combined those epidemiological studies into individuals exposed occupationally to radiation with the results on cardiovascular endpoints arising from research into atomic bomb survivors. The evidence for heightened cardiovascular risk relating to doses in excess of 0.5 Gy was assessed as fairly reliable, and the report explored a number of different possible mechanisms.

McGale and Darby (2005; 2008) focused in their summary on results from randomised breast cancer treatment studies involving cardiac doses of between 1 Gy and 20 Gy, during which a 27% increase in cardiovascular mortality risk was observed for patients in receipt of radiotherapy as opposed to those patients who were not given radiotherapy (Mc Gale and Darby 2005). The systematic overview used by the authors with respect to cardiovascular risk following exposure to ionising radiation gives an inconsistent picture, in which positive, negative and studies with a zero result are more or less balanced.

In a recent review dating from 2009, Little et al (2010) used meta-analytical methods to calculate summarised risk estimates (ERR/dose) for cardiovascular diseases, referencing existing studies into low and moderate doses. This included LSS data. The authors emphasised the considerable heterogeneity of the studies and the multiple potential distorting factors associated with studies on cardiovascular endpoints. Even if the analysis only involves studies with comparable endpoints, there is little decrease in the degree of heterogeneity. The ERR per dose calculated for all types of cardiovascular diseases varied depending on the studies included between 0.03 (95% CI: 0.00-0.07) Gy^{-1} and 0.19 (95% CI: 0.14; 0.24) Gy^{-1} and was highest in the separate consideration of the stroke as endpoint (ERR per dose = 0.27 (95% CI: 0.20; 0.34) Gy^{-1}). Similar results are to be found in other more recent papers published by the author (Little et al. 2008, Little 2009).

5.4 Limitations of the existing studies

Reference has already been made to the key limitations of the different studies. It should also be noted that only a few studies, including those on the atomic bomb survivors, ulcer patients and Mayak workers, offer sufficient data on key cardiovascular risk factors that are of significance when assessing the risk of ionising radiation. A handful of studies was at least able to include socioeconomic status in the analysis.

Only a few of the epidemiological studies, however, were able to reference dose values for those organs of relevance to cardiovascular diseases. As a result, considerable uncertainty is attached to the dose estimates. Furthermore, some exposure situations led to radiation incorporation to which it was either not always possible to give adequate consideration, or which was deemed negligible. More efforts were made in the case of the Mayak workforce cohort to quantify the degree of plutonium exposure and include the results in the dose estimate.

5.5 Conclusion and assessment

With the aim of assessing risk, the following summarises the results for those types of cardiovascular diseases for which a majority of the existing studies provided detailed risk estimates. Accordingly, in addition to all types of cardiovascular diseases (ICD9 390-459; ICD10 I00-I99), ischaemic heart diseases (ICD9 410-414; ICD10 I20-I25), which include myocardial infarction, and cerebrovascular diseases (ICD9 430-438; ICD10 I60-I69), which include strokes, are incorporated in the overall assessment.

The final section addresses estimates concerning the risks following exposure to low LET radiation, with absorbed doses of a few hundred milligray.

5.5.1 Cardiovascular diseases

The latest paper by Shimizu et al. (2010) on the atomic bomb survivors produced an ERR per dose of 0.11 (95% CI: 0.05; 0.17) Gy^{-1}. The other studies, with three exceptions, are consistent with this result (Table 5.2). One study produced a higher risk (BNFL workforce), two studies a lower risk (tuberculosis patients, uranium miners).

Overall the linear dose-response relationship analyses indicate that the ERR per dose for cardiovascular diseases is lower than that of cancer by a factor of 3-5.

Tab. 5.2: Results for the ERR per dose in the analysis of data on cardiovascular diseases using the linear dose-response model

Cohorts	**Reference**	**Endpoint**	**ERR per dose (Gy^{-1})**
Atomic bomb survivors LSS	Shimizu (2010)	Mortality	0.11 (95% CI: 0.05; 0.17)
BNFL workforce	McGeoghegan (2008)	Mortality	0.65 (90% CI: 0.36; 0.98)
Nuclear industry employees (15 countries)	Vrijheid (2007)	Mortality	0.09 (95% CI:-0.43; 0.70)
Semipalatinsk Historical Cohort	Grosche (2011)	Mortality	0.02 (95% CI: -0.32; 0.37)
Chernobyl accident relief workers	Ivanov (2006)	Incidence	0.18 (95% CI: -0.03; 0.39)
Tuberculosis patients	Davis (1989) Little (2008)	Mortality	-0.11 (95% CI: -0.20; -0.01)
UK Radiation Registry	Muirhead (2009)	Mortality	0.25 (95% CI: -0.01; 0.54)
Uranium miners	Kreuzer (2006)	Mortality	-0.26 (95% CI: -0.6; 0.05)

5.5.2 Ischaemic heart diseases

Results from the analyses of eight of the ten existing studies using the excess relative risk (ERR) model, which is linearly dependent on the dose, are consistent with ERR values per dose in the range 0.06 Gy^{-1} to 0.14 Gy^{-1} (Table 5.3). One study produced a higher risk value (BNFL workforce), one study a lower value (uranium miners). The range mentioned is consistent with the estimates given in Section 5.5.1 for all types of cardiovascular diseases.

Tab. 5.3: Results for the ERR per dose using the linear dose-response model in the analysis of ischaemic heart diseases data

Cohorts	Reference	Endpoint	ERR per dose (Gy^{-1})
Atomic bomb survivors, AHS	Yamada (2004)	Incidence	0.05 (95% CI: -0.05; 0.16)
Atomic bomb survivors, LSS	Shimizu (2010)	Mortality	0.14 (95% CI: 0.06; 0.23)*
BNFL workforce	McGeoghegan (2008)	Mortality	0.70 (90% CI: 0.33; 1.11)
Mayak workforce	Azizova (2011)	Incidence	0.10 (95% CI: 0.05; 0.15)
Mayak workforce	Azizova (2011)	Mortality	0.06 (95% CI: - 0.01; 0.13)
Nuclear industry employees (15 countries)	Vrijheid (2007)	Mortality	-0.01 (95% CI:-0.59; 0.69)
Semipalatinsk Historical Cohort	Grosche (2011)	Mortality	0.06 (95% CI: -0.39; 0.52)
Chernobyl accident relief workers	Ivanov (2006)	Incidence	0.41 (95% CI: 0.05; 0.78)
UK Radiation Registry	Muirhead (2009)	Mortality	0.26 (95% CI: -0.05; 0.61)**
Uranium miners	Kreuzer (2006)	Mortality	-0.35 (95% CI: -0.7; 0.01)*

* Result for all types of heart diseases, since a classification according to sub-type is unreliable (Shimizu), and/or no results for ischaemic heart diseases had been published (Kreuzer).

** Result for 'coronary heart disease' (ICD9 414)

5.5.3 Cerebrovascular diseases

Results from the analyses of eight of the ten existing studies using the excess relative risk (ERR) model, which is linearly dependent on the dose, are consistent with ERR values per dose in the range 0.11 Gy^{-1} to 0.17 Gy^{-1} (Table 5.4). The risk results for the Mayak workforce incidence data are inconsistent with this risk range (lower limit of confidence interval: 0.32 Gy^{-1}.) Moreover, the results for the Mayak workforce incidence data are also inconsistent with the ERR per dose for the mortality data (upper limit of confidence interval: 0.12 Gy^{-1}). Owing to the higher number of cases (7,266 vs. 1,494) and the better quality of data, the incidence result is to be valued higher than the mortality result.

The range mentioned is consistent with the estimates given in Section 5.5.1 for all types of cardiovascular diseases.

Tab. 5.4: Results for the ERR per dose using the linear dose-response model in the analysis of cerebrovascular diseases data

Cohorts	Reference	Endpoint	ERR per dose (Gy^{-1})
Atomic bomb survivors, AHS	Yamada (2004)	Incidence	0.07 (95% CI: -0.08; 0.24)*
Atomic bomb survivors, LSS	Shimizu (2010)	Mortality	0.09 (95% CI: 0.01; 0.17)
BNFL workforce	McGeoghegan (2008)	Mortality	0.43 (90% CI: -0.10; 1.12)
Mayak workforce	Azizova (2011a)	Incidence	0.41 (95% CI: 0.32; 0.50)
Mayak workforce	Azizova (2011a)	Mortality	0.03 (95% CI:-0.06; 0.12)
Nuclear industry employees (15 countries)	Vrijheid (2007)	Mortality	0.88 (95% CI:-0.67; 3.16)
Semipalatinsk Historical Cohort	Grosche (2011)	Mortality	-0.06 (95% CI: -0.65; 0.54)
Chernobyl accident relief workers	Ivanov (2006)	Incidence	0.45 (95% CI: 0.11; 0.80)
UK Radiation Registry	Muirhead (2009)	Mortality	0.16 (95% CI: -0.42; 0.91)
Uranium miners	Kreuzer (2006)	Mortality	0.09 (95% CI: -0.6; 0.8)

* for the 'stroke II' endpoint (ICD9 430, 431, 433, 434, 436)

5.5.4 Dose-response relationship below 500 mGy

Research into the dose-response relationship for heart diseases among the atomic bomb survivors of Hiroshima and Nagasaki produced no indication of non-linearity (Shimizu et al. 2010). The best threshold dose estimate was 0 Gy with the 95% confidence interval upper limit being 0.5 Gy. The ERR for cerebrovascular diseases in the low dose range was lower than the value produced in a data analysis using a linear dose-response relationship of the entire cohort. The best threshold dose estimate was 0.5 Gy with a 95% confidence interval of not more than 0 Gy - 2 Gy.

Schöllnberger et al. (2012) conducted an analysis of the LSS data using multi-model inference. This entails weighting the risk values drawn from several models according to the quality of fit. This resulted in a cerebrovascular diseases ERR for a dose of 400 mGy that was lower by a factor of 3.3 than the result produced by a linear dose-response relationship analysis (Fig. 5.1). The 90% confidence interval for the ERR at 400 mGy ranged from 0 (no excess risk) to 0.07. Models with a threshold above 400 mGy had a 55 % weighting, i.e. models with a dose-response relationship threshold and models without a threshold both produced an equally good depiction of the data.

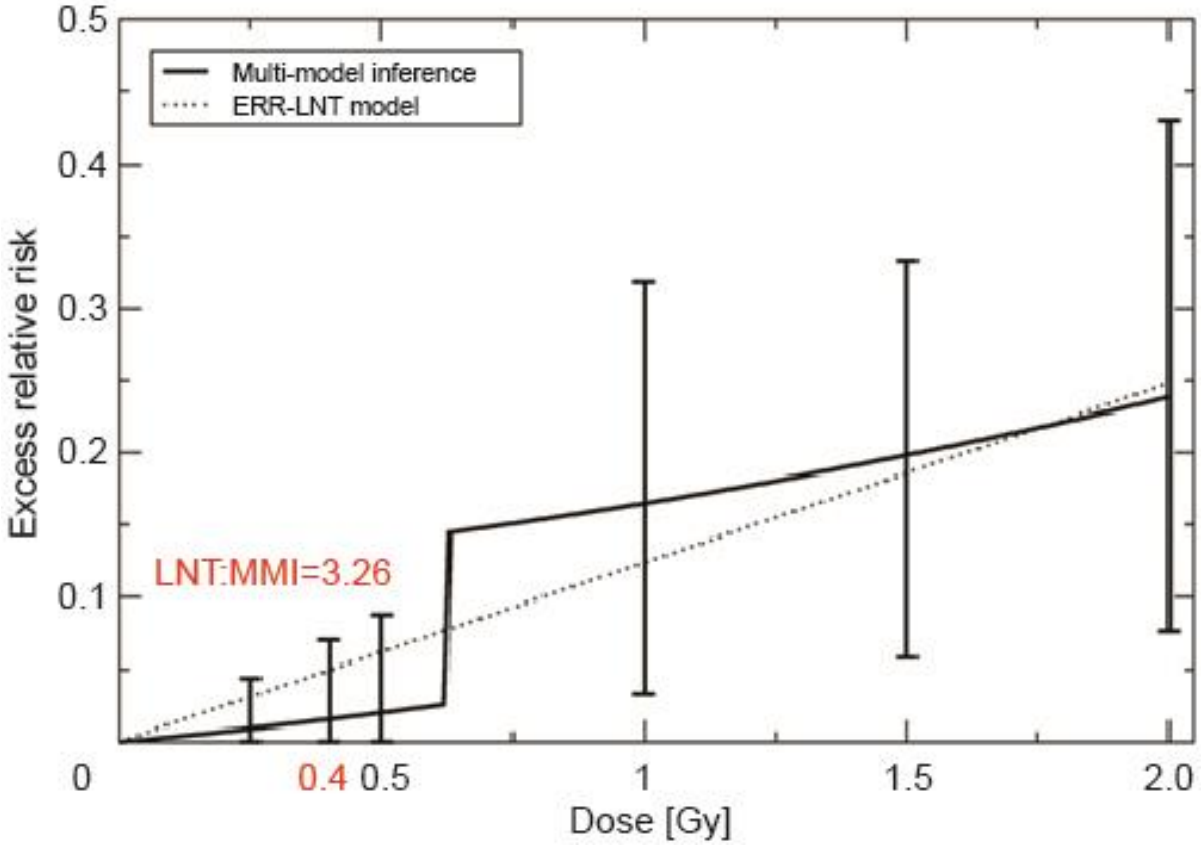

Fig. 5.1: Analysis of the LSS cerebrovascular diseases data using multi-model inference (according to Schöllnberger et al. 2012). According to this analysis the ERR at 400 mGy is lower by a factor of 3.3 than the result of the linear dose-response relationship analysis. The 90% confidence interval for the ERR at 400 mGy ranges from 0 (no excess risk) to 0.07.

In the multi-model inference analysis conducted by Schöllnberger et al. (2012) the EAR for cardiovascular diseases excluding cerebrovascular diseases at 400 mGy was lower by a factor of 2.4 than the result produced by the linear dose-response relationship analysis (Fig. 5.2). The 90% confidence interval for the EAR at 400 mGy ranged from 0 (no excess risk) to up to 5 cases per 10,000 person-years. Models with a threshold above 400 mGy had a 33 % weighting, i.e. although models without a dose-response relationship threshold gave a better data depiction than models with a threshold, it was nevertheless not possible to rule out the latter.

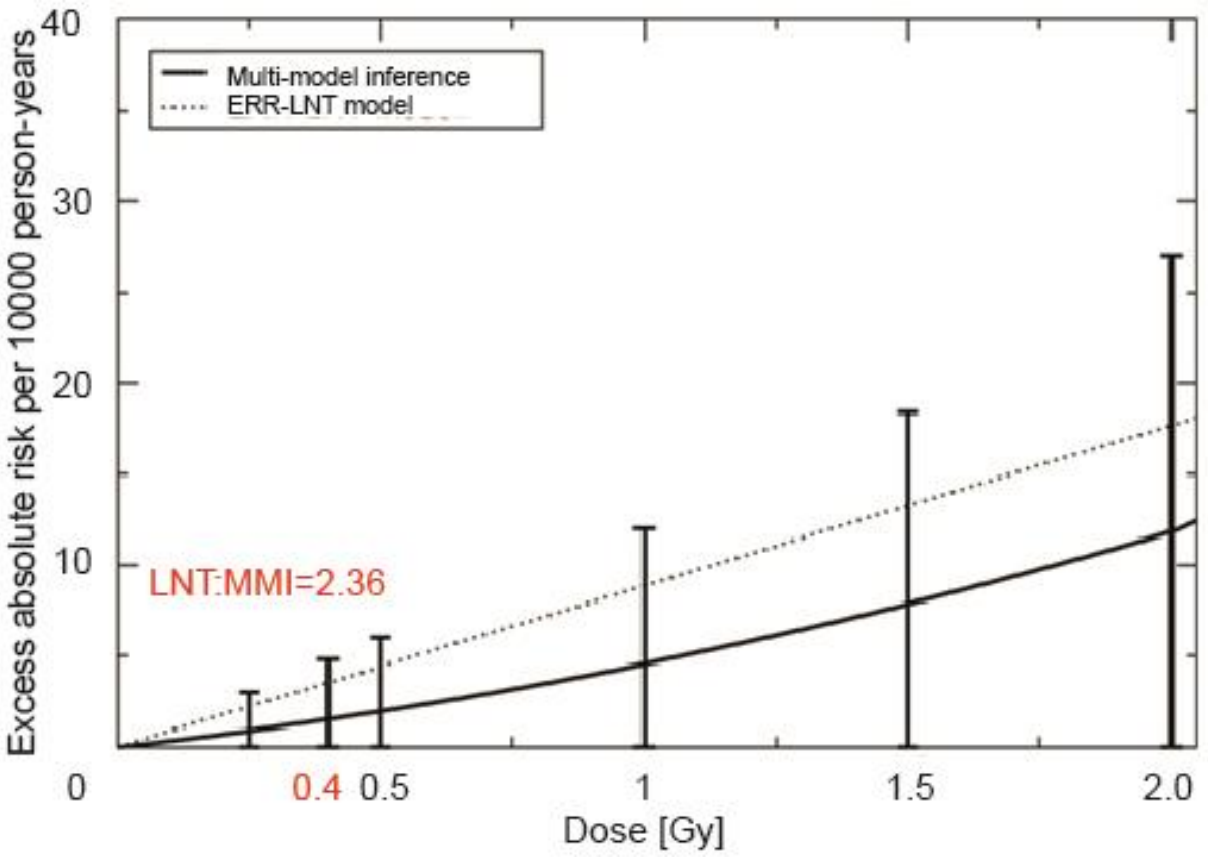

Fig. 5.2: Analysis of the LSS cardiovascular diseases data excluding cerebrovascular diseases using multi-model inference (according to Schöllnberger et al. 2012). According to this analysis the EAR at 400 mGy is lower by a factor of 2.4 than the result of the linear dose-response relationship analysis. The 90% confidence interval for the EAR at 400 mGy ranged from 0 (no excess risk) to up to 5 cases per 10,000 person-years.

The study into the BNFL workforce (McGeoghegan et al. 2008) produced an extremely high value for the ERR per dose. For the two highest dose groups (>400 mGy and 200 mGy - 400 mGy), the relation between observed and expected cases of cardiovascular mortality was consistent at 1.3; it varied in the range from 10 mGy - 200 mGy between 1.02 and 1.17, and at doses below 10 mGy was 0.96. The authors nevertheless advised caution when drawing conclusions from the study, since sub-groups of the cohort produced different results (p-value for inhomogeneity: 0.016).

Even though, when analysing the incidence of heart diseases among Mayak employees (Azizova et al. 2011a), the risk in the 200 mGy - 500 mGy dose group was significantly lower than that for the dose group below 200 mGy, it was significantly higher for cerebrovascular diseases (Azizova et al. 2011b).

For the overwhelming majority of workers (99.9 %) included in the international study of nuclear industry employees (Vrijheid et al. 2007) the cumulative dose was less than 500 mGy. Nevertheless, the results of the study into cardiovascular diseases are characterised by extreme uncertainty, thus allowing no conclusions to be drawn concerning the effect of radiation at doses below 500 mGy.

Overall the research into the Semipalatinsk historical cohort (Grosche et al. 2011) is of low statistical power. No statistically significant conclusions emerged for the individual dose categories.

In the study conducted on tuberculosis patients (Davis et al. 1989) 4,611 had not been exposed to radiation, 1,881 had received pulmonary doses of less than 500 mGy, and 2,416 pulmonary doses in excess of 500 mGy. The statistically significant negative coefficient found in the linear dose-response relationship (Little et al. 2008) is more likely to be attributable to the patients with pulmonary doses in excess of 500 mGy than to those with lower doses.

The study into the Chernobyl accident relief workers calculated the relative risk of cerebrovascular diseases in 9 dose groups, each with approx. 3,000 workers, all of whom had been deployed during the first year following the accident at Chernobyl, in relation to the 3,000 employees in the lowest dose group (absorbed dose less than 50 mGy). Although no increased risk was observed in the highest dose group (average dose 265 mGy), the best relative risk estimates were found in the four next highest dose groups (averages from 190 mGy to 230 mGy) and ranged from 1.05 to 1.12. Overall the ERR-per-dose values were lower for those workers who were deployed later. The study indicated that the excess risk per dose increases with the dose rate.

During the study into those individuals entered in the UK Radiation Registry (Muirhead et al. 2009), the group with doses above 100 mGy was not subdivided. It is therefore impossible to draw any conclusions about the effects of radiation exposure relating to doses in excess of and/or less than 500 mGy.

Of the 59,001 uranium miners included in the study by Kreuzer et al. (2006), 6,638 workers had received external doses of gamma radiation between 100 mGy and 500 mGy, and 124 workers doses of more than 500 mGy. Compared to those with no radiation exposure, the relative risk value for workers who had received doses in excess of 300 mGy was significantly negative. Despite the greater degree of statistical power and the commensurately narrow confidence interval range, the 100 mGy - 300 mGy dose group produced no statistically significant result.

There was a general tendency towards an increased risk of cardiovascular diseases following radiation exposure amounting to a few hundred milligray. Analyses using a linear dose-response relationship produced an ERR per dose of approx. 0.1 Gy^{-1}. Nevertheless the different studies provide contradictory evidence for or against a lower ERR-per-dose value or a threshold within the dose range below 500 mGy.

5.5.5 Estimating the risk associated with exposure to 400 mGy

There remains huge uncertainty about potential cardiovascular risks following exposure to an absorbed dose of radiation of a few hundred milligray. The above-mentioned observations do, however, allow a broad initial assessment of the potential risks of cardiovascular diseases following exposure to low LET radiation with an absorbed dose of 400 mGy. Analyses of existing data with a linear dose-response relationship provide the starting point for such an assessment. Within the context of these analyses, research into workers exposed to radiation produced ERR values per doses for cardiovascular diseases that were consistent with the results of Shimizu et al. (2010) for the atomic bomb survivors of Hiroshima and Nagasaki. There is therefore no evidence to suggest that, at this dose level, the excess risks following longer term exposure are any different to those associated with acute exposure.

The best ERR-per-dose estimates produced by the different studies into workers exposed to radiation are characterised by huge statistical uncertainty. The results of the study into the atomic bomb survivors (Shimizu et al. 2010), with a best ERR-per-dose estimate of 0.11 Gy^{-1}, was therefore selected as a basis for further deliberations. As far as the dose-response relationship is concerned within the moderate dose range, a similar degree of evidence exists

to suggest a linear dose-response relationship for both acute and longer term exposure, lower radiation effects, or even a threshold within the lower range of moderate doses. Owing to the potential non-linearity of the dose-response relationship, current knowledge therefore appears to indicate risk values for the few hundred milligray range that are lower than would be produced using the above-mentioned ERR-per-dose value. An analysis of LSS data using multi-model inference produced an ERR for cardiovascular diseases at a level of 400 mGy that was approximately three times lower than the result of analysis using the linear dose-response relationship. This means that the ERR for cardiovascular diseases at 400 mGy is an order of magnitude smaller than the ERR for cancer. Since the spontaneous risks associated with cardiovascular diseases are higher than those relating to cancer, the difference between the excess absolute risks is less pronounced than between the excess relative risks.

The comparison indicates that the absolute risks of cardiovascular diseases following exposure to a radiation dose of a few hundred milligray are lower than the corresponding risks of cancer, yet should nevertheless not be overlooked. Despite the fact that a total absence of risk cannot be ruled out, due consideration needs to be given in the drafting of statutory regulations – by way of precaution – to the potential for increase in cardiovascular disease risk following exposure to radiation doses of a few hundred milligray.

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6 Evidence of a correlation between cardiovascular diseases following prior exposure to ionising radiation with an absorbed dose of a few hundred milligray

Table 6.1 provides a summary assessment of the evidence of a correlation between cardiovascular diseases following prior exposure to ionising radiation with an absorbed dose of a few hundred milligray.

Tab. 6.1: Evidence of a correlation between cardiovascular diseases following prior exposure to ionising radiation with an absorbed dose of a few hundred milligray

Evaluation criteria	**Evidence**
Physico-chemical effects model	Ionising radiation causes damage to DNA and oxidative stress. The link with cardiovascular diseases is unclear.
Biological effects model	Ionising radiation causes cell death, genomic instability and affects inter-cellular communication. The link with cardiovascular diseases is unclear.
Dose-response relationship	Whereas a linear dose-response relationship was established for the physico-chemical effects, a mainly non-linear dose-response relationship was established for the biological effects of radiation exposure in the few hundred milligray range. The link with cardiovascular diseases is unclear. A few epidemiological studies into cardiovascular diseases following exposure to ionising radiation produced indications of a linear dose-response relationship, others of a possible threshold within this dose range.
In vitro studies	Sufficient evidence is provided by in vitro studies for the above-mentioned assessment models and dose-response relationships.
In vivo studies	There is little evidence within the few hundred milligray range to suggest a causal link between radiation effects and cardiovascular diseases. More detailed studies are needed.
Epidemiological studies	The LSS provided evidence of a dose-response relationship for ischaemic heart diseases following acute radiation exposure, without indicating a threshold, within the few hundred milligray range. A positive coefficient estimate was established within a linear dose-response relationship for six out of eight studies into longer term periods of radiation exposure; in three of these studies the increase recorded was significant. The LSS provided evidence of a threshold in the few hundred milligray range for cerebrovascular diseases; any increase in resulting mortality below this threshold was small and statistically insignificant. A positive coefficient estimate was established within a linear dose-response relationship for seven out of eight studies into longer term periods of radiation exposure; the increase recorded was only significant however in two of the studies. The studies into cardiovascular diseases following longer term exposure to radiation produced contradictory results with reference to the course of dose-response. Nevertheless, most indicated an increase in risk in the few hundred milligray dose range.

Appendix

Tab. A.1: Summary of cardiovascular disease code categories in ICD-9 and ICD-10 (WHO)

	ICD-9	**ICD-10**
Acute rheumatic fever	390-392	I00-I02
Chronic rheumatic heart diseases	393-398	I05-I09
Hypertensive diseases (high blood pressure)	401-405	I10-I15
Ischaemic heart diseases	410-414	I20-I25
Pulmonary heart disease and diseases of pulmonary circulation	415-417	I26-I28
Other forms of heart diseases	420-429	I30-I52
Cerebrovascular diseases	430-438	I60-I69
Diseases of arteries, arterioles and capillaries	440-448	I70-I79
Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	451-459	I80-I89
Other and unspecified disorders of the circulatory system		I95-I99

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