2. Studies of Cancer in Humans

2.1 Introduction

A wealth of information exists about the health consequences of human exposure to ionizing radiation (Committee on the Biological Effects of Ionizing Radiations, 1990 (BEIR V), 1998 (BEIR VIII); ICRP, 1991a; UNSCEAR, 1994; Boice, 1996, 1997; Upton, 1999). Important epidemiological studies of humans exposed to radiation are listed in Table 11. It is from these epidemiological studies that radiation risks are identified and quantified in humans.

Table 9. Main occupational populations exposed to X- and γ-radiation

Population	Major exposure	Individual lifetime dose (mSv)		Collective dose (person–Sv)
		Average	Maximum	
Mayak workers (8800)	External from short-lived fission products, ^{239}Pu inhalation	1300	> 5500	12 000 000
Nuclear workers (86 000, three countries)	External γ-radiation	40	> 500	3800
Chernobyl liquidators, 1986–87 (200 000)	External from fission products	100	Several Sv	20 000
Early radiologists (5000)		–	10 000	–
Bomb testing personnel (70 000)		1–4	–	100–200

From Seltser & Sartwell (1965); Smith & Doll (1981); Robinette *et al.* (1985); Darby *et al*. (1993); UNSCEAR (1993)

Table 10. Main populations of patients exposed to X- and γ-radiation

Disease	Major exposure	Individual dose to critical tissue (Gy)		Collective dose (person–Sv)
		Average	Maximum	
Ankylosing spondylitis	X-radiation to bone marrow	4.4		61 000
Bone-marrow eradication in leukaemia	X-radiation	2	14	–
Haemangioma	Soft X-radiation + ^{226}Ra γ-radiation	0.2	47	2800
Tinea capitis	X-radiation to head and neck	6.8	24	73 000
Mastitis	X-radiation to breast	3.8	14	2 300
Tuberculosis treated by fluoroscopy	X-radiation to chest, breast	0.8	6.4	2 000

From UNSCEAR (1993)

Table 11. Epidemiological studies that provide quantitative estimates of doses of radiation to specific organs and cancer risks

Outcome	Type of exposure	Study population
Cancer mortality	Atomic bombs	Japanese bomb survivors (Pierce *et al.*, 1996)
	Radiotherapy for benign disease	Patients with ankylosing spondylitis (Weiss *et al.*, 1994, 1995)
		Patients with benign gynaecological disorders (Inskip *et al.*, 1990a, 1993; Darby *et al*., 1994)
		Patients with peptic ulcer (Griem *et al.*, 1994)
	Occupation	Nuclear workers (Cardis *et al.*, 1995)
	Diagnostic procedures	Patients with tuberculosis examined by fluoroscopy (Davis *et al.*, 1989; Howe, 1995; Howe & McLaughlin, 1996)
Cancer incidence	Atomic bombs	Japanese bomb survivors (Preston *et al*., 1994; Thompson *et al.*, 1994)
	Radiotherapy for malignant disease	Patients with cervical cancer (Boice *et al.*, 1987, 1988)
		Patients with childhood cancer (Tucker *et al.*, 1987a,b, 1991; Hawkins *et al*., 1992, 1996; Wong *et al.*, 1997; de Vathaire *et al*., 1999a)
		Patients with breast cancer (Boice *et al.*, 1992; Curtis *et al.*, 1992; Storm *et al*., 1992)
		Patients with endometrial cancer (Curtis *et al.*, 1994)
		Patients with Hodgkin disease (Hancock *et al*., 1993; Bhatia *et al.*, 1996)
	Radiotherapy for benign disease	Patients undergoing bone-marrow transplantation (Curtis *et al*., 1997)
		Patients with breast disease (Shore *et al*., 1986; Mattson *et al.*, 1993, 1997)
		Patients with tinea capitis (Ron *et al.*, 1988a,b, 1989, 1991)
		Patients with an enlarged thymus (Shore *et al.*, 1993)
		Patients with enlarged tonsils (Schneider *et al.*, 1993)
		Patients with haemangioma (Lundell *et al.*, 1994; Lundell & Holm, 1995; Lundell *et al*., 1996, 1999)
	Diagnostic procedures	Patients with tuberculosis examined by fluoroscopy (Boice *et al.*, 1991a,b)

From UNSCEAR (1994); Boice (1996); Upton (1999)

The epidemiological studies that provided evidence that ionizing radiation, and X-rays and γ-rays in particular, are associated with cancer in humans are summarized below. The studies are divided into four categories of exposure: that due to military use, to medical use, to occupational exposure and environmental exposure. Not all studies are discussed: the Working Group emphasized those with large numbers, documented exposure and minimum influences of bias or confounding factors. Case reports are not included.

Radiation is unique among other known or suspected carcinogenic exposures in that standing committees have existed for over 50 years that periodically review the human and experimental evidence linking radiation to cancer. Table 11 indicates the wide range of studies, practically all of cohort design, that have provided quantitative estimates of cancer risk in human populations. Studies of both mortality and incidence have been conducted in populations around the world. The single most important investigation, that of the atomic bomb survivors, has been under way for over 45 years and provides quantitative risk estimates for use by committees in setting standards. Most information on the effects of radiation comes from studies of patients treated for malignant or benign conditions, and the most informative study of the medical use of radiotherapy is the International Cervical Cancer Patient Study (Day & Boice, 1984), which involved nearly 200 000 women who were followed for over 40 years. Studies of patients treated for benign conditions, such as ankylosing spondylitis, also provided data on the carcinogenicity of radiation. Studies of diagnostic examinations such as frequent chest fluoroscopies to monitor lung collapse, used in the treatment of tuberculosis, are important sources of information on the effects of fractionation, when a dose is spread over long periods as opposed to a brief period as occurred during the atomic bombings. The doses observed in studies of occupational exposure are much lower than those in studies of medical uses, except those of pioneering radiologists who must have received very high doses, although they were not recorded. As the doses to which most people are exposed occupationally and in the environment are very low, studies of such populations are uninformative for establishing a causal relationship with cancer. The final sections cover issues in quantitative risk assessment and a discussion of the many factors that affect the development of radiation-induced cancer, such as age at exposure.

2.2 Military uses

2.2.1 *Detonation of atomic bombs over Hiroshima and Nagasaki*

The Life Span Study is an on-going study conducted by the Radiation Effects Research Foundation (and its predecessor, the Atomic Bomb Casualty Commission (Shimizu *et al*., 1990)) to investigate the long-term health effects of exposure to radiation during the atomic bombings of Hiroshima and Nagasaki, Japan, in 1945. A number of features make this study a singularly important source of information for assessing the risks associated with exposure to radiation. These include the large size of the exposed population, consisting of both men and women of a wide range of ages who received various doses, long-term follow-up for mortality from and incidence of cancer, well-characterized estimates of the doses received by individual study subjects and the availability of clinical, biological and other information relevant for epidemiological studies. This study has resulted in hundreds of publications which are relevant to understanding various aspects of the effects of exposure to radiation on

human health and has served as the primary source of data for quantitative assessments of the risk due to exposure to ionizing radiation (see also sections 2.6 and 2.7).

The study has a number of limitations which must be considered in interpreting its results. The subjects were all Japanese exposed during wartime, and host and environmental factors may have modified their risk for cancer. In addition, the study sample includes only those still alive five years after the bombings. The effect of this initial selection on the estimated cancer risk is a subject of debate. Although it is known that the dose was predominantly from exposure to γ-radiation, the contribution of neutrons and the yield of the bomb dropped on Hiroshima are uncertain. Although these limitations may affect the estimated magnitude of the risk for radiation-induced cancers and their generalizability to other populations, they do not affect the overall conclusion of an association between exposure to radiation and cancer.

The Life Span Study cohort consists of approximately 120 000 people (UNSCEAR, 1994) who were identified at the time of the 1950 census, and individual doses have been reconstructed. Several versions of the dose estimates have been published (see Overall introduction). The current version, DS86, is available for 86 572 survivors who were in the cities at the time of the bombings, and most of the recent analyses (and all of the results presented here) were limited to this subcohort. Table 12 summarizes the distribution of doses among these subjects. Sieverts are used to express weighted organ doses, while grays are used for exposure (shielded kerma) unadjusted for attenuation by the body. Doses to organs, such as 'marrow dose', are given as weighted doses unless reference is made specifically to γ-rays or neutrons. When no specific type of cancer is mentioned, dose refers to weighted dose to the colon, chosen as representative of a more general dose.

A major strength of the Life Span Study is the virtually complete ascertainment of deaths ensured by use of the Japanese family registration system, known as *koseki*. Follow-up of the cohort began in 1950 and was updated at three-year cycles. The latest published data on mortality from cancer cover the period 1950–90 (Pierce *et al*., 1996). An additional source of information on leukaemia and related haematological disease is the Leukemia Registry (Brill *et al.*, 1962; Ichimaru *et al.*, 1978). It later became possible to analyse cancer incidence by linkage to the Hiroshima and Nagasaki tumour registries (Mabuchi *et al*., 1994; Thompson *et al*., 1994), which allows ascertainment of persons who remained in the two cities. A limitation of these data is that they do not include diagnoses of cancers before 1958 or for persons who migrated from the two cities. The incidences of haematological malignancies and of other cancers (referred to below as 'solid tumours') in 1958–87 have been published (Preston *et al*., 1994; Thompson *et al*., 1994). The main results of the latest analyses of cancer mortality and incidence are summarized below. The modifying effects of age at exposure, sex and time since exposure are addressed in section 2.7.

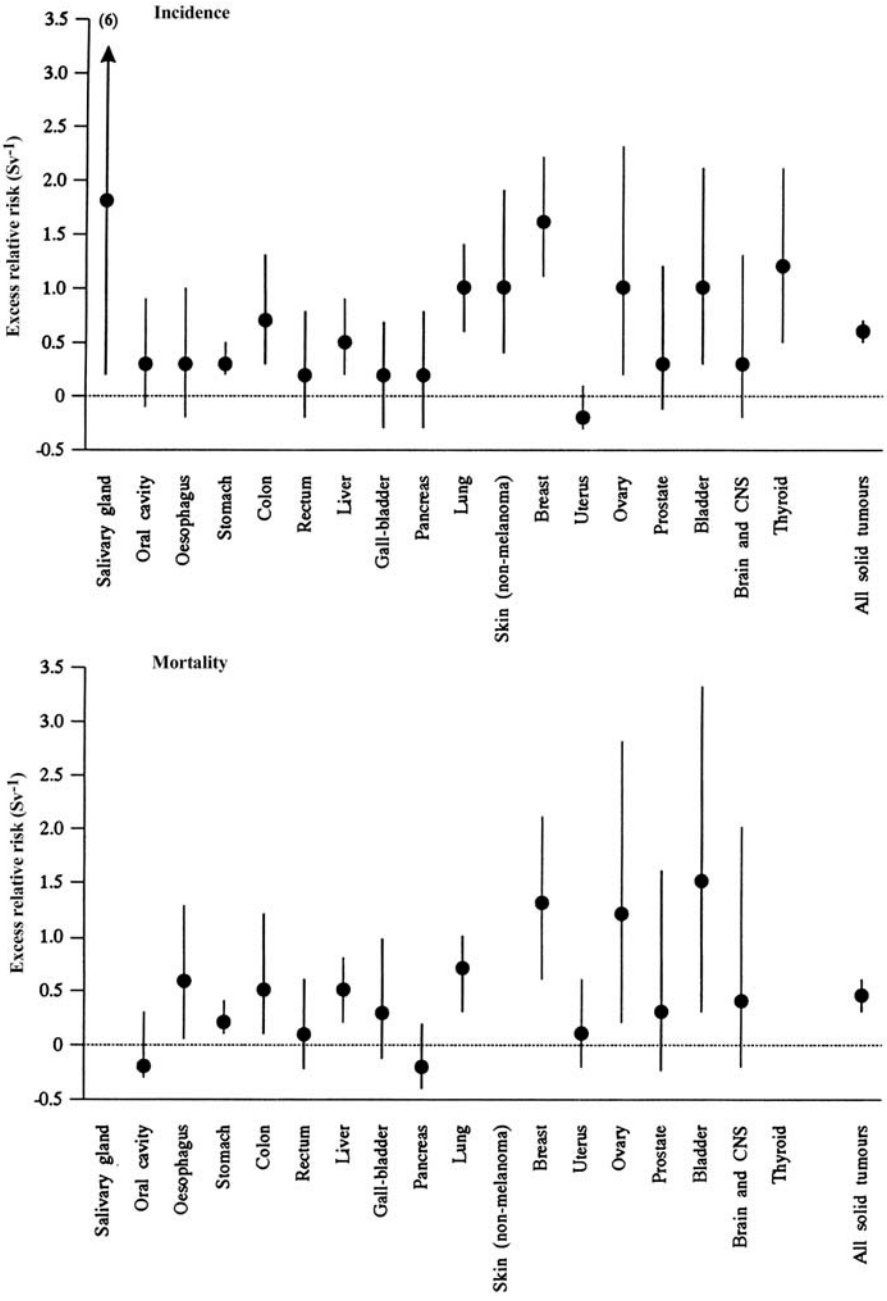
Figure 3 shows the excess relative risk (ERR; relative risk –1) per sievert for each of several cancers and for all solid tumours combined. Slightly more recent results for mortality (1950–90) were reported by Pierce *et al*. (1996); the only change is that the

Table 12. Numbers of subjects by radiation dose and city in the Life Span Study of survivors of the atomic bombings

City	Total no.	DS86 weighted dose to the colon (Sv)								
		< 0.005	0.005–0.02	0.02–0.05	0.05– 0.1	0.1– 0.2	0.2– 0.5	0.5– 1.0	1.0– 2.0	> 2.0
Hiroshima	58 459	21 370	11 300	6 847	5 617	4 504	5 078	2 177	1 070	496
Nagasaki	28 113	15 089	5 621	2 543	921	963	1 230	1 025	538	183
Total	86 572	36 459	16 921	9 390	6 538	5 467	6 308	3 202	1 608	679

From Pierce *et al.* (1996)

Figure 3. Excess relative risks per sievert and 90% confidence intervals for the incidence of solid tumours (1958–87) and mortality from solid tumours (1950–87) among survivors of the atomic bombings



From UNSCEAR (1994). CNS, central nervous system

ERR for cancer of the gall-bladder is closer to the level of statistical significance in the new data ($p = 0.06$) than in the older data ($p = 0.13$; Shimizu *et al.*, 1990). The most recent published estimates of the ERR and excess absolute risk (EAR; number of excess cases or deaths per 10 000 person-years Sv) for cancer incidence are shown in Table 13 for several sites of cancer. The findings for leukaemia, all solid tumours and cancers of the female breast and thyroid are presented below, followed by an indication of the extent to which cancers at other specific sites have been linked with radiation in the Life Span Study cohort.

(*a*) *Leukaemia*

Leukaemia was the first cancer to be linked with exposure to radiation after the atomic bombings (Folley *et al.*, 1952), and the ERR for this malignancy is by far the

Table 13. Estimates of risk for increased incidence of cancer by site, 1958–87, in the Life Span Study of survivors of the atomic bombings

Cancer site/organ system	No. of cases		ERR_{1Sv} (95% CI)	EAR per 10 000 person–years Sv (95% CI)
	Exposed[a]	Unexposed		
All solid tumours	4327	4286	0.63 (0.52, 0.74)	29.7 (24.7, 34.8)
Oral cavity and pharynx	64	68	0.29 (–0.09, 0.93)	0.23 (–0.08, 0.65)
Salivary gland	13	9	1.8 (0.15, 6.0)	NR
Oesophagus	84	101	0.28 (–0.21, 1.0)	0.30 (–0.23, 1.0)
Stomach	1305	1353	0.32 (0.16, 0.50)	4.8 (2.5, 7.4)
Colon	223	234	0.72 (0.29, 1.3)	1.8 (0.74, 3.0)
Rectum	179	172	0.21 (–0.17, 0.75)	0.43 (–0.35, 1.5)
Liver	283	302	0.49 (0.16, 0.92)	1.6 (0.54, 2.9)
Gall-bladder	143	152	0.12 (–0.27, 0.72)	0.18 (–0.41, 1.1)
Pancreas	122	118	0.18 (–0.25, 0.82)	0.24 (–0.36, 1.1)
Trachea, bronchus and lung	449	423	0.95 (0.60, 1.4)	4.4 (2.9, 6.0)
Non-melanoma skin	91	77	1.0 (0.41, 1.9)	0.84 (0.40, 1.4)
Female breast	289	240	1.6 (1.1, 2.2)	6.7 (4.9, 8.7)
Uterus	349	375	–0.15 (–0.29, 0.10)	–1.1 (–2.1, 0.68)
Ovary	66	67	0.99 (0.12, 2.3)	1.1 (0.15, 2.3)
Prostate	61	79	0.29 (–0.21, 1.2)	0.61 (–0.46, 2.2)
Urinary bladder	115	95	1.0 (0.27, 2.1)	1.2 (0.34, 2.1)
Kidney	34	39	0.71 (–0.11, 2.2)	0.29 (–0.50, 0.79)
Nervous system	69	56	0.26 (–0.23, 1.3)	0.19 (–0.17, 0.81)
Thyroid	129	96	1.2 (0.48, 2.1)	1.6 (0.78, 2.5)
Leukaemia[b]	141	67	4.4 (3.2, 5.6)	2.7 (2.0, 3.5)

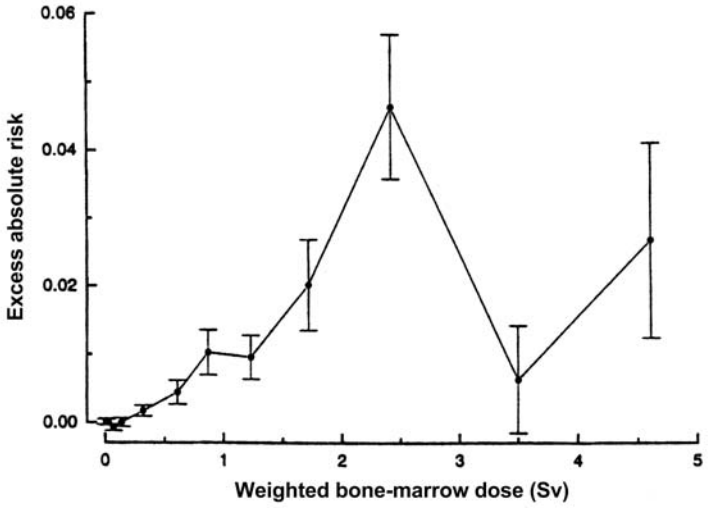
From Thompson *et al.* (1994). ERR_{1Sv}, excess relative risk at 1 Sv; EAR, excess absolute risk; CI, confidence interval

[a] Defined as a dose to the colon ≥ 0.01 Sv

[b] Based on data for 1950–87 and bone-marrow dose, from UNSCEAR (1994); 90% CI

highest (Table 13). Figure 4 shows the EARs for leukaemia plotted as a function of dose to the bone marrow, based on the most recent mortality analyses (Pierce *et al*., 1996). This Figure demonstrates a clear increase in risk with increasing dose over the range 0–2.5 Sv.

Figure 4. Excess absolute risks for death from leukaemia per person in the Life Span Study, 1950–90, of survivors of the atomic bombings



From Pierce *et al.* (1996); bars = standard error

Table 14, also based on the analysis of Pierce *et al.* (1996), presents the observed numbers of leukaemia deaths, the estimated expected background numbers and their differences, by dose category. The excess deaths are those estimated to be attributable to radiation. Because these values are estimates, they are subject to statistical variation, and thus negative values are possible; the negative excesses in the first dose category are well within sampling variation of a true value of zero. The excess of deaths among people whose dose was greater than zero, i.e. (87–9)/(249–73) = 44%, may be considered to correspond to the percentage of tumours due to exposure to radiation, or the attributable risk among exposed persons.

Although the temporal patterns of leukaemia risk are more complex than those of solid tumours (see below), the largest excess risks were generally seen in the early years of follow-up. For people exposed as children, essentially all of the excess deaths appear to have occurred early in the follow-up. For people exposed as adults, the excess risk was lower than that of people exposed as children and appears to have persisted throughout the follow-up. Detailed investigations (Preston *et al.*, 1994) have been made of the patterns of risk by time since exposure, age at exposure and sex for four major subtypes of leukaemia—acute lymphocytic leukaemia, acute myelogenous

Table 14. Observed and expected numbers of deaths from leukaemia in the Life Span Study, 1950–90, of survivors of the atomic bombings

Dose (Sv)[a]	No. of subjects	No. of deaths observed	No. of deaths expected	Excess no. of deaths
< 0.005	35 458	73	64	9
0.005–0.1	32 915	59	62	–3
0.1–0.2	5 613	11	11	0
0.2–0.5	6 342	27	12	15
0.5–1.0	3 425	23	7	16
1.0–2.0	1 914	26	4	22
> 2.0	905	30	2	28
Total	86 572	249	162	87

From Pierce *et al.* (1996)
[a] Dose to red bone marrow

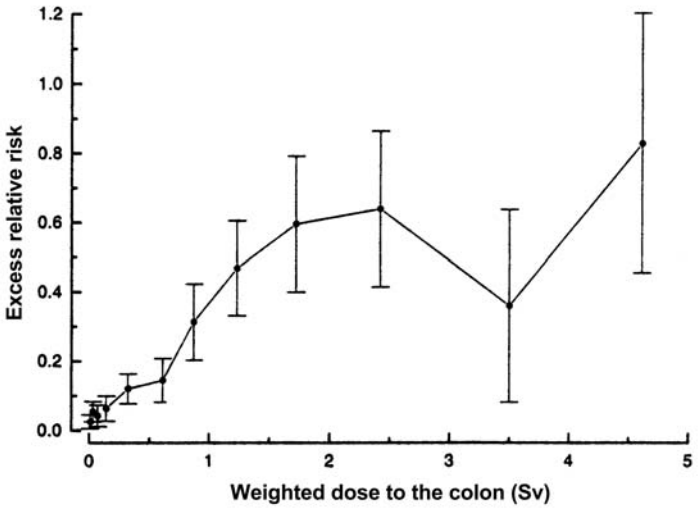
leukaemia, chronic myelogenous leukaemia and adult T-cell leukaemia—and dose–response relationships were seen for the first three. The other major type of leukaemia, chronic lymphocytic leukaemia, is infrequent in Japan, and no excess was seen in the Life Span Study cohort. One of the important recent developments in studies of leukaemia in the atomic bomb survivors was the reclassification of leukaemia cases by new systems and criteria, including the French–American–British classification after 1975 (Matsuo *et al.*, 1988; Tomonaga *et al.*, 1991), which made it possible to analyse the data on leukaemia in the Life Span Study by subtype.

(*b*) *All solid tumours*

Figure 5 shows the ERRs for all solid tumours by dose to the colon. As for leukaemia, an increase in risk with increasing dose over the range 0–2.5 Sv is seen.

Excess deaths from solid tumours are shown in Table 15. The attributable risk for solid tumours is estimated to be 8%—much smaller than the estimate of 44% for leukaemia. The temporal pattern of solid tumours differs from that of leukaemia as it includes a longer minimal latent period. The ERR for solid tumours remained remarkably constant from about 5–9 years after exposure to the end of the follow-up period, but the number of excess deaths increases monotonically with each successive five-year period of follow-up, and the EAR is roughly proportional to the rapid age-specific increase in background risk. For people who were exposed when they were under the age of 30, nearly half of the excess deaths during the entire 40 years of follow-up have occurred in the last five years.

Figure 5. Excess relative risks for solid tumours, adjusted to men aged 30 at the time of exposure, in the Life Span Study of survivors of the atomic bombings



From Pierce *et al.* (1996); bars = standard error

Table 15. Observed and expected numbers of deaths from solid tumours in the Life Span Study, 1950–90, of survivors of the atomic bombings

Dose (Sv)[a]	No. of subjects	No. of deaths observed	No. of deaths expected	Excess no. of deaths
< 0.005	36 459	3 013	3 055	–42
0.005–0.1	32 849	2 795	2 710	85
0.1–0.2	5 467	504	486	18
0.2–0.5	6 308	632	555	77
0.5–1.0	3 202	336	263	73
1.0–2.0	1 608	215	131	84
> 2.0	679	83	44	39
Total	86 572	7 578	7 244	334

From Pierce *et al.* (1996)

[a] Weighted dose to the colon used to represent all solid tumours

Of the 86 572 subjects for whom DS86 dose estimates are available, 56% were still alive at the end of 1990, the end of the period for which mortality has been reported. Of the 46 263 subjects who were under the age of 30 at the time of the bombings, 87% were still alive at the end of 1990 (Pierce *et al*., 1996). This indicates the importance of continued follow-up of the Life Span Study cohort.

(*c*) *Site-specific cancer risks*

Although the nearly complete ascertainment of mortality is a major strength of the Life Span Study, information from death certificates is not optimal for analyses of the risks for cancers in specific organs and tissues. The causes of death reported on death certificates are generally reliable for major groups of cancer but are less reliable for some specific sites, and provide only partial ascertainment of cancers that are less often fatal. The histological types of cancer are generally not recorded on death certificates. Data on cancer incidence from tumour registries fill these gaps and complement the data on mortality. The following discussion of site-specific cancer risks is therefore based primarily on incidence.

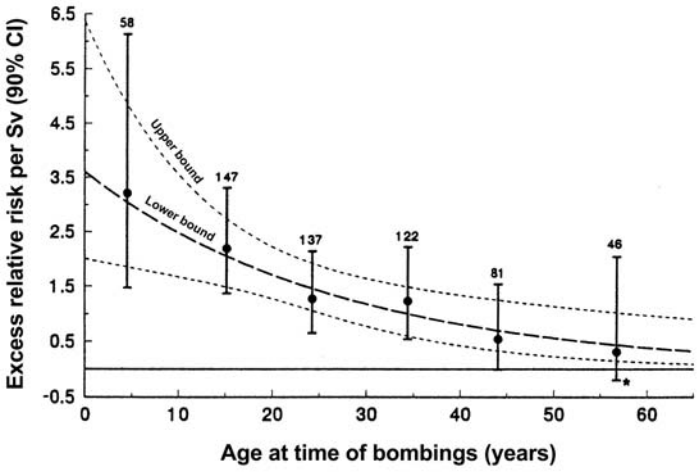
(i) *Female breast cancer*

The risk for breast cancer among women in the Life Span Study (Tokunaga *et al.*, 1994) shows a strong linear dose–response relationship and a remarkable age dependence (Figure 6). The ERR for this cancer is one of the largest of those for solid tumours (see Table 13), but it decreases smoothly and significantly with increasing age at the time of exposure. Figures on incidence from the tumour registries showed, for example, that the ERR of women who were under 10 years of age at the time of exposure was five times that of women who were over 40 years of age at that time. Land *et al.* (1994a,b) investigated the interaction between exposure to radiation and known risk factors for breast cancer in a case–control study nested in the Life Span Study and found a multiplicative relationship between exposure and age at the time of a first full-term pregnancy, the number of children and cumulative period of breast-feeding.

(ii) *Thyroid cancer*

After early reports of increased risks for thyroid cancer among atomic bomb survivors, a dose-related increase in the incidence of thyroid cancer was demonstrated in the early 1960s (Socolow *et al.*, 1963) from the results of periodic clinical examinations of a subcohort of approximately 20 000 persons (the ‘Adult Health Study’). More detailed analyses based on incidence in the Life Span Study cohort showed a strong dependence of risk with age at exposure, the risk being higher among people who had been less than 19 years old at the time of the bombings (Thompson *et al.*, 1994). In fact, no association was found for subjects who had been over the age of 14 when exposed (ERR/Gy, 0.4; 95% CI, –0.1, 0.2; n = 169), while the risk of people exposed as children (< 15 years) was significantly elevated (ERR/Gy, 4.7; 95% CI,

Figure 6. Estimated excess relative risks (ERRs) per sievert for breast cancer among women in the Life Span Study, according to age at the time of the atomic bombings



From Tokunaga *et al.* (1994). Derived from the model ERR (D;E) = $\alpha D \exp(\beta_1 E)$, where D is the equivalent dose in sieverts (relative biological effectiveness of neutrons = 10) and E is age at the time of the bombings. The estimates and 90% confidence intervals (CIs) are stratified on city, age at the time of the bombings, attained age and period of follow-up. The numbers above the CIs are the numbers of cases for each age interval.
*Minimum value feasible for lower confidence limit

1.7–11; n = 56) (Ron *et al.*, 1995). Among children who were under 15 at the time of the bombings, a steep decrease in risk with age at exposure was found, and children who were exposed between the ages of 10 and 14 had one-fifth the risk of those exposed when they were under 5.

(iii) *Other sites*

Cancers at other sites that are clearly linked with exposure to radiation in the Life Span Study include those of the salivary glands, stomach, colon, lung, liver, ovary and urinary bladder, and nonmelanoma skin cancer. For most of these sites, statistically significant associations were found for both mortality and incidence. A study of cancers of the salivary glands involving reviews of slides strengthened the evidence for an association (Land *et al.*, 1996). A similar study of nonmelanoma skin cancer showed a significant dose–response relationship for all nonmelanoma skin cancer as a group, for basal-cell carcinoma and for non-basal-, non-squamous-cell epithelial skin carcinoma, but not for squamous-cell carcinoma (Ron *et al.*, 1998a).

The evidence for an association with exposure to radiation is equivocal for cancers of the oesophagus, gall-bladder, kidney and nervous system and for non-Hodgkin lymphoma and multiple myeloma, as the results are either of borderline statistical significance or those for incidence and mortality conflict (UNSCEAR, 1994).

Cancers for which there is little evidence of an association with exposure to radiation include those of the oral cavity (except salivary glands), rectum, pancreas, uterus and prostate and Hodgkin disease. Small numbers of cases and diagnostic misclassification may have contributed to the failure to demonstrate an association, as all of the upper confidence limits of the risk estimates were positive. Therefore, the possibility of associations with these cancers cannot be excluded on the basis of the Life Span Study alone (UNSCEAR, 1994).

2.2.2 *Nuclear weapons testing*

A number of epidemiological studies have been carried out to assess the risks for cancer associated with exposure to radiation resulting from nuclear weapons tests. The populations that have been studied are those who were living near the tests sites and were thus exposed to radioactive fall-out, and military personnel who participated in the tests and were thus exposed primarily to external γ-radiation with possible internal exposure by ingestion or inhalation of radionuclides. Many of the results are inconclusive, largely because of the lack of individual doses and in some cases because the approaches used, such as population-based ecological (correlation) studies, are not adequate for assessing risk.

(*a*) *People living near weapons test sites*

(i) *Nevada test site*

Between 1951 and 1958, the US Atomic Energy Commission carried out more than 100 atmospheric tests of nuclear weapons at a test site in Nevada, resulting in the deposition of radioactive fall-out in regions surrounding the site. The heaviest exposure was in southwestern Utah and in adjacent areas of Nevada and Arizona. The cancer risks of residents of areas downwind of the test site have been the subject of studies of varying kind and quality. Studies of leukaemia clusters and risks and of the risks for thyroid disease led to a population-based case–control study in Utah of 1177 persons who had died of leukaemia (cases) and 5330 who had died of other causes (controls) (Stevens *et al.*, 1990). The median dose of cases and controls was estimated to be 3.2 mGy. A weak, nonsignificant association was found between dose to the bone marrow and acute leukaemias (excluding chronic lymphocytic leukaemia) when all ages and all periods after exposure were considered (odds ratio, 1.7; 95% CI, 0.94–3.1 for those exposed to ≥ 6 mGy; n = 17). [The Working Group noted that the dose estimates were largely determined by the doses assigned to the place of residence.]

(ii) *Semipalatinsk test site*

In 1949, the Semipalatinsk test site was created in northeastern Kazakhstan, then part of the USSR, and 118 atmospheric nuclear and thermonuclear devices were exploded before 1962, 26 of which were near the ground; between 1965 and 1989, 370 underground nuclear explosions were carried out, and two additional atmospheric tests were conducted in 1965. Most of the contamination and exposure resulted from the early atmospheric testing. The estimated effective doses from external and internal exposure attributable to the 1949 and 1953 tests (the two largest atmospheric tests) in villages near the test site range from 70 to 4470 mSv (Gusev *et al*., 1997), most local residents being exposed to an effective dose of 100 mSv. The incidence of cancer among children under the age of 15 during 1981–90 in four administrative zones of Khazakhstan in relation to distance from the test site was studied by Zaridze *et al*. (1994): the risk for acute leukaemia rose significantly with increasing proximity of residence to the testing areas, although the absolute value of the risk gradient was relatively small. [The Working Group noted that potential confounders, notably urban–rural and ethnic differences, were not considered in the analyses.]

(*b*) *Military personnel participating in weapons tests*

Follow-up of more than 20 000 participants in the 21 atmospheric nuclear tests conducted by the United Kingdom in 1952–58 in Australia and islands in the Pacific Ocean (Darby *et al*., 1988) and of an equally large control group of military personnel through 1991 showed that the rate of death from leukaemia among participants was similar to that of the general population (SMR, 1.0 [95% CI, 0.7–1.4]) but was higher than that of the control group (RR, 1.8; 95% CI, 1.0–3.1) (Darby *et al.*, 1993).

A small study, with follow-up for the period 1957–87, of approximately 500 personnel of the Royal New Zealand Navy involved in the test programme of the United Kingdom in the Pacific Ocean in 1957–58, showed that mortality from all cancers was similar (RR, 1.2; 95% CI, 0.8–1.7) to that of 1504 Navy personnel who were not involved in the tests (Pearce *et al.*, 1997); however, mortality from leukaemia was greater among participants than controls (RR, 5.6; 95% CI, 1.0–42; four cases).

In a cohort study of participants in five US nuclear bomb test series between 1953 and 1957 (Robinette *et al.*, 1985), more than 46 000 subjects were followed-up by linkage to Veterans' Administration records, which showed 5113 deaths. No increase in mortality from leukaemia was observed (SMR, 0.9; 95% CI, 0.6–1.2), suggesting that the findings of a previous smaller study of 3217 participants in a single test (Caldwell *et al.*, 1983), which showed a relative risk of 2.6 (95% CI, 1.1–5.1), were probably not due to exposure to radiation.

Approximately 8500 Navy veterans who had participated in the US 'Hard tack I' operation in 1958, which included 35 tests in the Pacific Ocean, were found to have had a median dose of 4 mSv (Watanabe *et al.*, 1995). The mortality rates from all cancers (RR, 1.1; 95% CI, 1.0–1.3) and leukaemia (RR, 0.7; 95% CI, 0.3–1.8) were

comparable to those for an unexposed group of veterans. In a study of 40 000 military veterans who had participated in a test in the Bikini atoll, Marshall Islands, in 1946, the mortality rates from all cancers (RR, 1.0; 95% CI, 0.96–1.1) and from leukaemia (RR, 1.0; 95% CI, 0.75–1.4) were similar to those for nonparticipants (Johnson *et al.*, 1997).

[The Working Group noted that the weaknesses of these studies include low doses and insufficient dosimetry, which obviate a quantitative risk estimation.]

2.2.3 *Production of materials for nuclear weapons*

Plutonium production for nuclear weapons in the former USSR started in 1949 in the closed city of Ozersk (the Mayak facility) situated 1200 km east of Moscow in the southern Ural Mountains. During the early 1950s, the Techa River was severely contaminated with radioactive wastes discharged directly into the water (Kossenko *et al*., 1997). Approximately 28 000 inhabitants of the river-bank villages were exposed, and 7500 were resettled. In 1957, a container of highly radioactive wastes exploded, resulting in a contaminated area known as the East Urals Radioactive Trace; this incident is referred to as the 'Kyshtym accident', after the name of a nearby village. About 11 000 individuals, including approximately 1700 who had previously lived in exposed areas along the River, were resettled. Systematic follow up of a cohort of almost 30 000 individuals who received significant exposure from the releases was begun in 1967.

The inhabitants of the riverside villages were exposed to both internal and external radiation (river water, sediments and soils). Doses are available at the village level (Degteva *et al*., 1994), but individual doses are being constructed (Degteva *et al*., 1996). ^{90}Sr, which accumulates in bone, was the largest component of the internal dose (Kozheurov & Degteva, 1994). The individuals living along the River thus received doses of external γ-radiation and of internal γ- and β-rays over several years. The preliminary results of follow-up from 1950 through 1989, which were analysed in linear dose–response models for excess relative risk, indicate an increased rate of mortality from leukaemia and solid tumours related to internal and external doses of ionizing radiation (Tables 16 and 17; Kossenko *et al*., 1997).

The authors emphasize that with continuing improvement of the quality of follow-up and dosimetry, the study of the Techa River cohort could provide important information on the effects of protracted exposure to low doses of ionizing radiation in an unselected population, and that this study supplements and complements the findings of the studies of atomic bomb survivors in Japan.

Table 16. Estimated excess numbers of cases of leukaemia[a] in the Techa River cohort and person–years of risk in relation to dose to red bone marrow

Dose category (Sv)	Person–years[b]	Observed	Excess
0.005–0.1	103 031	3	–1
0.1–0.2	194 858	13	4
0.2–0.5	200 144	16	6
0.5–1	93 873	9	5
> 1	49 398	9	7
Total	641 304	50	21

From Kossenko *et al*. (1997)
[a] Computed as the difference between the observed number of cases and an estimate of the number expected in the absence of exposure
[b] Computed through date of death, loss to follow-up or 31 December 1989

Table 17. Estimated excess numbers of deaths from solid tumours[a] in the Techa River cohort and person–years of risk in relation to dose to soft tissue

Dose category (Sv)	Person–years[b]	Observed	Excess
0.005–0.1	459 576	716	5
0.1–0.2	96 297	126	1
0.2–0.5	19 582	34	10
0.5–1	32 204	52	6
> 1	33 645	41	8
Total	641 304	969	30

From Kossenko *et al*. (1997)
[a] Computed as the difference between the observed number of cases and an estimate of the number expected in the absence of exposure
[b] Computed through date of death, loss to follow-up or 31 December 1989

2.3 Medical uses

Studies of patients irradiated for the treatment or diagnosis of diseases have contributed substantial evidence about the carcinogenic effects of X-rays and γ-rays. The often detailed radiotherapy records for cancer patients and those treated for benign conditions allow precise quantification of the doses to the organs of individuals, and dose–response relationships can be studied. Further, patients with the same initial disease treated by means other than radiation are often available for comparison. Large cohorts of patients who have been followed-up for long periods are available, allowing evaluation of late effects and cancer in particular. Population-based cancer registries around the world have been used to identify these patients; for example, the risks for a second cancer after individual primary cancers in Denmark and in Connecticut, USA, have been evaluated comprehensively (Boice *et al*., 1985a).

Studies of patients undergoing radiotherapy have provided information on the risks for cancer in relatively insensitive organs, such as the rectum, that appear to be associated with exposure to radiation only at therapeutic doses of the order of ≥ 10 Gy. Studies of organs outside the radiation treatment fields which received lower doses provide information on risks for cancer that are not influenced by the cytotoxic effects of radiation. Studies of long-term survivors of radiotherapy for benign conditions, such as past use for enlarged tonsils, have indicated that cancers such as those of the thyroid and breast can be induced, in the absence of confounding effects of the disease being treated or concomitant therapy. Studies of diagnostic procedures that involve much lower doses provide limited evidence for the carcinogenicity of radiation except when the cumulative exposure reaches a substantial level. Well over 100 studies of patients have linked exposure to radiation to increased risks for cancer (Boice *et al*., 1985a, 1996; UNSCEAR, 1994; Curtis, 1997). Only the most informative ones, which include assessments of radiation dose, are reviewed in this section and summarized in Table 11; more detailed listings are given in Tables 18–20.

2.3.1 *Radiotherapy for malignant disease*

Chemotherapy and/or hormonal therapy used in the treatment of cancers are potential confounding factors in investigations of the risk for a second cancer. Furthermore, patients with a malignant disease may develop a second primary cancer because of common risk factors for the two cancers or genetic predisposition for the second. Increased medical surveillance may contribute to the detection and reporting of new cancers. These studies are summarized in Table 18.

(*a*) *Cervical cancer*

External beam radiotherapy and radium and caesium applicators are used for the treatment of cervical cancer to deliver high local doses of X-rays and γ-rays to the cervix uteri and adjacent organs in the abdomen and pelvic area—notably the urinary

Table 18. Study characteristics and second cancers in patients receiving radiotherapy for a malignant disease

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Cohort studies						
Zippin *et al.* (1971)	Cervix (1932–51)	Women, 497/497	17–36	Bone marrow, 20	Leukaemia	No increase
Fehr & Prem (1973)	Cervix, squamous-cell carcinoma (1939–60)	Women, 627/627	> 9	NR	Pelvic girdle sarcoma	Pelvis: SIR = 650; *n* = 4
Clarke *et al.* (1984)	Cervix, invasive carcinoma (1960–75)	Women, 7083/7535	7.5	Cervix, 40	All	No increase
Boice *et al.* (1985b)*	Cervix (1920–78)	Women, 82 616/182 040	7.60; < 1–> 30	Stomach, 2 Colon, 5 Pancreas, 1.5 Lung, 0.35 Breast, 0.35 Kidney, 2.0 Bladder, 30 Thyroid, 0.15 Red bone marrow, 7.5	All, excluding cervical cancer	Oesophagus: SIR = 1.5; *n* = 40 Small intestine: SIR = 2.2; *n* = 21 Rectum: SIR = 1.3; *n* = 198 Pancreas: SIR = 1.3; *n* = 121 Lung: SIR = 3.7; *n* = 493 Bladder: SIR = 2.7; *n* = 196 Connective tissue: SIR = 1.9; *n* = 27 ANLL: SIR = 1.3; *n* = 52
Pettersson *et al.* (1985)	Cervix, carcinoma (1914–65)	Women, 5000[a]/13 041	>10–45	NR	Colon, rectum, corpus uteri, ovary, bladder	Rectum: O/E = 1.7; *n* = 118 Bladder: O/E = 3.4; *n* = 112

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Cohort studies (contd)						
Pettersson *et al.* (1990)	Cervix, invasive carcinoma (1958–80)	Women, 16 704/16 704	8	Pelvic wall, 35–50	All	Bladder: O/E 3.5; *n* = 55 Rectum: O/E = 1.8; *n* = 47 Uterus (not corpus): O/E = 1.9; *n* = 11
Arai *et al.* (1991)	Cervix (1961–81)	Women, 7694/11 855	8	Pelvis, 50	All	Leukaemia: SIR = 2.6; *n* = 9 Rectum: SIR = 1.9; *n* = 25 Bladder: SIR = 2.1; *n* = 9
Hancock *et al.* (1991)*	Hodgkin disease (1961–89)	Both sexes, 1677/1787	10	Cervical lymph node area, 44	Thyroid	Thyroid: SIR = 16; *n* = 6
Hancock *et al.* (1993)	Hodgkin disease (1961–90)	Women, 383/885	10	Radiotherapy alone, 7.5–≥ 40	Breast	Breast: SIR = 3.5; *n* = 12
Khoo *et al.* (1998)	Hodgkin disease (1970–89)	Both sexes, 320/320	9; 1–23	Thyroid, 40	Thyroid	Thyroid: RR = 6.7; *n* = 4
Harvey & Brinton (1985)	Breast (1935–82)	Women, 11 691/41 109	> 20	NR	All	Second breast cancer: RR = 3.9; *n* = 544
Yoshimoto *et al.* (1985)	Breast (1960–70)	Women, 733/1359	11	NR	All	Second primary cancer: SIR = 8.7; *n* = 61
Andersson *et al.* (1991)	Breast (1977–82)	Women, 846/3538	8	NR	All	Second breast cancer: SIR = 4.2; *n* = 47
Taghian *et al.* (1991)	Breast (1954–83)	Women, 6919/7620 > 1 year follow-up	7	Sarcoma, 45	Soft-tissue sarcoma	Soft tissue: SIR = 1.8; *n* = 11

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Cohort studies (contd)						
Neugut *et al.* (1997a)	Breast (1973–93)	Women, 62 453/251 750	< 20	NR	Pleural mesothelioma	No significant increase
Pride & Buchler (1976)	Gynaecological malignancies (1956–74)	Women, 4238/4238	> 10	NR	Vaginal, cervical carcinoma	No increase
Ahsan & Neugut (1998)	Breast (1973–93)	Women, 47 915/220 806	6	NR	Oesophagus	Oesophageal squamous-cell carcinoma: RR = 5.4; *n* = 20 (≥ 10 years after radiotherapy)
Maier *et al.* (1997)	Gynaecological carcinomas (1972–93)	Women, 10 709/10 709	22	Pelvis, 67.5	Urinary tract	Bladder: RR = 4.7; *n* = 6
Jacobsen *et al.* (1993); Møller *et al.* (1993)	Testis[b] (1943–87)	Men, 6187/6187	9.5	Lymph nodes, 20–45	All	Sarcoma: SIR = 4; *n* = 13 Stomach: SIR = 2.1; *n* = 34 Colon: SIR = 1.5; *n* = 28 Pancreas: SIR = 2.3; *n* = 21 Kidney: SIR = 2.3; *n* = 21 Bladder: SIR= 2.1; *n* = 47 Non-melanoma skin: SIR = 2.0; *n* = 68 Leukaemia: SIR = 2.4; *n* = 18
Horwich & Bell (1994)	Testicular seminoma (1961–85)	Men, 859/859	10	NR	All	Leukaemia: SIR = 6.2; *n* = 4

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Cohort studies (contd)						
Travis *et al.* (1997)*	Testis (1935–93)	Men, 8841/28 843	10	NR	All	Stomach: SIR = 1.95; *n* = 93 Bladder: SIR = 2.0; *n* = 154 Pancreas: SIR = 2.2; *n* = 66
Neugut *et al.* (1997b)	Prostate (1973–93)	Men, 34 889/141 761	0.5–> 8	NR	Bladder, rectal carcinoma, ANLL, CLL	Bladder: RR = 1.5; *n* = 38 (> 8 years after radiotherapy)
Maxon *et al.* (1981)	Head and neck (1963–67)	Both sexes, 554/1 266	21.5	Salivary gland, 5 ± 2	Salivary gland	Salivary gland: *p* = 0.049; *n* = 3
Potish *et al.* (1985)	Childhood cancer (1953–75)	Both sexes, 330/330	14 (5–30)	NR	All	None
Hawkins *et al.* (1987)*	Childhood CNS cancer[c] (1962–79)	Both sexes, 1101/9279	19	NR	All	All: RR = 6.2; *n* = 10
Eng *et al.* (1993)*	Retinoblastoma (1914–84) Bilateral	Both sexes, 965/1603 835/919	17	NR	All (results for bilateral retinoblastoma)	Bone: SMR = 630; *n* = 34 Soft tissue: SMR = 880; *n* = 15 Skin melanoma: SMR =180; *n* = 7 Brain: SMR = 45; *n* = 8
Bhatia *et al.* (1996)*	Childhood Hodgkin disease (1955–86)	Both sexes, 1270/1380 (897 girls)	11 (median); 0.1–37	Breast, < 20–> 40	All	Breast: 20–40 Gy; RR = 5.9; *n*, NR
de Vathaire *et al.* (1999a)*	Childhood cancer (1942–85)	Both sexes, 2827/4096	15; 3–45	Thyroid, 7.0	Thyroid	Thyroid carcinoma: SIR = 80; *n* = 14

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Cohort studies (contd)						
de Vathaire *et al.* (1999b)*	Childhood cancer (1942–85)	Both sexes, 3013/4400	15; 3–48	Brain, 8.6 Breast, 5.1 Colon, 8.1	All	Brain: O/E = 44; *n* = 8 Breast: O/E = 5.1; *n* = 4
Curtis *et al.* (1997)*	Bone-marrow transplantation for cancer (1964–92)	Both sexes, 14 656/19 229	5; 1–25	Whole body Single, ≥ 10 Total fractionated, ≥ 13	All	Melanoma: RR = 8.2; *n* = 7 Brain: RR = 4.3; *n* = 8 Thyroid: RR = 5.8; *n* = 6
Case–control studies						
Boivin *et al.* (1986)	All (1933–72)	Both sexes, 398/781	6; 1–28	NR	Leukaemia	Leukaemia excluding CLL (232 cases): RR = 1.6; *n* = 82
Nandakumar *et al.* (1991)	All (1974–86)	Both sexes, 97/194	NR	NR	Myeloid leukaemia	No increase
Zaridze *et al.* (1993)	All (1975–90)	Both sexes, 165/294	NR	NR	All	None

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Case–control studies (contd)						
Boice *et al.* (1988)*	Cervix (1920–78)	Women, 4188/6880	7.6; < 1–> 30	Stomach, 2 Small intestine, 10–20 Colon, 24 Rectum, 30–60 Uterus, 165 Ovary, 32 Vagina, 66 Bladder, 30–60 Bone, 22 Connective tissue, 7 Stomach, 2 Pancreas, 2 Kidney, 2 Breast, 0.3 Thyroid, 0.1 Red bone marrow, 7	All, excluding cervical cancer	Stomach: RR = 2.1; *n* = 338 Vagina: RR = 2.65; *n* = 100 Bladder: RR = 4.05; *n* = 267 Leukaemia excluding CLL: RR, 2.0; *n* = 133 Rectum: RR = 1.8; *n* = 465
Curtis *et al.* (1994)*	Corpus uteri (1935–85)	Women, 218/775	1–50	Bone marrow, 5.2	Leukaemia	Leukaemia excluding CLL (57 cases); RR = 1.9; *n* = 118
Kaldor *et al.* (1990a)*	Hodgkin disease (1960–87)	Both sexes, 163/455	1–≥ 10	Red bone marrow, < 10–> 20	Leukaemia	Risk increased with dose ≥ 20 Gy: RR = 8.2; *n*, NR
Kaldor *et al.* (1992)*	Hodgkin disease (1960–87)	Both sexes, 98/259	1–≥ 10	Lung, < 1–> 2.5	Lung	No significant increase

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Case–control studies (contd)						
van Leeuwen *et al.* (1995)	Hodgkin disease (1966–86)	Both sexes, 30/82	1–23	Lung, 7.2	Lung	No significant increase, but significant trend
Travis *et al.* (1994)	Non-Hodgkin lymphoma (1965–89)	Both sexes, 35/140	8; 2–18	Red bone marrow, 9.3	ANLL	No significant increase
Travis *et al.* (1995)	Non-Hodgkin lymphoma (1965–80)	Both sexes, 48/136	9; 2–21	Bladder, 12.0 Kidney, 12.8	Bladder and kidney	No increase
Basco *et al.* (1985)*	Breast (1946–82)	Women, 194/194	≥ 5–≥ 10	Contralateral breast, 2.0–3.3	Contralateral breast	No significant increase
Curtis *et al.* (1989)*	Breast (1935–84)	Women, 48/97	12; 1.6–27	Red bone marrow, 5.3	Leukaemia	No increase
Boice *et al.* (1992)*	Breast (1935–82)	Women, 655/1189	5–> 10	Contralateral breast, 2.8	Contralateral breast	For < 45 years old, RR = 1.6; *n* = 78
Curtis *et al.* (1992)*	Breast (1973–85)	Women, 90/264	5; 2–12	Red bone marrow, 7.5	All leukaemia & myelodys-plasia	ANLL: RR, 2.4; *n* = 12
Storm *et al.* (1992)*	Breast (1943–78)	Women, 529/529	8–> 25	Contralateral breast, 2.5	Contralateral breast	No significant increase
Inskip *et al.* (1994)*	Breast (1935–71)	Women, 61/120	10–46	Lung, 9.8	Lung	For ≥ 15 years after treatment, RR = 2.8; *n*, NR

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Case–control studies (contd)						
Neugut *et al* (1994)	Breast (1986–89)	Women, 121/1043	> 10	NR	Lung	Lung: OR = 2.8; *n*, NR
Karlsson *et al.* (1996)*	Breast (1960–80)	Women, 18/54	1–26	Breast (integral dose), 152 J	Soft-tissue sarcoma	Soft-tissue sarcoma: $p = 0.008$ with integral dose; $n = 16$
Kaldor *et al.* (1990b)*	Ovary (1960–85)	Women, 114/342	1–> 10	Red bone marrow, < 10–> 20	Leukaemia	No significant increase
Kaldor *et al.* (1995)*	Ovary (1960–87)	Women, 63/188	0–> 15	Bladder, 35	Bladder	No significant increase
Travis *et al.* (1999)*	Ovary (1980–93)	Women, 96/272	4 (max., 14)	Red bone marrow, 18.4	Leukaemia	No increased risk
Tucker *et al.* (1987a)*	Childhood cancer (1936–79)	Both sexes, 64/209	2–≥ 20	Bone, 27	Bone sarcoma	Bone: OR = 2.7; *n* = 54
Tucker *et al.* (1987b)*	Childhood cancer (1945–79)	Both sexes, 25/90	> 2	Red bone marrow, 10 (0–38)	Leukaemia	No increase
Tucker *et al.* (1991)*	Childhood cancer (1945–79)	Both sexes, 23/89	5.5; 2–48	Thyroid, 12.5 (0–76)	Thyroid	Thyroid: 2–< 10 Gy, RR = 13; *n* = 7 10–< 30 Gy, RR = 12; *n* = 7 > 30 Gy, RR = 18; *n* = 5
Hawkins *et al.* (1992)*	Childhood cancer (1940–83)	Both sexes, 26/96	7.7	Red bone marrow, 0.01–> 15	Leukaemia	No significant increase
Hawkins *et al.* (1996)*	Childhood cancer (1940–83)	Both sexes, 59/220	10	Red bone marrow, 0.01–≥ 50	Bone	No significant dose–response relationship

Table 18 (contd)

Reference	Index cancer (period of diagnosis)	Sex, no. of exposed and total no. of individuals (exposed + unexposed) or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy, except as noted)	Second cancers studied	Results
Case–control studies (contd)						
Wong *et al.* (1997)*	Retinoblastoma (1914–84)	Both sexes, 83/89	20	Bone, 32.8 Soft tissues, 20.4	Bone and soft-tissue sarcoma	Bone and soft-tissue sarcoma combined: RR (dose–response) = 1.9–10.7; *n* = 55
Le Vu *et al.* (1998)*	Childhood cancer (1960–86)	Both sexes, 32/160	9; 2–25	Red bone marrow, 6	Osteosarcoma	Osteosarcoma: linear increase with dose (ERR/Gy = 1.8)

ANLL, acute non-lymphocytic leukaemia; CLL, chronic lymphocytic leukaemia; CNS, central nervous system; ERR, excess relative risk; NR, not reported; O/E, observed/expected; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio

* Study cited in text

[a] Only patients who survived the treatment for > 10 years were taken into account.

[b] 53% seminomas

[c] Excluding second primary tumours for which there is a genetic predisposition

bladder, the rectum, the ovaries, the corpus uteri, and portions of the colon and bone marrow in the pelvis. The treatment is successful, and patients survive for many years after radiotherapy.

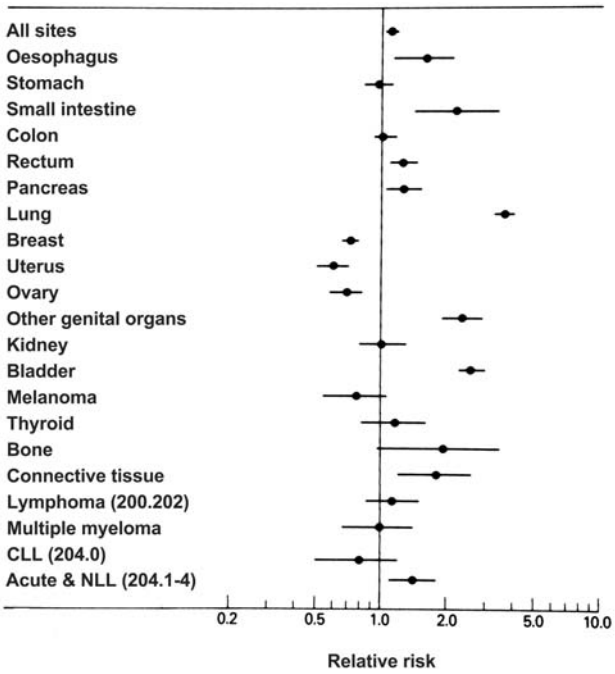
An international study of nearly 200 000 women treated for cervical cancer in 15 countries has provided information on dose-related risks of second cancers associated with radiotherapy (Day & Boice, 1984; Boice *et al*., 1985b, 1987, 1988, 1989). This study is one of those that provides quantitative information on the risk for cancer (UNSCEAR, 1988, 1994): it is a study of incidence, as opposed to mortality, with long and complete follow-up; the numbers of exposed and unexposed patients were large, and chemotherapy was rarely used; the existence of radiotherapy records allowed the development of a comprehensive programme for dose reconstruction to simulate actual individual doses. Estimates of the doses to specific organs were computed for selected cases and controls (Boice *et al*., 1987, 1988).

In the initial part of the study (Day & Boice, 1984; Boice *et al*., 1985b), 5146 second cancers were identified in cancer registries, whereas 4736 were expected from the rates for the general population. Radiotherapy with large doses in 82 616 women was associated with increased risks for cancers close to or within the field of radiation, but the authors concluded that these doses had not significantly altered the risk for developing a second cancer at a distant site, and at most only 162 (5%) of the 3324 second cancers in these women could be attributed to radiation.

The relative risks for developing a second primary cancer after radiotherapy for cervical cancer are shown in Figure 7 (Boice *et al*., 1985b). Some of the differences seen may be due to dose: those to organs in the pelvic area were of the order of tens of grays, those to the corpus uteri were > 200 Gy, those just outside the pelvic region were of the order of grays and those to organs at some distance from the pelvis were fractions of grays. Significantly increased risks were seen for cancers of the bladder, rectum, lung, pancreas, oesophagus, small intestine and connective tissue, and significantly decreased risks were seen for cancers of the corpus uteri and ovary. No excess risk was found within 10 years of radiotherapy for cancers at sites that received > 1 Gy. The risk rose after 10 years and remained elevated for up to 40 years of follow-up. A slight but significant excess risk for acute and nonlymphocytic leukaemia was found (RR, 1.3; $p < 0.05$); however, the radiation regimens used to treat cervical cancer were not as effective in inducing leukaemia as other regimens that have been studied, possibly because the bone marrow in the pelvis is destroyed by the very high doses of radiation used. There was little evidence that radiation affected the incidences of cancers of the colon, liver or gall-bladder or those of melanoma or chronic lymphocytic leukaemia, despite substantial exposure. The incidences of second cancers at other sites that received relatively low doses were either not increased over that expected or were increased due to other strong risk factors, such as cigarette smoking or alcohol drinking.

The expanded case–control study of this cohort involved 19 cancer registries and 20 oncology clinics, and 4188 women with second cancers were matched to 6880

Figure 7. Relative risks for developing a second primary cancer at selected sites one year or more after radiotherapy for cervical cancer, with 95% confidence intervals



From Boice *et al.* (1985b). CLL, chronic and unspecified lymphocytic leukaemia; NLL, non-lymphocytic leukaemia

controls. Doses of the order of several hundred grays significantly increased the risks for cancers of the bladder (RR, 4.0), rectum (RR, 1.8) and vagina (RR, 2.7), and doses of several grays increased the risks for stomach cancer (RR, 2.1) and for leukaemia (RR, 2.0). There was no evidence of a dose-dependent increase in risk for pancreatic cancer (Boice *et al*., 1988). The incidence of breast cancer was not increased overall, even though the average dose to this site was 0.3 Gy and 953 cases were available for evaluation; however, ovarian ablation during radiotherapy was a complicating factor (Boice *et al*., 1989). Radiation was not found to increase the overall risks for cancers of the colon, ovary or connective tissue or for Hodgkin disease, multiple myeloma or chronic lymphocytic leukaemia (Boice *et al*., 1988).

(*b*) *Hodgkin disease*

The large radiation therapy fields used in the treatment of Hodgkin disease by external beam radiotherapy, the young age of patients and their long survival provide

opportunities for investigating the risk for second cancer as a consequence of exposure to ionizing radiation. Most patients, however, are treated with a mixture of radiotherapy and chemotherapy (Henry-Amar, 1983; Blayney *et al*., 1987; Kaldor *et al*., 1987; Morales *et al*., 1992; Glanzmann *et al*., 1994; Beaty *et al*., 1995; Boivin *et al*., 1995), and many studies have convincingly linked exposure to alkylating agents to a high risk for leukaemia (see also IARC, 1987). A few have addressed the risks for solid tumours and the role of radiotherapy alone.

In a case–control study of 163 cases of leukaemia and 455 controls nested in an international cohort of 29 552 patients with Hodgkin disease in Canada and Europe, Kaldor *et al*. (1990a) found a ninefold increase in the relative risk for leukaemia associated with chemotherapy, whereas a dose–response relationship was suggested for patients treated with radiotherapy, the risk of leukaemia increasing with estimated dose to the red bone marrow: relative risk, 1 for < 10 Gy; 1.6 (95% CI, 0.26–10) for 10–20 Gy and 8.2 (95% CI, 1.7–39) for > 20 Gy.

Another case–control study nested in the same international cohort (Kaldor *et al*., 1992) involved 98 cases of lung cancer occurring after Hodgkin disease which were compared with 259 matched controls without lung cancer. Patients treated with chemotherapy had a higher risk than patients given radiotherapy only. Although the results indicated an increasing risk with dose of radiation to the lungs for those treated with radiation alone, neither the trend nor any of the relative risks by dose category was statistically significant.

In a cohort of 1677 patients in the USA who were treated for Hodgkin disease and received an average dose to the cervical lymph node area of 44 Gy, a significant excess risk for thyroid cancer was shown, based, however, on only six cases (standardized incidence ratio (SIR), 15.6; 95% CI, 6.3–32.5) (Hancock *et al*., 1991).

(*c*) *Breast cancer*

A case–control study of leukaemia was conducted within a cohort of 82 700 women with breast cancer in the USA (Curtis *et al*., 1992). Detailed information on therapy with alkylating agents and radiotherapy was obtained for 90 patients with leukaemia and for 264 matched controls. The mean dose of radiation to red bone marrow was 7.5 Gy. The risk for acute non-lymphocytic leukaemia was significantly increased after radiotherapy alone (RR, 2.4; 95% CI, 1.0–5.8; 12 cases), and a dose–response relationship was demonstrated after adjustment for the amount of chemotherapy. It was suggested that chemotherapy might interact with radiotherapy to enhance the development of leukaemia.

In a case–control study of 655 women in whom a second breast cancer developed ≥ 5 years after a primary breast cancer and 1189 controls nested in a cohort of 41 109 women in whom breast cancer was diagnosed between 1935 and 1982 in Connecticut, USA, an increased risk for contralateral breast cancer was found in association with radiotherapy (mean dose, 2.8 Gy) only among women who were under 45 years of age

at the time of treatment (RR, 1.6; 95% CI, 1.1–2.4; *n* = 78) (Boice *et al*., 1992). No excess risk was found among older women.

A similar study performed in Denmark comprised 529 cases of contralateral breast cancer and 529 controls with unilateral breast cancer nested in a cohort of 56 540 women with breast cancer diagnosed between 1943 and 1978; 82% of each group had received radiotherapy at a mean dose of 2.5 Gy. Radiation did not increase the risk for contralateral breast cancer (RR, 1.0; 95% CI, 0.7–1.5) (Storm *et al*., 1992). The dose to the contralateral breast of each case and each control was known from individual radiotherapy records in both the Danish and the US studies.

A case–control study nested in a cohort of 14 000 Canadian women with breast cancer diagnosed between 1946 and 1982 included 194 cases of contralateral breast cancer and 194 controls. The mean dose to the contralateral breast was 2.0–3.3 Gy, depending on the radiation source. This study showed no excess risk for contralateral breast cancer in association with radiotherapy (RR, 0.99; 95% CI, 0.76–1.3) (Basco *et al*., 1985).

In one study, an attempt was made to reconstruct the doses of radiation to the lung and to evaluate risk in a case–control fashion within a large cohort of breast cancer patients reported to the Connecticut Tumor Registry (USA; Inskip *et al*., 1994). The risk appeared to increase with estimated dose, but the dosimetry was complex and the location of the initial lung tumour was often unknown (RR for ≥ 15 years after radiotherapy, 2.8; 95% CI, 1.0–8.2).

In a cohort of 13 490 women with breast cancer in Sweden (Karlsson *et al*., 1996), 19 cases of soft-tissue sarcoma (SIR, 2.2; 95% CI, 1.3–3.4) were found, one of which had been misclassified and was in fact a melanoma. A matched case–control study was conducted with respect to radiation dose and the occurrence of sarcoma inside the radiation field. A significant correlation (p = 0.008) with the integral dose was observed. When the analysis was restricted to sarcomas that occurred inside the radiation field, the odds ratio was no longer significant.

(*d*) *Ovarian cancer*

A case–control study comprising 114 cases of leukaemia and 342 controls within an international cohort of 99 113 survivors of ovarian cancer showed no significant excess risk for leukaemia associated with radiotherapy alone (RR, 1.6; 95% CI, 0.51–4.8) (Kaldor *et al*., 1990b), and no significant risk for bladder cancer was observed (RR, 1.9; 95% CI, 0.77–4.9; *n* = 63) (Kaldor *et al*., 1995).

In a more recent international study in Europe and North America of 28 971 patients in whom ovarian cancer was diagnosed between 1980 and 1993, a case–control study of 96 cases of secondary leukaemia and 272 controls found no risk associated with exposure to radiotherapy at a median dose to the bone marrow of 18.4 Gy (RR, 0.4; 95% CI, 0.04–3.5) (Travis *et al*., 1999).

(*e*) *Testicular cancer*

In a study of 28 843 men with testicular cancer who survived for one year or more, identified in 16 population-based tumour registries in Europe and North America, 1406 patients developed a second primary malignancy (Travis *et al.*, 1997). The overall SIR was 1.43 (95% CI, 1.36–1.51), and a significantly increased risk was seen for acute leukaemia ([SIR, 3.4; 95% CI, 2.4–4.7]; $n = 36$) in relation to both chemotherapy and radiotherapy. Significantly increased risks seen for cancers of the stomach (SIR, 1.95; 95% CI, 1.6–2.4; $n = 93$), bladder (SIR, 2.0; 95% CI, 1.7–2.4; $n = 154$) and pancreas (SIR, 2.2; 95% CI, 1.7–2.8; $n = 66$) were mainly associated with radiotherapy. The dose of radiation was not estimated, and excess risks for cancer were noted among patients who did not receive radiotherapy.

(*f*) *Malignant disorders during childhood*

One of the great successes in the treatment of cancer is the increased survival of patients treated in childhood for malignancies. Radiotherapy, often in combination with chemotherapy, has prolonged the life expectancy of children with cancer, leaving open the possibility for the development of late effects and particularly second cancers. Because childhood cancer is rare, national and international groups have combined their data to evaluate the risks. The most informative studies were conducted by the Late Effects Study Group (Tucker *et al.*, 1984, 1987a,b, 1991) and several groups in the United Kingdom (Hawkins *et al.*, 1987, 1992, 1996) and France (de Vathaire *et al.*, 1989, 1999b). The cohort studies of children with cancer who survived for at least two years indicate that the risk for developing a second cancer 25 years after the diagnosis of the first cancer was as high as 12% (Tucker *et al.*, 1984); that for a second cancer 50 years after diagnosis of hereditary retinoblastoma was as high as 51% (Wong *et al.*, 1997).

High doses of radiotherapy have been associated with increased risks for brain cancer, thyroid cancer and bone and soft-tissue sarcomas, with dose–response relationships. The effect of radiation on the risk for leukaemia is less clear because it is difficult to control for the effect of concomitant chemotherapy (see IARC, 1987), which is associated with a much higher risk for leukaemia than radiation and is cytotoxic at therapeutic doses.

An international cohort study of 9170 children who developed a second malignant tumour at least two years after diagnosis of a first tumour, conducted by the Late Effects Study Group (Tucker *et al.*, 1984), provided information on risks associated with radiotherapy in three nested case–control studies involving 64 cases of bone cancer and 209 controls (Tucker *et al.*, 1987a), 23 cases of thyroid cancer and 89 controls (Tucker *et al.*, 1991) and 25 cases of leukaemia and 90 controls (Tucker *et al.*, 1987b). Although the doses to red bone marrow were accurately quantified, there was no evidence of a dose–response relationship for leukaemia, and the authors concluded that high doses to small volumes of tissue probably result in killing of stem cells rather

than carcinogenic transformation. When the doses to the site of secondary bone cancers were reconstructed, a dose–response relationship was demonstrated, but no increase in the risk for bone cancer was observed at doses < 10 Gy, consistent with the hypothesis that radiation-induced bone cancer occurs only after very high doses. The relationship between dose and the relative risk for bone cancer was similar among patients treated for bilateral retinoblastoma, who have a high risk for developing sarcoma, and among children treated with radiation for other malignancies. The dose–response curve for thyroid cancer (average dose, 13 Gy) was also relatively flat, suggesting to the authors that cancer induction and cell killing have competing roles at high therapeutic doses. In comparison with the general population, the SIR for thyroid cancer was 53 (95% CI, 36–80).

A British cohort study of 10 106 three-year survivors of childhood cancer (Hawkins *et al.*, 1987) showed an SIR of 5.6 (95% CI, 3.8–8.1; $n = 40$) for second tumours among 2668 children with cancer (except retinoblastoma) who received radiotherapy, in comparison with the general population. For children with hereditary retinoblastoma, the RR for second tumours was 26 (95% CI, 14–45). Two case–control studies were nested in this study, involving 59 cases of second bone cancer and 220 controls (Hawkins *et al.*, 1996) and 26 cases of second leukaemia and 96 controls (Hawkins *et al.*, 1992). A dose–response relationship was reported for bone cancer, but it was not statistically significant ($p = 0.065$). The risk for leukaemia increased with dose of radiation to the red bone marrow, but the confidence interval around the overall estimate of risk was wide (RR, 8.4; 95% CI, 0.9–81). [The Working Group underlined the difficulty in controlling for the effects of chemotherapy, which is associated with very high risks for leukaemia, in analyses of the effects of radiotherapy.]

A French–British cohort study comprised 4400 three-year survivors of childhood cancer (de Vathaire *et al.*, 1999b). As this cohort overlapped somewhat with those of the Late Effects Study and the British studies described above, it is not completely independent. The SIR for the development of any second cancer among the 1045 children who received radiotherapy alone was 5.6 (95% CI, 3.8–7.8) when compared with the general population. Brain cancer developed as a second cancer only in children who had received doses > 5 Gy (Little *et al.*, 1998a). Brain cancer had previously been linked to cranial radiotherapy for acute lymphoblastic leukaemia in children in the USA (Neglia *et al.*, 1991). Several case–control studies were nested in the French–British study: e.g. 32 cases of osteosarcoma and 160 controls (Le Vu *et al.*, 1998), and 25 cases of any second cancer and 96 controls, 23 and 74 of whom had received radiotherapy, respectively (Kony *et al.*, 1997). Thyroid carcinoma developed at a high rate (SIR, 80) among the 2827 children who received radiotherapy at a dose of 7 Gy (de Vathaire *et al.*, 1999a), and associations with radiation dose were reported for all types of second cancer together and for osteosarcoma, leukaemia and thyroid cancer.

In a cohort study of 1380 children (483 girls) treated for Hodgkin disease, the average dose to the chest region was 40 Gy for the girls who eventually developed breast cancer; 17 cases of breast cancer were observed after radiotherapy alone or

combined, giving an SIR of 75 (95% CI, 45–118) in comparison with the general population. In seven of these cases, only radiotherapy was used, but the SIR was not reported (Bhatia *et al*., 1996). The cumulative incidence of breast cancer at 40 years of age was 35% (95% CI, 18–52). [The Working Group noted that the incompleteness of the follow-up of persons with no medical problems could have biased the risk estimates upwards.]

Radiotherapy for retinoblastoma is associated with an increased risk for osteosarcoma (Jensen & Miller, 1971). In a cohort study of cancer mortality involving 1458 patients in the USA who were followed-up for retinoblastoma for an average of 17 years, 534 of whom received only radiotherapy, the SMR of children with bilateral disease who received radiotherapy was 2.9 (95% CI, 2.2–3.7; $n = 79$) (Eng *et al*., 1993).

In order to determine the long-term risk for new primary cancers among survivors of childhood retinoblastoma and to quantify the role of radiotherapy in the development of sarcomas, the incidence of cancer was studied in the same cohort, involving 1604 patients who had survived for at least one year after diagnosis (Wong *et al*., 1997). The children were treated at hospitals in Massachusetts and New York (USA) during 1914–84, and detailed records were available, allowing reconstruction of doses. The incidence of subsequent cancers was significantly increased only among the 961 patients with hereditary retinoblastoma, in whom 190 cancers were diagnosed, whereas 6.3 were expected in the general population (RR, 30). The cumulative incidence of a second cancer 50 years after diagnosis was 51 ± 6.2% for hereditary retinoblastoma and 5 ± 3% for non-hereditary retinoblastoma. All of the 114 sarcomas of diverse histological types occurred in patients with hereditary retinoblastoma, and the risk was associated with exposure to radiation at doses > 5 Gy, rising to 10.7-fold at doses > 60 Gy ($p < 0.05$). A dose–response relationship was demonstrated for all sarcomas and, for the first time in humans, for soft-tissue sarcomas; however, despite the role of genetic predisposition in the development of sarcomas, therapeutic doses < 5 Gy did not increase the risk for cancer.

(*g*) *Bone-marrow transplant*

Studies of patients given radiotherapy to the whole body or to part of the body at doses of about 10 Gy in conjunction with bone-marrow transplants show an increased risk for second cancers with evidence of a dose–response relationship (Curtis *et al.*, 1997). The effect of prior radiotherapy and chemotherapy could not be discounted, however.

2.3.2 *Radiotherapy for benign disease*

The studies of patients treated with X- and γ-rays for benign disease (Table 19) have provided valuable information about the role of radiotherapy in the risk for cancer. The doses used are not nearly as high as those used to treat malignant disease,

Table 19. Study characteristics and second cancers in patients receiving radiotherapy for a benign disease

Reference	Disease treated (period of treatment)	Sex, no. of exposed and total no. of individuals or, for the case–control study, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy)	Second cancers studied	Results
Cohort studies						
Shore *et al.* (1986)*	Post-partum acute mastitis (1940–57)	Women, 601/1840	29; 20–45	Breast, 3.8	Breast	Breast: RR = 3.2; *n* = 56
Mattsson *et al.* (1993, 1997)*	Benign breast disease (1925–61)	Women, 1216/3090	27; 0–61	Breast, 5.84 Lung, 0.75 Liver, 0.66 Stomach, 0.66 Pancreas, 0.37 Oesophagus, 0.28 Kidney, 0.13 Rectum, 0.008	All	Colon: RR = 1.8; *n* = 25 Breast: RR = 3.6; *n* = 183
Griem *et al.* (1994)*	Peptic ulcer (1973–65)	Both sexes, 1831/3609	21.5; 20–51	Stomach, 14.8 Colon, 0.1–12.3 Liver, 4.6 Lung, 1.8 Red bone marrow, 1.55	All	Stomach: RR = 2.8; *n* = 40 Pancreas: RR = 1.9; *n* = 28 Lung: RR = 1.7; *n* = 99 Leukaemia: RR = 3.3; *n* = 11
Alderson & Jackson (1971)	Uterine bleeding (1946–60)	Women, 2049/2049	15	NR	All	None
Inskip *et al.* (1990a,b)*	Uterine bleeding (1925–65)	Women, 4153/4153	27; < 60	Stomach, 0.2 Colon, 1.3 Liver, 0.2 Bladder, 6.0 Red bone marrow, 0.5 Uterus, 32 Vagina, 14	All	Colon: SMR = 1.3; *n* = 86 Pancreas: SMR = 1.5; *n* = 37 Uterus: SMR = 1.8; *n* = 105 Other genital sites: SMR = 1.5; *n* = 44 Leukaemia, excluding CLL: [SMR = 1.8]; *n* = 25

Table 19 (contd)

Reference	Disease treated (period of treatment)	Sex, no. of exposed and total no. of individuals or, for the case–control study, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy)	Second cancers studied	Results
Cohort studies (contd)						
Ryberg *et al.* (1990)*	Uterine bleeding (1912–77)	Women, 788/2007	28; 0–56	Pelvis, 6.5	All	Ovary, corpus uteri, cervix uteri, rectum and bladder combined: SIR = 1.6; *n* = 30
Inskip *et al.* (1993)*	Benign gynaecological disorders (1925–65)	Women, 9770/12 955	25	Red bone marrow, 1.2	All haematological malignancies	Leukaemia, excluding CLL: [RR = 4.7]; *n* = 47
Darby *et al.* (1994)*	Uterine bleeding (1940–60)	Women, 2067/2067	28; 5–30	Stomach, 0.23 Colon, 3.20 Liver, 0.27 Bladder, 5.20 Red bone marrow, 1.30	All	Colon: SMR = 1.4; *n* = 47 Bladder: SMR = 3.0; *n* = 20 Multiple myeloma: SMR, 2.6; *n* = 9 Leukaemia: SMR = 2.05; *n* = 12
Ron *et al.* (1994)*	Refractory hormonal infertility and amenorrhoea (1925–61)	Women, 816/816	35	Ovary, 0.88 Pelvis, 0.62 Uterus, 0.54 Sigmoid colon, 1.02 Red bone marrow, 0.29	All	Colon: SMR = 1.9; *n* = 15 Non-Hodgkin lymphoma: SMR = 2.8; *n* = 6

Table 19 (contd)

Reference	Disease treated (period of treatment)	Sex, no. of exposed and total no. of individuals or, for the case–control study, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy)	Second cancers studied	Results
Cohort studies (contd)						
Weiss *et al.* (1994, 1995)*	Ankylosing spondylitis (1935–57)	Both sexes, 14 556/15 577	25 (1–57)	Oesophagus, 5.55 Colon, 4.10 Stomach, 3.21 Liver, 2.13 Lung, 2.54 Bone, 4.54 Breast, 0.59 Bladder, 2.18 Kidney, 6.08 Thyroid, 1.41 Brain, 0.20 Red bone marrow, 5.10	All; ≥ 5 years since first treatment	Oesophagus: RR = 1.9; *n* = 74 Colon: RR = 1.3; *n* = 113 Pancreas: RR = 1.6; *n* = 84 Lung: RR = 1.2; *n* = 563 Bone: RR = 3.3; *n* = 9 Prostate: RR = 1.4; *n* = 88 Kidney: RR = 1.6; *n* = 35 Non-Hodgkin lymphoma : RR = 1.7; *n* = 37 Hodgkin disease: RR = 1.65; *n* = 13 Multiple myeloma: RR = 1.6; *n* = 22 Leukaemia, excluding CLL: RR = 3.1; *n* = 53
Damber *et al.* (1995)*	Benign lesions of the locomotor system or scoliosis (1950–64)	Both sexes, 20 024/20 024	1–38	Red bone marrow, 0.39	Haematological malignancies	Leukaemia: SIR = 1.2; *n* = 116; SMR = 1.2; *n* = 115
Shore *et al.* (1976, 1984)*	Tinea capitis (1940–59)	Both sexes, 2226/3613	26 (13–35)	Skin, 4.5 Thyroid, 0.1 Brain, 1.4	Thyroid, skin, brain, leukaemia, salivary glands, bone	Skin: RR = 3.8; *n* = 31

Table 19 (contd)

Reference	Disease treated (period of treatment)	Sex, no. of exposed and total no. of individuals or, for the case–control study, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy)	Second cancers studied	Results
Cohort studies (contd)						
Ron & Modan (1980); Ron *et al.* (1988a,b, 1989, 1991)*	Tinea capitis during childhood (1948–60)	Both sexes, 10 834/27 060	30; 26–39	Thyroid, 0.09 Brain, 1.5 Breast, 0.016 Skin, 6.8 Red bone marrow, 0.3	Thyroid, brain, skin, breast, leukaemia	Non-melanoma skin: RR = 4.2; *n* = 44 Brain: RR = 6.9; *n* = 60 Thyroid: RR = 4.0; *n* = 43 Leukaemia: RR = 2.3; *n* = 14
Janower & Miettinen (1971)	Thymus enlargement during childhood (1924–46)	Both sexes, 466/972	30	Thyroid, 4	Thyroid, breast	Thyroid: [SIR = 34]; *n* = 2
Hildreth *et al.* (1985, 1989); Shore *et al.* (1993)*	Thymus enlargement during childhood (1926–57)	Both sexes, 2657/7490	37; 29–60	Skin, 2.3 Breast, 0.69 Thyroid, 1.4	Thyroid, breast, skin, bone, nervous system, salivary gland	Skin: RR = 2.3; *n* = 11 Breast: RR = 3.6; *n* = 22 Thyroid: SIR = 24; *n* = 37
Li *et al.* (1974)	Skin haemangioma during childhood (1946–1968)	Both sexes, 4746/4746	7	NR	All	None
Fürst *et al.* (1988); Lundell & Holm (1995, 1996); Lundell *et al.* (1996)*	Skin haemangioma during childhood (1920–59)	Both sexes, 14 351/14 351	39; 1–67	Bone, 0.40 Thyroid, 0.26 Red bone marrow, 0.13 Breast, 0.39 Brain, 0.08 Stomach, 0.09 Lung, 0.12 Gonads, 0.05	All	Pancreas: SIR = 3.3; *n* = 9 Breast: SIR, 1.2; *n* = 75 Thyroid: SIR = 2.3; *n* = 17 Endocrine glands: SIR = 2.0; *n* = 16

Table 19 (contd)

Reference	Disease treated (period of treatment)	Sex, no. of exposed and total no. of individuals or, for the case–control study, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy)	Second cancers studied	Results
Cohort studies (contd)						
Lindberg *et al.* (1995); Karlsson *et al.* (1997)*	Skin haemangioma during childhood (1930–65)	Both sexes, 12 055/12 055	33; 1–59	Thyroid, 0.116 Breast, 0.155 Lung, 0.121 Brain, 0.07	All	Brain: SIR = 1.8; *n* = 47 Thyroid: SIR = 1.9; *n* = 15 Other endocrine glands: SIR, 2.6; *n* = 23
Maxon *et al.* (1980)	Various benign diseases of the head and neck (1963–67)	Both sexes, 1266/12 089	36.5	Thyroid, 2.9	Thyroid	Thyroid: [RR = 15.5]; *n* = 16
DeGroot *et al.* (1983)	Tonsil, thymus, acne (NR)	Both sexes, 263/416	26	Thyroid, 4.5	Thyroid	Thyroid: [SIR = 55]; *n* = 11 (results from physical examination)
van Daal *et al.* (1983)	Various benign diseases of the head and neck (1933–63)	Both sexes, 605/2400	38–43	Thyroid, 10.4–20.7 Skin, 10–19.5	Thyroid, skin	Skin: SIR, NR; *n* = 20
Fjälling *et al.* (1986)*	Tuberculous cervical adenitis (1975–82)	Both sexes, 444/444	43	Thyroid, 0.4–51	Thyroid	Thyroid: [SIR = 23]; *n* = 25
Schneider *et al.* (1993)	Infections and inflammatory diseases of the upper respiratory tract during childhood (1939–62)	Both sexes, 2634/2634	33; 12–51	Thyroid, 0.6	Thyroid	Thyroid: [SMR = 1.4]; *n* = 309

Table 19 (contd)

Reference	Disease treated (period of treatment)	Sex, no. of exposed and total no. of individuals or, for the case–control study, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy)	Second cancers studied	Results
Cohort studies (contd)						
Royce *et al.* (1979)	Various diseases of the head and neck (1937–70)	Both sexes, 214/457	28	Thyroid, 7.1	Thyroid	No increase
Refetoff *et al.* (1975)	Tonsils, adenoids, enlarged thymus (NR)	Both sexes, 100/100	24	Head and neck, 8	Thyroid	Thyroid: RR, NR; *n* = 7
Straub *et al.* (1982)	Lymphoid hyperplasia, acne, enlarged thymus (1940–60)	Both sexes, 553/553	23	Thyroid, 1	Thyroid	Thyroid: no significant increase (relatively late age at irradiation)
Pottern *et al.* (1990)	Lymphoid hyperplasia (1938–69)	Both sexes, 1195/2258	29	Thyroid, 0.24	Thyroid	Thyroid: [SIR = 2.4]; *n* = 13
Brada *et al.* (1992)	Pituitary adenoma (1962–86)	Both sexes, 334/334	11	Brain, 45	Brain	Brain: SIR = 9.4; *n* = 5
Bliss *et al.* (1994)	Pituitary adenoma (1962–90)	Both sexes, 296/296	8; 0.1–28	Brain, 45	All	Non-central nervous system tumours: SIR = 17.5; *n* = 30
Hanford *et al.* (1962)	Tuberculous adenitis (1920–50)	Both sexes, 162[a]/296	17	Thyroid, 8.2 (no standard dose)	Thyroid	Thyroid: [RR = 80]; *n* = 8

Table 19 (contd)

Reference	Disease treated (period of treatment)	Sex, no. of exposed and total no. of individuals or, for the case–control study, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy)	Second cancers studied	Results
Case–control study						
Fürst *et al.* (1990)	Skin haemangioma in childhood (1920–59)	Both sexes, 94/359	35 (0–59) (time since first treatment)	Thyroid, 0.3–0.8 Bone, 0.07–3 Breast, 0.2 Brain, 0.003–0.1	Breast, thyroid, brain, bone, soft tissue	Thyroid: linear trend $p < 0.05$; $n = 14$ Bone and soft tissue: OR = 19.5; $n = 3$ (≥ 0.5 Gy)

CLL, chronic lymphocytic leukaemia; NR, not reported; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio

* Studies cited in text

[a] Examined ≥ 10 years after irradiation

so that cell-killing effects do not predominate, survival after treatment is good and there is minimal confounding from concomitant treatment.

(*a*) *During adulthood*

(i) *Benign breast disease*

A cohort of 1216 women treated for benign breast disease with radiotherapy and 1874 women treated by other means in Sweden in 1925–54 were studied for subsequent cancer development (Baral *et al*., 1977; Mattsson *et al*., 1993, 1995, 1997). The mean age of the women at the time of radiotherapy was 40 years. The mean estimated dose of radiation to the breast was 5.8 Gy, and that to 14 other organs ranged from 0.01 to the rectum to 0.75 Gy to the lung. The mean follow-up time was 27 years. In an internal analysis, the incidence of breast cancers was increased (RR, 3.6; 95% CI, 2.8–4.6; *n* = 183) (Mattsson *et al*., 1993), with a linear dose–response relationship at low-to-medium doses. The risk for radiation-induced breast cancer was inversely related to age at exposure, the lowest risk being seen for women who were exposed at or after the menopause. The relative risk for all cancers together (excluding breast) was 1.2 (95% CI, 0.97–1.4; *n* = 189). In an analysis by site, the incidence of colon cancer was increased to a degree that approached statistical significance (RR, 1.8; 95% CI, 0.96–3.4; *n* = 25). The relative risk was 1.8 (95% CI, 0.75–4.5) for stomach cancer, at an average dose of 0.66 Gy, and 1.8 (95% CI, 0.65–5.0; *n* = 10) for lung cancer, at an average dose of 0.75 Gy. Deficits were noted for leukaemia (RR, 0.67; 0.18–2.1; *n* = 5) and several other cancers (Mattsson *et al*., 1997). [The Working Group noted that some benign diseases of the breast are independent risk factors for breast cancer, and this might have contributed to the excess risk if bias was present in the selection of those who received radiotherapy. The inconsistent patterns of cancer excesses for some sites, e.g. the colon, which received little exposure, were noted.]

A cohort of 601 women in the USA treated with radiotherapy for acute post-partum mastitis and 1239 treated by other means between 1940 and 1957 were followed-up for an average of 29 years. The average dose to the breast was 3.8 Gy, and a dose–response relationship was demonstrated. In an internal analysis, an increased risk for breast cancer was shown (RR, 3.2; 90% CI, 2.3–4.3; *n* = 56) (Mettler *et al*., 1969; Shore *et al*., 1986). In a combined analysis of this study with those of atomic bomb survivors and of tuberculosis patients who received repeated chest fluoroscopies, the risk was similar in the three populations, at least for people aged 10–40 years at the time of exposure (Boice *et al.*, 1979; Land *et al.*, 1980).

(ii) *Peptic ulcer*

A cohort of 1831 patients in the USA who received X-rays between 1937 and 1965 for the treatment of peptic ulcer and 1778 who did not were followed for an average of 22 years before 1985 (Griem *et al*., 1994). The dose to the stomach was about 15 Gy. In an internal analysis of cancer mortality, this treatment was associated with a significantly increased relative risk for death from cancers at all sites (RR, 1.5; 95% CI,

1.3–1.8; *n* = 341) and from stomach cancer (RR, 2.8; 95% CI, 1.6–4.8; *n* = 40). Cancers at the other sites studied were not convincingly linked to radiotherapy.

(iii) *Benign gynaecological diseases*

A cohort of 4153 women in the USA who received radiotherapy between 1925 and 1965 for uterine bleeding disorders were followed-up for an average of 27 years before 1984 (Inskip *et al.*, 1990a,b). The median dose to red bone marrow was estimated to be 0.5 Gy, and the median dose to the uterus was 32 Gy. By comparison with mortality rates for the general population of the USA, this treatment was associated with a significantly increased SMR for death from all cancers (SMR, 1.3; 95% CI, 1.2–1.4; *n* = 632). A significant increase was observed in deaths from cancer of the colon (SMR, 1.3 [95% CI, 1.0–1.6]; *n* = 86), cancers of the uterus (SMR, 1.8; 95% CI, 1.5–2.2; *n* = 105), cancers of other female genital organs (SMR, 1.5; 95% CI, 1.1–2.0; *n* = 44) and leukaemia (SMR, 2.0; 95% CI, 1.4–2.8; *n* = 34).

This cohort was expanded to 9770 women, for whom the average dose to red bone marrow was estimated to be 1.2 Gy (Inskip *et al.*, 1993). In comparison with 3185 women treated by other methods, radiotherapy was associated with a significantly increased relative risk for death from leukaemia (2.5; 95% CI, 1.4–5.2; *n* = 64 after exclusion of two cases of leukaemia diagnosed before radiotherapy), but no increase in mortality from non-Hodgkin lymphoma, Hodgkin disease or multiple myeloma was observed.

A cohort of 2067 women in the United Kingdom who received radiotherapy for uterine bleeding disorders between 1940 and 1960 was followed-up for an average of 28 years before 1990 (Darby *et al.*, 1994). The average doses ranged from 0.002 Gy to the brain to 5.3 Gy to the ovary and 5.2 to the uterus. In all, 331 deaths from cancer were observed (SMR, 1.1; 95% CI, 1.0–1.2), and significant excesses of deaths were observed from cancers at heavily irradiated sites in the pelvic area (SMR, 1.5; 95% CI, 1.2–1.7; *n* = 129), urinary bladder cancer (SMR, 3.0; 95% CI, 1.8–4.6; *n* = 20), colon cancer (SMR, 1.4; 95% CI, 1.05–1.9; *n* = 47), leukaemia (SMR, 2.05; 95% CI, 1.1–3.6; *n* = 12) and multiple myeloma (SMR, 2.6; 95% CI, 1.2–4.9; *n* = 9); whereas fewer deaths from breast cancer were observed than expected among women who received more than 5 Gy to the ovaries (SMR, 0.53; 95% CI, 0.34–0.78; *n* = 24).

A cohort of 788 Swedish women who received radiotherapy between 1912 and 1977 for uterine bleeding was followed-up for an average of 28 years before 1982 (Ryberg *et al*., 1990). By comparison with cancer incidence rates for the general population, those for women who underwent radiotherapy were slightly increased (SIR, 1.2; 95% CI, 1.0–1.5; *n* = 107); however, the SIR of an unexposed group of 1219 women with the same condition was similar (1.1; 95% CI, 0.94–1.3). The exposed group had a significantly increased SIR for cancers at heavily irradiated sites in the pelvic area (ovary, corpus uteri, cervix, rectum and bladder; SIR, 1.6; 95% CI, 1.1–2.3; *n* = 30) but not for cancers at other sites.

(iv) *Hormonal infertility*

A cohort of 816 women in the USA who received X-rays to the ovaries and/or pituitary gland for refractory hormonal infertility and amenorrhoea between 1925 and 1961 was followed-up for an average of 35 years before 1990 (Ron *et al.*, 1994). The average doses were 0.011 Gy to the breast, 0.88 Gy to the ovary and 1.02 Gy to the sigmoid colon. In an external analysis of cancer mortality, 78 deaths from cancer were observed (SMR, 1.1; 95% CI, 0.9–1.4). No increase in mortality rates was found for leukaemia or cancers of the ovary or brain, sites directly exposed to radiation.

(v) *Ankylosing spondylitis*

A cohort of 14 556 patients in the United Kingdom who received X-rays for the treatment of ankylosing spondylitis between 1935 and 1957 and 1021 patients who received other treatments were followed-up for an average of 25 years. This study, first reported in 1957 (Court Brown & Doll, 1957), provides strong evidence that radiation can cause leukaemia and other cancers in humans. Estimates were made of the doses received by persons who developed leukaemia and by a sample of the entire cohort, irrespective of mortality outcome. The average dose to red bone marrow was estimated to be 4.4 Gy, while those to other organs ranged from 0.2 to the brain to 5.55 Gy to the oesophagus; the doses were not uniform, and the lower spine received the highest dose. In a study of mortality (Darby *et al.*, 1987; Weiss *et al.*, 1994, 1995), the irradiated patients had a significantly greater mortality rate from cancer than expected from the national rates for England and Wales (SMR, 1.30; 95% CI: 1.2–1.35), and a significant increase was noted for leukaemia other than chronic lymphocytic leukaemia (SMR, 3.1; 95% CI, 2.4–4.1; $n = 53$), although a clear dose–response relationship was not evident. The excess cancers occurred predominantly in the tissues that were likely to have been exposed during radiotherapy, such as the oesophagus, lung, bladder, kidney, bone and connective and soft tissue. The relative risks of men were significantly increased for leukaemia (RR, 2.9; $p < 0.001$; $n = 55$), colorectal cancers (RR, 1.25; $p < 0.01$; $n = 148$) and other neoplasms (RR, 1.3; $p < 0.001$; $n = 1225$). The risks for prostate cancer, non-Hodgkin lymphoma and multiple myeloma were also increased. For lung cancer, the SMR associated with radiotherapy (average dose to the lung, 2.54 Gy) was 1.2 (95% CI, 1.1–1.3; $n = 563$), but the risk declined to near the expected level after 25 years. No excess risk for death from stomach cancer was found on the basis of 127 deaths and an average estimated dose of 3.2 Gy. No significant excess of deaths from breast cancer (average dose, 0.59 Gy) was found among the 2394 treated women (SMR, 1.1; 95% CI, 0.77–1.45). The treatment for ankylosing spondylitis involved various radiation fields, some covering only the neck region and others covering the entire spine. The dose–response relationship could be evaluated only for leukaemia and was found to be relatively flat over various categories of dose to the bone marrow, possibly because of cell killing effects. The condition being treated, ankylosing spondylitis, is known to be associated with increased rates of colon cancer, independently of exposure to radiation, and perhaps

with other conditions as well. It is unclear whether these factors influenced the time–response relationship and contributed to the return to levels of risk near those expected after 25 years.

A cohort of 20 024 Swedish patients who received X-rays between 1950 and 1964 for painful arthritic conditions such as spondylosis was followed-up for an average of 25 years before 1988 (Damber *et al.*, 1995; Johansson *et al*., 1995). The average dose to red bone marrow was estimated to have been 0.39 Gy. In analyses of both cancer incidence and cancer mortality, radiotherapy was associated with increased risks for leukaemia (SIR, 1.2; 95% CI, 0.98–1.42; n = 116 and SMR, 1.2; 95% CI, 0.99–1.45; n = 115). The reported dose–response relationship for leukaemia is not easily interpreted because chronic lymphocytic leukaemia was included and contributed 50 of the 116 cases, although this disease has not been associated with exposure to radiation. The numbers of cases of non-Hodgkin lymphoma (81 cases), Hodgkin disease (17 cases) and multiple myeloma (65 cases) were no greater than expected.

(*b*) *During childhood*

(i) *Tinea capitis*

The risk for cancer of children treated for tinea capitis (ringworm of the scalp) was studied in Israel among 10 834 patients (Ron *et al.*, 1989) and in New York (USA) among 2200 children (Shore *et al.*, 1976, 1984). In the Israeli cohort, the mean dose to the skin of the scalp was estimated to be several grays, and the scatter dose to the thyroid was estimated to be about 0.10 Gy. Significantly increased risks for thyroid cancer were seen in Israel (Ron *et al.*, 1989), and an association with non-melanoma skin cancer was seen in both Israel and New York (Shore *et al.*, 1984; Ron *et al.*, 1991). An interaction between sunlight and radiotherapy was suggested in the New York study. The Israeli study also revealed a significant relation between dose of radiation and tumours of the central nervous system (Ron *et al.*, 1988a). [The Working Group noted that although an increased risk for breast cancer after radiotherapy for tinea capitis was reported (Modan *et al.*, 1989), the increase was related to a deficit of breast cancer cases among the control subjects rather than to an increase among the exposed women.]

(ii) *Enlarged thymus gland*

A cohort of 2657 patients treated with radiotherapy for an enlarged thymus gland between 1926 and 1957 in Rochester, New York (USA), has been studied extensively (Shore *et al.*, 1993). Ninety per cent were treated before six months of age (Hildreth *et al*., 1985). The individual doses, estimated from radiotherapy records (Hempelmann *et al*., 1967), were 0.69 Gy to the breast (Hildreth *et al*., 1989) and 1.4 Gy to the thyroid (Shore *et al*., 1993). A significantly increased risk was found for cancer of the thyroid, with a dose–response relationship (Shore *et al*., 1980, 1985, 1993). Of the 1201 women who received radiotherapy, 22 developed breast cancer after a mean follow-up of 36 years, and the relative risk, in comparison with sibling

controls, was 3.6 (95% CI, 1.8–7.3); none of the cases occurred before 28 years after irradiation (Hildreth *et al.*, 1989). The relative risk for cancer of the skin was 2.3 (95% CI, 1.0–5.6), but no excess was found for cancers of the nervous system or salivary glands (Hildreth *et al.*, 1985).

(iii) *Skin haemangiomas*

Various techniques, most based on X-rays or applicators of ^{226}Ra, have been used to treat skin haemangiomas, usually in children under the age of two. Two cohort studies were performed in Sweden, which comprised 12 055 patients treated between 1930 and 1965 (11 807 followed-up) (Lindberg *et al.*, 1995; Karlsson *et al.*, 1997, 1998) and 14 351 treated between 1920 and 1959 (Fürst *et al.*, 1988, 1989; Lundell & Holm, 1995; Lundell *et al.*, 1996, 1999). Lundell *et al.* (1999) combined the data for women in the two cohorts (Lindberg *et al.*, 1995; Lundell *et al.*, 1996), for a pooled analysis of 17 202 women who had received a mean dose to the breast of 0.29 Gy (range, < 0.01–36 Gy). Between 1958 and 1993, 245 breast cancers were diagnosed in this cohort, yielding a SIR of 1.2 (95% CI, 1.1–1.4). The excess relative risk per gray was estimated to be 0.35 (95% CI, 0.18–0.59), which is somewhat lower than that reported in other studies. The risk for leukaemia was not associated with the dose of radiation to bone marrow (average, 0.13 Gy; range, < 0.01–4.6 Gy). During 1920–86, there were only 20 deaths from leukaemia, and the low dose to bone marrow implied a limited possibility of detecting an effect even among 14 624 irradiated infants (Lundell & Holm, 1996). The risk for cancer of the thyroid was evaluated for 14 351 irradiated infants (Lundell *et al.*, 1994; Lundell & Holm, 1995), among whom 17 cases were found (SIR, 2.3; 95% CI, 1.3–3.65) after a mean follow-up of 39 years. The mean dose to the thyroid of the patients with cancer was 1.1 Gy (range, < 0.01–4.3 Gy). The excess risk for thyroid cancer began to be seen 19 years after irradiation. The SIRs were similar for women (SIR, 2.2) and men (SIR, 2.9), but 15 of the 17 cancers occurred in women, such that the incidence rate in this cohort was nearly 10 times higher in women than in men.

In a study of intracranial tumours in 12 055 infants who were treated for skin haemangiomas (Karlsson *et al.*, 1997), 47 tumours developed in 46 persons (SIR, 1.8; 95% CI, 1.3–2.4). No dose–response relationship was observed, and the mean dose to the brain was low (0.07 Gy), although some children received > 1 Gy. In a pooled analysis of this cohort and that of Lundell and Holm (1995), for a total of 28 008 patients, 88 brain tumours were identified in 86 persons (SIR = 1.4; 95% CI, 1.1–1.8), to give an ERR of 2.7 per Gy (95% CI, 1.0–5.6). These results strongly indicate that a dose–response relationship exists (Karlsson *et al.*, 1998).

(iv) *Enlarged tonsils and other benign conditions*

A cohort of 2634 patients in the USA who received X-rays between 1939 and 1962 primarily for enlarged tonsils during childhood was followed-up for 33 years. The average dose to the thyroid was estimated to be 0.6 Gy. During screening of the

thyroid, 309 thyroid cancers were diagnosed. Successive follow-up of this cohort confirmed a strong dose–response relationship between the dose to the thyroid and the risk for thyroid cancer (Favus *et al*., 1976; Schneider *et al*., 1985, 1993).

A cohort of 444 patients in Sweden treated for cervical tuberculous adenitis received an average dose to the thyroid of 0.4–51 Gy. A significant excess of thyroid carcinoma was observed ([SIR, 23] $n = 25$) (Fjälling *et al*., 1986).

(v) *Combined analysis of studies of thyroid cancer*

Most of the available information on radiation-induced thyroid cancer comes from studies of cohorts of children who received radiotherapy for benign diseases. In 1995, a pooled analysis of seven studies was published (Ron *et al*., 1995), comprising the studies of atomic bomb survivors and six studies of patients who received radiotherapy: two case–control studies (Boice *et al*., 1988; Tucker *et al*., 1991) and four cohort studies (Ron *et al*., 1989; Pottern *et al*., 1990; Schneider *et al*., 1993; Shore *et al*., 1993). Five of the six studies concerned children who were ≤ 15 years old at the time of radiotherapy. The excess relative risk per gray after radiotherapy with X- or γ-rays during childhood was estimated to be 7.7 (95% CI, 2.1–28.7), and the excess absolute risk for thyroid carcinoma per 10^4 person–years Gy to be 4.4 (95% CI, 1.9–10.1), on the basis of 458 atomic bomb survivors and 448 exposed patients. The risk was strongly dependent on the age at exposure, being highest for people exposed when they were under the age of five years. No significant risk was found for exposure in adult life. A dose–response relationship was seen for persons exposed as children. The pooled study of irradiated children did not include several studies that had not been published at the time the analysis began (Lundell *et al*., 1994; Lindberg *et al*., 1995; de Vathaire *et al*., 1999a).

2.3.3 *Diagnostic X-radiation*

These studies are summarized in Table 20.

(*a*) *During adulthood*

(i) *Repeated chest fluoroscopies for pulmonary tuberculosis*

In a cohort study in Canada of 64 172 patients (32 255 men and 31 917 women) who had been treated for tuberculosis, 25 007 patients had been treated by lung collapse, which requires frequent monitoring by X-ray fluoroscopy. The number of such examinations ranged from one to several hundreds; the mean dose to the lung was 1.02 Sv, and the mean dose to the breast was 0.89 Sv. In 1987, the mean follow-up time was 37 years. Two main studies of cancer mortality in this cohort have been published: one on lung cancer (Howe, 1995) and one on breast cancer (Miller *et al*., 1989; Howe & McLaughlin, 1996). No increase in the risk for death from lung cancer was observed (RR, 1.0; 95% CI, 0.94–1.1; $n = 1178$). In contrast, an excess of breast cancer and a dose–response relationship were found (SMR, 1.5; 95% CI, 1.3–1.6;

Table 20. Study characteristics and second cancers in patients undergoing diagnostic X-ray procedures

Reference	Reason for examination (period)	Sex, no. of exposed and total no. of individuals or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy except as noted)	Second cancers studied	Results
Cohort studies						
Howe (1995); Howe & McLaughlin (1996)*	Tuberculosis; multiple chest fluoroscopies (1930–52)	Both sexes, 25 007/64 172	37; 0–57	Lung, 1.02 (0–24.2 Sv) Breast, 0.89 (0–18.4 Sv)	Lung, breast	Breast: SMR, 1.5; *n* = 349
Davis *et al.* (1989); Boice *et al.* (1991b)*	Tuberculosis; multiple chest fluoroscopies (1925–54)	Both sexes, 6285/13 385	30; 0–50	Oesophagus, 0.80 Lung, 0.84 Breast, 0.79 Red bone marrow, 0.09 Pancreas, 0.06 Stomach, 0.06	All	Oesophagus: SMR = 2.1; *n* = 14 Breast: SIR = 1.3; *n* = 147
Levy *et al.* (1994)	Scoliosis; multiple full spinal radio-graphies (1960–79)	Both sexes, 18 471/2181	NR	Breast, 0.03 Thyroid, 0.03	All	Excess risk, 2%
Hoffman *et al.* (1989)*	Scoliosis; multiple full spinal radiographies (1935–65)	Women, 973/1030	26; 3–> 30	Breast, 0.13	Breast	Breast: SIR = 1.8; *n* = 11

Table 20 (contd)

Reference	Reason for examination (period)	Sex, no. of exposed and total no. of individuals or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy except as noted)	Second cancers studied	Results
Cohort studies (contd)						
Spengler *et al.* (1983)	Childhood; cardiac catheterization; fluoroscopy (1946–68)	Both sexes, 4891	13	NR	All	None
McLaughlin *et al.* (1993a)	Cardiac catheterization; fluoroscopy (1950–65)	Both sexes, 3915	22; 0–36	NR	All	None
Case–control studies						
Storm *et al.* (1986)	Tuberculosis; multiple chest fluoroscopies (1937–54)	Women, 89/390	< 10–≥ 40	Breast, 0.27	Breast	No increase
Ron *et al.* (1987)*	All X-ray, including dental and radiotherapy (1978–80)	Both sexes, 159/285	< 20–≥ 40	NR	Thyroid	No significant increase

Table 20 (contd)

Reference	Reason for examination (period)	Sex, no. of exposed and total no. of individuals or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy except as noted)	Second cancers studied	Results
Case–control studies (contd)						
Hallquist *et al.* (1994)*	All X-ray, including dental and radiotherapy (1980–89)	Both sexes, 171/325	> 5	Thyroid, 0–> 0.6 mGy	Thyroid	Papillary thyroid cancer: OR = 2.3; *n* = 56 (for > 0.6 mGy)
Inskip *et al.* (1995)*	All X-ray (1980–92)	Both sexes, 484/484	54	6 mGy	Thyroid	No increase
Wingren *et al.* (1997)*	All X-ray, including dental (1977–89)	Women, 186/426	1–14	Thyroid, 0–> 1 mGy	Thyroid	Thyroid: OR = 2.6; *n* = 60 (for > 1 mGy)
Preston-Martin *et al.* (1980)	All X-ray, including dental and radiotherapy (1972–75)	Women, 185/185	< 7	NR	Intracranial meningiomas	No increase
Preston-Martin *et al.* (1989)*	All X-ray (1979–85)	Both sexes, 136/136	3–20	Red bone marrow, 0–≥ 2 mGy	Chronic myeloid and monocytic leukaemia	Leukaemia: OR = 2.4 (for ≥ 2 mGy)

Table 20 (contd)

Reference	Reason for examination (period)	Sex, no. of exposed and total no. of individuals or, for case–control studies, nos of cases and controls	Mean follow-up (years)	Organ dose (Gy except as noted)	Second cancers studied	Results
Case–control studies (contd)						
Boice *et al.* (1991a)*	All X-ray (1956–82)	Both sexes, 1091/1390	15–> 50	Red bone marrow, 0.00001–0.23	Non-Hodgkin lymphoma, leukaemia, multiple myeloma	No increase; dose–response relationship for multiple myeloma
Ryan *et al.* (1992)	Dental X-ray (1987–90)	Both sexes, 170/417	< 25	NR	Brain gliomas and meningiomas	No significant increase
Linos *et al.* (1980)	All X-ray (1955–74)	Both sexes, 138/276	> 10	Red bone marrow, < 3	Leukaemia	No increase
Thomas *et al.* (1994)	All X-ray (1983–86)	Men, 227/300	1–> 36	Estimate to breast, 0.18	Breast	Breast: RR = 3; n = 12, 10 and 10 when treated in 1940–54, for 20–35 years since first or last treatment, respectively

NR, not reported; OR, odds ratio; RR, relative risk; SIR, standardized incidence ratio; SMR, standardized mortality ratio
* Cited in text

n = 349). The excess relative risk per sievert decreased sharply with age at irradiation (Howe & McLaughlin, 1996).

In a cohort study in Massachusetts (USA) of 6285 patients (4940 women) who received repeated fluoroscopic examinations for tuberculosis in 1925–54 and 7100 who did not, the mean dose to the breast was 0.79 Gy. In a study of cancer incidence, an excess risk for breast cancer was observed (SIR, 1.3; 95% CI, 1.1–1.5; *n* = 147), which showed a linear dose–response relationship. The risk for radiation-induced breast cancer was inversely related to age at exposure, and no risk was seen for patients who had been over the age of 40 when first exposed (Hrubec *et al.*, 1989; Boice *et al.*, 1991b; Little & Boice, 1999). Significantly increased risks were found for death from cancer of the breast (SMR, 1.4; 95% CI, 1.1–1.8; *n* = 62) and oesophagus (SMR, 2.1; 95% CI, 1.2–3.6; *n* = 14), but not from lung cancer or, in an internal comparison of exposed and unexposed patients, from non-chronic lymphocytic leukaemia (RR, 0.9; 95% CI, 0.5–1.8; *n* = 17) (Davis *et al*., 1989). The average dose to red bone marrow was 0.09 Gy.

(ii) *Other uses of diagnostic X-rays in adults*

Other studies of the use of diagnostic X-rays have provided limited information on the effects of radiation, largely because of the low doses involved, the lack of dosimetry and problems of bias in studies involving interviews. In a case–control study of 136 pairs in Los Angeles, California (USA), the number of X-ray examinations and the associated dose to the bone marrow were associated with increased risks for chronic myeloid and monocytic leukaemia (Preston-Martin *et al*., 1989). [The Working Group noted that exposure was ascertained by telephone interview and not directly validated. The possibility of reporting bias and the uncertainty in the dosimetry make the results difficult to interpret.]

A case–control study of 565 patients with leukaemia, 318 patients with non-Hodgkin lymphoma, 208 patients with multiple myeloma and 1390 matched controls was conducted in the USA, in which information on exposure was extracted from medical records held by two prepaid health plans. When the first two years before diagnosis were excluded, no relation was found between the dose of radiation from diagnostic X-rays and the risks for leukaemia or non-Hodgkin lymphoma, whereas a dose–response relationship was found for multiple myeloma (Boice *et al*., 1991a). Exposure to diagnostic X-rays was not linked to multiple myeloma in a larger study of 399 patients and 399 controls who were interviewed in the United Kingdom (Cuzick & De Stavola, 1988).

In five case–control studies of the role of diagnostic radiation in the risk for thyroid cancer, all but one of which were performed in Sweden, exposure was assessed by interview in four studies, without validation. Of these, three found an association between the cumulative thyroid dose delivered by the diagnostic procedure and the risk for thyroid cancer (Wingren *et al*., 1993; Hallquist *et al*., 1994; Wingren *et al*., 1997), and one did not (Ron *et al*., 1987). The largest case–control study was based on data

from radiological records in hospitals and comprised 484 cases and 484 controls. No association was found with the estimated dose from diagnostic X-rays to the thyroid (Inskip *et al*., 1995). [The Working Group noted that studies based on interviews have potential recall bias, as persons with disease are more likely to recall past exposure than controls who do not have cancer.]

(*b*) *During childhood*

(i) *Multiple diagnostic X-rays for scoliosis*

A cohort study was conducted of 973 women in the USA who had received multiple diagnostic X-rays during follow-up for scoliosis between 1935 and 1965 (Hoffman *et al*., 1989). Follow-up was for an average of 26 years. The incidence of breast cancer was determined from mailed questionnaires. The average dose to the breast was estimated to have been 0.13 Gy (0–1.59 Gy); some women had received over 600 spinal X-rays during the adolescent growth spurt and after. Eleven women developed breast cancer, whereas 6.0 would have been expected in the general population (SIR, 1.8; 90% CI, 1.0–3.0) [The Working Group noted that pregnancy risk factors could not be accounted for, raising the possibility that confounding could have contributed partially to the small number of observed cases. Women with severe scoliosis were less likely to marry than women in the general population, and they also had difficulty in becoming pregnant. As nulliparity is associated with an increased risk for breast cancer, it may confound the reported association.]

(ii) *Exposure* in utero

The risks for cancer in childhood after exposure *in utero* have been studied (UNSCEAR, 1994; Doll & Wakeford, 1997). Prenatal X-rays were first associated with childhood leukaemia and cancer in the 1950s (Stewart *et al*., 1958), and most of the subsequent studies showed a consistent 40% increase in the risk for childhood cancer (excluding leukaemia) associated with intrauterine exposure to low doses. These studies have been reviewed extensively (Committee on the Biological Effects of Ionizing Radiation, 1972, 1980; UNSCEAR, 1972, 1986, 1994). The evidence for an association comes from case–control studies of the use of X-rays for pelvimetry, while none of the cohort studies has demonstrated an excess risk (Court Brown *et al*., 1960a; Boice & Miller, 1999). As a study of atomic bomb survivors who were exposed *in utero* showed no cases of childhood leukaemia, the causal nature of the association seen in the medical case–control studies has been questioned (Jablon & Kato, 1970).

The largest study of childhood cancer after prenatal exposure to X-rays is the Oxford Survey of Childhood Cancers, which is a national case–control study in the United Kingdom (Bithell & Stewart, 1975; Knox *et al*., 1987; Muirhead & Kneale, 1989; Doll & Wakeford, 1997). The study was started in 1955 and, up to 1981, the mothers of 15 276 children with cancer and the same number of matched controls had been interviewed. The relative risks associated with exposure just before birth were

about 1.4 for leukaemia and for all other childhood cancers, including Wilms tumour, neuroblastoma, brain cancer and non-Hodgkin lymphoma. It has been noted (Miller, 1969; UNSCEAR, 1994; Boice & Miller, 1999) that the similarity in the relative risks is unusual, given the difference in the incidence rates of these diverse tumours, their different origins and etiologies and the variation in risks for cancer after exposure to radiation in childhood and in adulthood (Thompson *et al*., 1994; UNSCEAR, 1994; Pierce *et al.*, 1996). It is also peculiar that embryonic tumours could be induced by exposure only a few moments before birth, and that the incidences of tumours such as lymphomas would be increased, since they have not been convincingly associated with exposure to radiation. The 1.4-fold increase in the incidence of each form of childhood cancer in the British studies may hint at an underlying bias in the case–control studies that has eluded detection (Miller, 1969; Boice & Miller, 1999).

Initial criticisms of the Oxford Survey of Childhood Cancer included the potential for recall bias, in that the mothers of children with cancer might remember their experiences during pregnancy better than mothers of control children. These concerns were minimized when a large study in the USA was published in 1962 (MacMahon, 1962), which was based on medical records of X-ray examinations and not on the mother's recall of events some years in the past. An extension of the study published in 1984, however, no longer showed an excess risk for solid tumours related to prenatal X-ray, although the risk for leukaemia remained (Monson & MacMahon, 1984).

Case–control studies of childhood cancer in twins have generally shown associations with prenatal exposure (Harvey *et al.*, 1985; MacMahon, 1985; Mole, 1990), but cohort studies of twins showed no excess of childhood cancer, and most reported deficits of childhood leukaemia (Inskip *et al*., 1991; Boice & Miller, 1999).

In 1997, Doll and Wakeford estimated that the excess risk associated with prenatal exposure to radiation was 6% per gray. Other interpretations of the same data, however, resulted in different conclusions about the causal nature of the association and the level of risk (Mole, 1974; MacMahon, 1989; Mole, 1990; Boice & Inskip, 1996; Boice *et al*., 1996). The association is not questioned, but its etiological significance is. The medical profession has acted on the assumption that the association is causal, and X-rays for pelvimetry have been largely replaced by ultrasound procedures.

2.4 Occupational exposure

The earliest observations of the effects of γ- and X-rays on health were associated with occupational exposure. Case reports of skin cancer among early workers with X-rays were published soon after Röntgen's discovery of X-rays in 1895, and increased numbers of deaths from leukaemia among radiologists were reported in the 1940s (Doll, 1995; Miller, 1995).

Occupational exposure to ionizing radiation is common in medicine, the production of nuclear power, the nuclear fuel cycle, and military and industrial activities.

Workers in these industries who are potentially exposed to radiation are monitored for exposure with personal dosimetry systems.

Epidemiological studies of occupational exposure to radiation have been conducted for surveillance and to complement risk estimates from studies of populations exposed to high doses. Studies of individual facilities are rarely large enough to provide substantial information, as the doses are low. Therefore, mainly combined analyses and the largest individual studies are presented here. The discussion is also limited primarily to studies in which most of the subjects were monitored for external exposure and in which internal comparisons were made by dose.

2.4.1 *Medical use of radiation*

Studies of medical personnel exposed to radiation rarely had information on individual doses, and surrogate measures, such as first year worked or duration of work, were sometimes used. Generally, comparisons were made with population rates or a control group, and risk could not be quantified. The studies of early radiologists provide substantial evidence that radiation at high doses can cause leukaemia and other cancers. Before the hazards of excessive exposure to radiation were recognized, severe skin damage and low leukocyte counts were reported. The doses are estimated to have been of the order of many grays.

The first reports of an increased incidence of leukaemia among US radiologists were based on death notices published in *The Journal of the American Medical Association* (Henshaw & Hawkins, 1944; March, 1944). The report of March covered the years 1929–43 and showed a significant, tenfold increase in the proportional mortality ratio for leukaemia among radiologists, on the basis of eight cases. These findings were confirmed in similar analyses in the same journal in 1935–44 (Ulrich, 1946) and 1945–57 (Peller & Pick, 1952). A more formal analysis was conducted by Lewis (1963), who reported increased risks for leukaemia (SMR, 3.0; 95% CI, 1.5–5.2; $n = 12$), multiple myeloma (SMR, 5.0; 95% CI, 1.6–11.6; $n = 5$) and aplastic anaemia (SMR, 17; 95% CI, 4.7–44.5; $n = 4$) in 1948–61. In the most recent study, a cohort of 6524 radiologists was followed-up during 1920–69 (Matanoski *et al.*, 1975a,b), and the risk for leukaemia was found to be statistically significantly increased among those who had joined a radiological society in 1920–29 (1117 persons; SMR, 3.0) or 1930–39 (549 persons; SMR, 4.1) [confidence intervals not reported] when compared with the general population. No such increase was observed for other physicians.

In a study of cancer mortality in 1977 among 1338 British radiologists who had joined a British radiological society in 1897–1954, statistically significantly increased risks for cancers of the skin (SMR, 7.8; $n = 6$), lung (SMR, 2.2; $n = 8$) and pancreas (SMR, 3.2; $n = 6$) and for leukaemia (SMR, 6.15; $n = 4$) were observed among radiologists who entered the study before 1921 [confidence intervals not reported]. No significant excess of these cancers was observed among radiologists who had joined the society after 1920 (Smith & Doll, 1981).

Similarly, an increased incidence of cancer was reported in a cohort study of 27 011 Chinese radiologists and X-ray technologists in 1950–85 when compared with 25 000 other physicians in the same hospitals (Wang *et al.*, 1990a). The overall relative risk for leukaemia was 2.4 ($p < 0.05$; $n = 34$), which was seen mainly among those first employed before 1970, aged < 25 at initial employment and who had been employed for 5–14 years. Increased risks for cancers of the skin, oesophagus and liver were also observed, but the risks for the last two were thought to be related to other factors, such as alcohol consumption.

[The Working Group noted that the findings in different countries are consistent, and the association of risk with the year of first employment suggests that the excess of leukaemia is likely to be related to occupational exposure to radiation.]

No excess cancer mortality was observed in a cohort of 143 517 radiological technologists in the USA who had been certified during 1926–80; however, the risk for breast cancer was significantly elevated relative to all other cancers in a test for homogeneity of the SMRs (ratio of SMRs, 1.3; $p < 0.0001$). Significant risks were correlated with employment before 1940 (SMR, 1.5; 95% CI, 1.2–1.9), when the doses of radiation are likely to have been highest, and among women who had been certified as radiological technicians for more than 30 years (SMR, 1.4; CI, 1.2–1.7), for whom the cumulative exposure is likely to have been greatest (Doody *et al.*, 1998). The risk for breast cancer in women was not associated with surrogate measures of exposure in a nested case–control analysis within this cohort (Boice *et al.*, 1995).

2.4.2 *Clean-up of the Chernobyl nuclear reactor accident*

Between 600 000 and 800 000 workers (‘liquidators’) are thought to have participated in cleaning-up after the accident in the restricted 30-km zone around the Chernobyl power plants and in contaminated areas of Belarus and the Ukraine between 1986 and 1989 (200 000 in 1986–87) (Cardis *et al.*, 1996). They came from all areas of the former USSR, the largest numbers from the Russian Federation and Ukraine. Many are registered in the national Chernobyl registries in each country. A small proportion (around 36 000) were professional radiation workers from other nuclear research centres and power plants, but the great majority were military reservists, construction workers and others.

In most of the papers published to date, the mortality rates and sometimes the morbidity due to cancer of the liquidators have been compared only with those of the general population (Buzunov *et al.*, 1996; Cardis *et al.*, 1996; Okeanov *et al.*, 1996; Ivanov *et al.*, 1997a; Rahu *et al.*, 1997). An increased incidence of leukaemia was reported among Belarussian, Russian and Ukrainian liquidators who worked in the 30-km zone, but no excess was found in a small Estonian study with complete follow-up (Rahu *et al.*, 1997). These results are difficult to interpret, however, because of the different intensities of follow-up of the liquidators and the general population (Cardis *et al.*, 1996).

Ivanov *et al*. (1997b, 1998) reported the results of a cohort study of 169 372 emergency workers, including 119 000 (71%) for whom individual doses of external exposure were available. The mean age of the workers during their period of duty in the 30-km zone was 33.4 years. Of the 46 575 persons with the highest exposure, who were exposed in 1986, 4.5% have been assigned doses in excess of 250 mGy. In a nested case–control study of leukaemia within the subcohort of emergency workers with officially documented doses, no significant difference was seen in dose between 34 cases occurring more than two years after first exposure and 136 controls matched on date of birth (± 3 years) and region of residence (Ivanov *et al*., 1997a). [The Working Group noted the uncertain dosimetry.]

2.4.3 *Nuclear industry workers*

These studies are summarized in Table 21.

(*a*) *United Kingdom*

A combined study of three cohorts of nuclear industry workers in the United Kingdom (Carpenter *et al*., 1994), including the Atomic Energy Authority (Fraser *et al*., 1993), the Sellafield plant (Douglas *et al*., 1994) and the Atomic Weapons Establishment (Beral *et al*., 1988), covered 75 006 employees who had started work between 1946 and 1988; 40 761 had ever been monitored for exposure to radiation, and the rest formed an unexposed control group. The mean cumulative dose equivalent was 56.5 mSv. The mean duration of follow-up was 24 years. A lag of two years for leukaemia and 10 years for other cancers was assumed for dose–response analysis. There were 1884 deaths from cancer, of which 60 were from leukaemia. When information on social class was used to adjust for potential confounding, a statistically significant association was found between cumulative dose and leukaemia (regardless of exclusion or inclusion of chronic lymphocytic leukaemia), skin cancer (including melanoma; 10-year lag) and ill-defined and secondary neoplasms (10-year lag). The excess relative risk for leukaemia (excluding chronic lymphocytic leukaemia) was 4.2 per Sv (95% CI, 0.4–13), and the estimate for other cancers was –0.02 (–0.5, 0.6) (10-year lag).

In one of the largest studies on the association between cancer and exposure to radiation, a cohort of 124 743 persons working in nuclear energy production, the nuclear fuel cycle or production of atomic weapons were identified from the National Registry for Radiation Workers in the United Kingdom (Muirhead *et al*., 1999), including all of those mentioned above and persons from several other facilities. Follow-up was begun between 1976 and 1983 and continued up to the end of 1992. Information on social class was available and adjusted for. The mean lifetime radiation dose equivalent was 30.5 mSv. The highest mean dose was that of Sellafield workers (87 mSv), who constituted half of all the workers and had a cumulative dose > 100 mSv (Douglas *et al*., 1994). The only exposure for which information was

Table 21. Cohort studies of nuclear industry workers

Facility or database (reference)	No. of subjects	Mean dose (mSv)	ERR for all cancers per Sv (except as noted) (lag period = 10 years)	ERR for leukaemia per Sv (except as noted)
Sellafield, United Kingdom (Douglas *et al.*, 1994)	14 282	128[a]	0.1 (90% CI, –0.4, 0.8)[b]	14 (90% CI, 1.9, 70.5)[c,d]
Atomic Energy Authority, United Kingdom (Fraser *et al.*, 1993)	39 718	40	0.8 (95% CI, –1.0, 3.1)[b]	–4.2 (95% CI, –5.7, 2.6)[d]
Atomic Weapons Establishment, United Kingdom (Beral *et al.*, 1988)	22 552	8	7.6 (95% CI, 0.4, 15)[e]	NR
National Registry of Radiological Workers, United Kingdom (Muirhead *et al.*, 1999)	124 743	30.5	0.09 (90% CI, –0.28, 0.52)	2.55 (90% CI, –0.03, 7.2)[c,d]
Hanford site, USA (Gilbert *et al.*, 1993a)	44 154	23	–0.1 (90% CI, < 0, 0.8)[e]	–1.1 (90% CI, < 0, 1.9)[d,e]
Oak Ridge X-10 and Y-12 plants, USA (Frome *et al.*, 1997)	28 347[f]	10	1.45 (95% CI, 0.15, 3.5)	< 0 (95% CI, < 0, 6.5)[d]
Oak Ridge nuclear power plant, USA (Wing *et al.*, 1991)	8 318	17	3.3 (95% CI, 0.9, 5.7)[e]	6.9 (95% CI, –15, 28)[e,g]
Atomic Energy Canada (Gribbin *et al.*, 1993)	8 977	15	0.36 (90% CI, –0.46, 2.45)[e]	19 (90% CI, 0.14, 113)[d,e]
International collaborative study (Cardis *et al.*, 1995)	95 673	40	–0.07 (90% CI, –0.4, 0.3)[b]	2.2 (90% CI, 0.1, 5.7)[c,d]

Table 21 (contd)

Facility or database (reference)	No. of subjects	Mean dose (mSv)	ERR for all cancers per Sv (except as noted) (lag period = 10 years)	ERR for leukaemia per Sv (except as noted)
Combined analyses				
Combined analysis of three facilities, United Kingdom (Carpenter *et al.*, 1994)	75 006	56.5	0.03 (95% CI, –0.5, 0.7)	4.2 (95% CI, 0.4, 13)[c,d]
Combined analysis, USA (Gilbert *et al.*, 1993b)	44 943	[27]	–0.0 (90% CI, < 0, 0.8)	–1.0 (90% CI, < 0, 2.2)[a,f]

ERR, excess relative risk; NR, not reported; < 0, negative value
[a] Muirhead *et al*. (1999) give 90 mSv
[b] Excluding leukaemia
[c] Excluding chronic lymphocytic leukaemia
[d] Lag period, 2 years
[e] % per 10 mSv
[f] Number of workers included in the dose–response analyses
[g] Lag period, 10 years

available was external radiation. This was lagged by two years for the analysis of leukaemia and by 10 years for other cancers. A total of 3598 deaths from cancer was observed in analyses without lagging, and 2929 in lagged analyses; leukaemia other than chronic lymphocytic leukaemia accounted for 90 and 89 deaths, respectively. No significant association was found between the dose of radiation and all cancers (ERR per Sv, 0.09; 90% CI, –0.28, 0.52; n = 2929) or leukaemia (other than chronic lymphocytic leukaemia; ERR per Sv, 2.55; 90% CI, –0.03, 7.2; n = 89). The only type of malignancy for which there was a significant association with radiation was multiple myeloma (ERR per Sv, 4.1; 90% CI, 0.03–15; n = 35), although a dose-dependent excess of 'ill-defined and secondary neoplasms' was reported (ERR per Sv, 2.4; 90% CI, 0.48–5.5; n = 201).

(*b*) *USA*

The most informative study in the USA of workers at nuclear sites is a large combined analysis of 44 943 monitored workers (Gilbert *et al*., 1993b) at the Hanford nuclear site (Gilbert *et al*., 1993a), the Oak Ridge National Laboratory (Wing *et al*., 1991) and the Rocky Flats nuclear weapons site (Wilkinson *et al*., 1987). The mean length of follow-up was 19 years and the average dose was 27 mSv. There were 1871 deaths from cancer. For all cancer sites combined, the excess relative risk estimate was –0.0 per Sv (with an upper 90% confidence limit of 0.8). There were 67 deaths from leukaemia other than the chronic lymphocytic type, and the excess relative risk estimate was negative (–1.0 per Sv; upper 90% confidence limit, 2.2). Statistically significant excesses associated with the radiation dose were observed for cancers of the oesophagus and larynx and for Hodgkin disease, but these were interpreted as likely to be due to chance, as negative correlations with dose were found for the same number of sites. There was a statistically significant association between dose and cancer risk for people aged ≥ 75. [The Working Group noted that the combined analysis was dominated by the data for workers at the Hanford site.]

A cohort study of mortality among 15 727 employees at the Los Alamos National Laboratory, a nuclear research and development facility, between 1947 and 1990, who had been hired in 1943–77 showed an association between the dose of radiation and cancers of the oesophagus and brain and Hodgkin disease, but not for leukaemia or all cancers combined (Wiggs *et al*., 1994). [The Working Group noted that no risk estimates per unit dose were given.]

A cohort study of mortality among 106 020 persons employed in 1943–85 at the four nuclear plants in Oak Ridge, Tennessee, showed a slight excess of deaths from lung cancer among white male employees (Frome *et al*., 1997). In a dose–response analysis restricted to 28 347 white men at two plants who had received a mean dose of 10 mSv, significant positive relationships were found with deaths from all causes (ERR per Sv, 0.31; 95% CI, 0.16–1.01), deaths from all cancers (ERR per Sv, 1.45; 95% CI, 0.15–3.5; n = 4673) and lung cancer (ERR per Sv, 1.7; 95% CI, 0.03–4.9; n = 1848) after adjustment for age, year of birth, socioeconomic status, facility and

length of employment; however, no information on smoking was available. For leukaemia, the excess relative risk per sievert was negative (upper 95% confidence limit, 6.5; *n* = 180).

(*c*) *Russian Federation*

A cohort study of people who had worked at the Mayak nuclear complex in the early years of its operation showed an increased mortality rate from all cancers and from leukaemia (44 cases; 38 men) (Koshurnikova *et al*., 1996). The mortality of 8855 workers who were first employed between 1948 and 1958 at the nuclear reactors, at the Mayak fuel reprocessing plants and at the plutonium manufacturing complex was followed-up for an average of 36 years. The mean cumulative dose of external radiation was 1 Gy. A control group was formed of 9695 persons who were employed during the same period but whose radiation doses did not exceed the maximum permissible level [unspecified]. The excess relative risk for leukaemia was estimated to be 1.3 per Gy [confidence interval not reported] for 26 men in the reprocessing plants, but no estimates were available for the other two groups. Tokarskaya *et al*. (1997) and Koshurnikova *et al*. (1998) evaluated the risk for lung cancer in relation to external γ-ray dose (1.8 Gy) and internal dose from plutonium of male workers at the radiochemical and plutonium plants, who had received an average equivalent dose to the lung from plutonium of 6.6 Sv. No evidence of an association with external dose was found (ERR = –0.16 per Gy [CI not reported]; *n* = 47), but this may have been due to inadequate adjustment for plutonium dose and lack of information on smoking. [The Working Group noted that the study was potentially very informative because the doses were much higher than those of other occupational cohorts, but there is uncertainty about the adequacy of the dose estimates, and follow-up may have been selective. Further, in the absence of information on potential confounding by exposure to plutonium, the extent to which external radiation contributed to the increased cancer risks is difficult to estimate.]

(*d*) *International collaborative study*

A combined cohort study of mortality from cancer among 95 673 nuclear industry workers in Canada (Gribbin *et al*., 1993), the United Kingdom (Carpenter *et al*., 1994) and the USA (Gilbert *et al*., 1993b) has been published (IARC Study Group on Cancer Risk among Nuclear Industry Workers, 1994; Cardis *et al*., 1995). The persons had been employed for at least six months and had been monitored for external exposure. The activities of the nuclear facilities included power production, research, weapons production, reprocessing and waste management. The mean cumulative dose was 40 mSv. Data on socioeconomic status were available for all except the Canadian workers, and adjustment was made for this variable in the analysis. The combined analysis covered 2 124 526 person–years and 3976 deaths from cancer. The risk for leukaemia other than chronic lymphocytic leukaemia was statistically significantly associated with the cumulative external dose of radiation (one-sided *p* value, 0.046).

The excess relative risk estimate for leukaemia other than the chronic lymphocytic type was 2.2 per Sv (90% CI, 0.1–5.7; *n* = 119). There was no excess risk for cancer at any other site, and the excess relative risk estimate for all cancers except the leukaemias was –0.07 per Sv (90% CI, –0.4, 0.3; *n* = 3830). Of the 31 specific cancer types other than leukaemia, only multiple myeloma was statistically significantly associated with the exposure (*p* = 0.04; ERR per Sv, 4.2; 90% CI, 0.3–14; *n* = 44).

2.4.4 *Various occupations*

An association between dose of radiation and the rate of mortality from cancer was found in a study of 206 620 Canadian radiation workers (Ashmore *et al*., 1998) identified from the National Dose Registry, established in 1951. All workers except uranium miners who were monitored for exposure to radiation between 1951 and 1983 were included in the study. Most of the participants were medical (35%) or industrial (38%) workers and the remainder were employed in dentistry (21%) or nuclear power production (6%). The workers had been monitored with a film or thermoluminescent dosimeter. Nearly half (45%) of the workers had received doses below the recording threshold (usually 0.2 mSv), and the mean external dose was 6.3 mSv. The mean length of follow-up was 14 years. A statistically significant association between dose of radiation and death from any cancer was detected among men (% ERR per 10 mSv, 3.0; 90% CI, 1.1–4.9) but not among women (% ERR per 10 mSv, 1.5; 90% CI, –3.3, 6.3). In addition, a dose–response relationship was found with lung cancer among men (% ERR per 10 mSv, 3.6; 90% CI, 0.4–6.9). No significant association was found with other cancers, including leukaemia and cancers of the thyroid and breast, but a dose–response relationship was found for all causes of death among both men and women and for deaths from circulatory disease and accidents among men. [The Working Group noted that a strong association was found with causes of death other than cancer, which suggests possible confounding, perhaps by factors such as smoking. The mortality rate from cancer was only 68% of that predicted from national rates, suggesting ascertainment bias.]

2.5 Environmental exposure

2.5.1 *Natural sources*

Most studies of natural radiation are based on comparisons of cancer incidence or mortality among populations living in areas with different background levels of radiation. A direct effect of background radiation is unlikely to be observed since it is likely to be small in comparison with that due to other causes. Furthermore, large populations must be studied in order to obtain sufficient statistical power, and it could be difficult to maintain the same standards of diagnosis and registration for large populations and areas. The studies that have been conducted to investigate the risk for cancer from naturally occurring radiation have generally found no association, but

they are not particularly informative because of their low power and because most are ecological studies, which are difficult to interpret causally. The overwhelmingly negative results do suggest, however, that the carcinogenic risk represented by the low natural levels of radiation is unlikely to be substantial. The most important studies are summarized in Table 22.

Court Brown *et al.* (1960b) studied mortality from leukaemia in Scotland and related it to residence at the date of death and estimated dose to the bone marrow. The substantial variation in rates among the 10 areas in Scotland was suggested to be due to incomplete ascertainment of cases, economic status or background radiation.

In a study of 369 299 persons living in western Ireland, 2756 outdoor and 145 indoor measurements of γ-radiation were performed (Allwright *et al.*, 1983). The mortality rates from cancer were not related to residence in regression analyses, and no risk was found in relation to background exposure.

The incidences of leukaemia and non-Hodgkin lymphoma among children who were < 15 years of age at the time of diagnosis were studied during 1969–83 in 459 county districts in England, Wales and Scotland (Muirhead *et al.*, 1991) in relation to indoor radon and terrestrial γ-radiation. The incidences were not found to increase significantly with dose rate. When essentially the same database was used to analyse 6691 cases of childhood leukaemia diagnosed between 1969 and 1983 (16.5% acute nonlymphocytic leukaemia) with respect to background γ-radiation (Richardson *et al.*, 1995), no association was found, but a positive association between leukaemia incidence and socioeconomic status was revealed.

In contrast to the studies of Muirhead *et al.* (1991) and Richardson *et al.* (1995), Gilman and Knox (1998) found increased mortality rates from childhood leukaemia and solid tumours in relation to exposure to radon and terrestrial γ-radiation. The study was based on the Oxford Survey of Childhood Cancers and comprised 9363 deaths from solid tumours (48%) and from leukaemia and malignant lymphoma (52%) among children < 15 years of age during the period 1953–64. Although indoor γ-radiation was associated with an increased risk, once radon was introduced into the regression model terrestrial γ-radiation did not contribute significantly to the risk.

Mortality from lung cancer was studied in an area of central Italy with high background radiation from outdoor sources of γ-radiation (2.4 mSv year^{-1}) and high doses of ^{226}Ra and ^{232}Th from building materials (Forastiere *et al.*, 1985). When villages on volcanic and non-volcanic soil were compared, no significant difference in mortality from lung cancer was noted after adjustment for tobacco sales. In an Italian case–control study, 44 men with acute myeloid leukaemia were compared with 211 male controls (Forastiere *et al.*, 1998) in relation to measurements of radon and indoor γ-radiation performed in 1993–94. A nonsignificantly decreased odds ratio was found for higher background exposure both to radon and to γ-radiation.

In an ecological study, standardized cancer rates for all 24 Swedish counties were correlated to the average background radiation based on measurements of γ-radiation in 1500 dwellings chosen at random (Edling *et al.*, 1982). Significant correlations

Table 22. Epidemiological studies of cancer associated with natural background radiation

Country/region (reference)	Characteristics of study	Main results
Scotland (Court Brown *et al.*, 1960b)	Mortality from leukaemia in 10 major areas of Scotland compared with natural background radiation in four areas	An effect of radiation could not be ruled out, but social and economic factors were considered to be at least as important.
Irelan (Allwright *et al.*, 1983)	Ecological study of cancer mortality rates and natural background radiation measured outdoors (n = 2756) and indoors (n = 145); highest and lowest doses differed by a factor of approximately 5 (McAulay & Colgan, 1980), and ~370 000 individuals included	No significantly elevated risk related to natural background radiation
United Kingdom (Muirhead *et al.*, 1991; Richardson *et al.*, 1995)	Incidence of childhood leukaemia in 459 county districts compared with exposure to indoor radon and γ-radiation and outdoor γ-radiation	No increased risk for leukaemia attributed to ionizing radiation, but a positive association of leukaemia incidence with socioeconomic status
United Kingdom (Gilman & Knox, 1998)	Mortality from childhood solid cancers and leukaemia in 1953–64 (9363 deaths) compared with residence, social class, radon and terrestrial γ-radiation	Increased incidences in areas of high socioeconomic status and in areas of high population density. Radon, but not significantly γ-radiation, affected the risk for dying from a solid tumour but not leukaemia or malignant lymphoma.
France (Tirmarche *et al.*, 1988)*	Cancer mortality in seven ‘départements’ with high background γ-radiation compared with national rates	Increased mortality linked to background radiation only for childhood leukaemia, which was statistically significant in only one ‘département’
Italy (Forastiere *et al.*, 1985)	Lung cancer mortality in 31 villages in volcanic and non-volcanic areas in central Italy correlated to outdoor γ-radiation and cigarette sales	No significant difference in lung cancer mortality between volcanic and non-volcanic villages after adjustment for tobacco sales
Italy (Forastiere *et al.*, 1998)	Five controls matched to each of 44 men who had died of acute myeloid leukaemia compared with indoor radon and γ-radiation	Nonsignificant decrease in odds ratio with increasing background radiation

Table 22 (contd)

Country/Region (reference)	Characteristics of study	Main results
Sweden (Stjernfeldt *et al.*, 1987)*	One control chosen for each of 15 cases of childhood cancer, and exposure to indoor ã-radiation and radon measured	No difference in cumulative exposure to γ-radiation or radon daughters; low statistical power
Sweden (Edling *et al.*, 1982)	Cancer incidence in 24 Swedish counties correlated to γ-radiation measured in 1500 homes	Correlation for lung and pancreatic cancer but borderline correlation for leukaemia. Degree of urbanization and smoking most likely influenced the results.
Sweden (Flodin *et al.*, 1990)*	172 controls randomly selected for 86 cases of acute myeloid leukaemia; background radiation approximated from construction materials in homes and work places	Significantly increased risk for leukaemia when 'high-dose' exposure was contrasted to 'low-dose'. Selection of controls, approximation of exposure, and lack of information on number of cases of chronic lymphocytic leukaemia preclude firm conclusions.
Yangjiang, **China** (Tao & Wei, 1986; Wei *et al.*, 1990; Chen & Wei, 1991; Wei & Wang, 1994)	Ecological study of cancer mortality rates in thorium–monazite areas and a control area	Nonsignificantly lower rates of leukaemia, breast and lung cancer in the high background area but increased prevalence of stable chromosomal aberrations
Japan Noguchi *et al.*, 1986)	Correlation between background radiation and cancer mortality during 1950–78	Increased mortality correlated to background levels in some sites and negative correlations in others. Findings considered to be unrelated to radiation.
India (Nambi & Soman, 1987)	Cancer incidence in 5 Indian cities correlated to background γ-radiation of 0.3–1 mSv	Decreasing incidence with increasing background dose
USA (Mason & Miller, 1974)	Correlation of cancer mortality and altitude in 53 counties at an altitude > 3000 ft [> 900 m]	No significant difference in comparison with US national rates

Table 22 (contd)

Country/Region (reference)	Characteristics of study	Main results
USA (Amsel *et al.*, 1982)	Relationship between altitude, urbanization, industrialization and cancer in 82 US counties	Generally, deficits in cancer mortality rates at high altitude
Connecticut, USA (Walter *et al.*, 1986)	Cancer incidence related to background radiation, population density and socioeconomic status in data for 1935–74	No relationship with background radiation, but a high cancer incidence in areas of high population density
USA (Weinberg *et al.*, 1987)	Correlation between cancer mortality, altitude and background irradiation in US cities at an altitude > 900 ft [> 250 m]	No overall correlation between background radiation and cancer or leukaemia

* Not described in text

were seen for cancers of the lung and pancreas in both men and women, but only a borderline correlation to leukaemia in men was seen. An association was found between degree of urbanization and γ-radiation. [The Working Group noted that cigarette smoking is more common in urban areas and among men, but no adjustment was made for smoking.]

In Yangjiang province, China, thorium-containing monazites have been washed down by rain from the nearby heights and raised the level of background radiation to three times that in adjacent areas of similar altitude. Several studies have been performed to derive indoor and outdoor doses, and individual doses have been measured with personal dosimeters. More than 80 000 individuals who live in the high background areas were estimated to receive an annual dose to the red bone marrow of 2.1 mSv, whereas the dose of those in the control area was 0.77 mSv. Nonsignificantly lower rates of mortality from all cancers and from leukaemia, breast cancer and lung cancer were found in the high background areas (Tao & Wei, 1986; Wei *et al.*, 1990; Chen & Wei, 1991; Wei & Wang, 1994). Although a significantly higher risk for cancer of the cervix uteri was found in the high background area, it was considered not to be due to the ionizing radiation. Nevertheless, a higher frequency of stable chromosomal aberrations (translocations and inversions) was found in the high-dose area (see section 4.4.1). [The Working Group noted that, in contrast to the previous studies, migration was not a potential problem and that both indoor and outdoor exposures were considered.]

The correlation between background radiation and cancer mortality was studied in 46 of 47 prefectures of Japan for the period 1950–78 (Noguchi *et al.*, 1986). Correlations were found only in women, with positive correlations for stomach cancer and uterine cancer and negative correlations for cancers of the breast, lung, pancreas and oesophagus. [The Working Group noted that only γ-radiation was considered and altitude was not taken into consideration.]

High natural background levels of radiation are also present in Kerala, India. Although studies have shown very little evidence for an excess cancer risk, they have been of limited quality. Cancer incidence and background γ-radiation were investigated in five Indian cities with background levels of 0.3–1 mSv (Nambi & Soman, 1987). A significantly decreased overall cancer incidence was observed with increasing dose, but the authors underlined the limited extent of cancer registration in India.

The association between cosmic radiation and cancer was investigated in two studies in the USA (Mason & Miller, 1974; Amsel *et al.*, 1982), which found no increased risk for leukaemia or solid tumours in relation to altitude.

The relationship between background radiation, population density and cancer was studied with data from the Connecticut Tumor Registry for the period 1935–74 (Walter *et al.*, 1986), and data from an airborne survey of γ-radiation to approximate the annual doses in 169 towns. No increased risks were found in relation to level of γ-radiation. [The Working Group noted that the advantages of the study were use of

incidence rather than mortality data, the fairly high level of background radiation and a reasonable variation in exposure between towns.]

In order to study the simultaneous effects on mortality rates of altitude and terrestrial background radiation, all cities in the USA situated at an altitude > 900 feet [> 250 m] were identified in the metropolitan mortality report for 1959–61 (Weinberg *et al*., 1987), and information on background radiation, including cosmic radiation, was added. Background radiation did not appear to affect the rates of leukaemia or of cancers of the breast, intestine or lung. When altitude was added, the association was negative.

2.5.2 *Releases into the environment*

(*a*) *The Chernobyl accident*

As noted above, the accident at the fourth unit of the Chernobyl nuclear power plant led to substantial contamination of large areas. [The dramatic increase in the incidence of thyroid cancer in persons exposed to radioactive iodine as children (Cardis *et al*., 1996) will be discussed during a forthcoming IARC Monographs meeting on radionuclides.] In a follow-up in the Ukraine, the incidences of leukaemia and lymphoma in the three most heavily contaminated regions (*oblasts*) were found to have increased during the period 1980–93 (Prisyazhniuk *et al*., 1995); however, the incidences of leukaemia (including chronic lymphocytic leukaemia) and other cancers in countries of the former USSR had shown an increasing trend before the accident, in 1981, which was most pronounced in the elderly (Prisyazhniuk *et al*., 1991). The findings are based on few cases, and increased ascertainment and medical surveillance are likely to have influenced them. [The Working Group emphasized the importance of taking the underlying increasing trend into account in interpreting the results of studies focusing on the period after the Chernobyl accident.]

In a study of the population of Kaluga *oblast*, the part of the Russian Federation nearest Chernobyl, in 1981–95, no statistically significant increase in trends of cancer incidence or mortality was seen after the accident, although a statistically significant increase in the incidence of thyroid cancer was observed in women (Ivanov *et al*., 1997c).

The European Childhood Leukaemia–Lymphoma Incidence Study was designed to address concerns about a possible increase in the risk for cancer in Europe after the Chernobyl accident. The results of surveillance of childhood leukaemia in cancer registry populations from 1980 up to the end of 1991 were reported by Parkin *et al*. (1993, 1996). During the period 1980–91, 23 756 cases of leukaemia were diagnosed in children aged 0–14 (655×10^6 person–years). Although there was a slight increase in the incidence of childhood leukaemia in Europe during the period studied, the overall geographical pattern of change bears no relation to estimated exposure to radiation from the Chernobyl fall-out.

All 888 cases of acute leukaemia diagnosed in Sweden in 1980–92, after the Chernobyl accident, in children aged 0–15 years, were examined in a population-based study in which place of birth and residence at the time of diagnosis were included (Hjalmars *et al.*, 1994). A dose–response analysis showed no association between the degree of contamination and the incidence of childhood leukaemia.

Auvinen *et al*. (1994) reported on the incidence of leukaemia in Finland among children aged 0–14 in 1976–92 in relation to fall-out from the Chernobyl accident, measured as external exposure in 455 municipalities throughout the country. The incidence of childhood leukaemia did not increase over the period studied, and the excess relative risk in 1989–92 was not significantly different from zero.

The incidence of leukaemia among infants in Greece after exposure *in utero* as a consequence of the Chernobyl accident was found to be higher in children born to mothers who lived in areas with relatively greater contamination (Petridou *et al*., 1996). On the basis of 12 cases diagnosed in infants under the age of one year, a statistically significant increase in the incidence of infant leukaemia was observed (rate ratio, 2.6; 95% CI, 1.4–5.1). No significant difference in the incidence of leukaemia among 43 children aged 12–47 months born to presumably exposed mothers was found. [The Working Group was unclear why the authors chose to limit their analysis to infants, as there is little etiological reason for doing so.]

In a study of childhood leukaemia in relation to exposure *in utero* due to the Chernobyl accident based on the population-based cancer registry in Germany (Michaelis *et al*., 1997; Steiner *et al*., 1998), cohorts were defined as exposed or unexposed on the basis of date of birth and using the same selection criteria as Petridou *et al*. (1996). Overall, a significantly elevated risk was seen (RR, 1.5; 95% CI, 1.0–2.15; $n = 35$) for the exposed when compared with the unexposed cohort. The incidence was, however, higher among infants born in April–December 1987 (RR, 1.7; 95% CI, 1.05–2.7) than among those born between July 1986 and March 1987 (RR, 1.3; 95% CI, 0.76–2.2), although the exposure of the latter group *in utero* would have been greater than that of the former group. The authors concluded that the observed increase was not related to exposure to radiation from the Chernobyl accident.

(*b*) *Populations living around nuclear installations*

A number of studies have been conducted of populations living near nuclear installations (Doll *et al*., 1994; UNSCEAR, 1994), and some have shown unexpected associations between exposure to radiation and cancer in either potentially exposed persons or their offspring.

A cluster of childhood leukaemias was reported around the Sellafield nuclear installation in the United Kingdom in 1983 (Black, 1984). Childhood leukaemia was subsequently reported to be occurring in excess in other regions of the United Kingdom where there were nuclear installations, although the incidence of all cancers was not increased (Forman *et al*., 1987). These observations were not replicated in Canada (McLaughlin *et al.*, 1993b), France (Hill & Laplanche, 1990; Hattchouel *et al.*, 1995),

Germany (Michaelis *et al.*, 1992) or the USA (Jablon *et al.*, 1991), although associations were reported around a reprocessing plant in France (Viel *et al.*, 1995; Pobel & Viel, 1997). More refined analyses in the United Kingdom gave little evidence that the incidence of childhood leukaemia was related to proximity to nuclear facilities, except for the Sellafield installation (Bithell *et al.*, 1994). Another study conducted in England and Wales showed that the incidence of childhood leukaemia was increased around sites selected for nuclear facility construction but in which the facilities had not been completed (Cook-Mozaffari *et al.*, 1989). An infectious agent associated with large migrations of people into these areas has been proposed as a possible explanation for the clusters (Kinlen *et al.*, 1991; Kinlen, 1993a). These ecological analyses are severely limited by the absence of information on individual doses of radiation, but they were probably lower than the dose of natural background radiation (Darby & Doll, 1987). [The Working Group noted that unknown factors associated with migration and selection of residence and occupation could play a major role in cancer occurrence.] Other studies around nuclear facilities have failed to provide clear insight into the reasons, other than chance or selection, for the apparent clusters of childhood cancer (MacMahon, 1992; Draper *et al*., 1993).

A case–control study of leukaemia and non-Hodgkin lymphoma among children around Sellafield raised the possibility that exposure of the fathers who worked at the facility might explain the cluster. Four cases of leukaemia were seen among children whose fathers received doses ≥ 10 mSv within six months of conception (Gardner *et al*., 1990). These findings were not replicated in a similar but smaller study at the Dounreay nuclear facility in Scotland (Urquhart *et al*., 1991) or in two further surveys in Scotland (Kinlen, 1993b; Kinlen *et al*., 1993) and one in Canada (McLaughlin *et al*., 1993c). Further, a study of 10 363 children who were born to fathers who worked at the Sellafield facility included an evaluation of the geographical distribution in the county of Cumbria of the paternal dose received before conception. The paternal doses were consistently higher for fathers of children born outside Seascale, a village close to Sellafield where the original cluster was found. Since the incidence of childhood leukaemia was not increased in these areas of West Cumbria, despite the higher preconception exposures, the authors concluded that paternal exposure to radiation before conception is unlikely to be a causal factor in childhood leukaemia (Parker *et al.*, 1993). The hypothesis was also not substantiated in further studies (Doll *et al*., 1994; Committee on Medical Aspects of Radiation in the Environment, 1996).

A further study of cancer among the children of nuclear industry employees in the United Kingdom was conducted with a questionnaire approach (Roman *et al.*, 1999). Employees at three nuclear establishments were contacted, and 111 cancers (28 leukaemias) were reported among 39 557 children of male employees and 8883 children of female employees. The incidences of all cancers and of leukaemia were similar to those in the general population; however, the rate of leukaemia in children whose fathers had accumulated a preconceptual dose ≥ 100 mSv was significantly higher (5.8; 95% CI, 1.3–25) than that in children born before their fathers'

employment in the nuclear industry, but this result is based on only three exposed cases. [The Working Group noted that two of these three cases were included in the study of Gardner *et al.* (1990) which generated the hypothesis, and should have been excluded in order that the study be considered an independent test of the hypothesis that paternal irradiation results in childhood leukaemia. Further, the approach used probably resulted in substantial under-ascertainment of the number of cases of childhood cancer because no effort was made to obtain information on children of workers who had died; ex-employees who were not on the pensions database were not contacted; ex-employees of one of the three nuclear establishments and persons over the age of 75 were not contacted at all; an unstated number of questionnaires was returned undelivered; and 18% of the male workers who received the questionnaires failed to return them. Comparison with a record linkage study that included all children of nuclear industry workers in the United Kingdom (Draper *et al.*, 1997) indicates that as many as two of every three childhood cancers may have been missed. The study is therefore susceptible to biases related to incomplete ascertainment of children with cancer and to the reasons for responding or failing to respond to the questionnaire.]

The nuclear reactor accident at Three-Mile Island, Pennsylvania (USA), released little radioactivity into the environment and resulted in doses to the population that were much lower than those received from the natural background. Any increase in the incidence of cancer would thus be expected to be negligible and undetectable (Upton, 1981). An ecological survey found no link between estimated patterns of radiation release and increased cancer rates (Hatch *et al*., 1990; Jablon *et al*., 1991). Other studies of the Three-Mile Island incident have given inconsistent results (Fabrikant, 1981; Wing *et al*., 1997) and provide little evidence for an effect of radiation.

2.6 Issues in quantitative risk assessment

The wealth of data and the availability of quantitative estimates of biologically relevant measures of dose or exposure have led to the development of intricate approaches for estimating the magnitude of risks due to exposure to γ- and X-rays. These approaches, which have drawn on information obtained from both epidemiological and experimental studies, have then been used to estimate the risks from various exposures. In this section, several measures of risk are defined, problems and uncertainties in estimating those risks are discussed, and recent efforts of major national and international groups to provide quantitative risk estimates are summarized. Several estimates of risks from particular sources of exposure are given as illustrations.

2.6.1 *Measures of risk*

In general, summary measures of risk are based on the assumption that variation in risk among individuals within a population can be ignored (at least for certain

purposes) and that the concept of an average risk for a population is meaningful. An important measure of risk is the lifetime risk that an individual will die from a cancer that has been caused by exposure to a carcinogenic agent such as radiation. The lifetime risk is sometimes referred to as the risk of exposure-induced death and differs from the excess lifetime risk (National Council on Radiation Protection and Measurements, 1997), which does not include deaths from cancers that would have occurred without exposure but which occur at a younger age because of the exposure (Thomas *et al*., 1992). Such risks are dependent on dose and thus must be expressed as a function of dose. In the most commonly used linear model, the risk is often expressed per unit of dose. Lifetime risk estimates may depend on sex, age at exposure and the pattern of exposure over time. Approaches have been developed that allow estimation of sex-specific lifetime risks resulting from various patterns of exposure with regard to age and time. For example, the risk from single exposures at various ages or from continuous exposure over a specified period can be estimated. Lifetime risks also depend on many individual characteristics, but too little is known about such dependence for it to be taken into account. Rigorous definitions and interpretations of measures such as attributable risk and the probability of causation have been discussed extensively (Greenland & Robins, 1988). Only a broad definition is given here.

Once a model for estimating the lifetime risks of individuals has been developed, it can be applied to all individuals in a population (such as an entire country) to estimate the total number of cancers that are expected to occur as a result of exposure to various specified doses. Since risks often depend on sex and age at exposure, such estimates require demographic data on the population for which the risk estimates are being made. Like individual risks, population risks can be expressed as a function of dose, or per unit of dose for a linear model.

If estimates of the doses or distribution of doses received by a population from a particular source of radiation are available, the models for estimating lifetime risks can be applied to estimating the number of cancer deaths associated with exposure from the source. This number is sometimes expressed as a fraction of the total number of cancer deaths that have occurred in the population and is known as the attributable risk. A closely related quantity is the probability of causation, which is identical to the ‘assigned share’, which is the probability that a cancer that has already occurred in an individual was caused by radiation (Lagakos & Mosteller, 1986). Radiation risks are commonly measured in terms of cancer mortality, but all of the above measures can also be used to estimate the risk for non-fatal cancer. None of these measures reflects the age at which death from cancer occurs. An additional measure that takes account of age is the loss of life expectancy, which was defined and discussed by Thomas *et al*. (1992). This is sometimes expressed as the number of years of life lost per radiation-induced cancer.

2.6.2 *Problems and uncertainties in quantifying risks due to radiation*

Models or sets of assumptions are needed to estimate any of the quantities described above, and their development and application are described below in general terms. For more rigorous treatment, the reader is referred to Bunger *et al*. (1981), Thomas *et al.* (1992) or any of the documents describing the specific risk models summarized below.

The most recent attempts at risk assessment are based on epidemiological data, so that age-specific cancer mortality or incidence rates are estimated as a function of baseline rates and parameters that characterize the relationship between risk and exposure to radiation. The risk from radiation is usually expressed as a function of dose, age at the time of exposure, time since exposure, sex and sometimes other factors. These functions are then used in combination with data on the characteristics of the population.

A commonly used model takes the form:

$$\lambda (a, s, D, e, t) = \lambda (a, s) [1 + f (a, s, D, e, t)]$$

where $\lambda (a, s, D, e, t)$ is the age-specific rate for age (a), sex (s), dose (D), age at exposure (e) and time since exposure (t); $\lambda (a, s)$ is the baseline risk at age (a) and sex (s) and $f (a, s, D, e, t)$ is the ERR associated with a, s, D, e and t. A key feature of this model is that risks are expressed relative to the baseline rather than in absolute terms. If life-table methods are used, the age-specific risks $\lambda (a, s)$ and $\lambda f (a, s, D, e, t)$ can be applied to demographic data for the population for which risk estimates are being made to obtain lifetime risk estimates or any of the other measures described above. In this application, the baseline risks $\lambda (a, s)$ are usually derived for the population of interest (Committee on the Biological Effects of Ionizing Radiation (BEIR IV), 1988).

Because the populations and exposures for which risk estimates are desired nearly always differ from those for which epidemiological data are available, assumptions are required, many of which involve considerable uncertainty. Some of the more important assumptions are discussed below, and the approaches used to address these problems in specific risk assessments are described in section 2.6.4.

Most situations for which risk estimates are desired involve exposure to low doses and dose rates. Because the estimates obtained directly from epidemiological data on populations exposed to low doses are imprecise, it is necessary to extrapolate from risks estimated for persons exposed to higher doses and dose rates than those of direct interest. Specifically, the data on the atomic bomb survivors have played a strong role in developing models for risk estimation, and estimates based on those data tend to be driven by doses > 1 Gy, which is much higher than the doses for which risk estimates are needed, < 0.1 Gy. Although many epidemiological findings are compatible with a linear dose–response function in which risk is proportional to dose, other forms, such as a linear–quadratic relationship, cannot be excluded. Because experimental data have suggested that the risk per unit of dose is lower when radiation is received at low rates than when it is received at high rates, linear estimates of risk at low doses and dose rates are often reduced by a factor known as the dose-and-dose-rate-effectiveness

factor. Although a factor of 2 has been used in several risk assessments, the magnitude of the factor, or whether it is needed at all, is uncertain. Because of the large uncertainty in the risks associated with exposures to < 0.1 Gy, some committees such as the Committee on the Biological Effects of Ionizing Radiations (BEIR V; 1990) have refrained from publishing estimates below this level and have noted the possibility that there is no risk at very low doses. Further discussion of this issue is given in section 2.7.

Although the risk for cancer associated with exposure to radiation has been found to depend on sex, age at exposure and the time between exposure and diagnosis or death, the available data are not adequate to determine the exact form and magnitude of such dependence, and risk estimates are usually based on relatively simple assumptions. For example, many estimates of the risk for solid tumours are based on the assumption that, for a given age at exposure, the ratio of the risk associated with radiation to the baseline risk, the ERR, remains constant as subjects are followed over time; however, some data suggest that this ratio declines over time, and populations have not yet been followed for their entire lifespans. The risks of people exposed at young ages are particularly uncertain, since follow-up of these persons is the least complete. The data on many cancer types indicate that the relative risk is greatest for people exposed early in life, but the magnitude of the increase and whether it persists throughout life is highly uncertain.

Another difficulty is that the baseline cancer risks of the population being studied may differ from those of the population for which risk estimates are desired. This has been a major concern in using data on Japanese survivors of the atomic bombings to estimate risks for white populations, especially for certain specific cancers, as the baseline rates of cancers of the breast, lung and colon are much lower in Japan than, for example, in the United Kingdom or the USA; in contrast, the rate of stomach cancer is much higher in Japan. In order to address this problem, some risk estimates (Committee on the Biological Effects of Ionizing Radiations (BEIR III), 1980) were based on the assumption that absolute risks do not depend on baseline risks, while others were based on the assumption that radiation risks are proportional to baseline risks (Committee on the Biological Effects of Ionizing Radiations (BEIR V), 1990). The risk for breast cancer can be estimated from the results of studies of white women (Abrahamson *et al.*, 1991), but adequate data on non-Japanese populations are not available for many other cancers. The problem is less severe for leukaemia and for all solid tumours combined, since the baseline rates for these categories do not vary as greatly among countries.

A closely related problem is that smoking and other life-style factors may modify risks. This is especially important in estimating risks for individuals, but also affects population risks if these factors differ in the population used to develop the risk models and in that for which risk estimates are desired. In fact, these differences are probably part of the reason for differences among baseline rates in different countries.

Ideally, risk models should take account of the modifying effect of other exposures and life-style factors, but in practice too little is known to allow this.

Increasing attention is being given to quantifying the uncertainties in risk estimates. The sources of uncertainty include lack of knowledge about the correct assumptions, as discussed above, and these uncertainties must often be assessed subjectively. Sampling variation is another important source of uncertainty, but it differs from most other sources in that it can be quantified by reasonably rigorous statistical approaches, although it may be necessary to use Monte Carlo computer simulations to address the complex dependence of lifetime risk on the parameters that are estimated (Committee on the Biological Effects of Ionizing Radiations (BEIR V), 1990). Still other sources of uncertainty are possible errors and biases in the epidemiological data used, including errors in the estimated doses. Methods are available for addressing these uncertainties, but they are often difficult to apply and require a thorough understanding of the magnitude and nature of the errors.

2.6.3 *Lifetime risk estimates by national and international committees*

The vast literature relevant to radiation risk assessment is reviewed periodically by national and international committees, and several such reviews have included summary estimates of lifetime risks. In this section, the more recent efforts of UNSCEAR (1988, 1994), the Committee on the Biological Effects of Ionizing Radiations (BEIR V; 1990) and the ICRP (1991a) are briefly summarized.

(*a*) *UNSCEAR*

In their 1988 report, UNSCEAR provided estimates of lifetime risk that served as the basis for recommendations of the ICRP (1991a). Estimates were given for death from leukaemia, from all cancers except leukaemia and from several other types of cancer. For all cancers, separate estimates were given for the total population, for a working population aged 25–64 years and for an adult population aged ≥ 25. The estimates were based on the data on mortality among survivors of the atomic bombings during 1950–85, as presented by Shimizu *et al.* (1990). The lifetime risk estimates were based on demographic data for the population of Japan in 1982. Alternative estimates based on patients with ankylosing spondylitis or cervical cancer who were exposed to radiation were also given.

UNSCEAR (1988) used two approaches for extrapolating risks beyond the period for which follow-up data were available: an additive model, in which it was assumed that the absolute risk is constant over time, and a multiplicative model, in which it was assumed that the ratio of the radiation-induced cancer risk to the baseline risk (ERR) is constant over time. Because baseline risks increase as persons age, the multiplicative model generally results in larger estimates than the additive model. The additive model is no longer thought to be appropriate for solid tumours. For leukaemia, it was assumed that risks persist for 40 years after exposure, while for solid tumours it was

assumed that the risks persist through the remainder of life. The estimates for most cancers were assumed not to depend on sex or age at exposure, but for leukaemia and the category 'all cancers except leukaemia' estimates based on age in categories of 0–9, 10–19 and ≥ 20 years were presented. The estimates were based on a linear model, but UNSCEAR recommended that the effects of low doses (< 0.2 Gy) and low dose rates (< 0.05 mGy/min) be reduced by a factor of 2–10, although no specific recommendation was made.

UNSCEAR (1994) presented lifetime risk estimates for leukaemia and several categories of solid tumour. The approach was similar to that used in 1988, in that the estimates were based on data on the mortality of atomic bomb survivors during 1950–87 and applied to the Japanese population in 1985 to obtain lifetime risks; however, the analyses used to derive the estimates were more refined than those used in 1988. In the model for leukaemia, the excess absolute risk was expressed as a linear–quadratic function of dose and was allowed to depend on sex, age at exposure (separate parameters estimated for 0–19, 20–34 and ≥ 35 years) and time since exposure (treated as a continuous variable that allowed the risk to decrease with time). Estimates were also presented for tumours of the oesophagus, stomach, colon, liver, lung, bladder, breast, ovary, other sites and all solid tumours. The ERRs were allowed to depend on sex and age at exposure, and the latter was treated as a continuous variable and evaluated separately for each cancer evaluated. The lifetime estimates were based on the assumption of constant relative risk, in which the ratio of the risk for radiation-induced cancer to the baseline risks was assumed to be constant over time. For the category of all solid tumours, lifetime risk estimates were also presented from two alternative models, in which the ERR was assumed to be constant for the first 45 years of follow-up and to then decline linearly with age. In the first alternative model, the risks were assumed to decline linearly until they reached the risk for exposure at the age of 50. In the second alternative model, the risks were assumed to decline linearly to reach zero risk at age 90. These alternatives yielded lifetime risks that were 20 and 30%, respectively, below those predicted by the constant relative risk model.

The resulting estimates of lifetime risk were compared with those given in the 1988 report by age-specific coefficients and multiplicative risk projection. The estimates for leukaemia were nearly identical in 1988 and 1994, whereas the 1994 estimate for all solid tumours based on the constant relative risk model was only slightly higher than that of 1988. UNSCEAR did not recommend that the estimates be modified but did recommend that the risks for solid tumours be reduced by a factor of about 2 for exposure to low doses (< 0.2 Sv).

(*b*) *Committee on the Biological Effects of Ionizing Radiations (BEIR V; 1990)*

Unlike the models of UNSCEAR, those of BEIR V were developed for application to the population of the USA, and thus demographic data for the 1980 population were

used in calculating lifetime risks. The BEIR V report provides estimates of the excess mortality from leukaemia and all cancers except leukaemia that would be expected to result from a single exposure to 0.1 Sv, from continuous lifetime exposure to 1 mSv per year and from continuous exposure to 0.01 Sv per year from the age of 18 until the age of 65, with separate estimates for men and women. Estimates of the number of excess deaths (with confidence intervals), the total years of life lost and the average years of life lost per excess death are given. For each exposure scenario, separate estimates are presented for leukaemia and for cancers of the breast, respiratory tract, digestive tract and other cancers, for each sex and for nine categories of age at exposure.

The estimates of BEIR V were based on models in which the ERR was expressed as a function of sex, age at exposure and time since exposure. Separate models were developed for leukaemia and the four categories of solid tumours listed above. The models were based primarily on analyses of data on the mortality of atomic bomb survivors, although the models for breast and thyroid cancers drew on data from several other epidemiological studies. The lifetime risk estimates were based on a multiplicative model in which the relative risks are assumed to be the same for the US population and Japanese survivors of the atomic bombings.

The ERR for leukaemia was found to depend on age at exposure and time since exposure, and separate estimates were made for each of several categories defined by these variables. The ERR for female breast cancer depended on time since exposure (treated as a continuous variable) and age at exposure (< 15, about 20 and ≥ 40 years); the risks increased and then declined with time since exposure and decreased with increasing age at exposure. The ERR for respiratory cancer depended on sex and time since exposure (treated as a continuous variable and indicating a decline with time) but not on age at exposure. The ERR for digestive cancers depended on sex and age at exposure (treated as a continuous variable with a decline starting at age 25) but not on time since exposure. For other cancers, the ERRs depended only on age at exposure (treated as a continuous variable with a decline starting at age 10), with no dependence on sex or time since exposure.

In order to estimate the risks for leukaemia at low doses and dose rates, a linear–quadratic model was used, which reduced the effect by a factor of 2 below the estimates that would have been obtained from a linear model. For cancers other than leukaemia, a linear model was used, with a non-specific recommendation to reduce the estimates obtained through linear extrapolation by a factor of 2–10 for doses received at low rates.

(*c*) *ICRP*

ICRP (1991a) reviewed the estimates provided by UNSCEAR (1988) and by the BEIR V Committee (1990) and recommended use of the estimates obtained from the UNSCEAR age-specific additive model for leukaemia and from the UNSCEAR age-specific multiplicative model for all cancers other than leukaemia. ICRP also recommended that the linear risk estimates obtained from data on high doses be reduced by

a factor of 2 for exposures to < 0.2 Gy or < 0.1 Gy h^{-1}. ICRP provided separate estimates for a working population and for the total population, including children.

ICRP was especially concerned with developing tissue weighting factors (w_T) to allow for their relative sensitivity to cancer. Such weighting factors are useful for estimating the detrimental effects of radiation received at non-uniform doses by various organs of the body (see section 1.4, Overall introduction). To develop these weighting factors, lifetime risks for several types of cancer were calculated from age-specific risk coefficients for the survivors of the atomic bombings. As the factors were to be applicable to the world population, separate calculations were made with reference populations from China, Japan, Puerto Rico, the United Kingdom and the USA on the basis of three sets of assumptions for projecting risks over time and across countries. In estimating risks for cancers of the thyroid, bone surface, skin and liver, ICRP (1991a) considered sources of data other than that on atomic bomb survivors. Other factors that were used in developing the weighting factors were the lethality of each type of cancer and the reduction in lifespan that would result.

(*d*) *Summary*

Table 23 summarizes the lifetime risk estimates per 10^4 person–Gy for a population of all ages and each sex. The reasons for the differences among these estimates were discussed by Abrahamson *et al*. (1991) and Thomas *et al.* (1992). Table 24 shows the contributions of specific cancers to total mortality from cancer as proposed by ICRP and as used in developing the weighting factors.

2.6.4 *Estimates of risk due to specific sources of radiation*

Estimates of the risks attributable to specific sources of radiation are often of interest. As discussed in section 2.6.1, this requires that the magnitude of the doses be estimated. For a linear model, the total exposure, often referred to as the collective dose, may be sufficient. For exposures that vary by age or sex (such as medical and occupational exposure), information is required on such variation, since the risks depend on these factors. For exposures that involve non-uniform doses to various organs of the body, doses to specific organs are required. A few illustrative examples are given briefly below; for details, readers should consult the references indicated. The Working Group made no judgement about the validity of the methods used or the results obtained.

(*a*) *Natural background*

Darby (1991) estimated the number of cancers expected to occur annually in relation to exposure to natural background ionizing radiation in the USA. The source of data on exposure was a report of the National Council on Radiation Protection and Measurements (1987a), which provided estimates of the effective dose equivalents received annually by an average member of the US population from various com-

Table 23. Estimates of lifetime risk for fatal cancer (excess deaths per 10^4 persons exposed to 1 Sv for a population of all ages and each sex)

Type of cancer	UNSCEAR (1988)[a]		BEIR V[b] (1990)	ICRP (1991a)
	Multiplicative[c]	Additive[d]		
Linear estimates[e]				
Leukaemia	97 (100)	93 (100)	[95]	100
All cancers except leukaemia	610 (970)	360 (320)	[695][f]	900
Total	707 (1070)	453 (420)	790	1000
Estimates for low dose and dose rate				
Leukaemia			47.5	50
All cancers except leukaemia				450

[a] The 1994 UNSCEAR report provided a linear–quadratic lifetime risk estimate of 110 for leukaemia after exposure to 1 Sv and linear estimates ranging from 750 to 1090 for solid tumours, but recommended continued use of the age-specific multiplicative estimates from the 1988 report. Based on constant (age-averaged) risk coefficients; those in parentheses were based on age-specific risk coefficients.

[b] Committee on the Biological Effects of Ionizing Radiations. Unlike estimates from other reports, those of BEIR V do not include radiation-induced cancer deaths in persons who would have died of cancer later.

[c] Based on a multiplicative model in which it is assumed that relative risks remain constant over time

[d] Based on an additive model in which it is assumed that the absolute risks remain constant over time

[e] Do not include modification for dose and dose rate reduction factors

[f] Sum of the BEIR V estimates for female breast cancer, respiratory cancer, digestive system cancers and other cancers

ponents of natural background radiation. The values used were 0.27 mSv from cosmic radiation, 0.22 mSv from terrestrial γ-radiation, 0.01 mSv from cosmogenic radionuclides, 2.0 mSv from inhaled radionuclides (mainly radon and its daughters) and 0.39 mSv from other radionuclides in the body. The first three sources irradiate the body uniformly, whereas the non-uniform nature of the remaining sources was taken into account in calculating the resulting effective dose equivalents. There is no important variation in such exposures by age or sex. The risk due to radon was evaluated separately from those due to other sources, and only the non-radon sources were considered, which provided a total dose of about 1.0 mSv per person per year.

Darby (1991) applied the BEIR V model to data on US mortality rates and populations in 1987 and estimated that each year about 6700 cancer deaths would be expected to occur in men and 7100 in women as a result of postnatal exposure to natural background radiation other than radon. She also estimated the numbers of deaths from leukaemia (men, 900; women, 700), respiratory cancers (men, 1800; women, 1800), female breast cancer (700), digestive cancers (men, 1300; women, 1900) and other cancers (men, 2700; women, 2000). These were then expressed as

Table 24. Contribution of cancers in specific organs to mortality from all cancers in a general population

Organ	Fatal probability coefficient (per 10^4 person–Sv)
Bladder	30
Bone marrow	50
Bone surface	5
Breast	20
Colon	85
Liver	15
Lung	85
Oesophagus	30
Ovary	10
Skin	2
Stomach	110
Thyroid	8
Remainder	50
Total	500

From ICRP (1991a)

attributable risks on the basis of the observation that they comprised 2.8% of all cancer deaths in men and 3.6% in women. She further noted that the BEIR V model for cancers other than leukaemia is based on linear extrapolation from risk estimates obtained from data on persons exposed to high doses and dose rates, and may require modification for application to the low doses and dose rates from natural background sources. If the risk estimates are halved to account for this modification, the attributable risks would be about 1.6% for men and 2.0% for women.

(*b*) *Medical diagnosis*

Kaul *et al*. (1997) estimated the annual collective effective dose from medical diagnostic radiation in Germany in 1990–92 in order to evaluate the risk associated with such exposure. They first used health insurance and hospital records to estimate the number of examinations with X-ray and diagnostic medical procedures that had been conducted in the former Federal Republic of Germany. The effective doses from each type of procedure were then estimated, by thermoluminescent dosimetry for the X-ray procedures and information provided in ICRP publications (1991a,b) for the nuclear medical procedures. The collective dose was estimated by multiplying the effective doses associated with each type of examination by the estimated annual frequency of the procedure, and then summing over all procedures. Using this approach, Kaul *et al*. (1997) estimated an annual collective effective dose of about

115 000 person–Sv from X-ray diagnosis and 5000 person–Sv from diagnostic nuclear medicine for the former Federal Republic of Germany, which had a population of 65 million in 1992.

The risk calculations were based on ICRP recommendations (1991a), although the authors noted that the ICRP risk estimate of 5.2% per Sv (lifetime probability of radiation-induced fatal cancer) for a population covering all ages is not fully appropriate because medical exposures are much more frequent at older than at younger ages. By taking into consideration both the age-specific risk calculations provided in an appendix to the ICRP report (1991a) and information on the age distribution of the recipients of the procedures in Germany, they concluded that the estimate of 5.2% per Sv could be reduced by a factor of 0.6–0.7 to estimate the risk from diagnostic medical examinations. Use of a 0.6 reduction led to an estimate of approximately 0.5% for the average additional lifetime risk of fatal cancer attributable to medical irradiation, which can be compared with a 'spontaneous' total fatal cancer risk of 25%. [The Working Group calculated that the attributable risk would then be 0.5/25, or 2%.]

(*c*) *Dental radiography*

White (1992) estimated the worldwide risk from dental radiography by adjusting the risk estimates from several sources so that they were all expressed in terms of full-mouth examinations and by substituting the ICRP (1991a) risk coefficient for the original risk coefficients, which were usually based on earlier data than used by ICRP. This standardization resulted in an average estimate of 2.5 fatal cancers per million full-mouth examinations. The worldwide risk was estimated on the basis of a United Nations report that 340 million dental radiographic procedures had been performed in 1980, with four films per procedure. The estimate of 2.5 fatal cancers per million full-mouth examinations was then converted to an estimate of 0.5 fatal cancers per million procedures, which resulted in an estimate of about 170 annual cancer fatalities worldwide due to dental radiography. White (1992) noted that the universal adoption of alternative films (E-speed films) and procedures (rectangular collimation) could reduce this estimate by a factor of 5.

(*d*) *Mammography*

Mammographic screening and treatment can reduce the risk for fatal breast cancer, but since the radiation involved can cause breast cancer, the procedure also involves risk. Comparisons of the risks and benefits are clearly of interest. Mettler *et al*. (1996) estimated the annual risks and benefits for women in the USA who had annual mammographies beginning at the age of 35, 40 or 50. They used ERR coefficients specific for age at exposure obtained from data on atomic bomb survivors (Tokunaga *et al.*, 1994) but adjusted for differences in the baseline risks for breast cancer in Japan and the USA. The coefficients were applied to data on breast cancer incidence in 1973–90 in selected areas of the USA that are covered by cancer registries. Assumptions were made about the dose per mammography, the reduction in the risk

for dying from breast cancer resulting from screening, the percentage of breast cancers that are fatal and the latency for breast cancer. On the basis of these assumptions and calculations, it was concluded that the benefits substantially outweigh the risks, with a 5% reduction in the rate of mortality from breast cancer with annual screening at the ages of 35–39 and a 25% reduction with screening at ages ≥ 40.

2.7 Other issues in epidemiological studies

The previous section dealt with quantitative issues in risk assessment. Other important epidemiological issues are the statistical power of a study to detect convincingly a cancer excess after exposure to radiation and other factors that modify the effect of radiation, such as age at the time of exposure.

The single most important study of radiation carcinogenesis in human populations is that of the Japanese atomic bomb survivors (Pierce *et al.*, 1996), as it is a long-term prospective cohort study in which a defined group of survivors have been followed forward in time since 1945 to determine their causes of death; more recently, cancer incidence has been evaluated (Thompson *et al.*, 1994). A single exposure to 2 Sv is estimated to double the risk, i.e. cause a 100% excess in the relative risk (RR, 2) for death from any solid tumour. The ability of epidemiological studies to detect such a twofold increase in risk is quite good. A single exposure to 1 Sv is estimated to be associated with a relative risk of about 1.4–1.5, and epidemiological methods are often sufficient to conclude causal associations of this magnitude. The excess absolute risk is about 10 extra cancers per year among 10 000 persons exposed to 1 Sv, and the lifetime risk is about 10% per Sv; i.e. 10 in 100 persons acutely exposed to 1 Sv of whole-body radiation would be predicted to develop a radiation-induced cancer sometime during their lifetime. At an exposure of only 0.1 Sv, the predicted relative risk is only 1.05, i.e. a 5% excess, and epidemiologists have difficulty in detecting such low risks. Sampling variability and inability to control for confounding factors provide ‘noise’ that swamps the small signal to be detected. Thus, estimates of effects at low doses are obtained by extrapolation from data on people exposed to high doses (Boice, 1996).

It is further assumed that estimates obtained from acute or brief exposures should be reduced by a factor of about 2 when exposure is spread over time and not instantaneous, although the possible range in the reduction factor is 2–10. Leukaemia is usually separated from other cancers because its minimum latency is shorter (about two years after exposure) and its mechanism of development may be different. The minimum latency before solid tumours appear after irradiation is about 5–10 years.

Summary estimates of risks associated with radiation can be used as guidelines for setting protection standards and health policy, although even estimates based on high doses are subject to uncertainty (National Council on Radiation Protection and Measurements, 1997). The five broad areas of uncertainty are: epidemiological uncertainties, dosimetric uncertainties, transfer of risk between populations, projection to a

lifetime model and extrapolation to low doses or low dose rates. Risk varies by age at exposure, sex, time after exposure, dose rate, type of radiation, total dose and the presence of other factors such as cigarette smoke. Some cancers, such as chronic lymphocytic leukaemia, have not been associated with exposure to radiation (Boice, 1996). The convention of combining all cancers to obtain a global estimate of risk is a source of error as some cancers have not been associated with radiation and the sites of other cancers differ appreciably in their sensitivity to induction. At very low doses, radiation damage may be repaired, which might influence risk. In the absence of reliable data on the effects of low doses, it is often assumed that extrapolation to low doses should be linear and without a threshold. This assumption remains controversial, some people contending that a threshold does exist, others contending that the risks are higher than those estimated from a linear relationship and still others contending that low exposures may be beneficial (Fry *et al*., 1998; Upton, 1999).

2.7.1 *Scale of measurement*

The scale of measurement is important in evaluating variation in the ability of radiation to induce specific cancers (tissue sensitivity) and the modifying effects of co-factors such as age. A relative scale is influenced by the baseline cancer incidence in the population being studied, and populations with different baselines have different risk coefficients. For example, the rate of naturally occurring breast cancer in Japan is much lower than that in western countries, and the relative risk for radiation-induced breast cancer per sievert is higher in Japanese atomic bomb survivors than in western women exposed to radiation (UNSCEAR, 1994). Differences in radiation-related relative rates between populations can thus be due to differences in the background incidence rates. On an absolute scale, the excess number of cancers occurring per person per year per dose is compared. If the relative risk for radiogenic cancers remains constant with this exposure, then the absolute risk will change at each follow-up period.

2.7.2 *Complicating factors*

Although perhaps more is known about radiation than any other carcinogen, with the possible exception of tobacco, there remain complicating factors which limit generalization of the findings (Table 25). Risk varies with dose, but not always in a linear fashion. The risk may be lower when low doses are delivered at low rates, but most of the evidence of effects comes from studies of high doses delivered at high rates. Risk depends on the sex of the individual exposed and the age at exposure. Risk varies by time since exposure. Exposure to high-LET radiation such as α-particles and neutrons appears to be associated with higher risks than exposure to low-LET radiation (X-rays, γ-rays and electrons). The presence of certain genetic, environmental or lifestyle factors may influence risk to an extent that is not yet well defined (Boice, 1996).

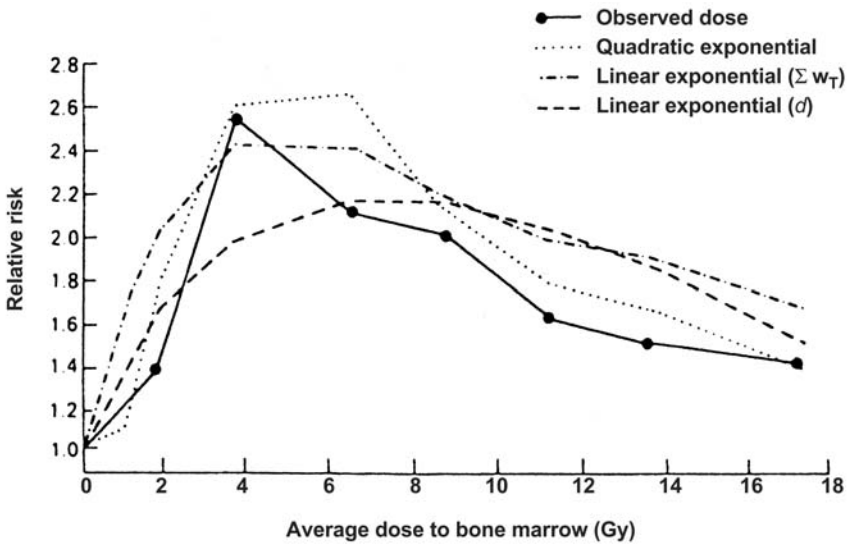
Table 25. Factors that complicate generalizations about estimates of risk associated with exposure to radiation

Factor	Comment
Dose dependence	Cell killing at high doses, repair at low doses
Dose rate	Higher risk for brief exposure, repair at low dose rates
Sex	Somewhat higher risk for women
Age	Somewhat higher risk for people exposed at a young age
Latency	Risk varies by time after exposure.
Co-factors	Smoking enhances the risk associated with radon and may potentiate the effect of radiotherapy; chemotherapy may interact with radiotherapy.
Genetic susceptibility	High-dose radiotherapy of susceptible patients may enhance their risk for malignancies, such as bone cancer after retinoblastoma.
Outcome	Cancer incidence may differ appreciably from cancer mortality, e.g. for the thyroid.
Background rates	Radiation risk varies for different cancers and in relation to the background rate (on a relative or absolute scale).
Tumour type	Cancer sites differ in inducibility, and some cancers have not been convincingly linked to radiation.
Cellular factors	Radiation damage can be repaired, but some errors occur. The extent of cellular repair at low doses is not known. The relevance of genomic instability and of the 'bystander effect' is yet to be determined

(*a*) *Dose*

The dose of radiation to an organ is the most important consideration for risk estimation, and dose–response relationships must be understood since it is necessary to extrapolate from high doses. If the relationship were linear, extrapolation to lower doses would be straightforward. Over a broad range of doses in experimental and human studies, however, the relationship is not always linear, either at the highest or the lowest doses. For example, women who have been treated with radiation for cervical cancer have an increased risk of developing leukaemia, but the dose–response relationship is complex (Day & Boice, 1984; Boice *et al.*, 1987; Blettner & Boice, 1991): the risk increases with doses up to about 4 Gy and decreases or levels off at higher doses (Figure 8). This reduction in risk at high doses has been attributable to cell killing, since so much energy is deposited into small volumes of bone marrow that the cells are destroyed or rendered incapable of division. Studies of atomic bomb survivors also show an apparent decrease in the risks for leukaemia and solid tumours at 2.5 Sv (Figures 4 and 5), although that may reflect dosimetric errors (Pierce *et al.*, 1996). Other studies that have shown a decrease or levelling off of risk at high doses include those of women irradiated for mastitis in whom the risk for breast cancer declines (Shore *et al.*, 1986), women irradiated for endometrial cancer in whom the

Figure 8. Dose–response relationships for leukaemia among women who have been treated with radiation for cervical cancer



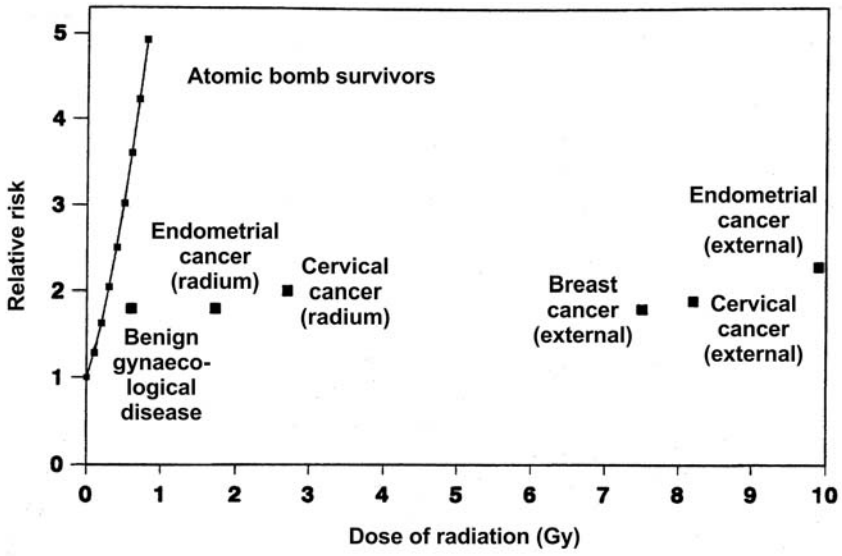
Adapted from Boice (1996)

risk for leukaemia reaches a plateau (Curtis *et al.*, 1994) and children given radiotherapy for cancer in whom the risk for thyroid cancer levels off and there is no increased risk for leukaemia (Tucker *et al.*, 1987b, 1991; Boice, 1996).

The risk coefficients and dose–response relationships for leukaemia vary appreciably among the populations studied. The data on atomic bomb survivors (Figure 4) show a linear–quadratic response to radiation in the low dose range (Preston *et al.*, 1994; Pierce *et al.*, 1996). Partial exposure of the body to high doses in medical procedures with various dose rates and various contributions of fractionation results in a variety of risk coefficients per gray (Figure 9). These differences among studies suggest a complex interplay between cell killing, fractionation, lengthened dose interval and neoplastic transformation in defining dose–response relationships.

For single whole-body exposures, the relationship between mortality from all cancers except leukaemia among the atomic bomb survivors is consistent with linearity up to about 3 Sv (Figure 10) (Pierce *et al.*, 1996). A significant excess is seen at 0.2–0.5 Sv, and is suggested down to 0.05 Sv; extrapolation to lower doses on the basis of a linear model appears reasonable. The authors caution, however, that reporting bias may have contributed to the shape of the dose–response curve at low doses in that Japanese physicians appeared to have been more likely to record cancer as the primary cause of death for people exposed to low doses than for those receiving high doses. The incidence data (Thompson *et al.*, 1994) are also consistent with linearity,

Figure 9. Relative risks for leukaemia by dose of radiation in survivors of the atomic bombings and patients receiving high doses in radiotherapy



Adapted from Boice *et al.* (1996)

Figure 10. Dose–response relationship for all cancer except leukaemia among atomic bomb survivors

Adapted from Boice (1996)

although cancers of the breast and thyroid may disproportionally influence the aggregate data.

One complicating factor in estimating the risk associated with low doses is the extent to which neutrons (see separate monograph in this volume) may have influenced the shape of the dose–response curve. The bomb dropped on Hiroshima resulted in exposure to neutrons in addition to γ-rays. While the exact contribution of neutrons to the total dose is under investigation, the greater effectiveness of neutrons in causing cancer at low doses could be responsible for the seeming linearity of the dose–response curve. The larger the fraction of the total dose attributed to neutrons, the smaller will be the estimate of the risk attributable to photons. In the absence of exposure to neutrons, the dose–response relationships would be expected to be curvilinear, consistent with the majority of experimental data for exposure to γ-rays (Kellerer & Nekolla, 1997). Some analyses of the incidence of cancer among atomic bomb survivors indicate that a threshold or non-linear dose–response model is more suitable than a linear model for some cancers (Hoel & Li, 1998) and especially leukaemia (Little *et al*., 1999) and skin cancer (Little *et al*., 1997).

At very low doses, the relationship between cancer and exposure to radiation becomes blurred because the excess number of cancers at low doses predicted from studies of exposure to high doses is so much smaller than the spontaneous incidence, i.e. one in three persons is expected to develop cancer during his or her lifetime. Extrapolation of risks derived from studies of exposure to high doses to lower levels requires use of a model selected on the basis of the fundamental principles of radiation biology (UNSCEAR, 1993). The model used in radiation protection is the linear–quadratic function, which is a derivative of the linear non-threshold model with allowance for effects of low doses and low dose rates (Beninson, 1997; Sinclair, 1998; Upton, 1999).

Some scientists contend that linearity exaggerates the risk of low doses. They base their arguments on phenomena such as the ability of cellular mechanisms to repair damage to DNA induced by radiation, the absence of an excess risk for leukaemia among atomic bomb survivors exposed to low doses and among US military personnel who participated in nuclear tests, the absence of a risk for lung cancer in ecological studies of indoor exposure to radon, the absence of an excess risk for thyroid cancer among patients given ^{131}I, the absence of an excess of cancer in populations living in areas with high background radiation and others (Yalow, 1994; Cohen, 1995; Pollycove, 1995; Yalow, 1995; IAEA, 1997; Pollycove, 1998). They contend that epidemiological findings for people exposed to high doses at high rates should not be extrapolated to low doses, where the risk may be negligible or non-existent. These arguments are being considered by various scientific committees (Fry *et al*., 1998; Upton, 1999).

(*b*) *Dose rate*

Dose rate, i.e. the time over which a radiation dose is delivered, may influence risk in a variety of ways. In experimental animals, the risk per unit dose is usually greater at higher dose rates, for the same cumulative dose of low-LET radiation (Fry, 1992; UNSCEAR, 1993). It is thought that increasing the duration of exposure may increase the opportunity for cellular repair.

Perhaps the most thoroughly studied cancer with regard to the effects of fractionating low-LET radiation is that of the breast (Boice *et al*., 1979; Land *et al.*, 1980; UNSCEAR, 1994). Large studies of patients with tuberculosis who were exposed to multiple chest fluoroscopies several times per month for three to five years in order to monitor lung collapse showed linear increases in the risk for breast cancer with increasing dose to the breast (Boice *et al.*, 1991a; Howe & McLaughlin, 1996; Little & Boice, 1999). The age-specific absolute risk estimates were similar to those seen in studies of women irradiated for acute post-partum mastitis and among atomic bomb survivors. While fractionation did not seem to lower the risk for breast cancer measurably in the patients with tuberculosis, fractionation may well have influenced the risk for lung cancer. Despite an average cumulative dose of nearly 1 Gy, no excess lung cancers have been observed in these large series (Davis *et al.*, 1989; Howe, 1995), and no excess risk for leukaemia has been reported after repeated chest fluoroscopies (Davis *et al*., 1989). Studies in experimental animals also indicate that the spectrum of tumour types may be different after protracted rather than brief exposure (see section 3; Fry, 1992; UNSCEAR, 1993; Upton, 1999).

Few studies have directly addressed the possible lowering of risk when exposure is protracted. No increase in the risk for thyroid cancer was seen in patients given diagnostic doses of ^{131}I, which has a half-life of only eight days, although the absence of risk may have been due to the older age of the patients when exposed or to the distribution of dose within the thyroid gland (Hall *et al.*, 1996). Leukaemia did not occur in excess after ^{131}I treatment for hyperthyroidism (Holm *et al.*, 1991; Ron *et al.*, 1998b), although the dose to the bone marrow was small. Studies of working populations may provide useful guidance about the risks of low, protracted doses, although the number of excess cancers attributable to radiation is so far small and was of the order of 10 in a combined series of nearly 100 000 workers (Cardis *et al*., 1995).

ICRP (1991a) assumes a dose and dose rate effectiveness factor of 2 for radiation protection, i.e. the risk coefficients available for the atomic bomb survivors are reduced by half. The Committee on the Biological Effects of Ionizing Radiations (BEIR; 1990) and UNSCEAR (1988, 1993, 1994) indicate that a factor between 2 and 10 might be used, although a value closer to 3 has been suggested (UNSCEAR, 1993). Since the sites of cancer vary in their inducibility by radiation, they would also vary with respect to the protective effect of protraction. The factor for breast might be close to 1, whereas that for lung might be 10 (Howe, 1995; Boice, 1996; Howe &

McLaughlin, 1996). Perhaps the most important unanswered question in radiation epidemiology is the level of risk after prolonged as opposed to brief exposure.

(*c*) *Age*

Age at exposure can affect the response to radiation. In general, children appear to be at somewhat greater risk than adults. For example, women who were < 20 when they were exposed are at greater risk for breast cancer than women who were older, and little risk is associated with exposure after the menopause (Land *et al.*, 1980; Boice *et al.*, 1991b; UNSCEAR, 1994). The data on atomic bomb survivors show the dependence on age at exposure of the subsequent risk for breast cancer, children being at highest risk and women over the age of 40 at small or minimal risk (see Figure 6). The risk for radiogenic thyroid cancer appears to be concentrated almost entirely among children under the age of 15 (Ron *et al.*, 1995). Studies of atomic bomb survivors reveal little risk for radiation-induced thyroid cancer among those exposed after the age of 20 (Thompson *et al.*, 1994), and large studies of adult patients given diagnostic doses of ^{131}I show no increased risk for thyroid cancer (Hall *et al.*, 1996). Increased risks for thyroid cancer reported in other studies of adults were either not statistically significant (Boice *et al.*, 1988) or were seen after administration of extremely high doses (> 10 Sv) in the treatment of an underlying thyroid disorder (Ron *et al.*, 1998b). The risks for only a few cancers, such as of the lung, appear to be higher after exposure as an adult rather than as a child to the atomic bombs. Because no childhood population has been followed for life, however, it is not known whether the apparent differences in effects by age will continue to be seen.

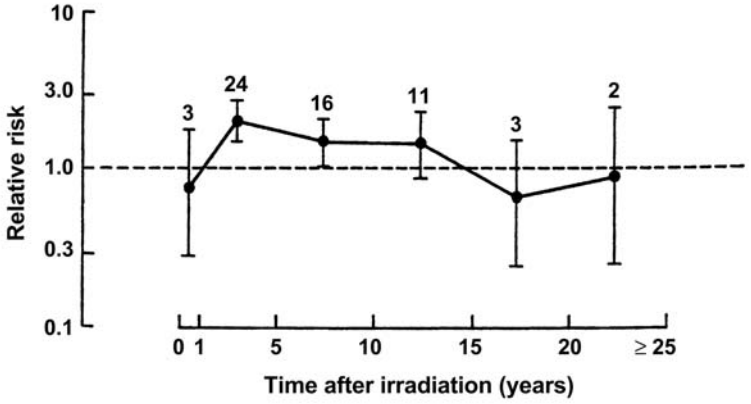
(*d*) *Sex*

On a relative scale, women appear to be somewhat more sensitive to the carcinogenic effects of radiation than men for most cancer sites except perhaps leukaemia (Thompson *et al.*, 1994). Since the baseline risks for many cancers are lower for women than for men, however, the absolute risks tend to be more comparable by sex. The breast is one of the most important radiogenic sites in women: the risk coefficient is high, and there is no evidence that radiation causes breast cancer in males. Females, who are at higher risk for naturally occurring thyroid cancer than males, also seem to be at higher radiogenic risk for cancer at this site. Although increased rates of ovarian cancer have been seen, cancers of male genital organs have not been convincingly linked to exposure to ionizing radiation (UNSCEAR, 1988). In the data on cancer incidence among the atomic bomb survivors, women had approximately twice the relative risk for developing solid tumours when compared with men (Thompson *et al.*, 1994).

(*e*) *Time*

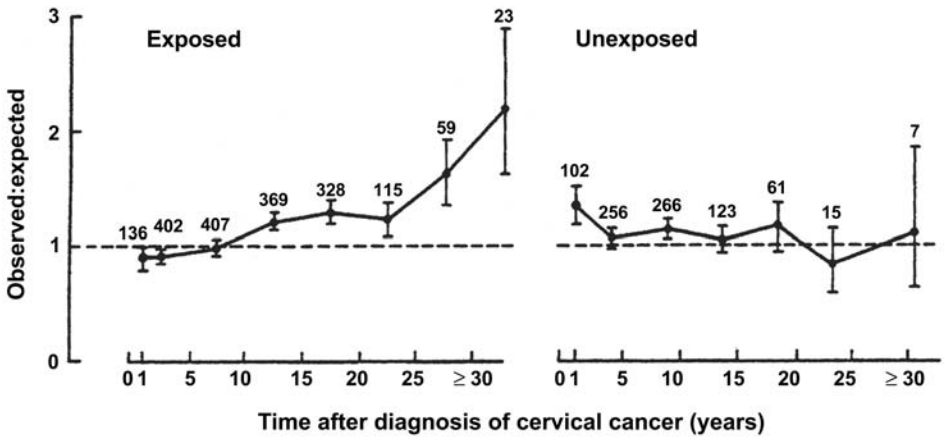
The period of observation is also an important determinant of risk (UNSCEAR, 1994). As the expression of radiation-induced solid tumours takes many years, studies with a short follow-up period might find different risk coefficients than those with longer periods of observation. Leukaemia has a relatively short minimal latency, an increase in risk first appearing about two years after exposure (Figure 11). The pattern of risk over time is then somewhat wave-like, peaking after about 10 years and decreasing thereafter, but not to control levels (Preston *et al.*, 1994). Solid tumours appear to have a minimal latency of five to nine years, and the risk may remain high for much of a lifespan, although there might be a decrease in the relative risk for radiogenic solid tumours after long follow-up periods. Studies of patients with ankylosing spondylitis treated with radiotherapy showed a risk close to background after 25 years (Weiss *et al.*, 1994). Atomic bomb survivors who were exposed while young have a reduced relative risk with time (Pierce *et al.*, 1996), as do children treated with radiation for medical conditions (Little *et al*., 1998b). Studies of cervical cancer patients treated with radiotherapy show no evidence for a decrease in risk after 30 years of observation (Figure 12), but the extremely high doses and the gynaecological tumours involved do not allow any generalizations to be made (Boice *et al.*, 1988).

Figure 11. Relative risks for acute and nonlymphocytic leukaemia with time after irradiation



Adapted from Boice *et al.* (1996). The numbers of cases are shown above the upper confidence limits.

Figure 12. Observed:expected numbers of second primary cancers at or near the pelvis, by time since diagnosis of cervical cancer, for patients treated with and without radiation



Adapted from Boice *et al.* (1996). The numbers of cases are shown above the upper confidence limits; 80% confidence intervals

(*f*) *Co-factors*

(i) *Environmental*

Co-factors are genetic, life-style or environmental conditions that influence a response to radiation. If co-factors differ appreciably between populations, it may be incorrect to extrapolate risk coefficients from one to the other. The risk estimates for the atomic bomb survivors were obtained after a brief exposure of a Japanese population with certain underlying disease rates who subsequently lived in a war-torn environment with severe malnutrition and poor sanitary conditions. Further, the striking excesses of mortality appear to be confined to a few cancer sites, such as the stomach, lung and breast, which account for about 70% of the total absolute risk (Pierce *et al*., 1996). In addition, the convention of combining all cancers has little biological justification, given the different etiological and radiation risk coefficients for individual cancers.

Smoking is an important co-factor, and studies of patients with Hodgkin disease (van Leeuwen *et al.*, 1995) and small-cell lung cancer (Tucker *et al.*, 1997) suggest that continued use of tobacco after radiotherapy potentiates the risk for a second cancer in the lung. In a study of leukaemia among breast cancer patients, there appeared to be a multiplicative interaction between chemotherapy and radiotherapy (Curtis *et al.*, 1992).

(ii) *Genetics*

An excess risk for skin cancers was seen in white but not black patients given radiotherapy for tinea capitis, suggesting that genetic factors act in concert with concomitant exposure to ultraviolet light (Shore *et al.*, 1984). Furthermore, the skin cancers in whites occurred on the face and around the edge of the scalp not covered by hair, suggesting that sunlight may potentiate the effects of X-rays. The role of ultraviolet light is not as evident for darker-skinned populations in Japan and Israel, however (Ron *et al.*, 1991, 1998a). The genetic susceptibility of people with inherited disorders is discussed in section 4.3.

Studies of radiotherapy in the treatment of childhood cancers suggest that underlying host factors might play an enhancing role in the carcinogenic process (de Vathaire *et al*., 1992). Most studies of genetic susceptibility, however, involved high therapeutic doses to treat tumours, and it is unclear whether similar responses would occur at low levels of exposure (ICRP, 1999).

2.7.3 *Variations in risk by cancer site*

Variation in cancer risk coefficients is seen in the data on incidence among atomic bomb survivors (Thompson *et al.*, 1994; Preston *et al.*, 1994) and in compilations of organ-specific risks in various studies (UNSCEAR, 1994). The study of atomic bomb survivors has a distinct advantage, in that the risks can be averaged for the two sexes, all ages, for whole-body exposure on the same day and among subjects followed prospectively in the same manner. As 56% of the atomic bomb survivors were still alive in 1991 (Pierce *et al*., 1996), however, the risk coefficients may change with further follow-up. In addition, the exposure was acute and not protracted, and studies in experimental animals suggest that the spectrum of tumour types is different after protracted and after brief exposure (Fry, 1992).

(*a*) *Excess relative risk*

Table 26 shows a ranking of cancers by ERR, i.e. the relative risk minus 1.0, for exposure to 1 Gy. For example, if the relative risk for breast cancer after exposure to 1 Gy is 2.74, the ERR is 1.74. Only cancers linked to exposure to radiation are presented. Leukaemia is seen to be associated with by far the highest ERR per Gy, whereas the stomach, which was strongly affected by the atomic bombs, is associated with a very low ERR per Gy (Boice, 1996).

(*b*) *Absolute excess risk*

The rankings change when an absolute scale is used (Table 27), reflecting the excess cancers per 10 000 persons per year per Gy. The estimate of absolute risk for breast cancer, for example, is 6.8×10^{-4} person–years Sv. Cancer of the female breast ranks first on an absolute scale, followed by cancers of the stomach and lung and then by leukaemia; cancers of the bladder and skin are at the lowest levels. These estimates

are based on new data on cancer incidence among atomic bomb survivors, which have been collected since 1958, so that a minimal latency of about 12 years is incorporated into the estimates. The rankings might be different for populations with different baseline risks (Boice, 1996).

Table 26. Ranking of cancers by excess relative risk (ERR) at 1 Gy from data on atomic bomb survivors

Cancer site	ERR per Gy
Leukaemia	4.37
Breast	1.8
Thyroid	1.2
Lung	1.0
Ovary	1.0
Skin	1.0
Bladder	1.0
Colon	0.72
Liver	0.49
Stomach	0.32

Adapted from Boice (1996)

Table 27. Ranking of cancers in survivors of the atomic bombings by excess absolute risks

Cancer site	Excess cases per 10 000 persons per year per Gy
Breast	8.7
Stomach	4.8
Lung	4.4
Leukaemia	2.7
Colon	1.8
Thyroid	1.6
Liver	1.6
Bladder	1.2
Ovary	1.1
Skin	0.84

Adapted from Boice (1996)

(*c*) *Attributable risk*

Sites can also be ranked by the percentage of tumours occurring in exposed survivors that could be related or attributable to exposure to the atomic bombings in 1945 (Table 28). These rankings are similar to those based on the ERR, since, as a first approximation, the attributable risk depends on the relative risk. More than half of the over 200 cases of leukaemia and 20–30% of the cancers of the breast, thyroid and skin could be attributable to exposure to radiation. The stomach has a very low attributable risk: only 6% of the over 1000 cases could be linked to exposure. For all solid tumours together, the attributable risk per cent is less than 10%, i.e. more than 90% of the cancers occurring in atomic bomb survivors were caused by factors other than atomic radiation (Boice, 1996). For all cancer deaths, the attributable risk is similar, about 8%, but for all deaths the attributable risk is about 1%. Overall, approximately 420 cancer deaths among the over 38 000 deaths among atomic bomb survivors can be attributed to the exposure to radiation received in 1945 (Pierce *et al.*, 1996).

Table 28. Ranking of cancers in survivors of the atomic bombings by attributable risk

Cancer site	Attributable risk (%)
Leukaemia	80
Breast	32
Thyroid	26
Skin	24
Lung	18
Ovary	18
Bladder	16
Colon	14
Liver	11
Stomach	8.5
Oesophagus	8.5

Adapted from Boice (1996)

(*d*) *Relative tissue sensitivity*

Human tissues vary in their sensitivity to cancer induction by radiation (Committee on the Biological Effects of Ionizing Radiations (BEIR V), 1990; Thompson *et al.*, 1994; UNSCEAR, 1994; Weiss *et al.*, 1994; Boice, 1996; Boice *et al.*, 1996). Cancers that appear to be highly susceptible to radiation, with relatively high risk coefficients, include leukaemia and those of the premenopausal female breast and the childhood thyroid gland. The risks for these cancers are frequently increased in exposed populations.

Tissues that are apparently less susceptible or in which cancers are induced only at relatively high doses include the brain, bone, uterus, skin and rectum. Some cancers have not been linked convincingly to exposure to radiation; these include chronic lymphocytic leukaemia, Hodgkin disease, multiple myeloma, non-Hodgkin lymphoma (Boice, 1992) and cancers of the cervix, testis, prostate, pancreas and male breast.