INTRODUCTION

1. The risks of cancer associated with exposure to ionizing radiation have been extensively studied and documented. Epidemiological data on the carcinogenic effects of exposure to ionizing radiation are the subject of continuing reviews by UNSCEAR (see annex A to this report, "Epidemiological studies of radiation and cancer", and, for example, references [U2, U4, U6]). The effects of exposure to radiation expressed as diseases other than cancer were most recently reviewed in the 1982 [U8] and 1993 UNSCEAR Reports [U5]. In these reports, the effects expressed as diseases other than cancer were regarded as "deterministic", resulting from "direct" changes occurring in cells. The deterministic model assumes the presence of a minimum dose—the threshold dose—below which radiation effects are not detected, although a threshold dose is difficult to define and may vary according to tissues, biological end points and measuring techniques [U8]. In 1992, the analysis of mortality data from the Life Span Study (LSS) cohort of survivors of the atomic bombings in Japan demonstrated a statistically significant association between radiation dose and some diseases other than cancer (non-cancer diseases) [S1]. Excess non-cancer disease mortality risks in the LSS were evident at levels of dose lower than those hitherto considered as a threshold, e.g. 4–5 Gy, for various deterministic effects. While some of these non-cancer diseases are neoplastic though benign in nature, significant excess risks are mostly seen for mortality from stroke, heart disease, and diseases of the respiratory and digestive systems, which are of a non-neoplastic nature.

2. The Committee considered it necessary to assess the epidemiological evidence of radiation effects expressed as diseases other than cancer at low doses, because the phenomenon is potentially important for radiation risk assessment at these dose levels, and there is a considerable lack of consistency among the available epidemiological data. The Committee considered it important to focus on cardiovascular disease as the major end point of interest, because cardiovascular disease is among the most common diseases in many populations worldwide and thus may be important for radiation risk assessment.

3. This annex first provides an overview of current epidemiological data on mortality from broad categories of non-cancer diseases obtained from studies of populations exposed to radiation at doses of less than 1–2 Gy. In assessing the evidence on radiation effects, the annex considers several methodological issues that are especially relevant for non-cancer data, such as cohort selection, quality of the mortality data, confounding and publication bias. It then provides a general overview of data currently available on major non-cancer disease categories from various irradiated populations. The annex goes on to consider radiation effects on diseases of the circulatory system and specifically on cardiovascular (heart) disease. Although the primary focus of this annex is the effect of exposure to low doses of radiation, the risks of cardiovascular disease associated with exposure to high doses are also addressed. This is because much is known about the clinical and biological effects of exposure at high dose levels, and this may be helpful for considering possible biological mechanisms of effects at low dose levels.

I. GENERAL ISSUES IN ASSESSING DATA ON NON-CANCER DISEASES

4. Annex A of this report describes features that are important in conducting or interpreting epidemiological studies. In addition, when assessing published epidemiological data on non-cancer diseases, several methodological issues are especially relevant. These include the selection of exposed populations (including the "healthy worker" effect and the presumed "healthy survivor" effect), the quality of the mortality data, the confounding effects of non-radiation risk factors and publication bias.

A. Cohort selection

5. The nature of an exposed population needs to be considered when study subjects are irradiated for medical reasons. Data on non-cancer diseases are reported from some of the medically exposed cohorts that have been studied to assess cancer risks. Groups of individuals with certain non-neoplastic medical conditions for which they were irradiated may have underlying rates of non-cancer diseases that may not be representative of the general population rates, even if the underlying cancer rates of these individuals are not affected by their medical conditions. For example, thyroid hormone exerts a major influence on the cardiovascular system, and patients with hyperthyroidism often have cardiovascular symptoms [L9]. Angina pectoris and congestive heart failure may develop when there is underlying heart disease. Women with some benign gynaecological disorders are in a hyper-oestrogenic status, and thus may have an increased underlying risk of cardiovascular disease. When the observed number of cases (or deaths) with the disease of interest is compared with the number expected from the general population (external comparison), estimates of the risk may be biased. However, comparison of disease rates in exposed and unexposed persons within the same cohort population (internal comparison) is less likely to produce biased risk estimates.

6. The "healthy worker effect" is an observed decrease in mortality in cohorts of workers when comparison is made with the general population. This effect occurs because of the initial selection process by which healthy people are more likely to be employed than unhealthy ones. Decreased mortality in workers may also occur for several other reasons, for example the beneficial effect from better health care (referred to as the "worker healthier effect"), or continuing selection due to healthier people remaining employed (referred to as the "healthy worker survivor effect") [C7]. The healthy worker effect is known to be particularly strong for chronic non-malignant diseases, such as cardiovascular disease, compared with cancer or precancerous conditions that are dormant or clinically less evident at the time of beginning or during employment. The empirical estimates are that the healthy worker effect represents a 20–30% reduction in comparison with the mortality rate of the whole population [C8]. Several features of the healthy worker effect are notable. The effect is greatest during the initial period of follow-up and diminishes with increasing follow-up time, and the length of time during which the effect persists has been reported to range from 5 to 30 years or longer [B9]. The magnitude of the healthy worker effect also varies among different occupational groups, and may be particularly large in nuclear worker cohorts because of the strict health selection associated with security clearances in the industry [B9]. Thus a simple ratio of the observed to the expected number of deaths, or standardized mortality ratio (SMR), is not a useful measure of radiation risk for non-cancer disease in occupational cohorts.

7. It has been suspected that a selection process that is similar to that underlying the healthy worker effect may have occurred in the cohort of the atomic bombing survivors [P4, S1]. This effect, called the "healthy survivor effect" is apparently different in nature from the healthy worker survivor effect seen in those who remain employed. Rather, several features suggest that it is similar in nature to the healthy worker effect caused by the selection of healthier persons at the time of cohort entry.

B. Quality of the mortality data

8. Mortality follow-up is the principal method used in most studies of radiation-exposed cohorts. Imprecise reports of the causes of death on death certificates often lead to misclassification of diseases from or with which subjects died. Since mortality rates for cancer generally increase with increasing radiation dose, the misclassification of death from cancer as death from non-cancer disease on death certificates can spuriously produce a dose-related increase in mortality rates for non-cancer disease or overstate the effect of radiation on non-cancer disease rates. In the analysis by Sposto et al. [S6] of the LSS death certificate data, correcting for the misclassification of cancer deaths as non-cancer deaths using autopsy diagnoses reduced the estimate of excess relative risk (ERR) for non-cancer disease by about 20% (although the non-cancer dose response still remained significant after this correction). The problem of

misclassification of causes of death is likely to exist in many of the radiation-exposed cohorts studied, but the LSS is the only study to date in which the impact of disease misclassification on the estimates for risk of non-cancer disease has been evaluated.

C. Confounding effects

9. Cardiovascular disease and the other non-cancer diseases with which this report is concerned are multifactorial diseases involving lifestyle and other personal factors. Underlying rates for major non-cancer diseases, especially circulatory diseases, are relatively high and vary among people with different socio-economic status, from different geographical locations and with different lifestyles. Because the risk of non-cancer effects associated with radiation exposure is relatively small—about one third the risk of cancer, as indicated by the atomic bombing survivor data—the power to detect radiation effects is reduced and the likelihood of the influence of confounding factors is increased. Simple comparisons of exposed versus unexposed groups are susceptible to confounding as well as selection bias and should be given limited credibility, while radiation dose–response analyses provide more credible evidence regarding the effect of radiation exposure.

D. Publication bias

10. Cancer has been the primary focus of epidemiological research on radiation effects. Radiation effects expressed as non-cancer diseases have been less systematically studied and reported. Only occasionally have associations of radiation with non-cancer diseases been reported as supplemental findings of studies designed to assess cancer risks. Findings related to non-cancer effects may have been reported because they are statistically significant or "interesting". On the other hand, non-cancer data may simply not have been analysed because the investigators were not interested in the data. Reviews of studies in the social and medical sciences show that studies with significant results or favourable results are more likely to be published, but the magnitude and nature of publication bias and other related biases are uncertain [S5]. Favourable results may be those findings that are congruent with ruling paradigms at the time. This also suggests that when positive results are unexpected, they may be rigorously analysed, while null results, when expected, may not be critically examined. For example, unexpected positive findings may cause investigators to examine the possible sources of bias or confounding, but null findings that are expected may be accepted at face value. While there is a concern for a potential publication bias in published non-cancer data, the direction of biases in published data is unpredictable.

II. NON-CANCER DATA IN RADIATION-EXPOSED COHORTS

11. The objectives of this annex include the identification of cohort studies that may provide epidemiological information for assessing the relationship of radiation exposure and non-cancer diseases and to judge the usefulness and consistency of their findings for various non-cancer disease categories. Table 1 lists cohort populations exposed to mostly low-linear-energy-transfer (LET) radiation and records any major non-cancer findings. These cohorts were selected from those considered in the UNSCEAR 2000 Report (table 2 in annex I, "Epidemiological evaluation of radiation-induced cancer") [U2], supplemented and updated by a separate literature search. The cohorts in table 1 were selected a priori on the basis of considerations of population size and reported radiation doses to relevant organs, and then data on non-cancer mortality were sought in published material.

12. In table 1, the LSS cohort of the survivors of the atomic bombings in Japan is presented together with the Adult Health Study (AHS) cohort, which is a subset of the LSS.[1] Cohort populations irradiated for treatment of cancer include those treated for cervical cancer, childhood cancer and childhood lymphoma. These patients received doses ranging between <1 Gy and 10 Gy to various organs, and they represent high-dose exposure populations. Table 1 excludes a large number of studies of cardiovascular disease risks following high-dose radiotherapy for Hodgkin's lymphoma or breast cancer, as these will be the focus of detailed examination later in this annex. Patients with a variety of benign diseases (childhood skin haemangioma, benign lesions in the locomotor system, ankylosing spondylitis, tinea capitis, post-partum mastitis, thymic enlargement, tonsil enlargement, benign breast disease, benign gynaecological disorders, lymphoid hyperplasia and peptic ulcer disease) who were irradiated at a range of moderate doses are considered next. Individuals irradiated for diagnostic purposes (fluoroscopic examination, scoliosis) were exposed to relatively low doses, as were occupationally exposed populations, and these are considered separately. The atomic bombing survivors and occupationally exposed populations are characterized by whole-body radiation exposure, whereas medically exposed populations had localized exposures with varying doses to different target organs. This should be kept in mind when comparing findings for different populations or when examining different non-cancer diseases within the same population.

13. Table 1 presents associations reported from these studies regarding radiation exposure and major non-cancer disease categories (infectious diseases, circulatory diseases, respiratory system diseases, digestive system diseases, genito-urinary system diseases and other diseases). The associations are described in terms of whether they were significantly positive (P, increased risk associated with radiation exposure), significantly inverse (I, reduced risk associated with radiation exposure), not significant (NS, no significant association) or lacking data on non-cancer disease (–). The types of analysis used in obtaining the results are described as follows: "dose–response analysis", including analyses using dose categories; "internal comparison" based on only a comparison of exposed versus unexposed groups with no dose data; or "external comparison" with SMRs or observed/expected (O/E) ratios for the exposed cohort only.

14. Of these cohort studies, 60% provided mortality or morbidity data for heart disease, cerebrovascular disease or diseases of the circulatory system as a whole. The use of different disease categories in different studies makes it difficult to assess the consistency of the associations. On the basis of dose–response analysis or trend analysis using dose categories, significant associations of radiation and circulatory disease (heart disease, cerebrovascular disease or both) were reported from nine cohort studies (atomic bombing survivors for both heart disease and cerebrovascular disease; peptic ulcer patients for coronary heart disease; scoliosis patients for diseases of the circulatory system; and six occupational cohort studies, i.e. the International Agency for Research on Cancer (IARC) three-country nuclear worker study for circulatory disease; studies in the United Kingdom on workers at Sellafield for ischaemic heart disease and at Springfields uranium production facility for cerebrovascular disease; the Canadian National Dose Registry study for circulatory disease; and studies on Chernobyl recovery operations workers for both ischaemic heart disease and cerebrovascular disease). The lack of a significant association for circulatory disease was reported from eight cohort studies (two populations of patients with benign gynaecological disorders and six occupational studies: in the United Kingdom, the National Registry for Radiation Workers (NRRW) and the studies of the Capenhurst uranium workers and the Chapelcross workers; in the United States, the

[1] Authors of atomic bombing survivor studies have provided dose estimates in terms of weighted colon doses, which are the sum of the gamma-ray dose estimate and 10 times the neutron dose estimate. Early papers often used grays (Gy) for the units of these weighted doses, while more recent papers use sieverts (Sv). Throughout this annex, the Committee uses the convention of sieverts for the units of the weighted colon doses when addressing the specific results of the atomic bombing survivor studies.

Hanford–Oak Ridge National Laboratory (ORNL)–Rocky Flats weapons plant study and the study at Hanford only; and in the Russian Federation, the study of workers at the Mayak nuclear complex). In one of the two studies of patients with benign gynaecological disorders, the association of heart disease with radiation exposure was of borderline significance. In the United States nuclear power utility worker study, dose–response analyses for circulatory disease and ischaemic heart disease showed significant associations, but trend analyses using dose categories showed the associations as not significant.

15. Fewer data were available for other non-cancer diseases. About half of the studies provide data on digestive diseases, 47% on respiratory diseases, 36% on infectious diseases and 33% on genito-urinary diseases. The specific disease categories analysed differed among the studies.

16. In addition to the evidence from the studies of the survivors of the atomic bombings, a significant association for diseases of the digestive system was reported from the follow-up of patients receiving X-ray monitoring for scoliosis, though no data were presented [D9], and from two occupational cohorts (the Springfields uranium production workers when exposures were lagged for 20 years, and the Chernobyl recovery operations workers). No significant association was found in seven cohort studies (the benign gynaecological disorder patients and six occupational cohorts: the IARC three-country cohort and the NRRW, Sellafield, Chapelcross, Capenhurst and Hanford cohorts).

17. A significant association for diseases of the respiratory system has been reported from studies on five cohorts: the atomic bombing survivors, patients with scoliosis (though data were not presented), NRRW workers (for respiratory diseases unrelated to smoking), Sellafield workers (for pneumonia) and Chapelcross workers (for bronchitis). The lack of a significant association was found for nine cohorts: benign gynaecological disorder patients, IARC three-country cohort, Chapelcross workers, Springfields uranium workers, Capenhurst uranium workers, Canadian National Dose Registry study, Hanford–ORNL–Rocky Flats workers, Hanford workers and Chernobyl recovery operations workers.

18. Data on infectious diseases or genito-urinary diseases were very scarce, with only one study reporting a significant association for each disease category: patients with scoliosis (for infectious diseases) and patients with benign gynaecological disorders (for genito-urinary diseases). The absence of a significant association was reported from several other cohort studies.

Table 1 Studies on radiation-exposed cohorts and reported associations with non-cancer diseases

Study	*Number of subjects*	*Doses: range and mean (Sv)*	*Non-cancer disease associations found*[a]							*Type of analyses performed for non-cancer diseases*
			All non-cancer diseases	*Infectious diseases*	*Circulatory diseases*	*Respiratory diseases*	*Digestive diseases*	*Genito-urinary diseases*	*Other diseases*	
Exposure to atomic bombings										
LSS [P4, S21]	50 113 exposed persons 36 459 unexposed persons	Individual estimates for several organs: colon dose[b], 0–4 Sv; mean 0.29 (exposed persons)	P	NS	P (stroke, heart disease)	P	P	NS	P (blood disease); I (suicide)	Dose–response analysis; confounding effects examined
AHS [K5, W5, Y3]	9 641 persons (subset of LSS)	Mean[b] 0.83 Sv (exposed persons)	–	–	P (hypertension, myocardial infarction)	–	P (liver disease, cirrhosis)	P (renal and ureteral stones)	P (uterine myoma, thyroid disease)	Dose–response analysis
Treatment of malignant disease										
Cervical cancer cohort [B10]	82 616 exposed women 99 424 unexposed women	Typical doses: oesophagus, 0.14–0.28; stomach, 0.7–1.2 [T1]	–	–	–	–	–	–		Non-cancer diseases not analysed
Hodgkin's lymphoma late mortality [H1]	2 001 exposed persons 231 unexposed persons	Mediastinum, <30–44	–	–	P (myocardial infarction, other heart disease)	–	–	–		Internal comparison (two dose categories: 0–30 Gy, >30 Gy)
Childhood cancers [D6] (France and United Kingdom)	3 109 exposed persons 1 291 unexposed persons	Individual doses: breast, 0.7–11; digestive tract, 0.5–13; brain, 0.3–25	–	–	–	–	–	–		Non-cancer diseases not analysed
Childhood Hodgkin's lymphoma [B11]	1 380 persons	Individual doses: oesophagus, 1.5–3.95; stomach, 10–28 [T1]	–	–	–	–	–	–		Non-cancer diseases not analysed
Treatment of benign disease										
Childhood skin haemangioma, Stockholm [L7, L8]	14 351 exposed persons	Individual organ doses, mean: lung, 0.15	–	–	–	–	–	–		Non-cancer diseases not analysed
Childhood skin haemangioma, Gothenburg	11 914 exposed persons		–	–	–	–	–	–		Non-cancer diseases not analysed
Benign lesions in locomotor system [D7]	20 024 exposed persons	Individual red bone marrow doses, mean: <0.2–>0.5	–	–	–	–	–	–		Non-cancer diseases not analysed

Study	*Number of subjects*	*Doses: range and mean (Sv)*	*Non-cancer disease associations found*[a]							*Type of analyses performed for non-cancer diseases*
			All non-cancer diseases	*Infectious diseases*	*Circulatory diseases*	*Respiratory diseases*	*Digestive diseases*	*Genito-urinary diseases*	*Other diseases*	
Ankylosing spondylitis [D3, L1]	13 914 exposed persons	1 in 15 sample of the population, mean: gastrointestinal tract, 2.43; heart, 2.49; pulmonary region, 1.64	NS	–	P (cerebrovascular disease, other circulatory diseases)	P (bronchitis)	P (peptic ulcer, other genito-urinary diseases)	–	P (violence)	O/E ratios, external comparisons
Israel tinea capitis [R11]	10 834 exposed persons 16 226 unexposed persons	Individual doses, mean: brain, 1.5; thyroid, 0.09		NS	NS	NS	NS	NS	NS	Internal comparison (exposed versus unexposed or sibling)
New York tinea capitis [S11]	2 226 exposed persons 1 387 unexposed persons	Individual doses	NS	NS	NS	–	–	–		Internal comparison (exposed versus unexposed)
New York postpartum mastitis [S12]	571 exposed persons 993 unexposed persons	Individual doses: breast, 0.6–11.5	–	–	–	–	–	–		Non-cancer diseases not analysed
Rochester thymic irradiation [H10]	2 652 exposed persons 4 823 unexposed persons	Individual doses, mean: breast, 0.69	–	–	–	–	–	–		Non-cancer diseases not analysed
Tonsil irradiation [S13, S14]	2 634 exposed persons	Individual doses, mean: thyroid, 0.58	–	–	–	–	–	–		Non-cancer diseases not analysed
Swedish benign breast disease [M10]	1 216 exposed persons 1 874 unexposed persons	Individual doses, mean: lung, 0.75; liver, 0.66; stomach, 0.66; oesophagus, 0.23	–	–	–	–	–	–		Non-cancer diseases not analysed
Metropathia haemorrhagica [D8, S3]	2 067 exposed persons	Individual doses, mean: lung, 0.04	–	–	NS (ischaemic heart disease)	–	–	NS (diseases of genitals, breasts, ovaries, etc.)		Internal comparisons (three dose categories)
Benign gynaecological disorders [I2]	4 483 exposed persons	Individual doses: lung, 0.04–0.06	–	NS	NS	NS	NS	P		Internal comparisons (four dose categories)
Lymphoid hyperplasia screening [P5]	1 195 exposed persons 1 063 unexposed persons	Individual doses, mean: thyroid, 0.24	–	–	–	–	–	–		Non-cancer diseases not analysed
Peptic ulcer [C9, G1]	1 831 exposed persons 1 778 unexposed persons	Individual doses, mean: heart, 2.1; left lung, 1.79; right lung, 0.55; left kidney, 14.2; right kidney, 2.07	–	NS	P (coronary heart disease); NS (other heart disease, stroke)	NS	NS	NS		Dose–response analysis for circulatory disease; internal comparison (exposed versus unexposed) for other diseases

Study	*Number of subjects*	*Doses: range and mean (Sv)*	*Non-cancer disease associations found*[a]							*Type of analyses performed for non-cancer diseases*
			All non-cancer diseases	*Infectious diseases*	*Circulatory diseases*	*Respiratory diseases*	*Digestive diseases*	*Genito-urinary diseases*	*Other diseases*	
Diagnostic examinations										
Massachusetts tuberculosis fluoroscopy [D4]	6 285 exposed persons 7 100 unexposed persons	Individual exposures, mean: lung, 0.84	NS (all except tuberculosis and respiratory)	NS (tuberculosis)	NS	NS	NS			O/E ratios, internal comparisons (exposed and unexposed)
Canadian tuberculosis fluoroscopy [H11, H12]	25 007 exposed persons 39 165 unexposed persons	Individual exposures: lung, 0–>3	–	–	–	–	–	–		Non-cancer diseases not analysed
Scoliosis [D9]	5 573 women with scoliosis receiving repeated radiographic examinations	Individual doses, mean: bone marrow, 0.01; lung, 0.041		P (infectious diseases)	P (circulatory diseases)	P (respiratory diseases)	P (digestive diseases)		P (musculoskeletal conditions)	Dose–response analysis
Occupational exposures										
Nuclear workers in Japan [I4]	119 484 workers	Recorded exposures to external radiation: mean cumulative dose, 0.0153	NS	–	–	–	–		P (external causes)	Dose–response analysis for total non-cancer mortality only
Nuclear workers in Canada, United Kingdom and United States [C6]	95 673 workers (Hanford, 32 595; Rocky Flats, 6 638; ORNL, 6 591; Sellafield, 9 494; United Kingdom other than Sellafield, 29 000; Atomic Energy of Canada Limited, 11 535)	Recorded exposures to external radiation: mean cumulative dose, 0.04	NS		P (circulatory diseases)	NS	NS (liver cirrhosis)		NS (external causes)	Dose–response analysis
NRRW, United Kingdom [M5]	124 743 workers	Recorded exposures to external radiation: mean cumulative dose, 0.03			NS (smoking-related diseases, including coronary heart disease, aortic aneurysm, bronchitis, emphysema, chronic obstructive pulmonary diseases)	P (non-smoking-related respiratory diseases)	NS	NS	I (unknown causes)	Dose–response analysis

Study	*Number of subjects*	*Doses: range and mean (Sv)*	*Non-cancer disease associations found*[a]							*Type of analyses performed for non-cancer diseases*
			All non-cancer diseases	*Infectious diseases*	*Circulatory diseases*	*Respiratory diseases*	*Digestive diseases*	*Genito-urinary diseases*	*Other diseases*	
Sellafield, United Kingdom Atomic Energy Authority (UKAEA) and Atomic Weapons Establishment (AWE) [C10]	40 761 monitored workers (Sellafield, 10 028; UKAEA, 9 389; AWE, 9 389)	Recorded exposures to external radiation: mean cumulative doses: Sellafield, 0.1329; AEA, 0.0406; AWE, 0.011	NS	–	–	–	–			Dose–response analysis
Sellafield [O1]	10 382 monitored workers	Recorded exposures to external radiation	–	I (tuberculosis)	P (ischaemic heart disease)	P (pneumonia)	NS	NS	P (mental disorders); I (accidents/ violence)	Dose–response analysis (ischaemic heart disease, pneumonia, mental disorders); internal comparisons (tuberculosis, digestive and genito-urinary diseases, accidents/ violence)
Chapelcross [M11]	2 628 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.0836	–	–	NS	P (bronchitis)	NS	NS		Internal comparisons (seven dose categories)
Springfields uranium production [M12]	13 960 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.0228	–	NS	P (cerebrovascular disease)	NS	P	NS	P (nervous and sense organ diseases, prostatic hyper-trophy, accidents/ violence)	Internal comparisons (seven dose categories)
Capenhurst uranium enrichment [M7]	3 244 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.0098	–	NS	NS	NS	NS	NS		Internal comparisons (seven dose categories)
Canadian National Dose Registry [A2]	206 620 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.06	–	NS	P (circulatory diseases)	NS	–	NS	P (accidents)	Dose–response analysis
Hanford, ORNL and Rocky Flats weapons plant [G6]	44 943 monitored workers (Hanford, 32 643; ORNL, 6 348; Rocky Flats, 5 952)	Recorded exposures to external radiation: mean cumulative doses: Hanford, 0.026; ORNL, 0.022; Rocky Flats, 0.041	NS	–	NS	NS	P (cirrhosis)		NS (external causes)	Internal comparison (six dose categories)

Study	*Number of subjects*	*Doses: range and mean (Sv)*	*Non-cancer disease associations found*[a]							*Type of analyses performed for non-cancer diseases*
			All non-cancer diseases	*Infectious diseases*	*Circulatory diseases*	*Respiratory diseases*	*Digestive diseases*	*Genito-urinary diseases*	*Other diseases*	
Hanford [G7]	37 971 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.0233	NS	–	NS	NS	NS (cirrhosis)		NS (external causes)	Internal comparison (five dose categories)
Portsmouth Naval Shipyard [R12]	8 960 monitored workers	Recorded exposures to external radiation: <1.5 (range)	–	–	–	–	–	–		–
Rocketdyne/ Atomics International [R13]	4 563 monitored workers	Recorded exposures to external radiation: cumulative dose 0–0.2	–	–	NS	NS	NS	NS	NS	External comparison, single SMR values
Mound facility [W6]	3 229 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.0297	–	NS	NS	NS	NS	NS	NS (injuries)	External comparison, single SMR values
Nuclear power utilities, United States [H13]	53 698 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.0257	P	NS	P (circulatory system, arteriosclerotic heart disease)	NS	NS	NS		Circulatory disease data significant by dose–response analysis; not significant by trend tests using dose categories
Chernobyl recovery operations workers, Russian Federation [I1]	68 309 workers	Assessed external radiation doses: 0–0.02+		NS	P (essential hypertension, cerebrovascular disease) NS (hypertensive heart disease, ischaemic heart disease)	NS	P	NS	P (endocrine/ metabolic diseases, mental disorders)	Dose–response analysis
Chernobyl recovery operations workers, Estonia [R14]	4 742 workers	Recorded radiation doses: mean, 0.11	–	–	NS	–	NS	–	P (suicide)	External comparisons, SMRs only
Mayak workers [B12]	15 601 persons monitored for external radiation	Recorded doses to external radiation, mean: lung, 3.8–35	–	–	NS (cardiovascular disease)	–	–	–		Internal comparisons (three dose categories)

Study	*Number of subjects*	*Doses: range and mean (Sv)*	*Non-cancer disease associations found*[a]							*Type of analyses performed for non-cancer diseases*
			All non-cancer diseases	*Infectious diseases*	*Circulatory diseases*	*Respiratory diseases*	*Digestive diseases*	*Genito-urinary diseases*	*Other diseases*	
Japanese radiologic technologists [Y2]	9 179 radiologic technologists	Recorded exposures to external radiation	–	–	–	–	–	–		–
Danish radiotherapy staff [A5]	4 151 radiotherapy workers	Recorded exposures to external radiation	–	–	–	–	–	–		–
Chinese X-ray workers [W2]	27 011 X-ray workers	Recorded exposures to external radiation	–	–	–	–	–	–		–
United States radiologic technologists [H3]	90 284 radiologic technologists	Recorded doses to external radiation		–	P (ischaemic heart disease, stroke)	–	–	–		Internal comparisons using exposure surrogates (periods of employment); adjusted for confounding effects
United Kingdom radiologists [B4]	2 698 radiologists		NS	NS	NS	–	–	–	NS (external causes)	Internal comparisons using exposure surrogates (periods of employment)
United States radiologists [M2]	6 500 radiologists			–	P (cardiovascular disease)	–	–	–		Internal comparisons among different medical professions and calendar years

a P = positive, I = inverse, NS = not significant; (–) indicates no published data.

b Dose estimates are provided in terms of weighted colon doses, which are the sum of the gamma-ray dose estimate and 10 times the neutron dose estimate. This annex uses as a convention sieverts for the units of weighted colon doses.

III. DATA ON NON-CANCER MORTALITY FOR SURVIVORS OF THE ATOMIC BOMBINGS

19. This section examines the LSS data on non-cancer mortality in some additional detail, because the analyses of the mortality data on the LSS cohort represent the most thorough evaluation to date of the association between radiation exposure and non-cancer disease risks. The LSS mortality data provide evidence of a dose response for mortality from heart disease, stroke, respiratory diseases (largely pneumonia, 67%) and digestive diseases (including a large proportion of liver cirrhosis, 44%). Non-cancer risk estimates and dose responses for different disease categories presented in table 2 and figure I are derived from the analysis of the full follow-up period from 1950 to 1990 [S20]. The LSS non-cancer mortality data were updated more recently, to 1997, and were analysed in more detail [P4, Z1], as discussed later in this annex, but the overall risk estimates for the full follow-up period remained essentially unchanged. There is no evidence of a dose response for mortality from infectious diseases (largely tuberculosis) and other diseases (including diseases of the genito-urinary system). Several potential sources of bias and confounding have been considered [S20], including: *(a)* the possibility that the construction of this cohort five years after the bombings may have led to the selection of study subjects in a manner that would bias the non-cancer disease outcomes; *(b)* possible misclassification of causes of death that may give rise to a spurious association between non-cancer mortality and radiation dose; and *(c)* the possibility that radiation dose, which is closely correlated with distance from the hypocentre, may be confounded by other factors affecting non-cancer disease rates. The impact of these potential biases, which was analysed by pooling non-cancer mortality (excluding blood diseases), is discussed below.

Figure I. Dose–response curve of mortality from all diseases except neoplasms and blood disease
Both cities, both sexes, all ages at the time of bombing, 1950–1985. Bars indicate 90% confidence interval of relative risk [S20]

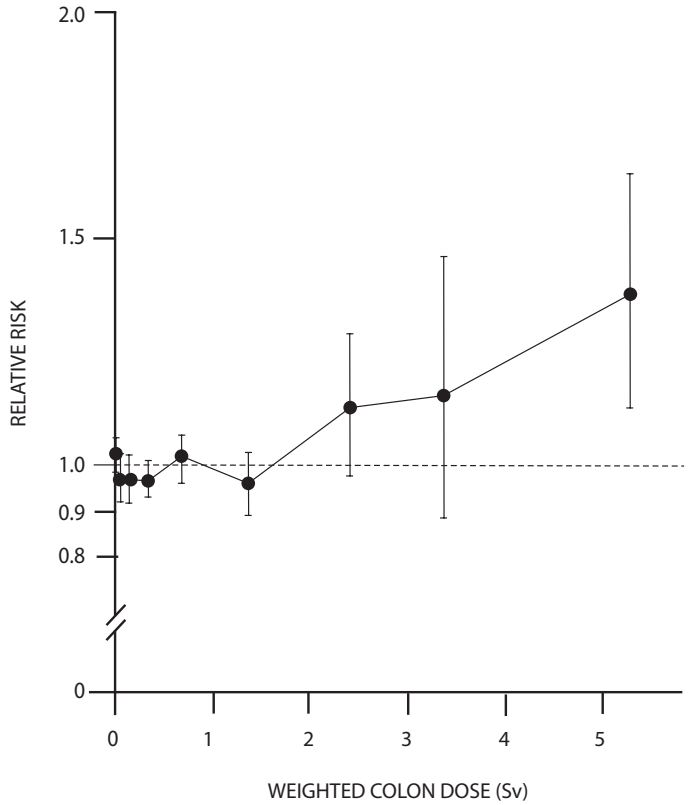


Table 2 Number of deaths and ERR estimates for major categories of non-cancer disease
Life Span Study 1950–1990 [S20]

Cause of death	*Number of deaths*	*ERR per unit weighted colon dose[a] (Sv^{-1})*	*90% confidence interval*	*p-value (1-sided)*
Stroke	7 859	0.09	(0.02, 0.17)	0.02
Cerebral haemorrhage	3 687	0.03	(–0.06, 0.14)	
Cerebral infarction	1 611	0.07	(–0.09, 0.25)	
Other	2 561	0.20	(0.06, 0.35)	
Heart diseases	6 826	0.14	(0.05, 0.22)	0.003
Coronary heart disease	2 362	0.06	(–0.06, 0.20)	
Hypertensive heart disease	1 199	0.21	(0.00, 0.45)	
Other	3 265	0.17	(0.05, 0.31)	
Respiratory diseases	3 163	0.18	(0.06, 0.31)	0.005
Pneumonia	1 828	0.20	(0.04, 0.37)	
Asthma	397	0.08	(–0.18, 0.45)	
Other	938	0.19	(–0.02, 0.43)	
Digestive diseases	2 742	0.11	(0.00, 0.24)	0.05
Liver cirrhosis	920	0.18	(0.00, 0.40)	
Other	1 822	0.07	(–0.07, 0.23)	
Infectious diseases	1 705	–0.002	(–0.13, 0.15)	>0.50
Tuberculosis	1 368	0.01	(–0.13, 0.19)	
Other	337	–0.07	(<–0.10, 0.29)	
Other diseases	4 822	0.01	(–0.08, 0.11)	0.41
Chronic renal disease	551	0.003	(–0.22, 0.30)	
Senility	1 906	0.09	(–0.08, 0.29)	
Other	2 365	–0.02	(–0.13, 0.10)	

[a] The authors express the weighted colon dose in sieverts as the sum of the gamma-ray dose and 10 times the neutron dose.

A. Misclassification

20. Using data from a large number of autopsies carried out in the LSS as the diagnostic reference, it was estimated that on average 20% of cancer deaths are misclassified on death certificates as being due to non-cancer causes ("cancer to non-cancer misclassification"), while 3.5% of deaths from causes other than cancer are mistakenly classified as cancer deaths ("non-cancer to cancer misclassification") [R5, S6]. Sposto et al. [S6] demonstrated that after correction for the cancer to non-cancer misclassification rates by age, sex, time and city, estimates for ERR of non-cancer mortality were reduced by about 20% relative to estimates that ignored the misclassification. In conclusion, in the LSS, disease misclassification on death certificates has an effect on estimates of risk for non-cancer disease, but the dose response for non-cancer disease remains highly significant even after correcting for this effect.

21. Because misclassification rates vary among different causes of death (they are especially high for respiratory diseases, for example), their impact on estimates for cause-specific mortality from non-cancer disease will vary but remains unassessed [R5]. Sposto et al. [S6] suggested two alternative ways to correct for misclassification for a specific disease entity. One was to create two disease categories, e.g. heart disease and all other causes combined, and to estimate the misclassification probabilities. Alternatively, more than two classifications could be used, pooling causes of death that are similar.

B. Biases and confounders

22. Because radiation doses were dependent on the distance from the hypocentre, a spurious dose effect could arise if proximal and distal survivors differed with respect to socio-economic status, lifestyle or other risk factors. First, this question was directly examined by assessing the possible confounding effect of smoking and other factors [S20] using data obtained from mail surveys conducted

among the LSS cohort subjects during the 1960s and 1970s. Potential factors, such as educational level, occupation, physical activity at work, house size per person (as a surrogate measure of socio-economic level), marital status, smoking status, regular alcohol use and percentage of Japanese food in diet, were analysed. Non-cancer underlying mortality rates varied significantly with each of these factors. The magnitude of the effects of many of these factors was comparable to, or even larger than, the difference in risk associated with exposure to 1 Sv. For example, smoking at the time of the mail surveys increased the non-cancer mortality rates by 37%. However, the associations between these factors and dose were not strong enough to significantly alter the risk associated with radiation doses; for example, there was only a 2% difference in the frequency of smoking associated with exposure to 1 Sv versus 0 Sv. Statistical adjustment for smoking reduced the estimate of ERR per unit dose only from 0.083 Sv^{-1} to 0.079 Sv^{-1} (table 3). In no case did the failure to allow for any of the other factors have an appreciable impact on the risk estimate for non-cancer disease from radiation exposure. When five factors (smoking, marital status, education, occupation and house size per person) were all taken into account, the estimate for ERR per unit dose for non-cancer disease was reduced from 0.097 Sv^{-1} to 0.087 Sv^{-1}. These findings indicate that the observed association between radiation and non-cancer mortality cannot be explained by the confounding effect of any of these factors, although the possibility of confounding by other unidentified or unmeasurable factors cannot be eliminated.

23. In further analysis [S20], the dose–response analyses for non-cancer disease were limited to the 61,000 proximal survivors (those exposed within 3 km of the hypocentre). The ERR estimate obtained from this subcohort was 0.11 Sv^{-1}, which was consistent with the estimate derived from the full cohort data. Furthermore, a significant radiation dose effect was found even when the analysis was limited to about 3,000 survivors who were between 0.9 and 1.2 km from the hypocentre, a span of 300 m in which weighted colon radiation dose estimates ranged from 0.35 to 5.8 Sv (median dose 1.1 Sv). It was considered implausible that there would be enough dose-correlated variation in socio-demographic characteristics over this narrow distance band to account for the observed dose response. It should be noted that atomic bombing survivors have shown a high prevalence of infection with the hepatitis C virus, an important cause of both liver cancer and liver cirrhosis [S19]. This may have played a cofactor role in the occurrence of liver disorders among exposed atomic bombing survivors.

C. Selection effects

24. The presence of cohort selection effects was suggested by temporal patterns of the LSS underlying rates of non-cancer diseases. The underlying rates of non-cancer disease in the year 1950 were about 15% lower for proximal survivors (i.e. those who were within 3 km of the hypocentre, generally an urban area, but for whom doses were estimated as zero because of shielding) than for distal survivors with zero dose (who were between 3 and 10 km of the hypocentre, generally a rural area), but this difference diminished to about 2% in the late 1960s [P4]. While this small difference in the rates of non-cancer disease seemed to persist, and may reflect the urban–rural, socio-economic or other differences affecting underlying rates, the diminishing difference in rates with time in the earlier years was considered to be due to the selection of healthy survivors, resembling the healthy worker effect seen in studies of occupational cohorts. Thus proximal survivors included in the LSS may have been initially healthier than the general

Table 3 Risk estimates for non-cancer disease due to radiation with and without adjustment for potential confounders
Life Span Study 1950–1990 [S20]

Risk factor	*Number of subjects with data available*	*ERR per unit dose*[a] *(Sv^{-1})*	
		Unadjusted	*Adjusted*
Highest education level	38 035	0.086	0.088
Occupation	36 766	0.098	0.097
Physical activity at work	7 364	0.088	0.097
House size per person	26 562	0.071	0.068
Current marital status	37 543	0.104	0.097
Current smoking status	38 975	0.083	0.079
Current alcohol use	34 470	0.133	0.144
Per cent of Japanese food in diet	7 292	0.085	0.084

[a] Weighted colon dose.

population, since they were able to survive the effects of the bombings and/or the difficult living conditions in the two cities in the immediate post-war period.

D. Dose response and risk estimates

25. The shape of the dose–response curve for non-cancer diseases is influenced by making allowance for the presumed healthy survivor effect, which depends on time and distance, and causes a small but persistent urban–rural difference in underlying rates [P4]. Because the effect is more pronounced in the earlier years of follow-up, the analysis restricted to the period before 1968 reveals significant curvature in the dose response (figure II, left panel), while there is no evidence of non-linearity in the later period, 1968–1997 (figure II, right panel). The small urban–rural (proximal–distal) differences in underlying rates add a smaller curvature to the dose response in the full cohort compared with the proximal survivors in both the pre-1968 and the 1968–1997 periods (figure II, left and right panels).

26. Figure III shows fitted linear and smoothed dose–response curves for the 1968–1997 period with no adjustment for proximal–distal differences in underlying rates [P4]. There is no indication of significant non-linearity in the dose response. However, there is considerable uncertainty regarding the dose response or even the existence of an effect at doses of below about 0.5 Sv. There is no evidence against a threshold of zero, and the maximum-likelihood estimate of the threshold in the adjusted analysis is about 0.15 Sv, with an upper 90% confidence bound of about 0.55 Sv. For the period before 1968, the data suggest a non-linear dose response. The non-linearity in the early LSS data is reduced but not totally accounted for by adjustments based on proximal–distal comparisons; this may be due to a residual proximal–distal effect that remains after the simple adjustment above [P4].

27. The non-cancer mortality data for the period of 1950–1967 show that a linear–quadratic or quadratic dose–response model may be adequate [P4]. However, since the distance-dependent selection effects among the proximal survivors are likely to have biased the estimates of values for dose–response parameters for this period, generalization of these estimates to other populations or different exposure situations may not be warranted.

28. Analysing the same LSS non-cancer mortality data for the period 1968–1997, Little used a variety of generalized relative risk models assuming 25%, 35% and 45% geometric standard deviation (GSD) dosimetric errors [L10]. When linear–threshold, quadratic–threshold, or linear–quadratic–threshold relative risk models were fitted, there was no evidence of threshold models significantly different from the linear, quadratic or linear–quadratic models. These findings were true irrespective of the assumed dosimetric errors. There was also little evidence of excess risk below 0.5 Sv. In general, these findings were true for the four major disease categories considered, i.e. stroke, coronary heart disease, digestive disease and respiratory disease.

29. Because the ERR for mortality from non-cancer disease is considerably smaller than that for mortality from solid cancers, and because underlying rates of non-cancer

Figure II. Fitted curves of mortality from non-cancer diseases in the LSS cohort for early (1950–1967, left panel) and late (1968–1997, right panel) periods of follow-up [P4]

Solid curve fits use only proximal survivor data; dashed curve fits are based on the full cohort without allowance for selection effects

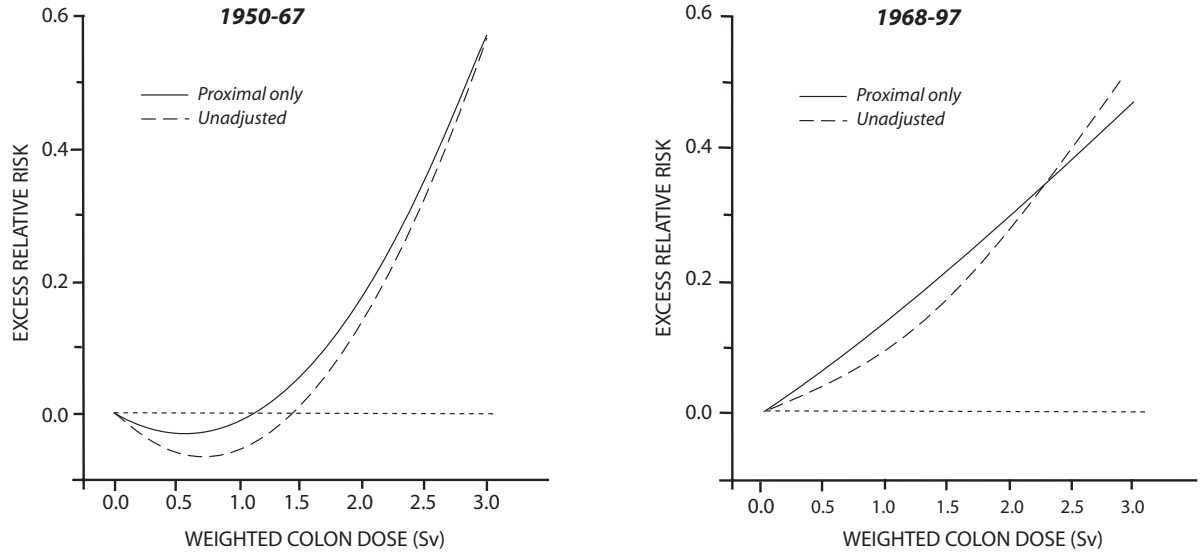
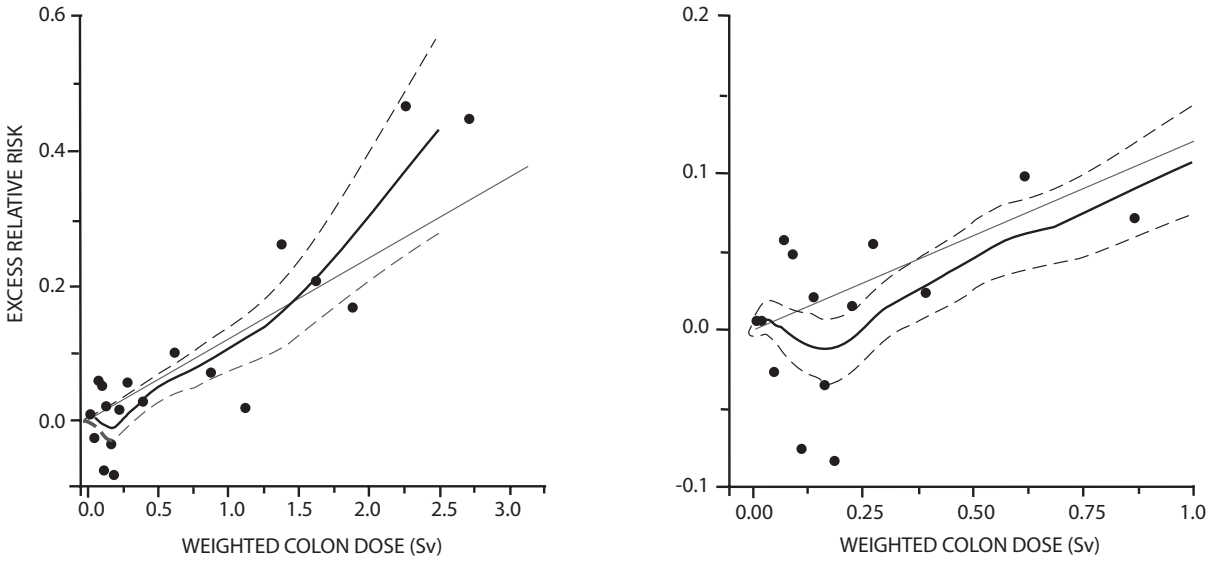


Figure III. Mortality from non-cancer disease in the LSS cohort versus dose for the period 1968–1997 [P4]
Individual points are dose-category-specific ERR estimates. The thin straight solid line is the fitted linear ERR model without any effect of age at exposure, sex or attained age. The thick solid curve provides a smoothed estimate derived from the individual points, with the two dashed curves indicating ±1SE (standard error). The right panel represents the same data as in the left panel, but shows the low-dose portion of the fitted curve in greater detail

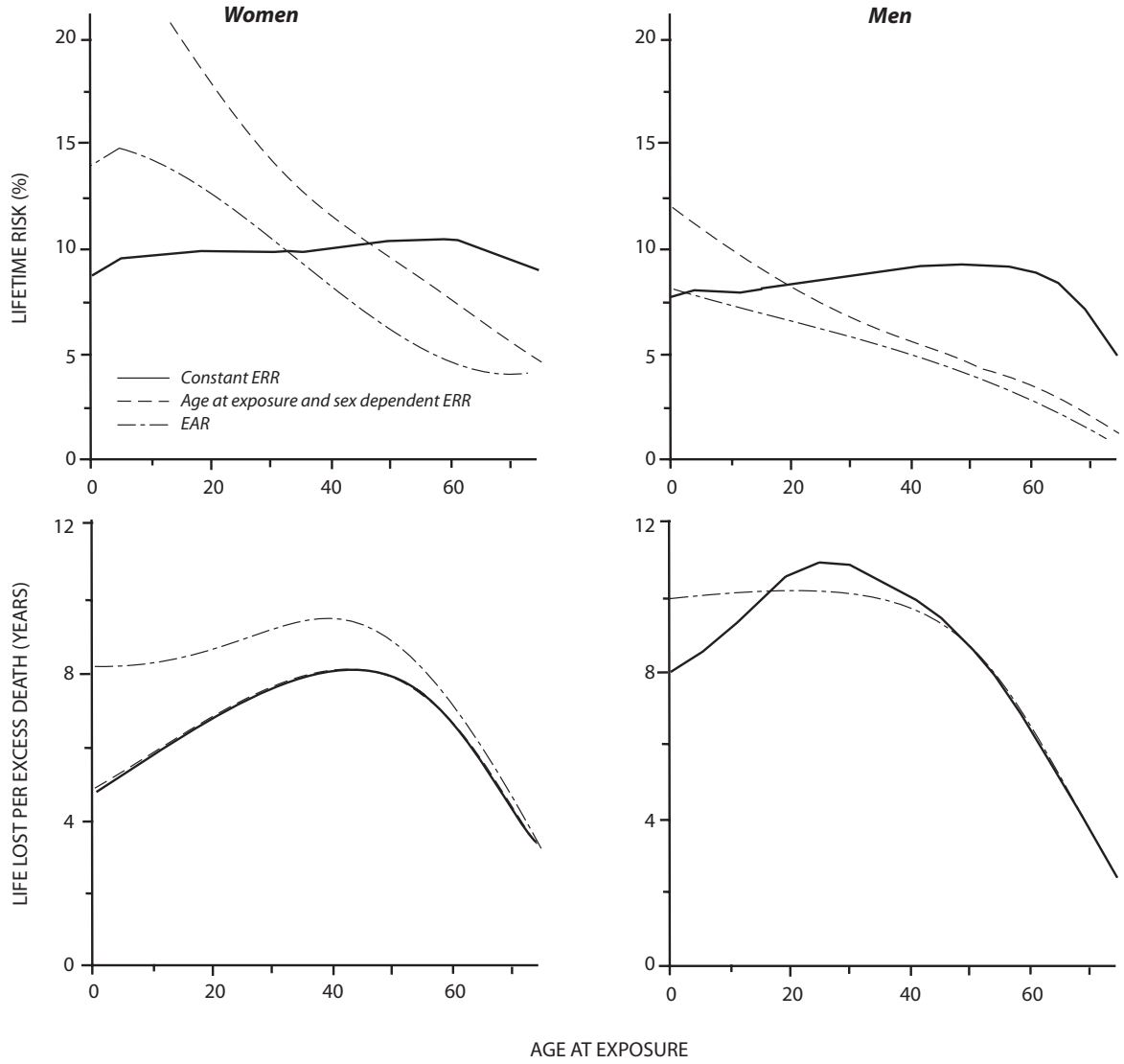


disease are much higher than rates of cancer, any modifying effect of age, time and sex on the risk is difficult to detect. The ERR for non-cancer disease decreases with increasing age at exposure, decreases with attained age and is lower for men than for women, although none of these effects is statistically significant [P4]. Others [L10, Z1] who have analysed the LSS data have also found that age at exposure has no significant effect on the risk of non-cancer disease.

30. There are two main sources of uncertainty in the current LSS dose–response data for estimating the lifetime risk of non-cancer disease due to radiation exposure. First, because of the uncertainty about how the risk varies with age, sex and age at exposure, three different risk models are used: *(a)* the constant ERR model; *(b)* an alternative ERR model with age-at-exposure and sex effects; and *(c)* an excess absolute risk (EAR) model with no age-at-exposure effects. Age-specific underlying rates of non-cancer disease have declined rapidly in Japan, but the time-constant ERR model provides lifetime risk estimates that are insensitive to age at exposure. In contrast, the other two models (ERR and EAR) depend on age at exposure, and predict decreasing risks with increasing age (figure IV). In any case, the results suggest that the lifetime risks of non-cancer disease among those exposed as children may be half the risks or less than those for solid cancer, while persons exposed at age 50 may have lifetime risks of non-cancer disease equal to those for solid cancer [P4]. Second, because there is great uncertainty about the shape of the dose–response relationship at low doses, the current estimates for lifetime risk are presented for exposure at 1 Sv, where the estimates are little affected by the shape of the dose–response curve. The magnitude of the risk of non-cancer disease at lower dose levels, e.g. 0.5 Sv, is at present very uncertain.

Figure IV. Estimates of lifetime risk (two upper graphs) and of years of life lost per excess death (two lower graphs) at 1 Sv weighted colon dose (from LSS Report 13 [P4])

The two left-hand graphs show the estimates for women, the two right-hand graphs those for men. Estimates represented by the dark solid curves are based on constant ERR models. Estimates based on age-at-exposure and sex-specific ERR models (dashed curves) or on an EAR model (dash-dotted curves) are also shown



IV. CIRCULATORY DISEASES

31. Diseases of the circulatory system (circulatory diseases) are leading causes of morbidity and mortality among adults worldwide, and are the cause of 30–50% of all deaths in many countries. In comparison, malignant neoplasms are the cause of 15–30% of all deaths. Atherosclerosis is a generalized underlying condition for the majority of circulatory diseases in adult populations and has three major clinical manifestations: cerebrovascular disease, coronary (or ischaemic) heart disease and peripheral vascular disease. Coronary heart disease and stroke are the major causes of death from circulatory diseases. Risk factors for atherosclerotic disease traditionally have included high blood pressure, cigarette smoking, hypercholesterolaemia (especially increased low-density lipoprotein (LDL) cholesterol) and diabetes. Factors such as obesity, family history of premature coronary heart disease and oestrogen replacement therapy have also been associated with coronary heart disease. Heavy alcohol intake increases mortality from coronary heart disease, but moderate intake appears to have a protective effect against the disease [T6].

32. Diseases of the heart may be broadly categorized as ischaemic heart disease (most importantly myocardial infarction), hypertensive heart disease, valvular heart disease, non-ischaemic (primary) myocardial disease and congenital heart disease. These different types of heart disease markedly differ in pathogenesis, aetiology, clinical presentation and prognosis. Ischaemic heart disease is the late manifestation of coronary atherosclerosis and is responsible for the majority (80–90%) of the cardiac deaths in most countries [S18]. The effects of radiation exposure at low doses on this category of heart disease and underlying atherosclerotic changes are of special concern in this annex. Hypertensive heart disease occurs in response to systemic hypertension, leading to heart dysfunction or congestive heart failure, among others. Valvular heart disease may be caused by congenital disorders or by various acquired diseases, including rheumatic heart disease. Primary myocardial disease may occur as a result of inflammatory disease (myocarditis), immunological disease, systemic metabolic disorders, muscular dystrophies, genetic abnormalities or other unknown causes. These different categories of heart disease can be coded using the International Classification of Diseases (ICD) scheme adopted by most epidemiological follow-up studies.

33. In the literature, the term "cardiovascular disease" is used interchangeably to refer to the broad category that includes all diseases of the circulatory system or more specifically to heart disease. This annex follows the nomenclature used in the International Classification of Diseases and Related Health Problems (ICD-10) [W7]. "Circulatory disease" will be used to refer to the entire group of diseases of the circulatory system (I00–I99), including any form of heart disease (I00–I02, I05–I09, I10–I15, I20–I25, I26–I28, I30–I52), cerebrovascular disease (I60–I69), and diseases of the arteries, diseases of other vessels and diseases not elsewhere classified (I60–I69, I70–I79, I80–I89). "Heart disease" will refer to any form of disease of the heart as defined above. "Ischaemic heart disease" (I20–I29), which is often used synonymously with coronary heart disease in the literature, will include angina pectoris, myocardial infarction and its complications. "Cerebrovascular disease" (I60–I69) includes stroke, haemorrhagic infarction or unspecified, and its sequelae. "Stroke" is used synonymously with this disease category.

A. Patients receiving radiotherapy for cancer

34. The heart at one time was considered to be a radiation-resistant organ; only isolated examples of radiation-induced carditis were available in the early literature. This was in part due to the limitations on thoracic irradiation posed by the much greater radiosensitivity of the lungs. In the mid-1960s, cases of radiation-induced heart disease began to be reported from a large series of Hodgkin's lymphoma patients who had survived irradiation of the mantle field. Therapeutic doses were very high, exceeding 30–40 Gy in most cases. Damage to the heart is considered to be due to tissue destruction from such high doses. The changes in heavily irradiated patients can involve all structures of the heart (including the pericardium, myocardium, valves, conduction system and coronary arteries), but most characteristically the pericardium, and can include pericardial effusion, fibrosis and constrictive pericarditis [A3, F1]. The term "radiation-induced heart disease" has been used to refer to such conditions [S2]. Initially, coronary heart disease or myocardial infarction was only occasionally reported, but starting in the early 1990s, an excess risk of myocardial infarction after radiation treatment began to be noted in patients with Hodgkin's lymphoma or breast cancer. Much information has since been accumulated on the risk of coronary heart disease subsequent to cancer radiotherapy.

1. Hodgkin's lymphoma patients

35. Until 1960, the treatment of Hodgkin's lymphoma was usually considered palliative, but starting around 1960,

curative treatment of this disease began to evolve rapidly with new radiotherapy and chemotherapy regimens. With the introduction of megavoltage radiotherapy, techniques to treat extensive fields became available. With the development of mantle field irradiation and total lymphoid irradiation, radiotherapy became the cornerstone of the treatment of Hodgkin's lymphoma [C1]. Megavoltage equipment delivered a dose to deeper parts of the body. In the 1960s, doses of 40–44 Gy were often given to involved fields [K1, N1]. Before 1960, if radiation was employed at all, smaller doses were used to treat early-stage Hodgkin's lymphoma, although at some medical centres doses of 25–30 Gy were administered to involved nodal and proximal areas [D1].

36. In the late 1970s and early 1980s, it became apparent that radiotherapy given to extended fields at high doses could induce late mortality from lung damage, myocardial infarction and second cancers. Modifications were then introduced to reduce radiotherapy fields and doses whenever possible. From the mid-1970s to 1994, 30–40 Gy was commonly given when radiotherapy was used without cytotoxic drugs, while an average of 30 Gy was administered when used in combination with chemotherapy [D2]. Before the early 1970s, similar therapy was given to paediatric and adult Hodgkin's lymphoma patients. Thereafter, treatment of Hodgkin's lymphoma in children was modified to use lower doses (15–25 Gy to involved fields); therapy regimens for fully developed adolescents still incorporated larger doses (35–44 Gy) [M1].

37. Some earlier literature linked coronary artery disease to cancer treatment [K2]. Among the earliest follow-up studies was one by Boivin et al. [B1]. In a cohort of 4,665 Hodgkin's lymphoma patients treated at 11 cancer treatment centres in the United States and Canada (Boston, Houston, Montreal and Toronto), 124 cases who died either directly from or with coronary heart disease were compared with 489 controls randomly selected from the entire cohort. The age-adjusted relative risk of death with any coronary heart disease after radiotherapy was non-significantly elevated (1.87), but the relative risk of death with myocardial infarction was significantly elevated (2.56). When the analysis was restricted to coronary heart disease as the direct cause of death, the age-adjusted relative risk associated with radiotherapy was significantly increased (3.11). The patients included both children and adults diagnosed between 1940 and 1985. Cardiac radiation doses were not available. The relative risk for those treated in the early period (before 1965–1970), when high-dose orthovoltage irradiation was used, was higher, but not significantly, than for those treated in later years.

38. To date, the most detailed analysis of risk of mortality from heart disease after radiotherapy for Hodgkin's lymphoma comes from the cohort study of 2,232 paediatric and adult patients irradiated during 1960–1990 at Stanford University Medical Centre (table 4) [H1]. The patients were followed on average for 9.5 years; 1,609 patients received mediastinal irradiation from mantle therapy; 369 received less extensive, limited field irradiation; 23 received irradiation for recurrent disease; and 231 received no mediastinal irradiation. Mean mediastinal doses were lower among patients treated before 10 years of age (21.5 Gy) and after 50 years of age (28.7 Gy) than for other age groups (36.7–40.5 Gy). Of the 88 deaths from heart disease, 55 were from acute myocardial infarction and 33 from other cardiac diseases.

39. The relative risk (RR) of death from acute myocardial infarction calculated on the basis of comparison with the United States Life Tables was 3.2 for the entire cohort, with no significant sex difference. The RR was higher for patients treated with radiation alone (RR = 4.1, mean dose 50.7 Gy) than for those treated with both chemotherapy and radiation (RR = 2.7, mean dose 43.3 Gy) or for those who received no mediastinal irradiation (RR = 1.7) (table 4). A significantly elevated RR of 3.5 was found for patients irradiated at ≥30 Gy (mediastinum dose); the RR of 4.2 for those irradiated at <30 Gy was derived from only two subjects.

40. Of the 33 deaths from cardiac diseases other than acute myocardial infarction, about half (15) were deaths from chronic pancarditis or pericarditis. The RR of other cardiac deaths was elevated both for patients treated with radiation alone (RR = 3.2) and for those treated with chemotherapy and radiation (RR = 3.6) (table 4).

41. In this cohort, very few patients were treated with combination chemotherapy, mostly MOPP, without radiotherapy. The relative risk for all cardiac disease mortality for this group of patients was elevated (1.6), but not significantly, and this was consistent with the earlier analysis by the same investigators, which indicated the absence of an excess risk of coronary heart disease in Hodgkin's lymphoma patients treated with chemotherapy [H14].

42. Several risk-modifying effects were noted. As discussed in more detail later, the most notable were the effects of age at treatment. A higher risk of heart disease, both myocardial infarction and other heart diseases, was found among patients treated at young ages, especially at less than 20 years. Also, the relative risk of acute myocardial infarction and other cardiac diseases increased with time after treatment. Blocking to limit cardiac exposure (subcarinal block) reduced the relative risk of cardiac diseases other than myocardial infarction from 5.3 to 1.4, but not that of acute myocardial infarction (RR = 3.7 versus 3.4). Subcarinal blocking reduces the volume of the heart exposed to irradiation but does not provide protection to the proximal part of the coronary arteries [A3].

43. Although information on smoking was not available for the entire cohort of Hodgkin's lymphoma patients, a subset of the subjects participated in a questionnaire and interview study. Among the Hodgkin's lymphoma patients, 52.6% had never smoked cigarettes and 24.5% had formerly

Table 4 Risks of death from myocardial infarction and other cardiac diseases after treatment for Hodgkin's lymphoma
Stanford Study [H1]

Group (number of patients at risk)	*Acute myocardial infarction*			*Other cardiac diseases*		
	Number observed/expected	*Relative risk (95% CI)*	*Absolute risk*	*Number observed/expected*	*Relative risk (95% CI)*	*Absolute risk*
All patients	55/17.3	3.2 (2.3, 4.0)	17.8	33/11.5	2.9 (1.9, 3.9)	10.2
Male (1 316)	47/14.3	3.3 (2.3, 4.2)	27.0	24/8.3	2.9 (1.7, 4.1)	13.0
Female (916)	8/3.0	2.6 (1.2, 5.0)	5.5	9/3.2	2.8 (1.4, 5.1)	6.4
Radiation alone[a] (1 183)	35/8.4	4.1 (1.2, 5.5)	25.7	17/3.3	3.2 (1.9, 4.0)	11.4
Combined treatment (1 119)[a]	14/5.2	2.7 (1.5, 3.8)	9.7	12/3.3	3.6 (2.0, 6.1)	9.6
Mediastinum radiation treatment:						
None (254)	6/3.6	1.7 (0.7, 3.5)	—[b]	4/2.9	1.4 (0.4, 3.4)	—[b]
0–30 Gy (131)	2/0.5	4.2 (0.7, 13.8)	—[b]	0/0.3	—[b]	—[b]
>30 Gy (1 830)	47/13.3	3.5 (2.5, 4.5)	18.6	29/8.4	3.5 (2.2, 4.7)	11.4
Before 1972 (553)	26/7.0	3.7 (2.3, 5.1)	24.7	23/4.3	5.3 (3.1, 7.5)	24.2
After 1972 (1 448)	23/6.8	3.4 (2.0, 4.8)	13.9	6/4.3	1.4 (0.6, 2.9)	—[b]
Age at irradiation, years:						
<20 (487)	6/0.14	44.1 (17.8, 91.6)	11.3	4/0.19	21.5 (6.8, 52)	7.3
20–29 (749)	8/1.1	7.3 (3.4, 13.8)	9.0	7/0.79	8.8 (3.8, 17.4)	8.1
30–39 (448)	14/2.7	5.1 (2.9, 7.4)	27.4	7/1.5	4.8 (0.5, 5.1)	13.4
40–49 (169)	9/3.0	3.0 (1.4, 5.5)	43.6	3/1.6	1.9 (0.5, 5.1)	—[b]
>50 (148)	12/6.8	1.8 (1.0, 3.0)	—[b]	8/4.6	1.7 (0.8, 3.3)	—[b]
Years after treatment:						
0–4 (NA)[c]	12/6.0	2.0 (1.1, 3.3)	6.4	6/4.1	1.5 (0.6, 3.0)	—[b]
5–9 (NA)	17/4.7	3.6 (2.2, 4.5)	20.1	10/3.1	3.2 (1.6, 5.7)	11.3
10–14 (NA)	11/3.7	3.0 (1.6, 5.2)	20.5	5/2.4	2.1 (0.8, 4.6)	—[b]
15–19 (NA)	11/2.2	5.0 (2.6, 8.7)	54.2	8/1.4	5.8 (2.7, 10.9)	40.7
>20 (NA)	4/0.7	5.6 (1.8, 13.6)	70.6	4/0.5	8.8 (2.8, 21.3)	76.1

[a] Includes mediastinum.
[b] Risk was not significantly elevated.
[c] NA = number of patients at risk not available.

smoked cigarettes. These figures were comparable to those reported for United States adults (of whom 51.2% had never smoked and 24.1% were former smokers), so it seems unlikely that the increased risk of acute myocardial infarction observed among the cohort of Hodgkin's lymphoma patients is explained by their smoking habits.

44. Other studies, generally of cohorts smaller in size than the Stanford cohort, have also reported increased risk (as measured by SMR) of mortality from myocardial infarction after radiotherapy for Hodgkin's lymphoma (table 5) [A7, C2, H9, K3, M6, R1]. Radiation doses received by the Hodgkin's lymphoma patients in these studies were in the range 35–45 Gy, except for the paediatric patients who were treated in 1980–1900 and received 20 Gy [H9].

45. Elevated SMRs ranging from 2 to 5 are in general agreement with the relative risks (which are actually SMRs) reported from the Stanford study [H1]. The very high SMR of 22 for cardiac death in paediatric patients irradiated between the ages of 3 and 22 years [H9] involved six deaths from cardiac disease, five of which were from myocardial infarction and occurred in males receiving 35–37 Gy from extended radiotherapy. Three of these six cases had received concomitant cyclophosphamide chemotherapy, which may also have contributed to cardiac myocyte injury.

46. Most results reported from follow-up of irradiated Hodgkin's lymphoma patients are based on external comparisons, with a few studies using limited internal comparisons. Nevertheless, the reported SMRs, which are sometimes

Table 5 Risks of heart disease after radiotherapy for Hodgkin's lymphoma, other than the Stanford study

Study and year	*Study population*	*Age at treatment (years)*	*Length of follow-up (years)*	*Dose (Gy)*	*Results*[a]
King et al., 1996 [K3]	326 patients treated between 1954 and 1989; Rochester, New York, United States	25.6 (mean); 5–72 (range)	13.3 (mean); 3–37 (range)	Central cardiac dose: 44.3 (mean); 35–60.4 (range)	Increased SMR (2.8) for fatal myocardial infarction among the irradiated patients
Reinders et al., 1999 [R1]	258 patients treated between 1965 and 1980; Netherlands	28 (median); 5–78 (range)	14.2 (median); 0.7–26 (range)	Mediastinum inferior dose: 37.2 (mean)	SMR = 5.3 for ischaemic heart disease among the irradiated patients
Cosset et al., 1991 [C2]	499 patients treated between 1971 and 1984; Villejuif, France	Not available	Not available	Mediastinal dose: 39–41 (68%); 35–37 (11%); 41–43 (7%)	Increased RR of 3.25 for pericarditis among patients irradiated at >41 Gy; no elevated RR of myocardial infarction
Mauch et al., 1995 [M6]	794 patients treated between 1969 and 1988; Boston, Massachusetts, United States	24 (median); 3–69 (range)	11 (median)	Mediastinal dose: 35–40 Gy	Increased SMR of 2.2 for cardiac deaths for the cohort
Aleman et al., 2003 [A7]	1 261 patients treated between 1965 and 1987; Netherlands	<40	17.8 (median)	Not available	Cardiovascular SMR: 7.2 (RT), 5.5 (RT and CT), 5.9 (salvage treatment); Myocardial infarction SMR: 1.3 (RT), 0.7 (RT and CT), 2.0 (salvage treatment)
Hudson et al., 1998 [H9]	387 paediatric patients diagnosed between 1968 and 1990; Memphis, Tennessee, United States	14.4 (median); 3–25 (range)	15.1 (median)	Mediastinal dose: 35–44 Gy (1968–1979); 20 Gy (1980–1990)	Increased SMR (22.2) for cardiac disease

[a] RT: radiotherapy; CT: chemotherapy.

referred to as relative risks in these studies, are in the range 2–5 in different populations (with the exception of paediatric patients), providing consistent evidence of the effects of high-dose radiotherapy (at about 30–40 Gy) on ischaemic heart disease. Modern radiotherapy for Hodgkin's lymphoma has incorporated newer techniques, exposing a smaller volume of the heart to a much lower dose, but little is known about the effects of the lower-dose radiotherapy currently in use (from 15 to 25 Gy). More information could be expected from follow-up studies of patients treated with modern radiotherapy, but analysis will be complicated by the combined use of doxorubicin and related drugs, which have been shown to have long-term cardiotoxic effects [K8, L11].

2. Childhood cancer patients

47. The long-term risk of heart disease following radiotherapy and chemotherapy for childhood cancer has been reported [A3], but few studies have examined a dose response. In a clinical follow-up of 229 patients treated for a variety of cancers before the age of 15 years at the Institut Gustave Roussy, Villejuif, France, between 1968 and 1985, cardiac disorders were diagnosed in 89 patients, including 24 with heart failures and 65 with other asymptomatic, echocardiographic changes (abnormal fractional shortening, ejection fraction and end systolic meridonal wall stress) [G10]. All these children had received anthracyclins and 125 had received radiotherapy. Radiation doses delivered to seven points in the heart were estimated for all patients who had received radiotherapy [D10]. Adjusted for potential confounders, the cardiac disorder risk was found to be linearly related to radiation dose; the RR was 1.63 for radiation doses of >0–5 Gy, 6.48 for doses of 5–20 Gy and 4.40 for doses of >20 Gy compared with patients with no radiotherapy [P6]. There was no indication of an interaction between radiation dose and cumulative dose of anthracyclins known to be cardiotoxic.

3. Breast cancer patients

48. Today, the majority of breast cancers diagnosed in women in most Western countries are detected at an early stage. Surgery is the primary treatment, but subsequently adjuvant therapy (including radiotherapy, chemotherapy or

hormonal treatment) is also given. The treatment fields used in irradiating the breast or chest wall include a portion of the heart. The radiation dose to the heart depends on the radiation treatment technique used. Especially in older series of post-mastectomy radiotherapy, a large portion of the heart was irradiated [F2, R2]. Early randomized trials of treatment for breast cancer, as discussed below, have demonstrated that radiotherapy is an effective treatment modality for reducing mortality from breast cancer, but they have also provided evidence of increased mortality from cardiovascular disease associated with the radiotherapy.

49. Recent radiation techniques used in conjunction with breast-conserving surgery deliver radiation to a smaller portion of the heart. The strategy for breast-conserving treatment is to remove the bulk of the tumour surgically and to use moderate doses of radiation to eradicate any residual cancer. The volume of the heart irradiated has been significantly reduced in patients treated with modern techniques (mostly megavoltage radiotherapy after conservative surgery) compared with patients treated with earlier techniques (mostly by post-mastectomy orthovoltage radiation) [F2]. However, even with contemporary megavoltage radiotherapy, left-side breast cancer may result in exposure of the left anterior descending coronary artery to a substantial radiation dose, because the artery lies within or near the target field [F2]. Several studies, also reviewed below, have attempted specifically to evaluate the risk associated with modern radiotherapy.

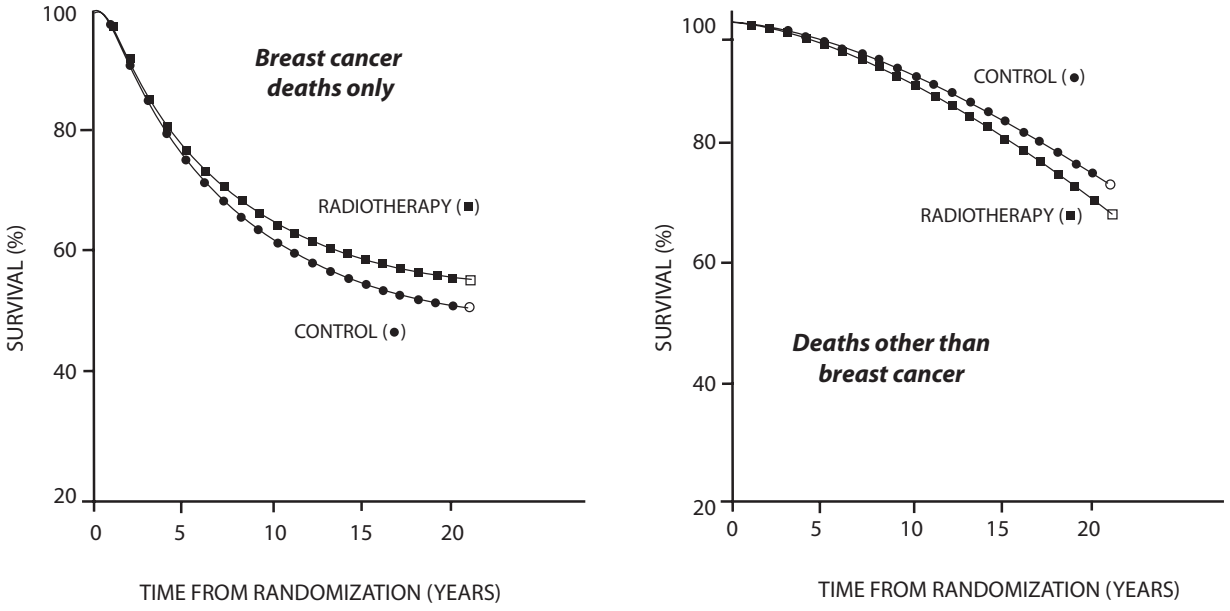
50. There are two major sources of data useful for assessing the risk of heart disease following radiotherapy in breast cancer patients: randomized clinical trials and laterality studies. In randomized clinical trials, breast cancer patients were randomly assigned to radiotherapy and other methods of treatment. Because of the random selection, results are expected to be unbiased, and thus well-executed randomized trials are regarded as the most credible. In "laterality studies", the risk of cardiac disease is calculated by comparing the disease rates after radiotherapy for left-sided breast cancer with that for right-sided breast cancer. This takes into account the fact that radiotherapy given for left-sided breast cancer exposes a larger volume of the heart to radiation and with a higher dose than treatment for right-sided breast cancer. Laterality studies are observational (not randomized), but they offer the advantage that differences in heart disease risk between left-sided and right-sided breast cancer patients are unlikely to be explained by possible confounding or patient selection.

(a) Randomized clinical trials

51. An increased risk of mortality from cancer other than breast cancer among irradiated breast cancer patients was initially suggested by Cuzick et al. [C3, C4], who reviewed data from several early breast cancer clinical trials—one comparing radical mastectomy without radiotherapy against simple mastectomy with radiotherapy in patients treated during 1951–1975, and the other evaluating post-operative adjuvant radiotherapy in breast cancer patients treated during 1949–1979. The data showed a detrimental impact on long-term (10–15 year) survival associated with radiotherapy, which was attributed to excess cardiovascular mortality [H2, H4, J3].

52. Radiotherapy regimens used in the initial series varied with respect to the energy of the beam, fields irradiated, duration of treatment and dose range. Cuzick et al. [C5]

Figure V. Effect of radiotherapy on cause-specific survival in breast cancer patients in the EBCTCG [E3]



subsequently extended the follow-up and showed that among the survivors of ≥10 years, cardiac-related deaths were increased in the radiotherapy arm by 82% compared with the control arm.

53. Since 1984–1985, data from randomized trials in early breast cancer, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), have been evaluated periodically. Results have shown reduced mortality from breast cancer in the adjuvant radiotherapy group [E2]. Mortality from diseases other than breast cancer, however, was increased among those who received radiotherapy. The meta-analysis of data from follow-up of the radiotherapy to 1995 in 40 unconfounded randomized trials involved 19,583 women with early breast cancer and showed that radiotherapy increased mortality from causes other than breast cancer by 21.2%; the 20-year survival was 69.5% among those who were allocated to radiotherapy compared with 73.8% among controls (figure V) [E3].

54. Vascular mortality was significantly increased by radiotherapy (radiotherapy/control death rate ratio = 1.30, standard error 0.09) (table 6). The relative excess of vascular deaths appeared to be similar during and after the first decade of follow-up, but the absolute rates were about three times higher in the latter period, reflecting the increasing underlying mortality with increasing follow-up time. No information was available, however, on radiation doses or on laterality of breast cancer (as a surrogate for cardiac exposure).

55. The latest analysis of the EBCTCG data involves 42,000 women in 78 randomized comparisons allowing analysis of 15 or more years of follow-up data [E4]. As with the previous analysis, there was a significant excess of mortality from non-cancer diseases in irradiated women, mainly involving heart disease (radiotherapy/control death rate ratio = 1.27, $p = 0.001$). The excess seemed to be less during the first 5 years of follow-up but was significant for the periods 5–14 years and 15 years or more after follow-up. The mean dates of randomization were 1975 and 1970, respectively, for those who died 5–14 years and 15 or more years after randomization. This is consistent with the possibly greater hazards of the radiotherapy regimens in the early 1970s versus the lower late hazards of modern radiotherapy.

56. More recent data, from the Danish Breast Cancer Cooperative Group, are relevant for assessing the risk associated with the most recent therapy techniques. In this trial, 3,083 women who were at high risk of breast cancer recurrence after mastectomy were randomly assigned to adjuvant systemic treatment with or without radiotherapy [H7]. Breast cancer patients were treated with electron-based techniques that minimized the portion of the heart volume irradiated. In the 12-year follow-up, the relative hazard (radiotherapy/non-radiotherapy ratio of the cumulative hazard function) of morbidity and mortality from ischaemic heart disease among women treated with radiotherapy was 0.86 (95% CI: 0.6, 1.3), which was not significantly different from that of 0.84 (95% CI: 0.4, 1.8) among those without radiotherapy (figure VI). The volume of the heart irradiated was considered small, but the exact heart volume in the radiation field was unknown. The conservative estimate was that less than 15 mm of the anterior surface of the heart received an absorbed dose per day of 1.7–1.9 Gy, given in 25 fractions, 5 fractions per week. The number of subjects (46 morbidity cases and 12 deceased cases with ischaemic heart disease) was rather small, and the authors cautioned that further follow-up would be necessary to assess the long-term effects on the heart.

(b) Laterality studies

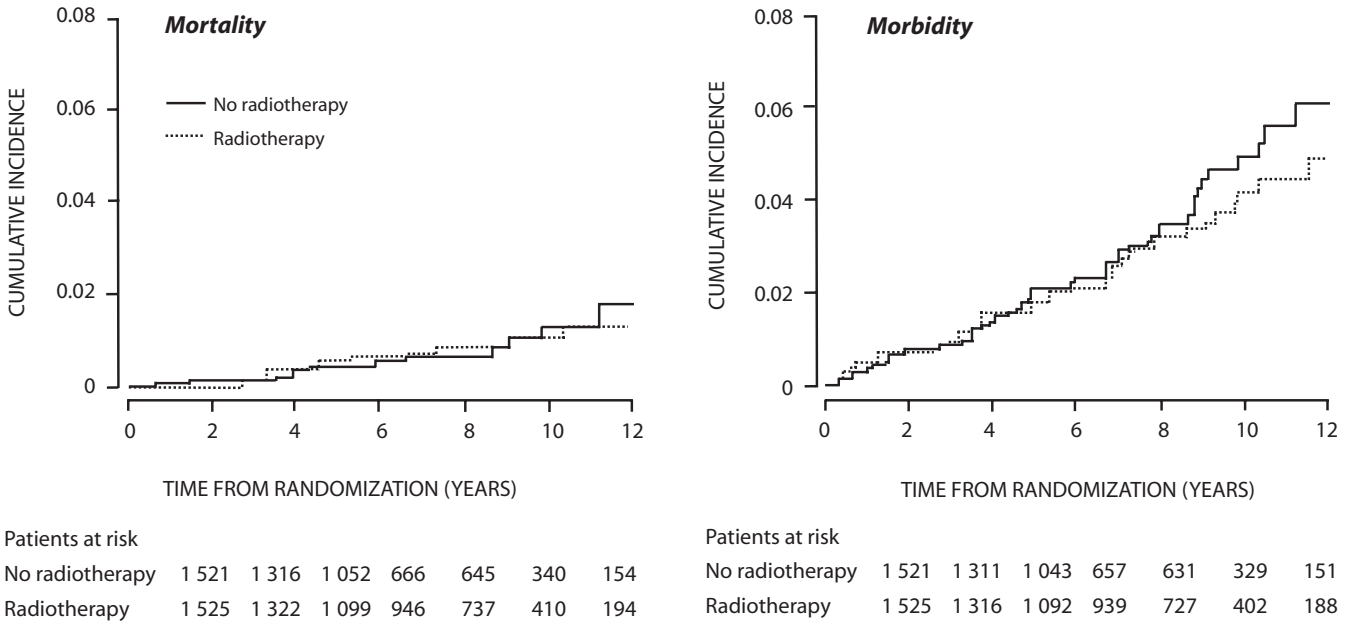
57. Laterality studies are methodologically innovative, taking advantage of the heart being closer to the left breast than the right. However, left- versus right-sided comparisons may lead to an underestimate of the radiation-related risk, because the heart also receives a low dose of scattered radiation from radiotherapy for the right-sided breast. In addition, most of the laterality studies lack information on the radiotherapy used, and radiation doses are rarely estimated.

58. Table 7 summarizes the main results regarding the risk of heart disease from laterality studies. The largest study of myocardial infarction after adjuvant radiotherapy for left- versus right-sided breast cancer was conducted by Paszat

Table 6 Non-cancer causes of death
Early Breast Cancer Trialists' Collaborative Group [E3]

Underlying cause of death when breast cancer had not recurred	*Number of deaths*		*Radiotherapy/control ratio of annual death rates (standard error)*
	Allocated to radiation treatment	*Adjusted control*	
Vascular	437	322	1.30 (0.09)
Non-vascular	382	313	1.15 (0.09)
Unknown	339	292	1.09 (0.09)
Total	1 158	927	1.18 (0.05)
Follow-up duration (10^3 woman-years before recurrence)	82.1	74.8	

Figure VI. Cumulative mortality (left) and morbidity (right) for ischaemic heart disease among patients treated with/without radiotherapy, from the Danish Breast Cancer Cooperative Group study of high-risk breast cancer patients after adjuvant post-mastectomy systemic treatment with/without radiotherapy [H7]



Patients at risk							
No radiotherapy	1 521	1 316	1 052	666	645	340	154
Radiotherapy	1 525	1 322	1 099	946	737	410	194

Patients at risk							
No radiotherapy	1 521	1 311	1 043	657	631	329	151
Radiotherapy	1 525	1 316	1 092	939	727	402	188

et al. [P1]. This was based on over 200,000 breast cancer patients identified by the Surveillance, Epidemiology and End Results (SEER) registries in the United States. The subjects were women aged 20 years or older and diagnosed between 1973 and 1992. A total of 703 deaths from myocardial infarction occurred during the follow-up, which averaged 74 months. Analysis of actuarial probability of deaths showed a greater likelihood of fatal myocardial infarction among women given adjuvant radiotherapy for left-sided breast cancer than for right-sided breast cancer (figure VII, two left-hand graphs). In contrast, there was no significant difference in the probability of death from myocardial infarction among non-irradiated women between left-sided and right-sided breast cancer (figure VII, two right-hand graphs). Since no individual information was available on the specific type of radiotherapy, the authors compared data for two time periods, 1973–1982 and 1983–1992, assuming major differences in radiation treatment practices (see table 7) between the two periods. The relative risk of myocardial infarction after irradiation for left-sided breast cancer patients was significant among those who were diagnosed before age 60 years during the earlier time period (table 7) but not among those aged 60 years or more at diagnosis, during either the earlier or the later period. Cardiac events were too few among breast cancer patients of less than 60 years of age and diagnosed in the later period, when use of post-lumpectomy (breast-conserving surgery) radiation treatment was more frequent.

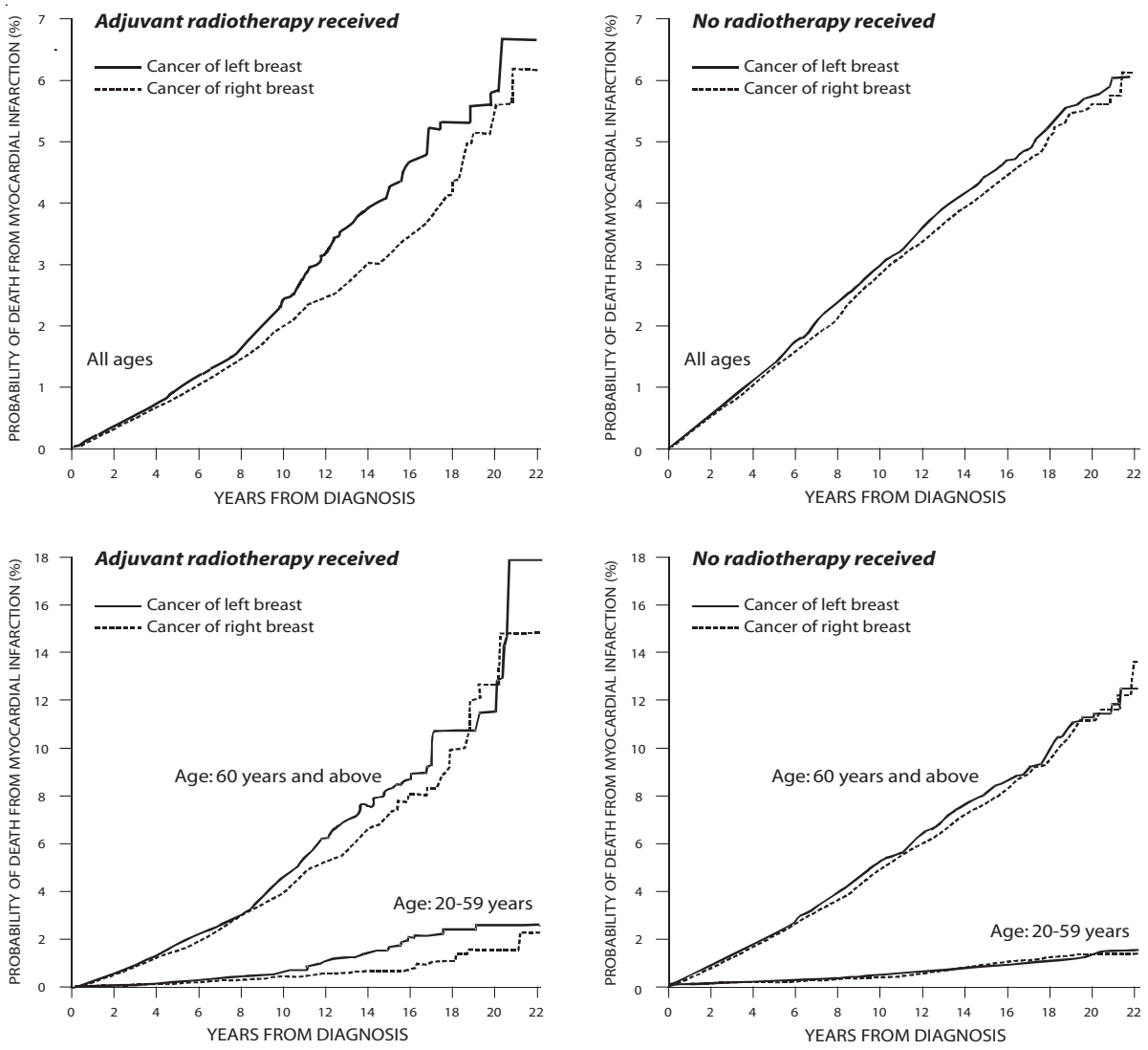
59. Rutqvist and Johansson [R3] analysed mortality data among about 55,000 breast cancer patients reported to the Swedish Cancer Registry during 1970–1985. The registry does not record information on treatment, but previous population-based surveys had indicated that about 50% of all breast cancer patients received radiotherapy, usually with supervoltage techniques. The relative risk of death from myocardial infarction was significantly elevated for left- versus right-sided tumours (1.09; 95% CI: 1.02, 1.17). The relative risk appeared to increase with follow-up time, but was not significant. Assuming that about half of all breast cancer patients in this study had radiotherapy, the relative risk associated with radiation was estimated to be 1.2. This magnitude of relative risk from the Swedish study was slightly lower than that previously reported from the United Kingdom Cancer Research Campaign (CRC) trial, in which the relative risk associated with treatment for left-sided tumours showed a twofold excess over that for right-sided tumours (2.26 versus 1.20) [H2]. However, in the latter study, the relative risk associated with orthovoltage radiation was higher (1.86) than that with megavoltage techniques (1.27). The Swedish relative risk value was similar to the value reported from the CRC trial for cardiac death associated with supervoltage radiation (1.35 for left-sided tumours).

60. Analysing mortality data for 89,407 women aged 18–79 years with unilateral breast cancer in Sweden between 1970 and 1996, Darby et al. [D5] reported an increased relative risk of death from cardiovascular disease (RR = 1.10) occurring more than 10 years after treatment (table 7). No information was available regarding the specific radiation techniques used, but most of the cardiovascular deaths involved women treated for breast cancer in the 1970s. For women treated in the 1980s, when radiation

Table 7 Breast cancer laterality studies

Study and year	*Number of breast cancer patients, years treated and country*	*Follow-up duration (years)*	*Treatment, breast tumour dose (Gy)*	*Heart disease*	
				Number of deaths or cases	*Relative risk (left- versus right-sided breast cancer)*
Mortality follow-up					
Paszat et al., 1998 [P1]	206 523 women 1973–1992 United States	Mean 6.2	1973–1982, adjuvant radiotherapy; 1983–1992, mostly post-lumpectomy radiotherapy	Total 361, aged 60+, 1973–1982; Total 125, aged 20–59, 1973–1982; Total 218, aged 60+, 1983–1992; Total 19, aged 20–59, 1983–1992	RR = 1.98 for age 20–59, 1973–1982; RR = 1.17 for age 60+, 1973–1982 (NS); RR = 1.02 for age 60+, 1983–1992 (NS)
Rutqvist and Johansson, 1990 [R3]	54 617 women 1970–1986 Sweden	Median 9; range 1–17	Usually supervoltage technique	1 803 (left) 1 566 (right)	RR (myocardial infarction) = 1.09
Darby et al., 2003 [D5]	89 407 women 1970–1996 Sweden	<10 10+	Unknown	5 739 3 426	RR (all cardiovascular disease) = 1.01 (95% CI: 0.96, 1.07) at <10 years, 1.10 at 10+ years after diagnosis
Nixon et al., 1998 [N2]	745 women 1968–1986 United States	Maximum 12	Breast-conserving surgery plus megavoltage, tangential; typically 45–50	Total 18 (9 left-sided; 9 right-sided)	RR (cardiac death) = 1.04 (NS)
Rutqvist et al., 1998 [R4]	684 women 1976–1987 Sweden	Mean 9; range 3–16	Breast-conserving surgery plus tangential photon field; 46–54 (96%), 10–16 (1.9%)	Total 12 (7 left-sided; 5 right-sided)	RR = 0.86 (NS)
Vallis et al., 2002 [V1]	2 128 women 1982–1988 Toronto, Canada	Median 10.2; range 7.7–15.1	Post-lumpectomy radiotherapy (coplanar tangential); typically 40	Total 49 (26 left-sided; 23 right-sided)	RR = 1.1 (NS), all ages; RR = 1.6 for age <60; RR = 0.9 for age 60+
Paszat et al., 1999 [P2]	3 006 women 1982–1997 Ontario, Canada	Median 8.8	Post-lumpectomy radiotherapy; mean 43	Total 74 (44 left-sided; 30 right-sided)	RR = 2.10 (all ages); RR = 8.76 (age 60+ versus 20–59)
Giordano et al., 2005 [G8]	27 283 women 1973–1988 United States	15		Not available	All patients (in situ, localized, regional disease): RR = 1.28 (13.1% versus 10.2%) for 1973–1979; RR = 1.08 (9.4% versus 8.7%) (NS) for 1980–1984; RR = 1.04 (5.8% versus 5.2%) (NS)
Morbidity follow-up					
Patt et al., 2005 [P7]	16 270 women (8 363 with left-sided breast cancer) 1986–1993 United States	mean 9.5; range 0–15	Primary surgical therapy and adjuvant radiotherapy	Total: Ischaemic heart disease (825 left-sided; 769 right-sided)	Hazard ratio = 1.05 (NS)

Figure VII. Probability of death from myocardial infarction in women of all ages (upper panels) and in women aged 20–59 years or 60+ years (lower panels) with cancer of the left or right breast who received adjuvant radiotherapy or no radiotherapy [P1]



doses to the breast were presumably lower, the relative risk was still elevated (1.1), but had a wide confidence interval.

61. Several studies (discussed below) attempted to assess the risk of myocardial infarction specifically associated with radiotherapy given after conservative surgery of the breast. The results are mixed. An absence of significantly increased relative risk of myocardial infarction following radiotherapy treatments for left- versus right-sided breast cancer has been reported by: Nixon et al. [N2], who followed 745 breast cancer patients in Boston, United States, for up to 12 years; Rutqvist et al. [R4], who followed 684 Swedish breast cancer patients from 3 to 16 years; and Vallis et al. [V1], who followed 2,128 breast cancer patients in Toronto, Canada, for about 8 to 15 years (table 7). The numbers of cases with myocardial infarction in these studies are generally small (fewer than 50).

62. An increased risk of myocardial infarction was reported from another study by Paszat et al. [P2], which included 3,000 breast cancer patients in Ontario, Canada, with a record of lumpectomy as maximal breast surgery and a record of post-lumpectomy radiotherapy. The relative risk of mortality from myocardial infarction for women who received post-lumpectomy radiotherapy for a left-sided cancer was 2.10 (95% CI: 1.11, 3.95) compared with those with right-sided cancer (table 7). The increased likelihood of mortality from myocardial infarction among the left-sided breast cancer patients was significant among women aged 60 years and older (table 7). There is an overlap in the breast cancer patients included in this study and the one by Vallis et al. [V1] cited above, which did not find an increased risk of myocardial infarction. While the subjects in the [P2] study were identified from a province-wide registry, the [V1] study included patients seen at a specialized

cancer centre. The patients included in the [V1] study had carcinoma in situ as well as invasive cancers and tended to be younger. Thus there may have been some differences in cardiac dose or dose volume between the two series of breast cancer patients.

63. More recently, Giordano et al. [G8] followed 27,283 women treated with adjuvant radiation for breast cancer identified from the SEER programme in the United States. These patients were stratified into three subcohorts on the basis of the year of diagnosis: 1973–1979, 1980–1984 and 1985–1989. To ensure an equal time of follow-up for the different subcohorts, follow-up was censored at 12–15 years. Among the women diagnosed between 1973 and 1979, there was a statistically significant difference in the 15-year mortality from ischaemic heart disease between patients with left-sided (13.1%) and right-sided (10.2%) breast cancer. No significant difference was found for women diagnosed between 1980 and 1984 (9.4% versus 8.7% for left- and right-sided, respectively) or between 1985 and 1989 (5.8% versus 5.2% for left- and right-sided, respectively). Thus the differences in rate for women with left- and right-sided breast cancer have diminished with time, but continued follow-up will be necessary to determine whether excess cardiovascular mortality disappears completely [C11, G8].

64. Also using the SEER database, Patt et al. followed 16,270 women with breast cancer who received adjuvant radiotherapy during 1986–1993 [P7]. The subjects were followed for up to 15 years by linkage to the Medicare database. This database provides morbidity information from hospitalization for individuals aged 65 years and older, but the completeness of coverage is not clear. No significant differences were found in left- versus right-sided breast cancer patients for hospitalization for ischaemic heart disease (9.7% versus 9.6%) or other heart disease, with the age-adjusted hazard ratios for ischaemic heart disease being 1.05 (95% CI: 0.94, 1.16).

65. Data on cardiac risks following breast cancer radiotherapy have also been reviewed by Taylor et al. [T3] and Prosnitz et al. [P9]. Both reviews concluded that modern radiotherapy techniques for breast cancer have reduced radiation exposure to the heart, but it is not clear whether current regimens are free from cardiac risks. Taylor et al. pointed out that none of the observational studies (mostly laterality studies) of breast cancer patients receiving radiotherapy have attempted to reconstruct dosimetric calculations for dose–response analysis for heart disease.

66. Subclinical vascular abnormalities have also been observed following thoracic irradiation. In breast cancer patients treated with modern radiotherapy, myocardial perfusion scintigraphy studies demonstrated perfusion defects to occur more frequently for left- than for right-sided breast cancers up to 18 years after radiotherapy [G9]. The frequency of perfusion defects was correlated with the volume of the left ventricle exposed to the radiation field, as these defects occurred in 25% of patients who had from 1 to 5% of the left ventricle in the tangent field compared with 55% of patients with >50% of the left ventricle in the field [M15]. The clinical significance of perfusion defects is unclear, but the findings suggest that subtle cardiac injury may still occur even with modern techniques [P8].

4. Testicular seminoma patients

67. About 15–25% of patients with stage I seminoma have metastases to the drainage lymphatics, and are treated with elective irradiation to the lumbar periaortic and ipsilateral ilioinguinal lymph nodes. Some patients are given bilateral pelvic irradiation. Previously, elective irradiation frequently was given to the mediastinum and supraclavicular areas of stage I patients, and elective mediastinal irradiation was administered to most patients with stage II disease. Currently, for patients with stage I disease, megavoltage irradiation is recommended using daily doses of 1.8–2 Gy, for a total of 20–25 Gy over 2–3 weeks, to the primary zone of nodal drainage in the lumbar and periaortic and ipsilateral ilioinguinal regions. When elective mediastinal irradiation is administered, 20 Gy is given over 2–3 weeks. For patients with stage II seminoma with metastases in lymph nodes below the diaphragm, irradiation is similar to that used in stage I patients, but the dose is increased to 30–40 Gy over 4–5 weeks. Elective mediastinal irradiation is administered to all stage II B patients [W3].

68. Early data from irradiated seminoma patients showed variable findings regarding heart disease risk [B6, P3, W4]. A more recent study of 124 patients with seminoma treated between 1968 and 1984 reported an increased risk of heart disease after mediastinal irradiation [L2]. Of the 124 patients, 57 had mediastinal as well as infradiaphragmatic irradiation, while others had treatment limited mostly to the infradiaphragmatic field only. The median dose to the mediastinum among the patients was 2.4 Gy. Four patients, all in the group that received mediastinal irradiation, developed heart disease (three with myocardial infarction or related heart disease and one with constrictive carditis), and two died from sudden death thought to be of cardiac origin. No cardiac disease was observed in the group not treated with mediastinal irradiation.

69. Huddart et al. [H8] analysed long-term risks of cardiovascular disease in a larger follow-up (up to 20 years) study of 992 testicular seminoma patients (390 with chemotherapy only, 130 with chemotherapy and radiotherapy, 230 with radiotherapy and 242 with surveillance only) treated between 1982 and 1992 at the Royal Marsden National Health Service Trust in the United Kingdom [H8]. The relative risk of cardiac events (myocardial infarction, angina or related cardiovascular episode) was significantly elevated (RR = 2.40) among patients treated with radiotherapy, with or without chemotherapy, compared with the reference surveillance group. No significant differences were found in smoking behaviour or cholesterol levels

between different treatment groups, but patients receiving radiotherapy and chemotherapy had a higher frequency of history of hypertension than the surveillance group. On the basis of computed tomography scans in six patients, the mean cardiac dose was estimated to be 0.76 Gy (range: 0.54–1.35 Gy), with a mean maximum cardiac dose of 3.36 Gy (range: 0.82–14.1 Gy), and on average 14% of the cardiac volume received a dose of 0.9 Gy or more, indicating that direct cardiac irradiation was uncommon. Only 30 patients received mediastinal irradiation, while the majority of the remaining patients received infradiaphragmatic radiotherapy. The risk of cardiovascular disease remained elevated after excluding patients who had mediastinal irradiation. These data suggest an elevated cardiac risk associated with partial irradiation and/or low scattered doses, although radiation-induced nephropathy (from infradiaphragmatic irradiation) could be an alternative explanation for the excess heart disease risk. This finding, however, is at odds with a more recent study of a larger cohort of 2,512 5-year survivors of testicular cancer in the Netherlands [V3]. After a medical follow-up of 18.4 years, 694 cardiovascular events occurred, including 141 acute myocardial infarctions. Mediastinal irradiation was associated with a 3.7-fold increase in myocardial infarction risk compared with surgery alone, but infradiaphragmatic irradiation was not associated with an increase in myocardial infarction risk.

5. Dose response and factors affecting risk

70. Dose–volume histograms and "normal tissue complication probability" models have been used to describe the cardiac response to irradiation. In these models, an organ is thought to consist of multiple functional subunits arranged serially or in parallel. For serially structured organs, such as the gastrointestinal tract or nervous tissue, damage to one portion of the organ may render the entire organ dysfunctional [H5]. In organs with parallel structure (e.g. lung and liver), damage to a small number of functional subunits may not impair the entire organ function, because the remaining subunits operate independently from the damaged subunits, and clinical injury occurs when a critical volume of the organ is damaged. When the dose distribution is inhomogeneous or when part of the organ is irradiated, the probability of a specific organ response can be estimated by a normal tissue complication probability model [G4]. In the case of the heart, little is known about structures within the heart that are liable to radiation-induced damage. However, dose–response curves have been constructed for radiation-induced heart disease, including coronary heart disease, assuming that the entire heart volume is equally radiosensitive. Applying the relative seriality model to the Stockholm and Oslo randomized trial data, Gagliardi et al. [G3] estimated a threshold dose of 20 Gy for ischaemic heart disease mortality. The serial assumption may not be valid because, as the Hodgkin's lymphoma data suggest (see the section on partial irradiation below), there may be differences in sensitivity to radiation by tissue type and location [H1].

71. In a study of a small number of Swedish breast cancer patients enrolled in a randomized trial of pre- or post-operative radiation therapy (45 Gy over 5 weeks) versus surgery alone [R2], the different radiotherapy techniques used were classified into three groups depending on the calculated dose volume: low (right-sided tangential ^{60}Co fields), intermediate (electron fields) and high (left-sided tangential ^{60}Co fields). The subset of patients who received the highest dose volume had significantly increased risk of death from ischaemic heart disease compared with surgical controls (table 8). Mortality from ischaemic heart disease in the groups with low and intermediate dose volume was similar to that among non-irradiated controls. No other differences were statistically significant. Since the dose and the irradiated heart volume were correlated, it was not possible to determine whether the dose, the volume or both were important for the increased cardiac mortality.

Table 8 Mortality by estimated radiation dose volume in breast cancer patients with adjuvant radiation therapy versus surgery alone

Rates in the table are deaths per 1000 persons per year; absolute numbers of deaths are given in parentheses [R2]

Cause of death	*Surgery alone (n = 321)*	*Radiation therapy: radiation dose volume*			*Trend test*
		Low (n = 164)	*Intermediate (n = 314)*	*High (n = 161)*	
Breast cancer	33.9 (120)	26.1 (51)	25.6 (93)	31.2 (57)	Not significant
Other cancer	4.2 (15)	3.6 (7)	3.6 (13)	1.6 (3)	Not significant
Ischaemic heart disease	2.3 (8)	1.5 (3)	2.2 (8)	7.1 (13)	$p < 0.05$
Other cardiovascular disease	2.8 (10)	2.6 (5)	2.5 (9)	1.6 (3)	Not significant
Other causes	2.5 (9)	2.0 (4)	3.0 (11)	3.3 (6)	Not significant
All causes	45.7 (162)	35.8 (70)	36.9 (134)	44.9 (82)	Not significant

(a) Partial irradiation

72. Gagliardi et al. [G3] reviewed data from two randomized breast cancer trials: the Oslo breast cancer trial of post-operative radiotherapy as an adjuvant to radical mastectomy [H4] and the Stockholm breast cancer trial of adjuvant pre- or post-operative radiotherapy versus surgery alone [R2]. The end points used were mortality from myocardial infarction in the Oslo trial and mortality from ischaemic heart disease in the Stockholm trial. Based on three-dimensional dose distributions reconstructed for different treatment techniques in 10 model breast cancer patients [G3], the dose–response curves were quite similar for different cardiac volumes irradiated (100%, 66% and 33%), suggesting that volume dependence is small.

73. Eriksson et al. [E1] further compared the dose response for heart disease mortality obtained from 157 Hodgkin's lymphoma patients with the five mean dose–volume histograms for breast cancer patients studied by Gagliardi et al. [G3]. The dose–response curve from the breast cancer radiotherapy was much steeper than that from the Hodgkin's lymphoma treatment. This was thought to be due to the different portions of the heart irradiated for the two types of treatment; the typical irradiation geometry for the Hodgkin's lymphoma treatment is almost complementary to that of the breast cancer treatment. These findings suggest the presence of heterogeneity in tissue response to radiation within the heart.

74. Heterogeneity in tissue response was also suggested by the Stanford study of Hodgkin's lymphoma [H1], in which subcarinal blocking was associated with a reduction of the relative risk for non-myocardial infarction from 5.3 to 1.4, but not of the relative risk for myocardial infarction (3.7 versus 3.4). Subcarinal blocking reduces the irradiated volume for the entire heart but does not protect the proximal part of the major coronary arteries from irradiation. This finding, however, is also consistent with possible susceptibility to coronary artery injury at lower radiation doses [H1].

(b) Dose fractionation

75. Cosset et al. [C2] followed 499 patients irradiated for Hodgkin's lymphoma during 1971–1984 at the Institut Gustave Roussy; 75% of the patients were treated using 4 weekly fractions of 2.5 Gy, 6% received 3 weekly fractions of 3 Gy, 16% received 3 weekly fractions of 3.3 Gy, and the remaining patients received an unusual fraction schedule and thus were not analysed. The 5-year cumulative incidence of pericarditis increased significantly with increasing total cumulative dose (4.1%, 5.8% and 10.4% in dose groups 35–37 Gy, 39–41 Gy and 41–43 Gy, respectively). After adjustment for fractionation, the same increasing trend was observed but was no longer significant. Multivariate analysis adjusting for age, sex, mediastinal involvement and type of chemotherapy showed the pericarditis risk to be significantly increased with total doses of 41 Gy or higher and at 3.0 Gy or higher per fraction. Although the cumulative incidence of myocardial infarction in the irradiated patients was significantly increased compared with that in 138 Hodgkin's lymphoma patients without mediastinal radiotherapy, neither a dose nor a fractionation effect could be demonstrated, possibly owing to there being only a small number of events (13 cases of myocardial infarction). The data suggest that dose fractionation may reduce the risk of radiation-induced pericarditis, but the effect of dose fractionation on the risk of coronary heart disease is not clear. In the study of irradiated Hodgkin's lymphoma patients, Reinders et al. [R1] failed to construct the "biologically equivalent dose", accounting for variations in total dose, fraction dose and treatment techniques, as a predictor of ischaemic heart disease risk, but this may have been in part due to the small variation in these parameters.

(c) Age and time

76. The earlier case–control study by Boivin et al. of Hodgkin's lymphoma patients [B1] found the relative risks of myocardial infarction associated with mediastinal irradiation to be homogeneous among subgroups classified by age at diagnosis of Hodgkin's lymphoma (0–39, 40–59 and 60+ years) or by number of years after diagnosis (0–4, 5–9 and 10+ years). However, variations in the radiation-related risk of heart disease were evident in the Stanford Hodgkin's lymphoma data [H1], which included a large number of patients treated at a wide range of ages and follow-up years. Most remarkably, the relative risk of acute myocardial infarction was highest (RR = 44) among those treated at an age of <20 years and decreased significantly with increasing age at treatment (irradiation) (see table 4). The absolute risk, i.e. the excess number of cases per 10,000 persons, increased significantly with increasing age at treatment, reflecting the increasing underlying rate for this disease with increasing age. The relative risk of acute myocardial infarction was already significantly elevated during the first 5 years after the initiation of therapy and remained elevated 20 years or more after treatment, and the risk increased with time after treatment (table 4). Generally similar patterns were observed for the risk of heart disease other than myocardial infarction. The relative risk of heart disease other than myocardial infarction was highest among patients treated at an age of <20 years, decreased significantly with increasing age at treatment (table 4), and increased significantly with increasing years after treatment.

77. Because of the narrow age range of breast cancer patients, ages at irradiation were grouped into two age categories, i.e. <60 and 60+ years, in most studies of breast cancer patients. In the study by Paszat et al. of breast cancer patients who received adjuvant radiotherapy [P1], the relative risk (left-sided versus right-sided breast cancer) of fatal myocardial infarction was significantly elevated for women diagnosed at ages 20–59 years and treated during 1973–1982 (RR = 1.98). The relative risk for women diagnosed at ages 60+ years was elevated but not significantly so. This is in disagreement with the results from another study by Paszat

et al. of the Ontario, Canada, cohort of Hodgkin's lymphoma patients [P2], which reported that the relative risk (left-sided versus right-sided breast cancer) of myocardial infarction after post-lumpectomy irradiation was increased for women diagnosed at age 60+ years (RR = 8.76) but not for women who were diagnosed at <60 years of age.

(d) Smoking and other risk factors

78. Animal studies have provided varying results as to whether general atherogenic risk factors modify the effect of radiation on coronary heart disease. In an early study by Fajardo and Stewart [F3, S15], irradiation of the heart in several hundred rabbits failed to produce coronary heart disease; a high-fat diet was found to be necessary for irradiation to induce atherosclerosis [A4]. However, in dogs, plaques developed with a normal diet [L4]. In general, however, results from these and other studies [A6, B3] are in agreement that the combination of irradiation and a high-fat diet accelerated atherogenesis.

79. Few human data are available on the possible modifying effects of non-radiation risk factors. In the study by Boivin et al. [B1], the relative risks of myocardial infarction after irradiation for Hodgkin's lymphoma did not differ with history of cigarette smoking (yes or no), hypertension, diabetes and previous coronary heart disease. Glanzmann et al. [G5] followed 352 irradiated Hodgkin's lymphoma patients with or without chemotherapy in Zurich, Switzerland, and found the incidence of ischaemic heart disease to be higher than expected in the subgroup with cardiovascular risk factors (18 observed versus 7.60 expected) but not in the subgroup without the risk factors (3 observed versus 3.13 expected).

B. Patients receiving diagnostic radiation or radiotherapy for non-neoplastic diseases

80. Patients irradiated for diagnostic purposes or treatment of non-neoplastic conditions are exposed at doses lower than those treated with radiation for cancer. Among the numerous patient populations in this category that have been studied, populations of special interest are patients with thymic enlargement, mastitis, skin haemangioma, benign gynaecological disorders, tinea capitis and peptic ulcer (see table 1). Most of the study results on circulatory diseases are based on the comparison of observed numbers of events (mostly deaths) with expected numbers derived from the general population (i.e. external comparisons). Very few studies have compared disease rates between irradiated and non-irradiated patients in the cohort (i.e. internal comparisons). Causal inferences of findings from external comparisons alone are problematic because of the possibility that individuals with disease may have underlying disease rates that differ from those of the general population. Certain conditions for which patients were irradiated may also influence the subsequent risk of circulatory disease.

81. Ankylosing spondylitis patients received a total mean cardiac dose of 2.5 Gy, with a 10–90% range of 0.04–4.75 Gy, from a single course of X-ray treatment [L1]. Doses relevant for cerebrovascular disease are not clear but are assumed to be much lower if a mean thyroid dose of 0.99 Gy is used as the surrogate. Cerebrovascular and other circulatory diseases (presumably mostly heart disease) were among the causes of death that originally were considered to be normal among patients with spondylitis (referred to as Class D). The ratios of observed to expected deaths (O/E ratios) from cerebrovascular and other circulatory diseases (based on age-, sex- and period-adjusted mortality rates in England and Wales) were significantly elevated (the O/E ratios were 1.14 for cerebrovascular disease and 1.25 for other circulatory disease) (table 9). The finding was interpreted as not being attributable to the radiation treatment because: *(a)* increased mortality was observed in Class D for many other causes of death, including bronchitis, peptic ulcer, other gastrointestinal disease and violence; *(b)* a similar excess had been observed in another population of non-irradiated spondylitis patients [R7]; and *(c)* the increased risk of Class D diseases was more closely associated with attained age than with time since treatment, i.e. the risk tended to decrease with time. When relative risks were estimated by comparing the O/E ratios for the irradiated spondylitis cohort with those for a separate non-irradiated spondylitis cohort [R7], the calculated relative risks were below unity for cerebrovascular disease (RR = 0.66; 95% CI: 0.40, 1.10) and other circulatory diseases (RR = 0.97; 95% CI: 0.70, 1.33) [M13].

82. Between the 1940s and the 1960s, radiation therapy was frequently used at the University of Chicago, United States, to treat peptic ulcers. Radiotherapy for peptic ulcers consisted of daily fractions of 1.5 Gy given in one or two 6-day to 14-day courses, with a total mean cardiac dose of 2.10 Gy. The heart received scattered radiation, and it was estimated that up to 5% of the heart (the apex) was within the direct irradiation field. In the earlier analysis of mortality data of 3,609 peptic ulcer patients, a significantly increased relative risk of circulatory disease of 1.20 was observed among the irradiated group [G1]. The relative risk was based on the internal comparison of irradiated and non-irradiated patients with peptic ulcer and was adjusted for age, sex and other demographic variables as well as smoking. More recently, Carr et al. conducted an analysis of the dose–response relationship for mortality from coronary heart disease [C12]. Among those who survived 10 or more years after the treatment, the relative risk (adjusted for demographic variables, smoking and other risk factors) increased significantly, from 1.00 for the lowest cardiac dose category (mean volume-weighted dose of 1.6 Gy, with mean in-field dose of 7.6 Gy) to 1.51 for the highest cardiac dose category (mean volume-weighted dose of 3.9 Gy with mean in-field dose of 18.4 Gy) (table 9). There was no indication of a dose response for heart disease other than coronary heart disease. A statistically significant increased relative risk for coronary heart disease of 1.54 was seen for persons with a mean volume-weighted dose

Table 9 Populations receiving diagnostic radiation or radiotherapy for non-cancer diseases

Cohort, country	*Cohort description*	*Dose (Gy)*	*Number of deaths*	*O/E ratio or relative risk*
Heart disease				
Ankylosing spondylitis, United Kingdom [D3, L1]	14 000 patients treated with a single course of X-rays	Heart: 2.49 (mean); 0.04–4.75 (10–90% range)	Circulatory disease other than cerebrovascular disease: 990 observed/794 expected	O/E = 1.25
Peptic ulcer, United States [C12, G1]	1 859 irradiated patients and 1 860 non-irradiated patients (men and women)	Heart: 1.6–3.9 (volume-weighted mean); 7.6–18.4 (assumed 5% in direct X-ray beam)	Coronary heart disease among 10+ year survivors: 551 exposed 546 unexposed	RR = 1 (referent, non-irradiated) RR = 1.00 (1.6 Gy, 7.6 Gy) RR = 1.23 (2.3 Gy, 10.6 Gy) RR = 1.54 (2.8 Gy, 12.9 Gy) RR = 1.51 (3.9 Gy, 18.4 Gy) (volume-weighted mean dose, in-field dose)
Metropathia haemorrhagica, Scotland, United Kingdom [D8, S3]	2 068 women treated with X-irradiation for metropathia haemorrhagica	Bone marrow: 1.34 (mean); 0.07–1.9 (range)	Coronary heart disease: 102 observed/100.9 expected	O/E = 0.70 (<1.25 Gy) O/E = 1.27 (1.25–1.49 Gy) O/E = 1.17 (>1.5 Gy)
Menorrhagia, Manchester, United Kingdom [A1]	2 049 women irradiated for menorrhagia	Ovary: 4.5–5; 12.5–15 (age <40 years)	Coronary heart disease: 44 observed/36.9 expected	O/E = 1.19, not significant
X-ray menopause, Cambridge, United Kingdom [B2]	277 women with X-ray-induced menopause	Pelvis: approx. 7–10	Coronary heart disease: 16 observed/9.68 expected	O/E = 1.65 (p = 0.04)
Cerebrovascular disease				
Ankylosing spondylitis, United Kingdom [D3, L1]	14 000 patients treated with a single course of X-rays	Thyroid: 0.99 (mean); 0–2.06 (10–90% range)	Cerebrovascular disease: 231 observed/202 expected	O/E = 1.14
Circulatory disease				
Metropathia haemorrhagica, Sweden [R15]	788 exposed and 1 219 unexposed women treated for benign bleeding disorders	Ovary: 6	Circulatory system disease: 308 exposed 257 unexposed	O/E = 0.92 exposed O/E = 0.88 unexposed RR = 1.05
New England benign gynaecological disorders, United States [I2]	4 483 women irradiated for benign gynaecological disorders; 10 hospitals in New England, 1925–1965	Bone marrow: 0.53–2.5 (tissue-weighted mean); Lung: 0.04–0.06	Circulatory system disease: 1 685 observed/1 734.6 expected	O/E = 0.8 (0.01–0.25) O/E = 1.0 (0.26–0.50) O/E = 1.0 (0.51–0.75) O/E = 1.0 (≥0.76) O/E = 1.1 (unknown)
Scoliosis, United States [D9]	5 573 women with scoliosis receiving repeated radiographic examinations	Lung: 0.041 (mean)	Circulatory system disease: number not reported	Significant dose response (no data presented)
Massachusetts tuberculosis fluoroscopy, United States [D4]	6 285 patients (men and women) fluoroscopically examined for an average of 77 times; 7 100 unexposed non-irradiatedpatients	Lung: 0.84 (mean);	Circulatory system disease: Number (SMR) Female: 309 (1.0) exposed 440 (1.1) unexposed Male: 517 (1.0) exposed 925 (1.1) unexposed	RR = 0.9 for both women and men (estimated by ratio of SMR for exposed to unexposed)

of 2.8 Gy or in-field dose of 12.9 Gy (to 5% of the heart volume). These relative risk values translate into an excess relative risk of 0.13–0.19 at 1 Gy (volume-weighted dose). It had previously been thought that peptic ulcer patients who were selected for radiotherapy may have had other conditions that made them unsuitable for surgical treatment, e.g. disposition for cardiovascular disease [G1], and that this may have caused the apparent increased rate of heart disease. However, such selection seemed unlikely. If such selection had occurred, the excess risk would have been observed sooner, within 10 years after treatment, and it was not.

83. During the 1930s and 1940s, the uterus and ovaries of female patients were irradiated to treat abnormal uterine bleeding. The conditions involved were mostly hyperplasia of the endometrium, uterine fibroids, endometrial and cervical polyps, and chronic cervicitis; the underlying cause

for many of these lesions was thought to be excessive secretion of oestrogen relative to progesterone from the ovaries. The target organ for radiotherapy was the ovary or uterus. Typical doses for women treated with X-rays were of the order of 6–15 Gy to the ovaries and 0.7–1.3 Gy to the bone marrow. Cardiac doses were not estimated but were presumably very low because the dose dropped sharply with increasing distance from the source and was very low for organs outside of the pelvis or abdomen [I2, I3]. Because the underlying condition (i.e. hyperoestrogenic status) may affect cardiovascular disease rates, a simple comparison of observed numbers of cardiovascular events in irradiated populations with numbers expected from rates in the general population is likely to be an inadequate measure of the risk associated with exposure.

84. Data on mortality from circulatory disease have been reported in several studies of patients with benign gynaecological disorders. Interpretation of the results presented in table 9 and summarized in the next paragraph is difficult because the underlying rates of circulatory disease may be influenced by the presumed hyperoestrogenic condition for which these patients were treated. Cell-killing effects of high-dose irradiation on the ovaries may affect the oestrogenic status, further complicating the assessment of radiation effects.

85. Early studies of women irradiated for gynaecological conditions generally reported mortality from heart disease close to the expected rate, although some studies suggested an increased risk of coronary heart disease after radiotherapy. In the cohort of 2,068 women X-irradiated for metropathia haemorrhagica at three Scottish radiotherapy centres, the observed number of deaths from coronary heart disease (102) was similar to the expected number (100.9) [D8, S3] (table 9). In this study, however, analysis based on internal comparison showed the ratio of observed to expected deaths from coronary heart disease to increase with an increasing bone marrow dose, with borderline significance for trend. The bone marrow dose ranged from 0.7 to 1.9 Gy [S3].

86. In another study of 2,049 women irradiated for menorrhagia at a Manchester (United Kingdom) hospital [A1], the observed number of deaths from coronary heart disease (44) was slightly higher than the expected number (36.9), but the difference was not significant. Radiation doses were not estimated for this group, but are presumed to be similar to those in the Scottish metropathia series. Significant excess mortality from coronary heart disease was found in a study of 277 women who had an X-irradiation-induced menopause in Cambridge, United Kingdom [B2]; 16 deaths were observed when 9.68 were expected (table 9). No internal comparison was carried out. Most of the higher than expected mortality occurred within 5 years after radiotherapy. Women in these series were mostly treated at ages close to their natural menopause, and therefore it was thought unlikely that results were explained by radiation-induced premature menopause.

87. The largest and most recent study of women irradiated for gynaecological disorders was conducted by Inskip et al. It originally involved 4,483 women irradiated at one of 10 hospitals in New England (Massachusetts or Rhode Island), United States, between 1925 and 1965 and followed up until 1985 [I2]. Cardiac doses were not estimated, but lung doses were estimated to be 0.04–0.06 Gy. The observed number of deaths (1,685) from circulatory disease was similar to the expected number (1,734.5) (SMR = 0.97; 95% CI: 0.93, 1.02). SMRs for circulatory disease did not differ with bone marrow dose (table 9). Bone marrow doses ranging from 0.1 to >0.76 Gy in this cohort were somewhat lower than the doses in the Scottish cohort. In a smaller study of patients irradiated for metropathia haemorrhagica in Sweden, the ratio of observed to expected deaths from circulatory disease was slightly higher in the exposed group than the unexposed group [R15]. The broad category of circulatory disease used is a weakness of the data from these two studies.

88. No evidence of excess risk of cardiovascular disease is available from a study of 6,285 tuberculosis patients who received multiple chest exposures to fluoroscopic X-rays at Massachusetts hospitals (fluoroscopy cohorts). Fluoroscopic examinations were given on average 77 times. Doses to the heart were not estimated, but doses to the lungs were estimated to be 0.84 Gy (mean). Doses relevant for cerebrovascular disease were not estimated. The SMRs for circulatory disease in the exposed patients were almost equal to the SMRs for the unexposed patients [D4], with ratios of the exposed to unexposed SMR being 0.9 for both men and women (table 9). However, no dose–response analysis was performed, and the disease category used was broad.

C. Radiologists and radiologic technologists

89. Radiologists were among the earliest occupational groups exposed to excessive amounts of radiation. There are eight cohorts of radiologists and medical radiological personnel documented in the literature: three from the United States (radiologists, army X-ray technologists and radiologic technologists) and one each from Canada, China, Denmark, Japan and the United Kingdom. Of these, published data on mortality from circulatory disease are available from only three studies: United Kingdom radiologists, United States radiologists and United States Army technologists. The published Canadian medical radiation cohort data do not distinguish medical from non-medical workers and thus are reviewed in section D below, together with studies of other radiation workers.

90. The cohort of about 2,700 United Kingdom radiologists, the data for which were most recently updated by Berrington et al. [B4], includes radiologists who worked in the earliest years of radiological practices. Those who worked during 1897–1920 were largely pioneer British

radiologists who were exposed to excessive amounts of radiation. The authors estimated that radiologists in the 1920s and 1930s could have received exposures of 100 roentgens (equivalent to absorbed doses of approximately 1 Gy) each year [B5]. Smith and Doll previously stated that annual exposure in this population was 0.1 Gy before the 1950s and perhaps 0.05 Gy in the early 1950s [S4]. SMRs for specific causes of death were compared for different calendar years of first registration with a radiological society. The comparison indicates the declining levels of radiation exposure among radiologists over time. Compared with the rates of mortality in the general population, significantly lower than expected numbers of deaths from all causes were found among the radiologists (SMR = 0.77) and among those who first registered after 1920. Compared with the mortality rates for Social Class I (professional occupations) males or male medical practitioners, a significant deficit in all-cause mortality was found for the entire group (SMR = 0.94 and 0.92, respectively), and this was primarily driven by the deficit for those who registered most recently (i.e. during 1955–1979) (SMR = 0.69 and 0.68, respectively). The deficit in all-cause mortality appears largely to be due to a deficit in non-cancer mortality, as the numbers of deaths from cancer were generally close to expectation but were higher than expectation among those entering the profession in the early years, especially before 1920. The observed numbers of deaths from circulatory disease were generally close to or lower than expectation (table 10). Compared with the mortality for male medical practitioners, the number of deaths from circulatory disease was significantly lower than expected among those who first registered before 1920 (SMR = 0.79), during 1921–1935 (SMR = 0.83) and most recently (1955–1979) (SMR = 0.59) (table 10). The authors concluded that the absence of an elevated SMR for non-cancer diseases in the earliest radiologists indicated the lack of evidence of a radiation effect.

91. It has been reported elsewhere, however, that general medical practitioners have higher mortality on average, largely from diseases associated with smoking (ischaemic heart disease, respiratory disease and several types of cancer, etc.), when compared with hospital physicians and surgeons; on average general practitioners smoked 37% more cigarettes than did hospital physicians and surgeons [S4]. This complicates the interpretation of SMR values using medical practitioners as the comparison.

92. In the study of United States radiologists, mortality rates were compared between radiologists and other physician specialists (who were considered less exposed to radiation) stratified by different calendar years of entry into their specialty organization. In an earlier analysis of cause-specific mortality data, the authors noted a significant difference in the cardiovascular–renal disease mortality of radiologists (RSNA) and physicians (ACP) compared with that of ophthalmologists and otolaryngologists (AAOO) in the earliest subcohort (1920–1929) and of ophthalmologists in the 1930–1939 subcohort [M2]. Further analysis of mortality data [M3] showed that radiologists had 15% higher mortality from cardiovascular disease than did other physicians (table 10). Interpretation of the findings is difficult. On one hand, the excess cardiovascular disease mortality seen for all cohorts of radiologists tended to argue against radiation effects. On the other hand, survival data showed that the increased mortality from circulatory disease occurred after age 55, as did the increased mortality from cancer [M3], and this was thought to suggest a common factor, such as radiation, for both cancer and cardiovascular disease. These facts clearly illustrate the limitations of the "ecological" nature of both the United States and the United Kingdom radiologist data, owing to the lack of data on individual doses, and emphasize the need for caution in inferring a causal association.

93. Mortality data from a cohort of United States radiologic technologists showed an overall SMR of less than unity for circulatory disease for the entire cohort [M14]. More detailed analyses of ischaemic heart disease and cerebrovascular disease risks by work history were carried out in a subset of this cohort for which data on work history were available from the mail survey conducted in the mid-1980s [H3]. Relative risks of mortality from circulatory-system diseases increased significantly among the technologists who started working in earlier years, when radiation exposure was higher. For both ischaemic heart disease and cerebrovascular disease, the relative risks (adjusted for confounding variables) increased significantly with decreasing calendar year in which the subjects started working as technologists (table 10). There was no association with the cumulative number of years worked for either ischaemic or cerebrovascular disease, but the relative risk of circulatory system diseases and the subset of cerebrovascular disease increased significantly with increasing number of years worked before 1950. In this analysis, the underlying risk was estimated internally using stratified models. Since the year first worked correlated with attained age and calendar year, which also correlated with the underlying rates of circulatory disease, this can induce intrinsic confounding leading to collinearity in extreme situations. This possibility was considered unlikely since similar results were obtained when external rates were used to estimate the underlying rate. The strength of this study is the analysis based on internal comparison, taking into account confounding effects of smoking, alcohol consumption and socio-economic variables. Surrogate measures of radiation exposure based on work history and calendar year of employment are limitations.

94. In the 1946–1974 follow-up study of a smaller cohort of United States Army radiologic technologists, a non-significantly higher frequency of arteriosclerotic and degenerative heart disease was reported among the technologists (4.31%) than among the controls (3.90%) (table 10) [J1]. The 1946–1963 follow-up data of the same cohort had shown a significantly higher than expected number of deaths from respiratory cancer (17 observed versus 10.5 expected), while there was no significant excess of any other cancer, including leukaemia [M4].

Table 10 Radiologists and radiologic technologists

Cohort	*Cohort description*	*Type of disease*			
United Kingdom radiologists [B4]	2 698 male radiologists registered from 1897 to 1979	**Circulatory disease**			
		Year of first registration:	SMR		
			(i)	(ii)	(iii)
		1897–1920	1.03	0.94	0.79**
		1921–1935	0.96	0.96	0.83*
		1936–1954	0.82**	1.03	0.98
		1955–1979	0.41***	0.60***	0.59***
		Expected deaths using rate for: (i) all men in England and Wales; (ii) all Social Class I males; and (iii) all male medical practitioners. *$p < 0.05$; *$p < 0.01$; ***$p < 0.001$			
United States radiologists [M2, M3]	6 500 male radiologists and 3 cohorts of other physician specialists	**Atherosclerotic heart disease**			
		1920–1939:	SMR		
		RSNA (radiologists)	1.15		
		ACP (physicians)	1.00		
		AAOO (ophthalmologists and otolaryngologists)	0.91		
		1940–1969:			
		RSNA	1.15		
		ACP	0.95		
		AAOO (otolaryngologists)	1.06		
		AAOO (ophthalmologists)	0.93		
United States radiologic technologists [H3]	90 284 radiologic technologists (predominantly female)	**Ischaemic heart disease**			
		Year of first work:	Relative risk[a] (number of deaths)		
		<1940	1.22 (116)		
		1940–1949	1.00 (214)		
		1950–1959	0.98 (157)		
		1960+	1.00 (111)		
		Cerebrovascular disease			
		Year of first work:	Relative risk[a] (number of deaths)		
		<1940	2.40 (52)		
		1940–1949	1.54 (54)		
		1950–1959	0.90 (27)		
		1960+	1.00 (32)		
United States Army technologists [J1]	6 560 male X-ray technologists during Second World War and 6 826 controls	**Arteriosclerotic and degenerative heart disease**			
		X-ray technologists	283 (4.3%)		
		Controls	266 (3.9%)		
		Vascular lesions of the central nervous system			
		X-ray technologists	37 (0.6%)		
		Controls	42 (0.6%)		

[a] Age- and time-adjusted.

95. There are three other cohorts of medical radiation workers that have been followed: 27,000 diagnostic X-ray workers in China [W2], 4,100 persons who worked in radiotherapy departments in Denmark [A5] and 12,000 male radiologic technologists in Japan [Y2]. There have been no published data on non-cancer disease from these studies.

D. Radiation workers

96. Studies of nuclear workers and other populations exposed at low doses can provide valuable information on risks of non-cancer disease at levels of dose less than 0.5 Gy. However, there are important limitations. At low doses, the disease risk attributable to radiation may be so small relative to the underlying risk that it may be undetectable. Furthermore, because the underlying disease rates vary by amounts that are greater than the risk related to low-dose exposure, it will be extremely difficult to reject the possibility that any observed difference arises from biases or other factors related to the disease of interest, even in a population large enough for a small risk to be detected. These limitations are well recognized in assessing the risk of cancer at low doses, but they become even more serious in assessing the risk of circulatory diseases. This is because the relative risk of non-cancer disease associated with radiation exposure is expected to be much smaller than the risk of cancer, and because underlying rates of circulatory disease are influenced by numerous lifestyle and socio-economic factors.

97. In the three-country study of combined cohorts of nuclear industry workers from Canada (Atomic Energy of Canada Limited (AECL)), the United Kingdom (Atomic Weapons Establishment (AWE), United Kingdom Atomic Energy Authority (UKAEA) and Sellafield) and the United States (Hanford, ORNL and Rocky Flats), a positive association was found between mortality from circulatory disease and radiation dose (table 11) in the range 0–≥0.4 Gy [C6]. The analysis was adjusted for socio-economic status within the facility as well as for age and other demographic variables. The association with mortality from circulatory disease was observed in three cohorts (AECL, Rocky Flats and Sellafield). Since the information on socio-economic status available for these three cohorts was less detailed than that for the other cohorts in this study, the authors suspected residual confounding by lifestyle factors for which the measure used for socio-economic status was an inadequate proxy. Only limited information was available on smoking and other lifestyle factors for workers in this study, but there was little evidence for an association between cumulative dose and mortality from smoking-related cancers, respiratory disease or liver cirrhosis.

98. Data from the United Kingdom NRRW demonstrated an inverse, though not significant, association between radiation dose (with the dose range comparable to that in the above three-country study) and smoking-related non-malignant diseases, which included coronary heart disease, aortic aneurysm, emphysema and chronic obstructive pulmonary disease (table 11) [M5]. A non-significant inverse association was also found for circulatory diseases not related to smoking.

99. The radiation workers of British Nuclear Fuels Limited (BNFL) plants were included in the NRRW analyses [M5], but mortality and morbidity data for the Sellafield workers, including plutonium workers, were analysed in a separate study [O1]. Compared with the mortality rates for England and Wales, there was significantly higher than expected mortality from ischaemic heart disease among all workers (1,354 observed versus 1,217.7 expected), but the excess was not apparent when compared with the Cumbrian mortality rates. Rate ratios (radiation-exposed to non-exposed) based on internal comparison showed a significant excess mortality from cerebrovascular disease (rate ratio = 1.28), though not from ischaemic heart disease (rate ratio = 0.96), for radiation workers compared with non-radiation workers (table 11). Analysis of mortality data against cumulative external dose showed a significant external-dose-related trend for ischaemic heart disease, but data were not presented. Plutonium workers also had higher mortality from cerebrovascular disease (rate ratio = 1.27), but not from ischaemic heart disease (rate ratio = 1.01), than did non-radiation workers (rate ratio = 1.27). Another separate analysis of mortality data among 470 male Sellafield employees who were involved in the 1957 Windscale accident showed a higher than expected mortality from circulatory disease (SMR = 1.21) and ischaemic heart disease (SMR = 1.28) when compared against the national rates, though not when compared against the Cumbrian rates [M8]. The elevated mortality for circulatory disease and ischaemic heart disease occurred among the workers involved in managing the fire, but was also evident for those not involved. No dose–response analysis was performed.

100. Among the other BNFL sites, analysis of the mortality data of about 14,000 workers at the Springfields uranium production facility demonstrated a significant dose-related trend for cerebrovascular disease when the cumulative external dose was lagged by 10, 15 or 20 years, but not for ischaemic heart disease (table 11). Studies of about 3,200 workers at the Capenhurst uranium enrichment facility and 2,600 workers at the Chapelcross plant showed no significant trends for mortality from ischaemic heart disease or cerebrovascular disease (table 11).

101. Large values for the excess relative risk per unit dose, apparently incompatible with the data from the survivors of the atomic bombings, have been reported for the Canadian National Dose Registry and for Chernobyl recovery operations workers (see table 11). The estimates of ERR for circulatory disease from the Canadian National Dose Registry are 2.3 (90% CI: 0.9, 3.7) Gy^{-1} for males and 12.1 (90% CI: –0.4, 24.6) Gy^{-1} for females [A2]. The authors indicated several sources of uncertainty, including dose estimation and record linkage errors for follow-up. In particular, underestimation of lifetime dose may have occurred

because of the manner in which dosimeter data under a reporting threshold were treated and because of incomplete dose records. It has also been noted that the ERR estimates for "all causes" (ERR = 2.5 Gy^{-1} for males and 5.5 Gy^{-1} for females) were as high as for "all cancer" (ERR = 3.0 Gy^{-1} for males and 1.5 Gy^{-1} for females) and that the ERRs for accidents were strikingly high (ERR = 8.8 Gy^{-1} and 6.1 Gy^{-1} for males and females, respectively). These results, together with the very low standardized mortality ratio for all causes (0.59 Gy^{-1} in males and 0.58 Gy^{-1} in females), raise the possibility of some bias, perhaps related to the ascertainment of deaths [G2].

102. An analysis by Gilbert et al. [G6] of mortality data for workers at the Hanford site, ORNL and Rocky Flats involved a total of about 45,000 monitored workers with mean cumulative doses of 22–41 mGy (table 11). No significant effects of radiation on circulatory disease were found in the combined mortality data. A separate analysis of the mortality data for workers at the Hanford site also found no significant association of radiation dose with circulatory disease [G7]. Two other studies, of workers at the Mound facility and at Rocketdyne/Atomics International, reported only SMRs for circulatory disease [R13, W6] (table 11).

103. More recently, Howe et al. analysed mortality data of United States nuclear power industry workers [H13]. This cohort of 53,698 individuals employed in 15 nuclear utilities in the United States was followed for up to 18 years between 1979 and 1997. Cumulative dose from whole-body radiation was estimated from dose records available at the facilities, supplemented by the dose information maintained by the United States Nuclear Regulatory Commission and the United States Department of Energy. While the analysis using dose categories revealed no significant trends for circulatory disease (table 11) or arteriosclerotic heart disease, linear analysis indicated a strong significant association between radiation dose and circulatory disease, which was driven primarily by the association for arteriosclerotic heart disease. The ERR was 8.32 (95% CI: 2.30, 18.2) Gy^{-1} for circulatory disease and 8.78 (95% CI: 2.10, 20) Gy^{-1} for ischaemic heart disease. These estimates were higher than those from the LSS data, although the ERR estimates for leukaemia and solid cancer from this cohort were comparable to the LSS data. The authors pointed out that an artificially high or low ERR estimate may have resulted from outliers, and emphasized that caution is needed when interpreting the results.

104. Incidence data from the first 11-year follow-up (1986–1996) of the Chernobyl liquidators showed large risks for some non-cancer disease categories [I1]. The ERRs were not significantly elevated for diseases of the circulatory system, hypertensive disease or ischaemic heart disease. However, significantly elevated relative risks were found for essential hypertension (ERR = 0.52; 95% CI: 0.07, 0.98 Gy^{-1}) and cerebrovascular disease (ERR = 1.17; 95% CI: 0.45, 1.88 Gy^{-1}). Furthermore, significantly increased ERRs were observed for many other disease categories, including endocrine and metabolic diseases (ERR = 0.58 Gy^{-1}), mental disorders (ERR = 0.40 Gy^{-1}) and diseases of the nervous system and sensory organs (ERR = 0.24 Gy^{-1}). Incidence data derived from health examinations are liable to potential bias. The authors also noted that psychological and emotional stress immediately after the accident was especially strong among these liquidators. The exceedingly large risks for many different disease categories are consistent with the possible presence of bias and confounding effects. Without consideration of lifestyle and other factors, the causal nature of the apparent excess risks is currently unclear. Cardiovascular and cerebrovascular data were recently updated up to the end of 2000 [I5]. ERR estimates were 0.41 Gy^{-1} for ischaemic heart disease, 0.45 Gy^{-1} for cerebrovascular disease and 0.36 Gy^{-1} for essential hypertension. These risk estimates were not adjusted for smoking, alcohol consumption, weight and other risk factors.

105. About 9000 male workers employed at the Mayak radiochemical plant during 1948–1972 were followed to the end of 1991 for cardiovascular disease mortality [B12]. The age-adjusted mortality rates for the male workers were lower than the general population rates ("controls" in table 11), possibly reflecting the healthy worker effect. Among the Mayak workers, the age-adjusted rates for those exposed to gamma irradiation of greater than 1 Gy were not significantly different from the rates for those with less than 1 Gy (table 11).

106. Although doses from inhaled radon and radon decay products to cardiovascular organs are very low, data from a study of miners in Newfoundland, Canada, showed an association between mortality from coronary heart disease and radon exposure [V2]. This involved 1,772 underground miners and 352 surface workers employed at two fluorspar companies. The relative risk of coronary heart disease mortality adjusted for smoking habits increased with cumulative radon exposure (table 11), but the trend test was of borderline significance ($p = 0.09$). The coronary heart disease risk also decreased with increasing duration of exposure (employment), suggesting the possible influence of the healthy worker effect. Results from other miner populations with radon exposure are also mixed. No associations with radon exposure were found for circulatory disease in the French or Czech miners [T4, T5]. The joint effects of radon and arsenic exposures on circulatory disease mortality found in Chinese tin miners were difficult to interpret, since radon exposure tended to increase the risk while arsenic exposure tended to decrease the risk. In a large cohort study of 59,000 miners employed between 1946 and 1989 at a uranium mine in Wismut, Germany, 5,417 deaths from circulatory disease (3,719 from heart disease and 1,297 from cerebrovascular disease) were identified in a follow-up to the end of 1998 [K9]. Exposure to radon and its progeny, external exposure to gamma radiation and long-lived alpha emitters were estimated by a job–exposure matrix. No significant trend was found in the mortality risk of all circulatory diseases in relation to cumulative exposure to radon, external gamma radiation or long-lived radionuclides.

Table 11 Findings on circulatory diseases in studies of radiation workers

Study	*Cohort*	*Exposure characteristics*	*Follow-up duration (years)*	*Radiation dose or exposure*	*Circulatory disease statistic (number of cases)*	*Comments*
Nuclear workers in Canada, the United Kingdom and the United States [C6]	95 673 workers (AECL, Sellafield, UKAEA, AWE, Hanford; Rocky Flats, ORNL)	Recorded exposures to external radiation: mean cumulative dose, 0.04 Gy	23.7 (mean)	Cumulative dose (mGy) <10 10–<20 20–<50 50–<100 100–<200 200–<400 ≥400	Circulatory disease O/E (deaths): 1.01 (4 689) 0.93 (908) 0.97 (954) 0.96 (487) 1.01 (372) 1.11 (313) 1.07 (132) Trend $p = 0.045$	Positive association observed in Rocky Flats, Sellafield and AECL cohorts where information on socio-economic status was least detailed; suggestion of residual confounding, but little evidence of smoking and alcohol strongly associated with cumulative dose
NRRW, United Kingdom [M5]	124 743 monitored workers exposed in nuclear power plants and in fuel processing and research facilities (AWE, BNFL, CLRC, MOD, MRC-RBU, NRPB, Nuclear Electric, Magnox Generation, Nycomed Amersham, PMS, RRA, Scottish Nuclear, UKAEA)	Recorded exposures to external radiation: mean cumulative dose, 0.03 Gy		Cumulative dose (mGy) <10 10–<20 20–<50 50–<100 100–<200 200–<400 ≥400	Smoking-related non-malignant diseases — heart disease, aortic aneurysm, respiratory disease O/E (deaths): 1.00 (1 888) 0.99 (477) 0.99 (698) 1.00 (431) 0.93 (288) 1.15 (244) 0.90 (102) Trend: NS	
Sellafield [O1]	10 382 monitored workers employed during 1947–1975	Recorded exposures to external radiation	29.0		Rate ratio: radiation-exposed versus non-exposed (deaths), trend: IHD: 0.96 (371), NS CVD: 1.28 (111), $p < 0.05$	Significant positive trend with external cumulative dose for IHD (data not published)
Sellafield plutonium workers [O1]	5 203 workers monitored for plutonium exposure	Monitored for plutonium by urine samples			SMR (deaths), trend: IHD: 110 (498), $p < 0.05$; CVD: 127 (137), $p < 0.01$	

Study	*Cohort*	*Exposure characteristics*	*Follow-up duration (years)*	*Radiation dose or exposure*	*Circulatory disease statistic (number of cases)*	*Comments*
Chapelcross [M11]	2 628 monitored workers employed during 1955–1995	Recorded exposures to external radiation: mean cumulative dose, 0.0836 Gy	24.3	Cumulative external dose (mGy)	O/E (deaths):	ERR (95% CI) estimates: IHD: 0.51 (-0.81, 2.54) Gy^{-1} CVD: -0.96 (<-2.95, 2.34) Gy^{-1}
					IHD / CVD	
				<10	0.99 (27) / 0.75 (6)	
				10–<20	1.25 (20) / 1.23 (4)	
				20–<50	1.11 (35) / 1.57 (11)	
				50–<100	1.07 (38) / 0.97 (8)	
				100–<200	0.70 (23) / 1.04 (9)	
				200–<400	1.03 (33) / 0.72 (6)	
				≥400	0.86 (5) / 0.71 (1)	
					Trend: NS / Trend: NS	
Springfields uranium production [M12]	13 960 monitored workers employed during 1946–1995	Recorded exposures to external radiation: mean external cumulative dose, 0.0228 Gy	24.6	Cumulative external dose (mGy)	O/E (deaths):	
					IHD / CVD	
				<10	1.02 (513) / 1.08 (144)	
				10–<20	1.01 (207) / 1.06 (62)	
				20–<50	0.96 (273) / 0.85 (71)	
				50–<100	0.98 (136) / 0.80 (30)	
				100–<200	1.10 (58) / 1.23 (16)	
				200–<400	0.77 (4) / 1.94 (2)	
				≥400	0.00 (0) / 8.00 (2)	
					Trend: NS / $p < 0.05$	
					(10-, 15- and 20-year lag)	
Capenhurst uranium enrichment [M7]	3 244 monitored workers employed during 1971–1991	Recorded exposures to external radiation: mean external cumulative dose, 0.0098 Gy	26.7	Cumulative external dose (mGy)	O/E (deaths):	
					IHD / CVD	
				<10	0.98 (143) / 0.87 (23)	
				10–<20	1.22 (32) / 1.45 (7)	
				20–<50	1.10 (31) / 1.27 (5)	
				50–<100	0.57 (5) / 0.76 (1)	
				100–<200	0.35 (1) / 3.70 (1)	
				200–<400	1.15 (1) / 0.00 (0)	
				≥400	0.00 (0) / 0.00 (0)	
					Trend: NS / NS	

Study	*Cohort*	*Exposure characteristics*	*Follow-up duration (years)*	*Radiation dose or exposure*	*Circulatory disease statistic (number of cases)*	*Comments*
Canadian National Dose Registry [A2]	206 620 monitored workers, including dental, medical, industrial and nuclear power plant workers	Recorded exposures to external radiation: mean cumulative dose, 0.06 Gy	13.8 (mean)		Circulatory disease O/E (deaths): Male: 0.61 (1 708), NS; Female: 0.49 (243), NS	ERR (% for 10 mGy) for circulatory disease: Male: 2.3 (95% CI: 0.9, 3.7) Female: 12.1 (95% CI: -0.4, 24.6)
Hanford, ORNL and Rocky Flats [G6]	44 943 monitored workers: Hanford: 32 643 ORNL: 6 348 Rocky Flats: 5 952	Recorded exposures to external radiation: mean cumulative dose, Hanford: 0.026 Gy ORNL: 0.022 Gy Rocky Flats: 0.041 Gy		Cumulative external dose (mGy) <10 10–<50 50–<100 100–<200 200–<400 ≥400	Circulatory disease O/E (deaths): 1.03 (2 719) 0.92 (846) 0.92 (143) 0.93 (99) 1.02 (78) 1.53 (22) Trend: NS	
Hanford [G7]	37 971 monitored workers employed during 1944–1978	Recorded exposures to external radiation: mean cumulative dose, 0.0233 Gy		Cumulative external dose (mGy) <10 10–<50 50–<100 100–<200 ≥200	Circulatory disease O/E (deaths): 1.03 (2 193) 0.92 (642) 0.91 (102) 0.91 (76) 1.05 (81) Trend: NS	
Mound facility [W6]	3 229 monitored workers	Recorded exposures to external radiation: mean cumulative dose, 0.0297 Gy			SMR for circulatory disease (deaths), trend: 0.82 (149), NS	
Rocketdyne/Atomics International [R13]	4 563 monitored workers	Recorded exposures to external radiation: cumulative doses, 0–0.2 Gy			SMR (deaths), trend: Circulatory disease: 0.63 (356), NS; ASHD: 0.56 (223), NS; Vascular lesions of CNS: 0.57 (33), NS	

Study	*Cohort*	*Exposure characteristics*	*Follow-up duration (years)*	*Radiation dose or exposure*	*Circulatory disease statistic (number of cases)*	*Comments*
Nuclear power utilities, United States [H13]	53 698 workers in 15 nuclear power utilities	Recorded exposures to external radiation: mean cumulative dose, 0.0257 Gy	13 (mean)	Dose (mGy) <1 1–<50 50–<100 ≥100	Relative risk (deaths): ASHD / CNS lesions 1.00 (141) / 1.00 (9) 0.70 (72) / 1.89 (4) 1.76 (20) / 3.27 (0) 1.65 (15) Trend: NS / Trend: NS	ERR (95% CI): circulatory disease: 8.32 (2.30, 18.2) Gy^{-1}; ASHD: 8.78 (2.10, 20.0) Gy^{-1}; vascular lesions of CNS: -2.05 (<-2.06, 353) Gy^{-1}
Chernobyl recovery operations workers, Russian Federation [I1, I5]	61 017 workers participating in clean-up work after the Chernobyl accident	Assessed external radiation doses, 0.109 Gy (mean)	14		IHD (10 942); CVD (12 832)	ERR (95% CI): IHD: 0.41 (0.05, 0.78) Gy^{-1}; CVD: 0.45 (0.11, 0.80) Gy^{-1}
Mayak workers [B12]	15 601 persons monitored for external radiation	Recorded doses for external radiation: lung, 3.8–35 Gy		Total external gamma irradiation (mGy): 0 (controls) >0–<1 000 ≥1 000	CVD mortality (age-adjusted): 513.3 ± 36.1 497.4 ± 18.0 504 ± 25.7	
Fluorspar miners, Newfoundland, Canada [V2]	1 772 underground and 352 surface workers employed at fluorspar companies between 1933 and 1960; cumulative exposure, 379 WLM	Internal exposure to inhaled radon and its decay products	To 1985	Cumulative radon exposure (WLM) 0 >0–<250 250–<500 500–<1 000 ≥1 000	CHD relative risk 1.0 0.90 1.12 1.57 1.46 Trend $p = 0.09$	
Uranium miners, France [T4]	1 785 uranium miners with underground mining experience between 1946 and 1972	Internal exposure to inhaled radon and its decay products	To 1985	Total cohort First exposure 1946–1955 First exposure 1956–1972	Circulatory disease SMR (number of deaths) 0.85 (69) 0.87 (40) 0.82 (29)	
Uranium miners, Czech Republic [T5]	4 320 male uranium miners, West Bohemia	Internal exposure to inhaled radon and its decay products	25 (mean)		779 deaths from circulatory disease other than rheumatic heart disease; O/E = 1.16	No significant trend with cumulative radon exposure

Study	*Cohort*	*Exposure characteristics*	*Follow-up duration (years)*	*Radiation dose or exposure*	*Circulatory disease statistic (number of cases)*	*Comments*
Tin miners, China [X1]	17 143 tin miners	Internal exposure to inhaled radon and its decay products	NA		CHD (47 deaths); CVD (302 deaths)	Significant joint effects of radon and arsenic exposure
				Radon exposure	CHD relative risk	
				Low (referent group)	1.0	
				Medium	0.8	
				High	1.7	
				Radon exposure	CVD relative risk	
				Low (referent group)	1.0	
				Medium	1.1	
				High	1.3	
Uranium miners, Wismut, Germany [K9]	59 001 male uranium miners, employed between 1946 and 1989	Cumulative exposure to radon, external exposure to gamma radiation and long-lived alpha particle emitters estimated by a job–exposure matrix	30.5 (mean)		Circulatory disease (5 417 deaths)	
				Radon exposure (WLM)	All circulatory disease relative risk	ERR for 100 WLM = 0.0006 (95% CI: -0.004, 0.006)
				0	1.00	
				>0–100	0.96	
				>100–400	0.93	
				>400–800	0.98	
				>800–1 600	0.92	
				≥1 600	1.11	
				Exposure to long-lived radionuclides (kBq·h/m^3)	All circulatory disease relative risk	ERR for 100 kBq·h/m^3 = -0.02 (95% CI: -0.5, 0.06)
				0	1.00	
				>0–<1.0	0.98	
				1.0–<3.0	1.02	
				3.0–<10.0	0.91	
				≥10.0	0.94	
				Exposure to gamma radiation (mSv)	All circulatory disease relative risk	ERR = -0.26 (95% CI: -0.6, 0.05) Sv^{-1}
				0	1.00	
				>0–<50	0.97	
				50–<100	0.92	
				100–<300	0.95	
				≥300	0.85	

Note: ASHD: arteriosclerotic heart disease; CHD: coronary heart disease; CNS: central nervous system; CVD: cerebrovascular disease; IHD: ischaemic heart disease; NA: not available; WLM: working level month.

E. Survivors of the atomic bombings in Japan

1. Mortality (Life Span Study)

107. In the latest LSS report [P4], deaths from heart disease and stroke together accounted for 58% (8,431) of the 14,459 deaths from all non-cancer diseases (except for diseases of the blood and blood-forming organs) that occurred during the period 1968–1997. The analysis of mortality data from 1968 or later indicated significant linear dose responses for heart disease and stroke. The ERR was 0.17 (90% CI: 0.08, 0.26) Sv^{-1} for heart disease and 0.12 (95% CI: 0.02, 0.22) Sv^{-1} for stroke. Estimated numbers of radiation-related deaths were 101 (2.2%) of the 4,477 deaths from heart disease and 64 (1.6%) of the 3,954 deaths from stroke during the above follow-up period. As described earlier in this annex, detailed analyses of the dose–response curve and the modifying effects of age, sex and time were performed for non-cancer disease mortality as a group [P4, S1] and also specifically for stroke and coronary heart disease [L10] (see section II).

2. Incidence and morbidity data (Adult Health Study)

108. The AHS is a long-term clinical follow-up investigation of a subset of the LSS cohort. This subset consists of 20,000 subjects who have been undergoing biennial health examinations since 1958. Morbidity data and longitudinal clinical data from this study are useful for studies of specific non-cancer diseases and related clinical end points.

109. An increased prevalence of coronary heart disease in proximally exposed survivors was first noted in 1958–1960 [Y1] but was not confirmed by subsequent studies of incidence of stroke and coronary heart disease in the first years (1958–1964) of the AHS follow-up [J2]. Cases were few and radiation doses were not available at that time. The studies of stroke and coronary heart disease continued and the data were updated several times, i.e. to 1974 [R6], to 1978 [K4] and to 1990 (or later) in the latest study, which is currently under way. The latest AHS incidence data from biennial health examination records show a significant quadratic dose–response relationship for myocardial infarction among those exposed at age ≤40 years, with a relative risk of 1.25 (95% CI: 1.00, 1.69) at 1 Sv, although the linear dose response for overall myocardial infarction was not significant [W5, Y3]. It should be noted that the morbidity data described above are based on biennial health examinations and thus may have missed some of the interim events, especially fatal events. Date from surviving cases may have been biased.

110. In an attempt to ascertain all incident cases of cardiovascular disease, additional efforts have been made to identify cases from a variety of AHS and other sources (i.e. self-reported diagnoses, electrocardiograms, death certificates and autopsy reports) and to apply standardized diagnostic criteria. Cardiologists review records to identify cases on the basis of standardized criteria. [R6]. Cases of coronary heart disease were defined as those with evidence of angina pectoris, myocardial infarction or death from coronary heart disease [R6]. The analysis of 288 incident cases of myocardial infarction (163 male and 125 female) that had been ascertained up to the end of 1990 by this intensive search [K5] showed a significant dose response. The relative risk at 1 Sv was estimated to be 1.17 (95% CI: 1.01, 1.36). The association between myocardial infarction and radiation dose remained significant after adjusting for blood pressure and serum cholesterol levels as well as age and sex.

3. Subclinical changes

111. While morbidity or incidence data on clinically overt disease from routine health examinations are prone to potential selection bias, subclinical (asymptomatic) end points or clinical laboratory data are less likely to be affected by selection bias. A number of subclinical cardiovascular changes or precursor lesions have been studied in the AHS cohort. Growth curve models were applied to the analysis of repeated longitudinal cholesterol measurement data among 9800 AHS subjects for the period 1958–1986 [W1]. The growth curves of individual subjects are assumed to vary randomly about a population growth curve, and are appropriate for assessing a radiation effect, taking into account the changing serum cholesterol levels in the Japanese population. For each sex, temporal trends of cholesterol levels were characterized with respect to age, body mass index, city and birth year, and the question was examined as to whether the temporal trends differed by radiation dose. The mean growth curve of cholesterol levels was significantly higher in exposed than in non-exposed subjects. There was no difference in dose response between Hiroshima and Nagasaki, and cigarette smoking did not alter the dose–response relationship.

112. Using similar growth models, Sasaki et al. [S17] found that systolic and diastolic blood pressure levels increased with radiation dose in subjects exposed at young ages (≤16 years), but this trend was reversed in older subjects. A significant quadratic, but not linear, dose response was also found for hypertension diagnosed at the AHS clinical examinations [Y3]. Other end points studied in the AHS cohort include the prevalence of aortic arch calcification [K6], isolated systolic hypertension [K7] and pulse wave velocity [U16], all of which have been found to be associated with radiation.

113. The AHS findings regarding the radiation effects on hypercholesterolaemia and other cardiovascular end points, which are well correlated with each other, offer little insight into a possible role of radiation in the process of atherogenesis, but they are consistent with the possibility of accelerated atherogenesis associated with radiation exposure.

114. A statistically significant association between radiation dose and increased inflammatory responses, as

measured by leukocytosis, accelerated erythrocyte sedimentation rates or acute phase proteins, has been noted in this population for some time [N3, S7]. This association has been re-examined with updated clinical data using various inflammatory response markers. Among 7,463 subjects examined during 1988–1992, the relationship between radiation dose and a series of inflammatory tests (including leukocyte counts, neutrophil counts, erythrocyte sedimentation rate (ESR), α-1 globulin, α-2 globulin and sialic acid) was examined [N4]. ESR is influenced by a variety of serum components, including acute phase proteins, which comprise α-1 globulin and α-2 globulin. Sialic acid is a glycoprotein component related to the surface membrane in the inflammatory process. After allowing for the effect of covariates such as city, age, sex and smoking, radiation dose was found to be associated with increased leukocyte counts per unit bone marrow dose (71.0 mm^{-1} Gy^{-1}), ESR (1.58 mm h^{-1} Gy^{-1}), corrected ESR (1.14 mm h^{-1} Gy^{-1}), α-1 globulin level (0.0057 g dL^{-1} Gy^{-1}), α-2 globulin level (0.0128 g dL^{-1} Gy^{-1}) and sialic acid level (1.2711 mg dL^{-1} Gy^{-1}), though not with neutrophil counts. No confounding effects of the presence of dose-related inflammatory diseases, i.e. clinically detectable chronic thyroiditis or chronic liver disease, were found.

115. Blood samples from 453 Hiroshima study participants between 1995 and 1997, excluding those with a history of cancer or an inflammatory disease, were studied by Hayashi et al. [H6]. C-reactive protein (CRP) levels were associated with age, sex, body mass index and a history of myocardial infarction. After adjusting for these factors, CRP levels increased significantly with bone marrow dose (an increase of about 28% at 1 Gy), as did IL-6 levels, by 9.3% at 1 Gy. CRP is an acute phase reactant that increases during an inflammatory response, and recent epidemiological evidence indicates increased CRP levels as an independent risk predictor for cardiovascular disease [R8, R9]. IL-6, a primary inducer of CRP, has also been found to be a predictor of myocardial infarction.

F. Mechanistic models

1. Microvasculature theory

116. High-dose irradiation is capable of damaging all structures of the heart, including the pericardium, myocardium, valves, conduction system and coronary arteries, as reviewed by Adams et al. [A3]. Histologically, radiation-induced tissue damage is characterized by marked diffuse fibrosis, especially of the pericardium and myocardium [A3, B7, F4, S9]. In an autopsy study of 16 young patients (aged 15 to 33 years) with heart disease who received over 35 Gy and 10 controls, the arterial plaques in patients treated with radiotherapy were largely composed of fibrous tissues, with the media more frequently replaced by fibrous tissues and more focal thickening of the intramural coronary arteries, than in the controls. Radiation-induced microvascular injuries can contribute to late damage of normal tissue. Capillaries are the most radiosensitive component of the vasculature [T2]. In a classic study of experimental radiation-induced heart disease in rabbits by Stewart [S10], electron microscopy studies of changes taking place during the latent stage of disease development indicated changes in endothelial cells of the myocardial capillaries with progressive obstruction of the lumen, resulting in formation of thrombi.

117. The dose–volume histogram and normal tissue complication models described in section IV.A.5 above [B7, S9] are used to describe the pathophysiology for heart disease induced by direct tissue damage from irradiation. These models are primarily applicable to damage from high-dose exposures. On the basis of data from patients treated for Hodgkin's lymphoma, a fractionated dose of 40 Gy was previously considered as a threshold for clinical radiation-induced heart disease [F3, S16]. The extent to which these models can explain heart disease, especially atherosclerotic coronary heart disease induced by low-dose irradiation, is not clear [T2]. It has been suggested [B7, J4] that damage to coronary artery endothelial cells may be a primary event in the pathogenesis of coronary heart disease. Irradiation may cause fibrointimal hyperplasia, which leads to thrombus formation and potentially to lipid deposition. Subtle changes to the blood vessels, such as abnormal vascular permeability, can occur at lower doses (down to 5 Gy) ([U8] p. 626, para. 496).

2. Inflammation theory

118. There have been a number of hypotheses for the pathogenesis of atherosclerosis, which underlies the development of ischaemic heart disease and cerebrovascular disease. Recent evidence suggests that atherosclerotic plaques arise from endothelial injury or dysfunction induced by cardiovascular risk factors and develop through a series of highly specific cellular and molecular responses, which can best be described as an inflammatory process [L3, L6, R10]. Initial endothelial injury may be induced by endotoxins, hypoxia, infection or other agents, but it is generally thought that haemodynamic disturbances and the adverse effects of hyperlipidemia are most important. Among the processes involving lipids in atherogenesis is their oxidative modification by free radicals, yielding oxidized low-density lipoprotein (LDL). Oxidized LDL is taken up by macrophages, contributes to monocyte recruitment and leads to foam cell formation. Fibrous plaques then develop as a growing mass of extracellular lipid with accumulating extracellular matrices derived from smooth muscle cells. Cytokines and growth factors secreted by macrophages and T-cells play multiple roles in this process.

119. Infection by cytomegalovirus and other viruses has recently been linked to atherosclerosis. Infectious organisms may incite a chronic inflammatory process. Another

plausible mechanism is stimulation of smooth muscle cell migration by the virus-coded chemoine receptor [L6]. It has been speculated that radiation-induced genomic instability and/or bystander effects may set off inflammatory responses that may persist for many years [H6, L5, N4].

3. Monoclonal theory

120. It was some 20 years ago that the monoclonal origin of the atherosclerotic lesion was proposed. In studies using the X-linked enzyme glucose-6-phophatase dehydrogenase (G6PD) to determine X chromosome inactivation patterns, aortic media were found to contain a mixed pattern of G6PD expression, whereas most atherosclerotic plaques contained a single isoform of G6PD [B8]. This was interpreted as providing evidence that atherosclerotic plaques arise from single progenitor cells. However, it has not been clear when monoclonal expansion occurs and what cell types give rise to the clone, owing in part to limitations in the G6PD methods [M9]. It was originally suggested that the monoclonal patchiness of atherosclerotic lesions may involve a transformation of smooth muscle cells [L6]. However, recent data indicated that the monoclonal populations result from patches of pre-existing clones of cells [M9, S8]. There is some evidence, however, consistent with oncogene activation, of loss of heterozygosity and microsatellite instability in human lesions [L6].

V. SUMMARY

121. Until recently, the effects of ionizing radiation on diseases other than cancer (non-cancer diseases) had been regarded as having a threshold in the dose response. Threshold doses vary by tissues and other factors, but are below a few grays for clinically evident diseases of the circulatory, digestive and respiratory systems following radiotherapy. Recent data from the follow-up of the LSS cohort of atomic bombing survivors indicated that excess risk of mortality from non-cancer diseases occurs at a level below these threshold doses. The excess risk of fatal non-cancer disease in the LSS was not explained by confounding, selection bias or disease misclassification, to the extent that these factors were evaluated. The effects on several specific non-cancer diseases were also supported in part by morbidity and clinical data from the AHS subset of the LSS population. The primary purpose of this annex was to evaluate epidemiological data on various fatal non-cancer disease outcomes from radiation-exposed populations. The annex specifically focuses on circulatory diseases, as these are among the most common non-cancer causes of disability and mortality in many populations.

122. Although non-cancer diseases have not been the subject of primary interest in major epidemiological studies of populations exposed to radiation at low doses, many of the existing cohort studies are potential sources of data on non-cancer risk. A review of the literature, however, indicated that non-cancer disease data are currently available for only a portion of these cohorts. However, data on circulatory disease mortality are the most frequently reported and are the most informative non-cancer data currently available for assessing the association with radiation exposure. Epidemiological data on other fatal non-cancer diseases are limited. Generally, published non-cancer findings are variable and inconsistent, and interpretation of the results is problematic because of the possible selection of data published, differences in analytical methods used, differences in data quality and, in several studies, the difficulty in dealing with the effects of potential confounders.

123. Radiation-induced heart disease after high-dose radiotherapy for cancer has long been recognized as a medical sequela. It can involve all parts and structures of the heart. Long-term follow-up and randomized trials of patients receiving radiotherapy for Hodgkin's lymphoma or for breast cancer have demonstrated an increased risk of heart disease, including coronary heart disease. Increased risk of heart disease has been linked to mediastinal doses in excess of 40 Gy from early radiotherapy for Hodgkin's lymphoma, but few data exist regarding the risk from the lower-dose radiotherapy currently in use (30–35 Gy for adults and 15–25 Gy for children). Increased risk of heart disease has been linked to breast tumour doses of 40–50 Gy from an early series of post-mastectomy radiotherapy. More recent radiotherapy used for early-stage breast cancer typically exposes up to 5% of the left ventricle to about 25 Gy. Studies show a diminished risk of heart disease associated with modern adjuvant radiotherapy for breast cancer, but longer follow-up is needed because of the persistence of the risk, possibly lasting for more than 3–4 decades, suggested by previous studies. Additional information on the risk for heart disease after low-dose radiotherapy may be expected from studies of patients irradiated for other cancers.

124. Some useful insights into factors that affect radiation-related heart disease risk have also been obtained from high-dose radiotherapy studies. Among the most prominent is the persistence of excess heart disease risk that may span over 3–4 decades, and this is consistent with the data on the atomic bombing survivors. The effects of partial organ irradiation differ from those of whole-organ irradiation, and there may be heterogeneity in response to radiation in different locations of the heart. The radiation-related heart disease risk is strongly related to age at irradiation and is especially high when exposure occurs during childhood or adolescence. Little is known about the possible effects of smoking and other risk factors on the radiation-related risk of heart disease.

125. Patients irradiated for treatment of benign diseases or for diagnostic purposes received much lower doses than cancer patients. In the ankylosing spondylitis patients, who received an estimated mean cardiac dose of 2.5 Gy, the observed numbers of deaths from cerebrovascular and other circulatory diseases were higher than expected from the general population, but the relative risks compared with a separate group of non-irradiated spondylitis patients were not elevated. Detailed dose–response characterization was reported from the follow-up study of patients irradiated for peptic ulcer disease. Coronary heart disease mortality risk adjusted for possible confounders among 10-year survivors increased with increasing cardiac dose ranging from 1.6 to 3.9 Gy (volume-weighted cardiac organ) and from 7.6 to 18.4 Gy (5% of the heart). The elevated risk associated with about 13 Gy to 5% of the heart indicates that excess coronary heart disease risk can occur at doses lower than the 30–40 Gy received from earlier radiotherapy for Hodgkin's lymphoma or breast cancer. A combined study of tuberculosis patients who received multiple fluoroscopic exposures

is of interest as there was a mean cumulative lung (surrogate cardiac) dose of about 1 Gy and the follow-up was for up to 50 years. Circulatory disease (including both cardiovascular and cerebrovascular disease) mortality was not elevated in the irradiated group compared with non-irradiated tuberculosis patients or the general population. No dose–response analysis was performed.

126. Radiologists and other medical radiation workers from the early half of the twentieth century received excessive doses of radiation. Cohort studies of radiologists provide conflicting evidence regarding the radiation effects on mortality due to circulatory disease (including heart and/or cerebrovascular disease). The results from the United States radiologic technologists using work history (e.g. calendar periods or length of employment) as a surrogate measure of exposure provide only indirect evidence regarding radiation effects. The lack of individual dose estimates in these cohorts is a common weakness.

127. Several major studies of occupationally exposed workers at nuclear facilities provide little evidence for increased risk of cardiovascular or cerebrovascular disease related to radiation exposure. Few of the occupational studies have sufficiently controlled for possible confounding effects.

128. Biological mechanisms by which low-dose radiation exposure might increase circulatory disease risks are currently unclear. Although several plausible biological models have been suggested, more research is needed to explore possible mechanisms.

VI. CONCLUSIONS

129. There is an increased risk of circulatory disease associated with high doses to the heart that may be incurred with radiotherapy, but newer treatment techniques resulting in lower cardiac doses have reduced the risk substantially. To date, the evidence for an association between fatal cardiovascular disease and radiation doses in the range of less than 1–2 Gy comes only from the analysis of the data on the survivors of the atomic bombings in Japan. Other studies have provided no clear or consistent evidence of a fatal cardiovascular disease risk at radiation doses of less than 1–2 Gy. It is the judgement of the Committee that, given the inconsistent epidemiological data and the lack of a biologically plausible mechanism, the present scientific data are not sufficient to establish a causal relationship between ionizing radiation and cardiovascular disease at doses of less than about 1–2 Gy. There also are insufficient epidemiological data for constructing appropriate risk models relative to these end points.

130. Circulatory diseases, which are multifactorial and heterogeneous in nature, occur commonly in non-exposed populations. Numerous risk factors, including tobacco use, genetics and cholesterol level, need to be taken into account when attempting to assess the risk associated with radiation. Given the relatively small increase in risk associated with radiation at doses of less than 1–2 Gy, it is uncertain whether epidemiological studies of mortality alone will be able to make a significant contribution to understanding the potential for and the nature of any relationship between circulatory diseases and radiation at these levels of dose.

131. For mortality from diseases other than circulatory diseases and cancer, evidence for an association with radiation at doses of less than about 1–2 Gy also comes only from the atomic bombing survivor data. Studies of other radiation-exposed populations linking other fatal non-cancer diseases to radiation at doses of less than about 1–2 Gy have yielded even less evidence than that which exists for circulatory diseases. For other non-cancer diseases, much less epidemiological information is available than for circulatory diseases, and the evaluation of the causal association is more difficult, owing to the greater heterogeneity in disease aetiology and pathology and the more numerous risk factors involved.

VII. FUTURE RESEARCH

132. Further studies of other irradiated populations are needed. A clear conclusion derived from this epidemiological review is that, apart from the studies of the survivors of the atomic bombings in Japan, there is a lack of data, in terms of both quality and quantity, on non-cancer disease risk. Not only are there few data on non-cancer disease outcomes reported from potentially informative cohorts, but also the disease outcomes addressed by published data are disparate and mostly based on varying methods and analyses not relevant for risk assessment. Individual investigators should be encouraged to revisit non-cancer data available in existing radiation cohorts and to conduct detailed dose–response analysis. A combined analysis pooling non-cancer data from a large number of exposed populations would also be desirable.

133. In future, reporting of epidemiological studies of non-cancer disease end points should include clear descriptions of any limitations of the statistical methods used. Underlying rates for non-cancer disease entities that can be used for risk estimation are quite high, and the indications are that the proportional increase (excess relative risk) per unit dose is low in comparison with that for solid cancers. This reduces the power to detect effects and limits the usefulness and credibility of exposed versus unexposed or external comparisons, because confounding factors are more likely (than for cancer) to distort inference. Vague statements about potential and unspecified confounding factors or bias should be avoided. If an argument is made that an observed association arises because of confounding, it would be useful to provide some indication of the nature and extent of the confounding that could give rise to such an association. The effects of potential bias should be evaluated. Confounding is less likely to markedly bias results from dose–response analyses than from exposed versus unexposed comparisons. Thus, to the extent possible, analyses should make use of doses or dose surrogates, with attention to the effects of uncertainty in these dose estimates on the risk estimates.

134. Mortality data are generally inadequate as the measure of the risk of non-cancer diseases, because of variable case fatality. Incidence or morbidity data are preferred, provided that systematic ascertainment of morbidity data is possible. When using mortality data, consideration should also be given to addressing the effect of disease misclassification on risk estimates. More attention should be given to results for other disease entities, such as digestive or respiratory diseases, in addition to circulatory diseases.

135. To the extent possible, future epidemiological studies should be designed to assess clinical and subclinical end points as well as biomarkers, since this information is more likely to lead to insights useful for developing mechanistic models than simple epidemiological data limited to case counts and rates. Mechanistic leads suggested by the studies of the atomic bombing survivors and others should be tested in other irradiated populations, and radiation-related subclinical changes suggested from therapy experience should be investigated in larger epidemiological cohorts. Laboratory and clinical scientists should be consulted to generate alternative and novel mechanistic hypotheses that can be tested in epidemiological studies.

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