X-RADIATION AND γ-RADIATION

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Röntgen received the Nobel Prize in Physics in 1901,
for the discovery of X-rays.

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1. Exposure data

1.1 Occurrence

1.1.1 *X-radiation*

X-rays are electromagnetic waves in the spectral range between the shortest ultraviolet (down to a few tens of electron volts) and γ-radiation (up to a few tens of mega electron volts) (see Figure 2, Overall introduction). The term γ-radiation is usually restricted to radiation originating from the atomic nucleus and from particle annihilation, while the term X-radiation covers photon emissions from electron shells. X-rays are emitted when charged particles are accelerated or decelerated, during transitions of electrons from the outer regions of the atomic shell to regions closer to the nucleus, and as *bremsstrahlung*, i.e. radiation produced when an electron collides with, or is deflected by, a positively charged nucleus. The resulting line spectra are characteristic for the corresponding element, whereas *bremsstrahlung* shows a continuous spectrum with a steep border at the shortest wavelengths.

Interaction of X-rays with matter is described by the Compton scattering and photoelectric effect and their resulting ionizing potentials, which lead to significant chemical and biological effects. Ions and radicals are produced in tissues from single photons and cause degradation and changes in covalent binding in macromolecules such as DNA. In other parts of the electromagnetic spectrum, below the spectra of ultraviolet and visible light, the single photon energies are too low to cause genotoxic effects. The intensity (I) of X-rays inside matter decreases according to $I = I_0 \times 10^{-\mu \cdot d}$, where d is the depth and μ a coefficient specific to the interacting material and the corresponding wavelength. The ability to penetrate matter increases with increasing energy and decreases with increasing atomic number of the absorbing material. When X-rays penetrate the human body, they are absorbed more effectively in the bones than in the adjacent tissue because of the greater density of bone and the larger proportion in bone of elements with higher atomic numbers, such as calcium.

X-rays are usually generated with X-ray tubes in which electrons emitted from a cathode are accelerated by a high electric potential and hit a target which emits *bremsstrahlung* and a line spectrum characteristic for the material of the target. The expression ‘kVp’ refers to the applied voltage (kV) of an X-ray machine and is given as the maximum (p for peak) voltage that the machine can produce. According to the

applied voltage, ultrasoft (5–20 kVp), soft (20–60 kVp), medium hard (60–120 kVp), hard (120–250 kVp) and very hard (> 250 kVp) X-rays can be distinguished. Extremely hard X-rays are generated with betatrons, synchrotrons and linear accelerators and are in the mega electron volt range.

X-rays are used in many medical and technical applications. The most common are X-ray examinations of the human body and analysis of technical materials. In X-ray therapy, the biological effect of X-rays is used to destroy malignant tissue. It is applied mainly to treat cancer patients, when high doses are delivered to a limited area of the body, with restricted irradiation of adjacent tissue.

1.1.2 γ-*radiation*

Ernest Rutherford in 1899 found that the radiation from radioactive sources consisted of several components, which he called α-, β- and γ-rays. In 1914, he proved by interference experiments that γ-rays were electromagnetic waves. They are emitted by γ-transitions in atomic nuclei. The corresponding photons, called γ-quants, have widely different energies, ranging from 0.01 to 17.6 MeV, which reflect the fact that the energy of the transitions in the atomic nucleus is higher than that of the transitions of the orbiting electrons. The emission of γ-rays usually follows nuclear transformations, which place an atomic nucleus in a state of enhanced energy during processes of radioactivity and during capture of particles. Unlike α- and β-radiation, γ-rays cannot be deflected by electric and magnetic fields. The γ-transition, also called γ-decay, is not radioactive decay in the usual sense, because neither the charge nor the mass number of the nucleus changes.

Electromagnetic radiation in the same energy range can also be produced by the decay of elementary particles, annihilation of electron–positron pairs and acceleration and deceleration of high-energy electrons in cosmic magnetic fields or in elementary particle accelerators. γ-rays, especially those with high energy, can penetrate matter easily, and their absorption and deflection follow an exponential law, as in the case of X-rays. Their physiological effect is also similar to that of X-rays.

Interaction of γ-rays with matter is described by the Compton scattering and photoelectric effect. At energies above 1.02 MeV, pair production occurs, resulting in emission of electron and positron radiation. At even higher energies, in the range of several mega electron volts, absorption of γ-quants results in neutron emission.

1.2 Exposure

Electromagnetic waves in the ionizing range are ubiquitous in the human environment and are responsible with α- and β-rays and to a lesser extent with particle radiation, such as neutrons or muons, for the total radiation dose to which the average person is exposed.

Exposure to X-rays and γ-rays can be external or internal, depending on the location of the source with respect to the human body. External exposure occurs, for example, during X-ray examinations or during natural irradiation from building materials containing γ-ray emitters. Most of the dose from external irradiation is due to X- or γ-rays, because α- and β-particles are readily absorbed by the clothes covering the body or by the superficial layer of skin, whereas X- and γ-rays can penetrate the body and even traverse it if their energy is sufficiently high (see Figure 1, Overall introduction). Internal irradiation occurs during the decay of radionuclides absorbed in the body, usually after ingestion or inhalation. In this case, α- and β-particles are more important than X- or γ-rays, because α- and β-emitters lose most or all of their energy in the tissues or organs in which they decay, while the energy of X- and γ-rays, which is usually lower than those of α- and β-rays, is diffused throughout the body or even leaves the body without creating any damage.

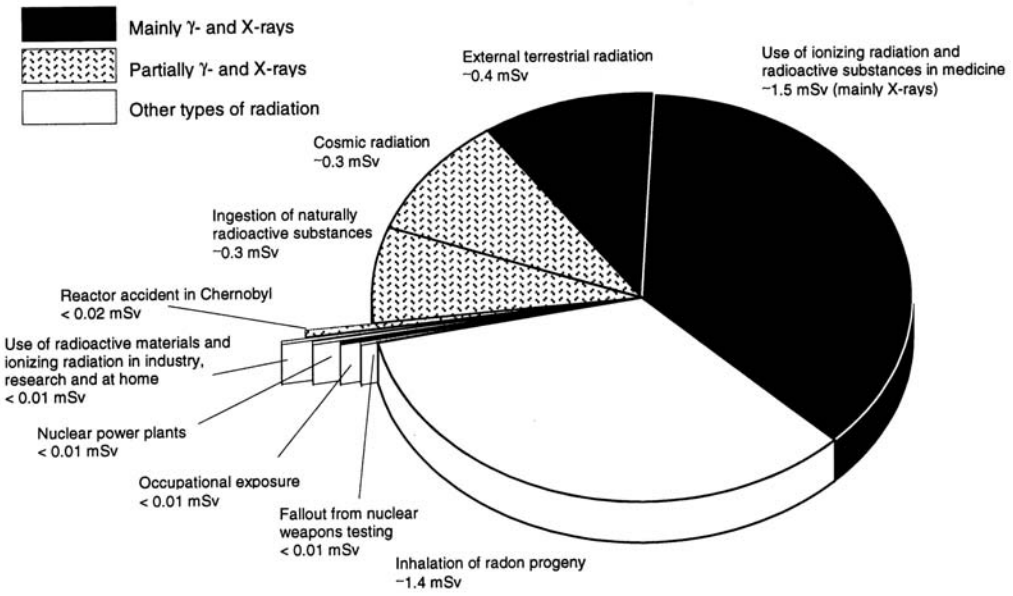
Doses of all types of radiation from external and internal exposure are summarized in the Overall introduction. In this chapter, only external exposure to X and γ-rays is discussed.

Although it is difficult to evaluate the relative contribution of electromagnetic radiation in mixed radiation fields, it can be estimated to be about 50% (Figure 1). There are major natural and man-made sources of exposure, some of which are increasing. Estimates of the average doses received by the general population are reviewed regularly by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and by many national bodies, such as the Bundesministerium für Umwelt, Naturschutz und Reaktorsicherheit in Germany, the National Council on Radiation Protection and Measurements in the USA and the National Radiological Protection Board in the United Kingdom. Medical exposure and natural terrestrial exposure are due mainly to X- and γ-rays. Other important components of these estimates are mixed radiation fields, such as internal β-emitters with a considerable γ-ray component, whereas the important man-enhanced exposure from indoor radon and its short-lived daughter products is mainly internal exposure to α-radiation. Cosmic radiation at ground level consists of particle radiation (mainly muons), with increasing contributions from neutrons at higher altitudes (see section 4.4.1, Overall introduction).

1.2.1 *Natural sources*

Most natural exposure to X- and γ-rays is from terrestrial sources, with a small part from extraterrestrial sources. Exposure from terrestrial sources depends on the geological properties of the soil, which vary significantly. The average annual external exposure to γ-rays worldwide from terrestrial sources is 0.46 mSv (UNSCEAR, 1993). This value is derived from the average indoor (80 nGy h^{-1}) and outdoor (57 nGy h^{-1}) absorbed dose rates in air, assuming an indoor occupancy factor of 0.8 and a conversion factor from the absorbed dose in air to the effective dose of 0.7 Sv Gy^{-1}.

Figure 1. Estimated average exposure to ionizing radiation from various sources in Germany



From Bundesamt für Strahlenschutz (1998)

UNSCEAR (1993) also gives detailed data for exposure in various regions of the world. The lowest outdoor dose rates in air are reported for Canada (24 nGy h^{-1}) and the lowest indoor rates for Iceland and New Zealand (20 nGy h^{-1}). The maximum average values are found in Namibia (outdoors, 120 nGy h^{-1}; indoors, 140 nGy h^{-1}). In a survey of terrestrial γ-radiation in the USA, 1074 measurements were made in and around 247 dwellings (Miller, 1992). The absorbed dose rate in outdoor air was 14–118 nGy h^{-1} with an average of 46.6 nGy h^{-1}, whereas the average indoor rate was 12–160 nGy h^{-1} with an average of 37.6 nGy h^{-1}. The last value is considerably lower than the worldwide average reported by UNSCEAR (1993) and apparently results from the predominant use of wood-frame construction and other building materials with a low content of radionuclides in the USA. The average exposures in eight countries of Europe ranged from 50 to 110 nGy h^{-1} in buildings and from 30 to 100 nGy h^{-1} in the open air (Green *et al.*, 1992; Commission of the European Communities, 1993).

Little exposure is derived from X- and γ-rays in extraterrestrial natural sources (i.e. cosmic rays), as muons and electrons are the most important contributors to the average annual effective dose at ground level of about 0.4 mSv (UNSCEAR, 1993).

1.2.2 *Medical uses*

The medical uses of radiation include diagnostic examinations and treatment. The dose to individual patients undergoing radiotherapy is much higher than that experienced during diagnosis, although the number of patients is much smaller. As treatment with radiotherapy is intended to deliver high doses to target organs, mostly in elderly patients, attempts to transform collateral doses to non-target organs into effective doses are open to criticism. For this reason, data on exposure during radiotherapy are not described, although UNSCEAR (1993) made the crude estimate that the effective collective dose of the world population due to radiotherapy is comparable to that due to diagnostic applications (see section 4.2, Overall introduction).

Medical diagnosis involving ionizing radiation is based mainly on X-rays. Although the dose per examination is generally low, the extent of the practice makes diagnostic radiography the main source of radiation from medical use. The use of X-rays and γ-rays for medical purposes is distributed very unevenly throughout the world, being closely associated with general health care level (see section 4.2, Overall introduction). A survey undertaken by UNSCEAR in 1990–91, in which responses to a questionnaire were received from 50 countries, indicated that at that time there were 210 000 radiologists worldwide, 720 000 diagnostic X-ray units, 1.6 thousand million X-ray examinations performed in 1990 and 6 million patients undergoing some form of radiotherapy. Seventy per cent of these services were available in countries with a well-developed health-care system. In highly developed countries, most plain-film examinations of the chest and extremities involve relatively low doses (effective doses of about 0.05–0.2 mSv), whereas the doses used to examine the abdomen and lower back are higher (about 1–3 mSv). The approximate doses to the skin and the effective doses from a number of diagnostic procedures in developed countries are shown in Table 1. Computed tomography scanning has become widely available in many developed countries. In the USA, even though it accounts for less than 10% of procedures, it provides more than 30% of the absorbed dose since the effective dose is about 2.5–15 mSv, which is higher than that from most procedures in which plain- film X-rays are used for diagnosis (UNSCEAR, 1993). The estimated annual effective dose from all diagnostic uses of radiation in those countries was estimated to be 1.0 mSv per person, while that averaged over the whole world was about 0.3 mSv per person (UNSCEAR, 1993).

A source of uncertainty in these estimates is the use of fluoroscopy, which results in much higher doses than radiography; furthermore, its prevalence is not fully known and is changing with time. The doses may vary widely: modern equipment with image amplifiers results in lower doses than older equipment with fluorescent screens, but high doses may still be received when fluoroscopy is used in interventional radiology as a means of guidance during surgical procedures, although this practice is infrequent. The effective dose from most procedures is about 1–10 mSv. The collective dose is due mainly to the more frequent fluoroscopic examinations of the gastrointestinal tract. In the USA, the average effective doses are 2.4 mSv during examination of the upper

Table 1. Approximate mean effective doses from diagnostic radiology procedures in highly developed countries

Procedure	Average effective dose (mSv) per examination	Average number of examinations per 1000 population per year
Chest radiograph	0.14	197
Lumbar spine radiograph	1.7	61
Abdominal radiograph	1.1	36
Urography	3.1	26
Gastrointestinal tract radiograph	5.6	72
Mammography	1.0	14
Radiograph of extremity	0.06	137
Computed tomography, head	0.8	44
Computed tomography, body	5.7	44
Angiography	6.8	7.1
Dental X-ray	0.07	350
Average	1.05	887

From UNSCEAR (1993). Doses may vary from these values by as much as an order of magnitude depending on the technique, equipment, film type and processing.

gastrointestinal tract and 4.1 mSv during a barium enema. These two types of examination are the source of about 40% of the annual collective dose due to diagnostic X-ray application, whereas chest examinations account for over 5% of the *per caput* effective dose equivalent from medical X-rays in the USA (National Council on Radiation Protection and Measurements, 1989). The dose from chest examinations in a Canadian study was 0.07 mSv (Huda & Sourkes, 1989).

1.2.3 *Nuclear explosions and production of nuclear weapons*

The atomic bombings of Hiroshima and Nagasaki, Japan, in 1945 exposed hundreds of thousands of people to substantial doses of external radiation from γ-rays. Estimates of the doses are available for 86 572 persons in the Life Span Study out of about 120 000 persons who were in one of the cities at the time of the explosions. The collective dose to the colon for the 86 472 persons for whom dosimetry is available was 24 000 person–Sv (Burkart, 1996; see section 4.1, Overall introduction), to give an average of about 300 mSv. The doses decreased with distance from the epicentres, but the highest doses to the colon were > 2000 mSv.

Atmospheric nuclear explosions were carried out at several locations, mostly in the Northern Hemisphere, between 1945 and 1980. The most intense period of testing was between 1952 and 1962. In all, approximately 520 tests were carried out, with a

total yield of 545 Mt. Since 1963, nuclear tests have been conducted mainly underground, and the principal source of worldwide exposure due to weapons testing is the earlier atmospheric tests. The total collective effective dose of X- and γ-rays committed by weapons testing to date is about 2.2×10^6 person–Sv. The radionuclides that contribute the most to this dose are listed in Table 2. With the exception of ^{137}Cs and ^{125}Sb, all of these radionuclides have radioactive half-lives of less than one year, and therefore delivered their doses soon after the explosions. ^{137}Ce, with a radioactive half-life of about 30 years, is still present in the environment and continues to deliver its dose at a low rate. For the world population of 3.2×10^9 in the 1960s, the average effective dose from global fall-out resulting from external irradiation was about 0.7 mSv (UNSCEAR, 1993).

Table 2. Collective effective doses of the world population from external radiation committed by atmospheric nuclear testing

Radionuclide	Radioactive half-life	Collective effective dose (1000 person–Sv)
^{137}Cs	30 years	1210
^{95}Zr	64 days	270
^{54}Mn	310 days	180
^{106}Ru	370 days	140
^{95}Nb	35 days	130
^{125}Sb	2.7 years	88
^{140}Ba	13 days	49
^{144}Ce	280 days	44
^{103}Ru	39 days	39
^{131}I	8.0 days	4.4
^{141}Ce	33 days	3.3
Total (rounded)		2200

From UNSCEAR (1993)

People living near the sites where nuclear weapons were tested received higher doses than the average, but the magnitude of the local dose varies according to the conditions under which the tests were conducted. In the USA, about 100 surface or near-surface tests were conducted at a test site in Nevada between 1951 and 1962. The collective dose to the local population of about 180 000 persons has been estimated to be approximately 500 person–Sv (Anspaugh *et al*., 1990), corresponding to an average dose of about 3 mSv.

After a US test in 1954 at Bikini atoll in the Marshall Islands, the residents of Rongelap and Utirik atolls, located 210 and 570 km, respectively, east of Bikini,

received high external exposures, mainly from short-lived radionuclides, with doses of 1900 mSv on Rongelap (67 persons, including three *in utero*), 1100 mSv on nearby Ailinginae atoll (19 persons, including one *in utero*) and 100 mSv on Utirik (167 persons, including eight *in utero*) (Conard *et al*., 1980).

At the Semipalatinsk test site in the Kazakh region of the former USSR, atmospheric tests were conducted from 1949 through 1962, exposing 10 000 people in settlements bordering the test site. The collective dose from external irradiation was estimated to be 2600 person–Sv, corresponding to an average dose of 260 mSv (Tsyb *et al*., 1990).

γ-ray fields resulting from production of weapons material and chemical separation can be considerable, and, as in the case of testing, some local exposures have been substantial. For example, the release of nuclear wastes into the Techa River from a military plant of the former USSR near Kyshtym, in the Ural Mountains, resulted in a cumulative effective dose in the early 1950s of up to 1 Sv (Trapeznikov *et al*., 1993; Bougrov *et al*., 1998).

1.2.4 *Generation of nuclear power*

The generation of electrical energy in nuclear power stations has also contributed to exposure to radiation. The collective effective dose committed by the generation of 1 GW–year of electrical energy has been estimated by UNSCEAR (1993) for the entire fuel cycle, from mining and milling, through enrichment and fuel fabrication, reactor operation, to fuel processing and waste disposal, including transport of radioactive materials from one site to another. The doses of X- and γ-rays have not been estimated explicitly as most of the exposure is due to internal irradiation. The local collective effective dose from X- and γ-rays from external irradiation can be crudely estimated to be about 0.2 person–Sv per GW–year. If it is assumed that about 2000 GW–year of electricity have been generated by nuclear reactors throughout the world, the local collective effective dose from external irradiation is about 400 person–Sv, corresponding to an average dose for the world's population of about 0.1 μSv. An additional component of the exposure is the long-lived radionuclides that are distributed worldwide; the only one that contributes significantly to external irradiation, however, is ^{85}Kr, which has a radioactive half-life of about 10 years. UNSCEAR (1993) indicated that the global component of the collective effective dose due to environmental releases of ^{85}Kr is 0.1 person–Sv per GW–year, corresponding to an average dose for the world's population of about 0.05 μSv.

1.2.5 *Accidents*

The production and transport of nuclear weapons have resulted in several accidents. The two most serious accidents in nuclear weapons production were at Kyshtym and at the Windscale plant at Sellafield in the United Kingdom, both occurring in 1957 (see

section 4.1.3, Overall introduction). A major accident in a nuclear power plant occurred in Chernobyl, Ukraine, in 1986 (see section 4.4.2, Overall introduction).

The Kyshtym accident was a chemical explosion that followed failure of the cooling system in a storage tank of highly radioactive fission wastes. The highest doses were received by 1150 people who received an estimated effective dose from external irradiation of about 170 mSv (UNSCEAR, 1993; Burkart & Kellerer, 1994; Burkart, 1996).

The Windscale accident was caused by a fire in the uranium and graphite core of an air-cooled reactor primarily intended for the production of plutonium for military use. An important route of intake was through milk consumption, which was controlled near the accident, although it was a significant source of exposure further away. The total collective effective dose from external irradiation received in northern Europe was 300 person–Sv (Crick & Linsley, 1984). The total collective effective dose from the release is estimated to have been 2000 person–Sv (UNSCEAR, 1993).

The Chernobyl accident consisted of a steam explosion in one of the four reactors and a subsequent fire, which resulted in the release of a substantial fraction of the core inventory of the reactor. The collective effective dose from the accident is estimated to have been about 600 000 person–Sv, approximately half of which was due to external irradiation (UNSCEAR, 1988). The main contributor to the dose from external irradiation was ^{137}Cs. The doses to individuals throughout the Northern Hemisphere varied widely, some staff and rescue workers on duty during the accident receiving fatal doses > 4 Sv and the most affected people in the evacuated zone receiving effective doses approaching 0.5 Sv (Savkin *et al*., 1996).

Sealed sources used for industrial and medical purposes have occasionally been lost or damaged, resulting in exposure of members of the public. Examples include the sale of a ^{60}Co source as scrap metal in the city of Juarez, Mexico, in 1983 (Marshall, 1984); the theft and breaking up of a ^{137}Cs source in Goiânia, Brazil, in 1987 (IAEA, 1988); and the retrieval of a lost ^{60}Co source in Shanxi Province, China, in 1992 (UNSCEAR, 1993). While these incidents resulted in significant individual doses to a small number of people, the collective effective doses were not large. Tables 3 and 4 are based on recently published data and summarize radiation accidents and resulting early fatalities. Table 4 shows that the steady increase in the use of sources of ionizing radiation has led to an increase in the number of fatalities, despite progress in radiation protection.

1.2.6 *Occupational groups*

Occupational exposure to radiation occurs during nuclear fuel recycling, military activities and medical applications. The doses, including those from internal exposure, are given in Table 5.

Table 3. Major radiation accidents (1945–97) and early fatalities in nuclear and non-nuclear industries

Year	Place	Source	Dose (or activity intake)	No. of persons with significant exposure[a]	No. of deaths
1945–46	Los Alamos, USA	Criticality	≤ 13 Gy	10	2
1958	Vinèa, Yugoslavia	Experimental reactor	2.1–4.4 Gy	8	1
1958	Los Alamos, USA	Criticality	0.35–45 Gy	3	1
1960	USSR	^{137}Cs (suicide)	~15 Gy	1	1
1960	USSR	Radium bromide (ingestion)	74 mBq	1	1 (after 4 years)
1961	USSR	Submarine accident	10–50 Gy	> 30	8
1961	Switzerland	^{3}H	3 Gy	3	1
1961	Idaho Falls, USA	Explosion in reactor	≤ 3.5 Gy	7	3
1962	Mexico City, Mexico	^{60}Co capsule	9.9–52 Sv	5	4
1963	China	^{60}Co	0.2–80 Gy	6	2
1964	Federal Republic of Germany	^{3}H	10 Gy	4	1
1964	Rhode Island, USA	Criticality	0.3–46 Gy	4	1
1966	Pennsylvania, USA	^{198}Au	Unknown	1	1
1967	USSR	X-radiation medical diagnostic facility	50 Gy	1	1 (after 7 years)
1968	Wisconsin, USA	^{198}Au	Unknown	1	1
1968	Chicago, USA	^{198}Au	4–5 Gy (bone marrow)	1	1
1972	Bulgaria	^{137}Cs (suicide)	> 200 Gy (local, chest)	1	1
1975	Brescia, Italy	^{60}Co	10 Gy	1	1
1978	Algeria	^{192}Ir	≤ 13 Gy	7	1
1982	Norway	^{60}Co	22 Gy	1	1
1983	Constitu, Argentina	Criticality	43 Gy	1	1
1984	Morocco	^{192}Ir	Unknown	11	8
1985	China	^{198}Au (mistake in treatment)	Unknown, internal	2	1

Table 3 (contd)

Year	Place	Source	Dose (or activity intake)	No. of persons with significant exposure[a]	No. of deaths
1985–86	USA	Accelerator	Unknown	3	2
1986	Chernobyl, USSR	Nuclear power plant	1–16 Gy	134	28
1987	Goiânia, Brazil	^{137}Cs	≤ 7 Gy	50[b]	4
1989	El Salvador	^{60}Co irradiation facility	3–8 Gy	3	1
1990	Israel	^{60}Co irradiation facility	> 12 Gy	1	1
1990	Spain	Radiotherapy accelerator	Unknown	27	≤ 11
1991	Nesvizh, Belarus	^{60}Co irradiation facility	10 Gy	1	1
1992	China	^{60}Co	> 0.25–10 Gy	8	3
1992	USA	^{192}Ir brachytherapy	> 1000 Gy (local)	1	1
1994	Tammiku, Estonia	^{137}Cs	1830 Gy (thigh) + 4 Gy (whole body)	3	1
1996	Costa Rica	Radiotherapy	Unknown	110	≤ 40
1997	Kremlev, Sarov, Russian Federation	Criticality experiment	5–10 Gy	1	1

From IAEA (1998)

[a] 0.25 Sv to the whole body, haematopoietic or other critical organs: < 6 Gy to the skin locally; < 0.75 Gy to other tissues or organs from an external source, or exceeding half the annual limit on intake

[b] The number of persons who received significant overexposure is probably lower, as some of the 50 contaminated persons received doses < 0.25 Sv.

Table 4. Time trends in numbers of major radiation accidents and early fatalities, 1945–97

Years	Nuclear or military installations		Other installations	
	Accidents	Fatalities	Accidents	Fatalities
1945–54	3	2	0	0
1955–64	12	14	15	10
1965–74	9	0	38	6
1975–84	1	0	35	12
1985–97	3	29[a]	20	66[b]

From IAEA (1998)

[a] Including 28 fatalities after the reactor accident in Chernobyl, 1986

[b] Including 40 fatalities after a radiotherapy accident in Costa Rica, 1996

Table 5. Annual occupational exposures of monitored workers to radiation, 1985–89

Occupational category	Annual collective effective dose (person–Sv)	Annual average effective dose per monitored worker (mSv)
Mining	1100	4.4
Milling	120	6.3
Enrichment	0.4	0.08
Fuel fabrication	22	0.8
Reactor operation	1100	2.5
Reprocessing	36	3.0
Research	100	0.8
Total	2500	2.9
Other occupations		
Industrial applications	510	0.9
Military activities	250	0.7
Medical applications	1030	0.5
Total	1800	0.6
All applications	4300	1.1

From UNSCEAR (1993). Radiological, terrestrial and most occupational exposures are dominated by X- and γ-radiation.

1.2.7 *Summary of collective effective doses*

Typical collective effective doses from all significant sources of exposure over the period 1945–92 are presented in Table 6, which indicates that the two largest sources of X- and γ-rays are natural radiation and the use of X-rays in medicine. Exposures from atmospheric testing have diminished, and only small contributions to the collective dose are made by the generation of electrical energy from nuclear reactors, from accidents and from occupational exposure. These contributions can, however, result in significant exposure of small groups of individuals.

Table 6. Collective doses from X- and γ-radiation committed to the world population by continuing practices or by single events, 1945–92

Source	Basis of commitment	Collective effect dose from X- and γ-rays (million person–Sv)
Natural	Current rate for 50 years	120
Medical use	Current rate for 50 years	
Diagnosis		80
Treatment		75
Atmospheric nuclear weapons tests	Completed practice	2.5
Nuclear power generation	Total practice to date	0.2
	Current rate for 50 years	2
Severe accidents	Events to date	0.3
Occupational exposure	Current rate for 50 years	
Medical		0.05
Nuclear power		0.12
Industrial uses		0.03
Military activities		0.01
Non-uranium mining		0.4
Total		0.6

From UNSCEAR (1993)

Variations in individual doses over time and place make it difficult to summarize individual doses accurately, although some indications can be given. The average annual effective dose from γ-rays from natural sources is about 0.5 mSv, with excursions up to about 5 mSv. Medical procedures in developed countries result in an annual effective dose of about 1–2 mSv, of which about two-thirds results from diagnostic radiology. The annual effective doses of monitored workers are commonly 1–10 mSv (UNSCEAR, 1993).

1.2.8 *Variations in exposure to X- and γ-radiation*

Figure 1 shows the estimated average exposures to ionizing radiation in a developed country. As described in the Overall introduction, some of the components may vary by a factor of up to 10, and the distribution is almost log-normal. The distribution of doses from X- and γ-irradiation in medical diagnosis is extremely skewed, as the majority of the population receives no exposure in a given year, while the effective dose may be up to 100 mSv for a small number of people receiving computed tomography scans of the abdomen. Table 7 lists the exposure of the general population that includes considerable X- or γ-ray components.

1.3 Human populations studied in the epidemiology of cancer due to X- and γ-radiation

In view of the large, often poorly understood fluctuations in natural and non-occupational artificial radiation, studies of the carcinogenic potential of ionizing radiation should concentrate on populations with known exposures well above the background load of 2–4 mSv per year from all qualities of radiation from internal and external sources. Many such populations were exposed in the past either routinely or during accidents. A number of persons are still irradiated at high doses in the course of radiation therapy to eradicate tumour tissue. Figure 2 shows those organs and systems in which significant health effects have occurred in such population groups. Although these cohorts are often well characterized with respect to the dose and dose rate they received, possible confounders such as increased susceptibility to toxicants and accompanying chemical treatment must be considered. In addition, patients undergoing cancer therapy are usually in an age distribution that excludes the early years of life, which are of special importance in view of the assumed greater sensitivity of children to radiation. Unselected populations of all ages are therefore of particular interest. In view of the many instances of high exposure to radiation at the workplace in the past, occupational exposure is another important facet of risk (Schneider & Burkart, 1998).

1.3.1 *Unselected populations*

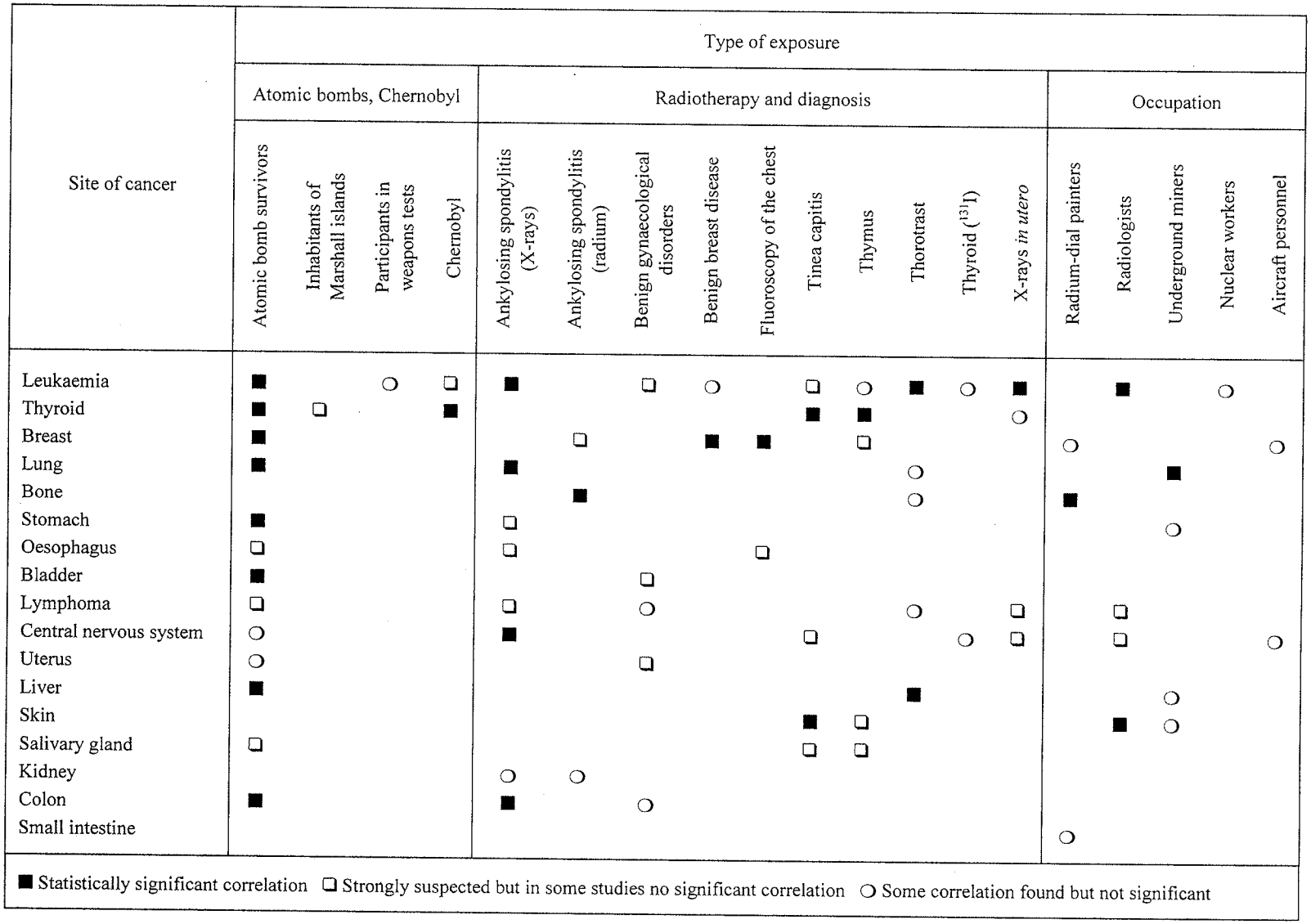
Entire communities received heavy exposure through military action, accidents and poorly controlled releases from weapon material production facilities. Table 8 lists the doses received by the cohorts that have been studied in order to quantify the carcinogenic potential of X- and γ-rays, the study of radiation effects in the survivors of the atomic bombs contributing a major element. Several populations exposed during the nuclear programme of the former USSR are now potentially accessible for epidemiological study, although it is unclear whether reliable retrospective dosimetry will be feasible. Nevertheless, except for partially unconfirmed high collective doses, the dose rates to which these populations were exposed are closer to those that

Table 7. Lifetime exposure of the general public to X- and γ-radiation, with doses and variations

Population	Route of exposure	Individual lifetime (75 years) dose (mSv)		Collective dose (person–Sv per year)	Variation
		Average	Maximum		
World (5800 million)	All	180	750	13 920 000	
Medical diagnosis, health-care level I (1500 million)	Diagnostic radiology	75	500	1 500 000	Highly skewed distribution
Medical diagnosis, health-care levels III and IV (1200 million)	Diagnostic radiology	3	380	48 000	Highly skewed distribution

From UNSCEAR (1993). For a description of health-care levels, see the Overall introduction, section 4.2.

Figure 2. Populations who received heavy exposure to ionizing radiation and were followed for cancer and other long-term effects on health



From Schneider and Burkart (1998)

Table 8. Major human populations exposed to considerable doses of X- and γ-rays

Population	Main exposure	Individual lifetime dose (mSv)		Collective dose (person–Sv)
		Average	Maximum	
Survivors of atomic bombs, Japan (86 000)	Acute γ-rays, neutron component for subcohort with low exposure	280	4000	24 000
Chernobyl: population in 'contaminated areas' (7 million in Belarus, Ukraine and Russian Federation)	External from ^{137}Cs (deposition density of ^{137}Cs, 37 Bq/m^2)	6–17	> 100	45 000–120 000
Population along the Techa River, Russian Federation (80 000)	External and internal ^{90}Sr	200	3000	15 000
Population in area near Semipalatinsk, Kazakhstan	External and internal ^{131}I, ^{137}Cs, ^{103}Ru			
Near Polygon test field (10 000)		(1000)	3000	(20 000)
Altair area (northeast of test field) (90 000)		(300)	1500	(30 000)

From UNSCEAR (1993); Burkart (1996); Cardis *et al.* (1996). Values in parentheses are highly uncertain estimates.

contribute to current exposure to radiation than to those experienced during the atomic bombings in Hiroshima and Nagasaki (UNSCEAR, 1993).

1.3.2 *Workers*

Large work forces experienced considerable individual exposures during the first few decades of the nuclear age. Whereas uranium mining results in internal exposure to α-particles from radon daughter products, reactor operation and reprocessing result mostly in external exposure to X- and γ-rays. In the past, radiologists and other medical personnel were exposed to considerable doses of radiation. In the clean-up operations near Chernobyl, a workforce of several hundred thousand persons was exposed to a cumulative effective dose of up to 250 mSv, and even higher doses were received immediately after the accident. Several tens of thousands of military personnel were exposed primarily to external γ-radiation when they participated in the atomic bomb tests conducted by the United Kingdom and the USA in the 1950s and 1960s, but the individual doses were typically a few millisieverts. Table 9 lists the doses received by cohorts used to assess the effects of radiation among workers.

1.3.3 *Patients*

Even optimized tumour therapy results in high doses of X- and γ-rays to healthy tissue adjacent to or overlying the target volume. Whole-body irradiation before bone-marrow transplantation in leukaemia patients is an example of treatment used in younger patients with potentially long survival and a concomitant risk for a second cancer. Ionizing radiation was also used in the past against fungal infections by inducing epilation of the scalp, to reduce inflammatory processes and against enlarged thymuses. Patients with tuberculosis who underwent multiple fluoroscopies also received high doses (UNSCEAR, 1993). Table 10 gives an overview of the doses received by some of the cohorts used in studies to assess cancer risks in patients exposed to X- and γ-rays.

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.

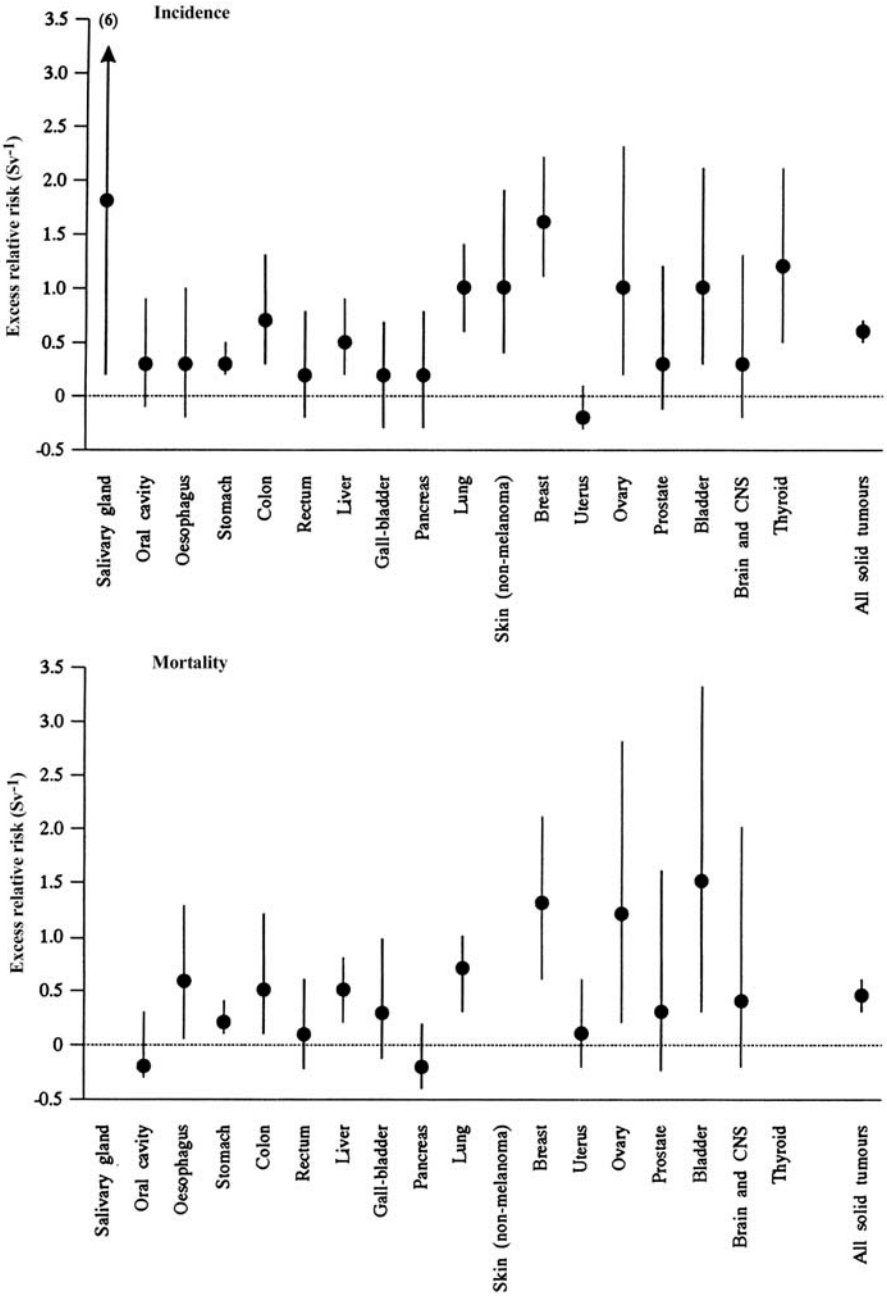
Figure 3 shows the excess relative risk (ERR; relative risk –1) per sievert for each of several cancers and for all solid tumours combined. Slightly more recent results for mortality (1950–90) were reported by Pierce *et al*. (1996); the only change is that the

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)

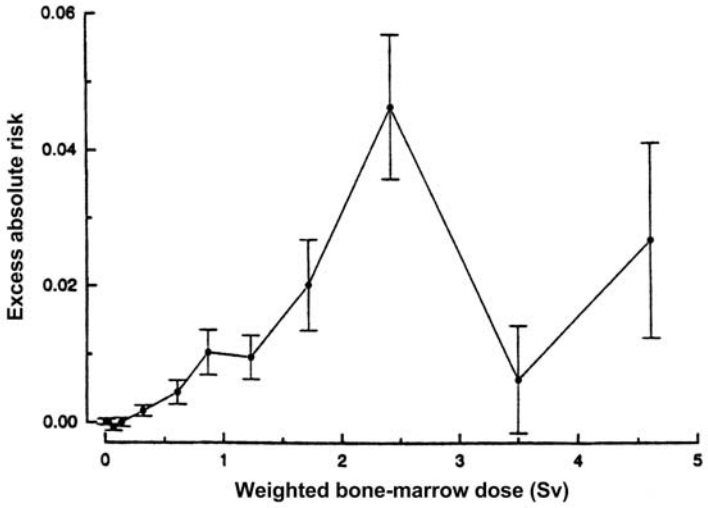
From Thompson *et al.* (1994). ERR_{1Sv}, excess relative risk at 1 Sv; EAR, excess absolute risk; CI, confidence interval

[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

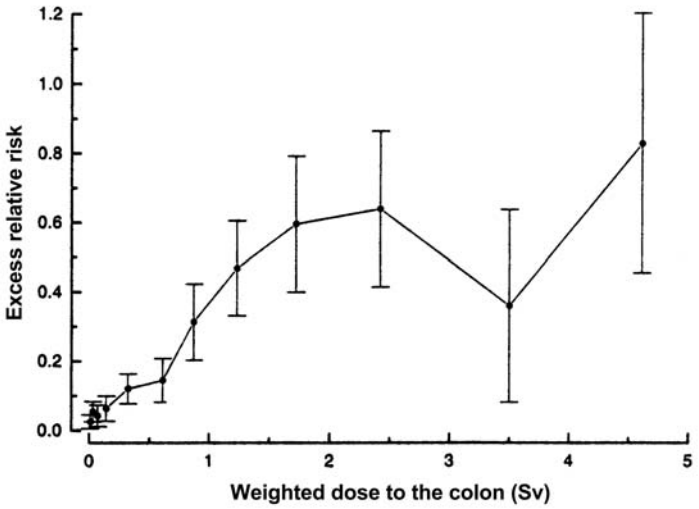
leukaemia, chronic myelogenous leukaemia and adult T-cell leukaemia—and dose–response relationships were seen for the first three. The other major type of leukaemia, chronic lymphocytic leukaemia, is infrequent in Japan, and no excess was seen in the Life Span Study cohort. One of the important recent 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.

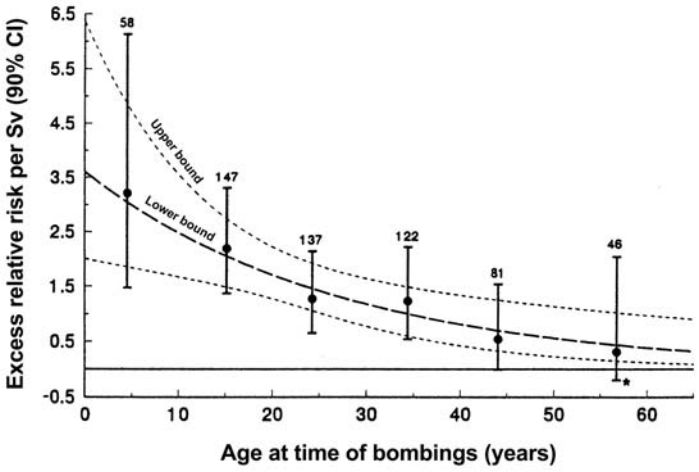
(i) *Female breast cancer*

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.

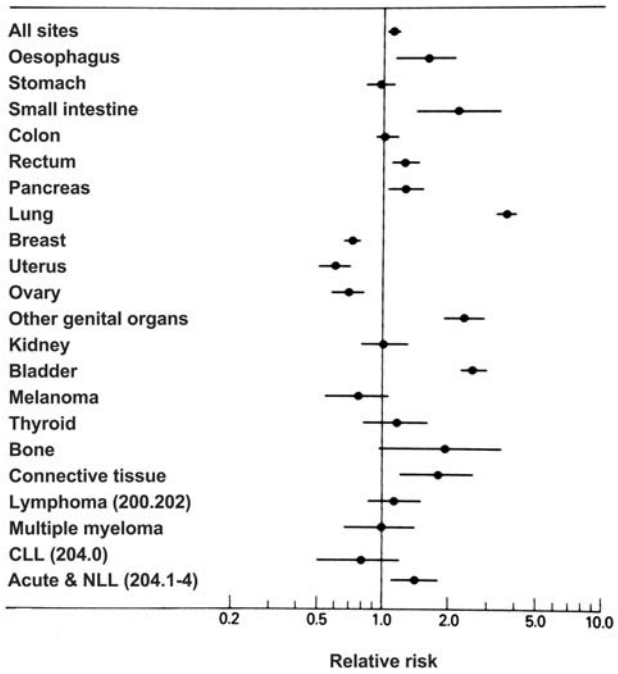
An international study of nearly 200 000 women treated for cervical cancer in 15 countries has provided information on dose-related risks of second cancers associated with radiotherapy (Day & Boice, 1984; Boice *et al*., 1985b, 1987, 1988, 1989). This study is one of those that provides quantitative 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 radiographies (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).

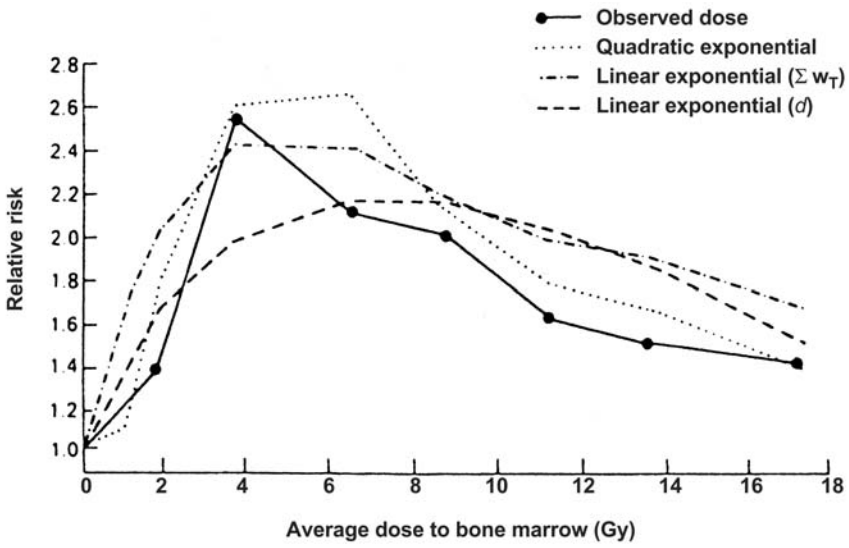
Table 25. Factors that complicate generalizations about estimates of risk associated with exposure to radiation

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



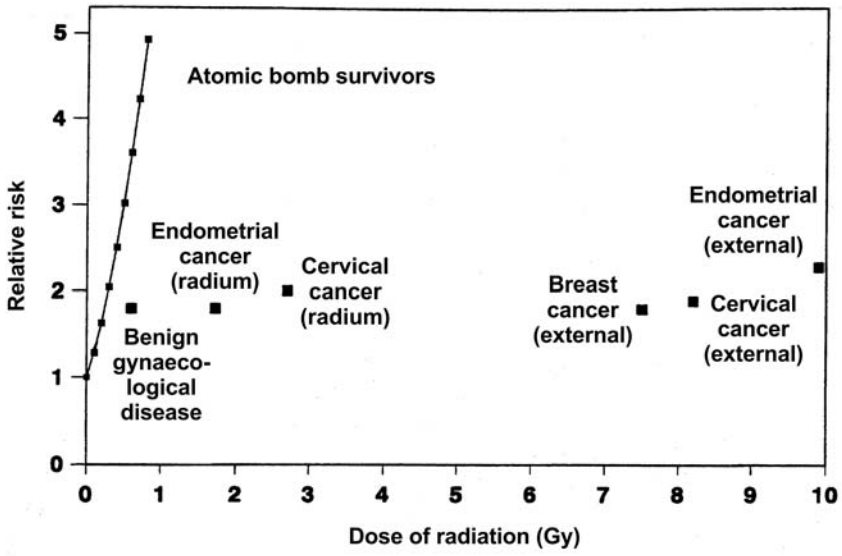
Adapted from Boice (1996)

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.

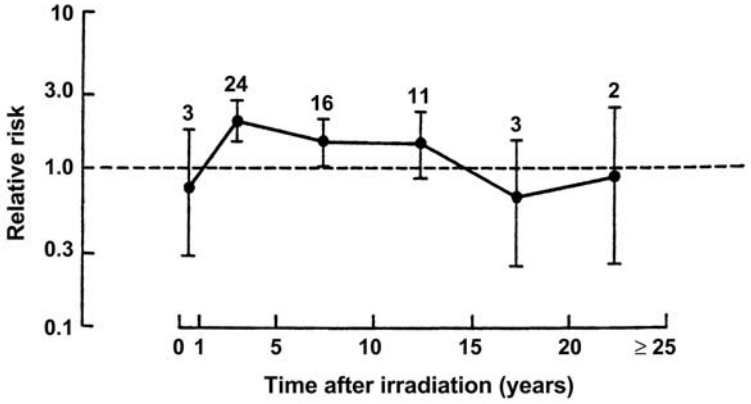
(*d*) *Sex*

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*

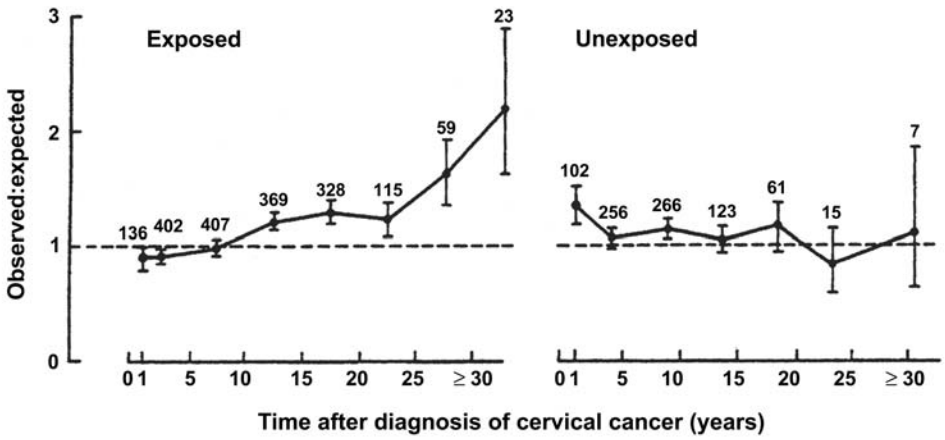
The period of observation is also an important determinant of risk (UNSCEAR, 1994). As the expression of radiation-induced solid tumours takes many years, studies with a short follow-up period might find different risk coefficients than those with longer periods of observation. Leukaemia has a relatively 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.

3. Studies of Cancer in Experimental Animals

The ability of X-rays and γ-rays to induce neoplasms in experimental animals has been known for many years. The types and frequencies of radiation-induced tumours observed in experimental studies depend on the strain and species used, the total dose of radiation and whether the radiation is delivered as a single dose or over a longer time as either fractionated or low doses. Because the carcinogenic effects of X-rays and γ-rays are well recognized, most reports have emphasized the quantitative aspects of radiation carcinogenesis in experimental animals. This section is not meant to be comprehensive; the studies summarized are those that provide both qualitative and quantitative information and address critical issues in radiation carcinogenesis.

3.1 Carcinogenicity in adult animals

3.1.1 *Mice*

In a large series of studies, Upton *et al*. (1970) examined the induction of neoplasms in male and female RF/Un mice after irradiation with 250-kVp X-rays or ^{60}Co γ-rays over a range of doses and dose rates. Whole-body irradiation was initiated when the animals were 10 weeks of age, and the animals were allowed to live out their lifespan or were killed when moribund. All animals were fully necropsied, but only selected lesions were examined histopathologically, as needed to confirm diagnoses. A total of 4100 female and 2901 male mice were used, with 554 female and 623 male controls. The doses ranged from 0.25 to 4.5 Gy for acute X-irradiation and from ~1 Gy to 98.75 Gy for chronic ^{60}Co γ-irradiation. An increased frequency of all neoplasms was observed even at the lowest acute dose. The specific tumour types found included myeloid leukaemia and thymic lymphoma in both males and females, and an increased incidence of ovarian tumours was observed in females. As shown in Table 29, male mice exposed to X-rays were more sensitive to the induction of myeloid leukaemia than to thymic lymphoma, whereas females exposed to γ-rays were more sensitive to the induction of thymic lymphoma. Under conditions of a continuous low dose rate of ^{60}Co γ-irradiation for 23 h daily, the incidences of all neoplasms, myeloid leukaemia, thymic lymphoma and ovarian cancer were reduced when compared with acute X-irradiation. [The Working Group noted that the comparison of dose rate effects of X-rays and ^{60}Co γ-rays is complicated by the fact

Table 29. Incidences of leukaemia and lymphoma in male mice exposed to γ- and X-radiation

Exposure	Mean accumulated dose (Gy)	Average dose rate (mGy/min)	Myeloid leukaemia			Thymic lymphoma		
			Incidence		Mean age at death (days)	Incidence		Mean age at death (days)
			%	SE		%	SE	
Control	0	–	4	1	463	4	1	502
X-rays	0.25	800	11	2	481	4	1	436
	0.5	800	12	2	481	6	2	334
	0.75	800	12	2	468	5	2	365
	1.0	800	22	3	407	5	2	363
	1.5	800	32	2	428	6	1	357
	3.0	800	42	3	370	15	2	309
	4.5	800	27	3	346	16	2	317
γ-rays	1.48	0.038	4	2	560	3	2	542
	1.53	0.106	6	2	582	4	2	408
	1.55	0.560	6	3	622	10	3	575
	3.29	0.038	10	3	597	3	2	598
	3.03	0.101	14	3	536	9	3	417
	3.08	0.159	12	4	473	10	4	433
	3.05	0.221	15	3	597	6	2	326
	3.15	0.570	10	3	487	5	3	472
	6.03	0.037	6	2	490	10	3	454
	6.21	0.098	10	4	533	12	4	401
	6.24	0.565	9	3	382	12	4	423
	58.1	0.115	5	4	679	26	7	382

From Upton *et al.* (1970); SE, standard error

that X-rays are slightly more effective than ^{60}Co γ-rays at low doses (relative biological effectiveness = 2). The frequency of myeloid leukaemia was reduced after exposure to a low dose rate, by a factor substantially greater than 2; it is therefore clear that the decreased effect is due to the lowering of the dose rate.]

Sensitivity to induction to myeloid leukaemia varies as a function not only of the sex of the animal but also of a number of other host factors, including genetic background, hormonal status, age, proliferative state of the bone marrow and the conditions under which the animals are maintained (Upton, 1968; Walburg & Cosgrove, 1969; Ullrich & Storer, 1979a).

One of the most comprehensive series of studies on the induction of cancer by γ-rays was reported by Ullrich and Storer (1979a,b,c). The induction of neoplastic disease was studied in male and female RFM/Un mice and in female BALB/c mice exposed to a range of doses of ^{137}Cs γ-rays at acute (0.4 Gy min^{-1}) and low dose rates (0.08 Gy per 20-h day). A total of 17 610 female and 1602 male RFM mice and 5659

female BALB/c mice were used; groups of 4762 female and 430 male RFM mice and 865 female BALB/c mice served as controls. The doses ranged from 0.1 to 3 Gy for the RFM mice and 0.5 to 2 Gy for BALB/c mice. As shown in Table 30, male and female RFM/Un mice showed dose-dependent increases in the frequencies of myeloid leukaemia and thymic lymphoma; females were more sensitive to the induction of thymic lymphoma. Significantly increased frequencies of thymic lymphomas were observed at doses as low as 0.25 Gy in both male and female RFM mice. Dose-dependent increased frequencies of ovarian, pituitary and Harderian gland tumours were observed in female RFM mice (Table 31), with an almost threefold increase in the frequency of ovarian cancer at 0.25 Gy. Higher doses were required to increase the frequencies of tumours at other sites. In male RFM mice, only the frequency of Harderian gland tumours was clearly increased in a dose-dependent manner, and males and females were equally sensitive to the induction of these tumours. Lowering the dose rate reduced the carcinogenic effectiveness of the radiation (Ullrich, 1983; Ullrich *et al.*, 1987). In the same study, female BALB/c mice were not sensitive to the induction of leukaemia or lymphoma over the dose range used (0.5–2.0 Gy), but dose-dependent increased frequencies of ovarian tumours and significant increases in the frequencies of lung and mammary adenocarcinomas were observed even at the lowest dose. Again, lowering the dose rate markedly reduced the carcinogenic effect.

Table 30. Incidences of thymic lymphoma and myeloid leukaemia in γ-irradiated RFM/Un mice

Dose (Gy)	Incidence (% ± SE)							
	Thymic lymphoma				Myeloid leukaemia			
	Male		Female		Male		Female	
	Obs	Adj	Obs	Adj	Obs	Adj	Obs	Adj
0	6.6	6.6 ± 1.3	13.4	13.4 ± 0.6	1.3	1.3 ± 0.59	0.77	0.77 ± 0.14
0.1	6.5	6.5 ± 1.7	14.2	14.2 ± 0.63	0.86	0.8 ± 0.56	0.80	0.72 ± 0.15
0.25	9.6	9.6 ± 3.4	20.8	20.8 ± 1.3	1.2	1.2 ± 0.92	0.85	0.84 ± 0.30
0.5	12.9	9.1 ± 2.8	27.6	27.6 ± 1.2	3.6	4.5 ± 1.5	1.1	1.1 ± 0.32
1.0	9.2	15.9 ± 2.2	30.3	30.3 ± 1.3	9.2	9.1 ± 2.2	1.4	1.6 ± 0.41
1.5	20.2	20.3 ± 3.6	38.3	38.3 ± 1.2	9.5	10.2 ± 2.7	2.5	3.6 ± 0.76
2.0	NT	NT	44.4	44.4 ± 3.1	NT	NT	3.0	3.5 ± 0.78
3.0	25.8	25.9 ± 2.6	52.4	52.4 ± 1.3	17.7	19.5 ± 2.4	3.0	5.2 ± 0.56

From Ullrich & Storer (1979a). Obs, observed incidence; Adj, age-adjusted incidence; NT, not tested; SE, standard error

Table 31. Incidences of solid tumours in γ-irradiated female RFM/Un mice

Dose (Gy)	No. of animals	Incidence (% ± SE)					
		Ovarian tumours		Pituitary tumours		Harderian gland tumours	
		Obs	Adj	Obs	Adj	Obs	Adj
0	4014	2.4	2.4 ± 0.55	6.6	6.6 ± 0.87	1.2	1.2 ± 0.38
0.1	2827	2.2	2.0 ± 0.61	6.0	5.8 ± 1.0	1.5	1.3 ± 0.45
0.25	965	7.0	6.4 ± 1.7	6.2	5.5 ± 1.5	1.2	1.6 ± 0.88
0.5	1143	33.3	35.5 ± 2.8	8.0	9.1 ± 1.8	1.8	2.3 ± 1.0
1.0	1100	31.7	35.1 ± 1.9	8.2	9.5 ± 1.9	6.0	6.6 ± 1.6
0.15	1043	32.2	42.4 ± 3.0	6.5	9.4 ± 2.1	3.5	5.3 ± 1.7
0.2	333	28.8	43.9 ± 6.8	6.7	10.2 ± 4.1	8.5	15.4 ± 2.4
0.3	4133	27.2	47.8 ± 1.9	7.7	20.9 ± 1.8	7.5	16.2 ± 1.6

From Ullrich & Storer (1979b); Obs, observed incidence; Adj, age-adjusted incidence; SE, standard error

Subsequent studies by Ullrich and co-workers (Ullrich, 1983; Ullrich *et al*., 1987) provided extensive data on the dose–response and time–dose relationships of ^{137}Cs γ-rays in the induction of both lung and mammary adenocarcinomas in female BALB/c mice at doses as low as 0.1 Gy. For mammary adenocarcinoma, a linear–quadratic dose–response relationship ($I = 7.7 + 0.035\ D + 0.015\ D^2$; where I = tumour incidence and D = dose) was observed over the 0–0.5-Gy dose range, while the response tended to flatten over the 0.5–2-Gy dose range. [The Working Group noted that the flattening is probably related to the effects of radiation on the ovary, since this organ is essentially ablated at doses ≥ 0.5 Gy.] Chronic exposure at a low dose rate (0.08 Gy day^{-1}) reduced the risk, while the effects of fractionated doses depended on the fraction size. In mice exposed chronically to ^{137}Cs γ-rays delivered at a dose rate of 0.01 Gy day^{-1} up to a total dose of 2 Gy, a linear dose–response relationship ($I = 7.7 + 0.035\ D$) was seen for mammary tumours. [The Working Group noted that the linear term of this response was consistent with the linear–quadratic model for acute exposure.] When multiple small acute daily fractions of 0.01 Gy were given, the results were similar to those with the low dose rate, whereas the cancer incidence after the same total doses were delivered as 0.05-Gy daily fractions was similar to that after single acute doses. For lung adenocarcinomas, single exposure to ^{137}Cs γ-rays over a 0–2-Gy dose range showed a linear–quadratic dose–response relationship ($I = 11.8 + 0.041\ D + 0.00043\ D^2$). Delivery of γ-rays at a dose rate of 0.08 Gy day^{-1} resulted in a diminution of the D^2 portion of the dose–response curve, such that it was linear over the entire dose range ($I = 12.5 + 0.043\ D$). When the doses were fractionated, the

response was dependent on the dose per fraction. When the dose per fraction was < 0.5 Gy, the response was similar to that with low dose rates; when the dose per fraction was > 0.5 Gy, the tumour incidences were similar to those after acute exposure.

Grahn *et al.* (1992) reported the results of a large series of experiments with more than 8000 male and female $B6CF_1$ (C57BL/6JAn1 × BALB/CJAn1) hybrid mice, which were irradiated with ^{60}Co γ-rays at 0.225–7.88 Gy at high dose rates, at 0.225–24.6 Gy at low dose rates or in fractionation regimens. Increased frequencies of lymphoreticular tumours, tumours of the lung and Harderian gland and all epithelial tumours were observed in male mice, which appeared to increase as a linear function of dose. In addition, increased frequencies of ovarian tumours were observed in female mice [frequencies at each dose not reported]. Protraction or fractionation of the dose reduced the carcinogenic effects of the radiation.

Maisin *et al*. (1983) exposed 1267 male BALB/c mice to single doses of ^{137}Cs γ-rays at doses of 0.25–6 Gy. The incidences of thymic lymphoma were increased at 4 and 6 Gy. Maisin *et al.* (1988) examined the effects of acute and 8 × 3 h or 10 × 4 h fractionated doses of ^{137}Cs γ-rays over the same dose range in male C57BL/6 mice. While the greatest effect was to cause early death [considered by the Working Group to be due mainly to death from cancers], increased frequencies of leukaemia and all malignancies were found after acute doses of 4 and 6 Gy. Fractionation resulted in an earlier and more frequent appearance of tumours at 1–2 Gy, but the results were not statistically significant.

The induction of myeloid leukaemia in 951 male CBA/H mice exposed to 250-kVp X-rays at 0.25–6 Gy was compared with that in 800 controls. The frequency of myeloid leukaemia increased with increasing doses up to 3 Gy and then decreased at higher doses (Mole *et al*., 1983).

Di Majo *et al*. (1996) examined the influence of sex on tumour induction by irradiation with 250-kVp X-rays (half-value layer, 1.5 mm Cu). After irradiation of 289 male and 259 female three-month-old CBA/Cne mice with doses of 1–7 Gy, increased incidences of myeloid leukaemia and malignant lymphomas were observed in males, and the incidence of Harderian gland tumours was increased in a dose-dependent manner and to a similar degree in males and females.

In 153 female RFM mice given a single localized thoracic X-irradiation at doses of 1–9 Gy, the incidence of pulmonary tumours at nine months increased as a linear–quadratic function of dose, but significant increases in the frequency of lung tumours over that in 88 controls and in the numbers of lung tumours per mouse were observed only at 6.5 and 9 Gy. While no data were available on low dose rates, experiments in which the doses were fractionated into two equal portions and given at intervals of 24 h or 30 days were conducted in 311 female RFM mice. A reduction in the carcinogenic effect was observed in animals given the high doses (6.5 and 9 Gy) at a 24-h interval, but no significant difference was observed with an interval of 30 days (Ullrich *et al*., 1979; Ullrich, 1980).

Lung tumours developed in male and female SAS/4 mice after local exposure to thoracic X-rays at doses of 0.25–7.5 Gy (Coggle, 1988). A total of 557 male and 551 female mice were irradiated, and the animals were killed 12 months after irradiation and their lungs examined for tumours. As shown in Table 32, a dose-dependent increase in the frequency of lung tumours was found in both males and females with increasing frequencies over the range of 0.25–5 Gy.

Table 32. Incidences of primary lung tumours in SAS/4 mice given 200-kVp X-irradiation at 0.6 Gy/min

Sex	Dose (Gy)	No. of mice exposed	No. of mice with tumours	Incidence ± SE
Males	0	291	48	16.5 ± 2.2
	0.25	61	12	19.7 ± 5.1
	0.5	62	11	17.7 ± 4.8
	1.0	67	13	19.4 ± 4.8
	2.0	56	15	26.8 ± 5.9
	2.5	69	23	33.3 ± 5.7
	3.0	32	12	37.5 ± 8.6
	4.0	45	17	37.7 ± 7.2
	5.0	45	22	48.9 ± 7.5
	6.0	48	18	37.5 ± 7.0
	7.5	72	16	22.2 ± 4.9
Females	0	210	19	9.0 ± 2.0
	0.5	62	7	11.3 ± 4.0
	1.0	61	6	9.8 ± 3.8
	1.5	64	8	12.5 ± 4.1
	2.0	63	10	15.9 ± 4.1
	3.0	60	16	26.7 ± 5.7
	4.0	61	23	37.7 ± 6.2
	5.0	59	21	35.6 ± 6.2
	6.0	60	15	25.0 ± 5.6
	7.5	61	9	14.8 ± 4.5

From Coggle (1988); SE, standard error

3.1.2 *Genetically engineered mice*

Genetically engineered mice are used in radiation carcinogenesis mainly to study the genes that may affect susceptibility and as a means of elucidating mechanisms. Mice lacking the *p53* gene are useful because of the role of *p53* in damage recognition

and response mechanisms. In addition, *p53* is known to be mutated in Li–Fraumeni syndrome, a genetic syndrome that affects sensitivity to radiation.

Thirty-three *p53* heterozygous (+/–) and 28 *p53* wild-type (+/+) mice were exposed by whole-body irradiation to 4 Gy of ^{60}Co γ-rays at 7–12 weeks of age and observed until they were moribund, when they were killed and autopsied. Eighteen null (–/–) and 14 heterozygous mice served as controls. None of the irradiated wild-type mice developed tumours within 80 weeks, but radiation significantly reduced the latency for tumour development (mainly lymphomas and sarcomas) in *p53* heterozygous mice. Approximately 90% of the heterozygous mice developed tumours with a mean latency of 40 weeks, before any of the unirradiated heterozygous mice developed tumours (mean latency, > 70 weeks). In the same study, a dose of 1 Gy of γ-rays given to two-day-old *p53* null (–/–) mice also decreased the latency for tumour development (Kemp *et al*., 1994).

Radiation-induced thymic lymphoma has also been studied in Eμ-*pim*-1 mice. The *pim*-1 gene was discovered as a preferential proviral integration site in murine leukaemia virus-induced T-cell lymphomas (Cuypers *et al.*, 1984) and can act as an oncogene in mice (Van Lohuizen *et al.*, 1989). The transgenic mice have a low incidence of spontaneous T-cell lymphomas before the age of seven months but are highly susceptible to genotoxic carcinogens. In this study, groups of 12 female and 14 male heterozygous Eμ-*pim*-1 transgenic mice and 15 female and 11 male non-transgenic littermates, four to seven weeks of age, were irradiated with four fractions of 1.5 Gy of X-rays. The fractions were given one week apart for four weeks. Groups of 15 female and 11 male Eμ-*pim*-1 transgenic mice and 15 female and 16 male non-transgenic mice were irradiated with four fractions of 1 Gy of X-rays. Groups of 32 female and 31 male Eμ-*pim*-1 and 25 female and 38 male littermates were irradiated with four fractions of 0.5 Gy. Thirteen female and 12 male transgenic and 13 female and 11 male non-transgenic mice served as controls. The animals were monitored for lymphoma development for 250 days after the last exposure. All 26 Eμ-*pim*-1 mice exposed to four fractions of 1.5 Gy of X-rays developed lymphomas within 250 days. At the lower doses per fraction, 20/22 effective mice developed lymphomas after exposure to four fractions of 1.0 Gy and 17/61 after exposure to four fractions of 0.5 Gy. In the non-transgenic littermates, 12/31, 6/31 and 0/62 irradiated mice developed lymphomas (Van der Houven van Oordt *et al*., 1998).

3.1.3 *Rats*

A total of 398 female adult Sprague-Dawley rats were divided into seven groups and exposed to γ-rays at different ages: to single doses of 5 Gy at 40 days of age or 160 days of age or to four fractionated doses of 1.25 Gy; to eight fractions of 0.62 Gy; to 16 fractions of 0.3 Gy or to 32 fractions of 0.15 Gy at 40 days of age. One group was sham-irradiated. All of the fractionated doses of ^{60}Co γ-rays were delivered twice weekly at a dose rate of 0.40 Gy/min. The incidence of mammary tumours (adeno-

carcinomas, adenofibromas and fibroadenomas) was determined histologically up to the age of 1000 days. An increased frequency of mammary fibroadenomas and, to a lesser extent, adenocarcinomas, was observed, with 64 in controls and 92, 90, 96, 89, 85 and 87% with the different regimes, respectively. No significant difference between single and fractionated exposures was reported (Shellabarger *et al*., 1966).

A total of 191 female adult Sprague-Dawley rats, 61–63 days of age, were given single whole-body doses of 0.28, 0.56 or 0.85 Gy of 250-kVp X-rays at a dose rate of 0.30 Gy min^{-1}. A group of 167 controls was available. The animals were observed over their lifespan (1033–1053 days) for the induction of mammary tumours, and the neoplasms were identified histopathologically as adenocarcinomas or fibroadenomas. The incidences of mammary tumours were 67% in controls and 72, 77 and 79% in the irradiated groups, showing a dose-dependent increase in all mammary tumours and in particular in fibroadenomas. The principal effect of the irradiation was to cause an earlier time of onset of fibroadenomas, which was dose-dependent (Shellabarger *et al*., 1980).

Groups of 40 control and low-dose and 20 mid- and high-dose female WAG/Rij, BN/Bi and Sprague-Dawley rats, eight weeks of age, were exposed by whole-body irradiation to a single dose of 300-kVp X-rays (Sprague-Dawley rats, 0.1, 0.3, 1 or 2 Gy; WAG/Rij and BN/bi rats, 0.5, 1 and 4 Gy [dose rate not given]). In another experiment, the numbers of animals in these groups were increased to 40 and 60, respectively. The animals were observed for life, and the mammary tumour incidences were determined by gross and histopathological observations. A dose-dependent increase in the incidence of all mammary tumours was observed: Sprague-Dawley rats, 30 (control), 70, 72, 75 and 86%; WAG/Rij rats, 27 (control), 26, 35 and 76%; and BN/Bi rats, 8 (control), 15, 86 and 88% (Broerse *et al*., 1986, 1987).

Groups of 40 female WAG/Rij inbred rats were exposed to a single dose of 1 or 2 Gy of ^{137}Cs γ-radiation at 8, 12, 16, 22, 36 or 64 weeks of age at a dose rate of 0.75 Gy min^{-1} to study the effect of age at exposure. A group of 120 controls was available. The animals were observed for life, and tumours of the mammary gland were classified histologically as fibroadenoma or carcinoma. No statistically significant difference in the incidence of mammary tumours was found by age on the basis of crude incidences, but examination of normalized excess risk demonstrated a reduced risk after exposure at 64 weeks of age (Barstra *et al*., 1998).

Lee *et al.* (1982) studied the induction of thyroid tumours in young, female Long-Evans rats after localized external irradiation of the thyroid glands with X-rays (250 kVp; half-value layer, 0.55 mm Cu) at estimated doses of 0.94, 4.1 or 10.6 Gy. The incidences of both follicular thyroid adenomas and carcinomas were increased with dose: 9/281 (control), 11/275, 35/282 and 74/267.

In 115 Sprague-Dawley rats, eight weeks of age, that received nerve isografts on the right posterior tibial nerve, exposure of the thigh region to 0 (control), 46, 66, 86 or 106 Gy ^{60}Co-γ radiation as 2-Gy fractions at a dose rate of 73 cGy/min, resulted in

osteosarcomas and/or fibrous histiocytomas in 0/7 (controls), 0/20, 2/27, 2/20 and 8/41 rats in the respective groups (Tinkey *et al*., 1998).

3.1.4 *Rabbits*

A group of 21 male and female Dutch rabbits were irradiated with 4.4–14.1 Gy of 2.5-MeV γ-rays at a dose rate of 17.6 Gy h^{-1}; a control group of 17 unirradiated rabbits was available. The animals were allowed to die naturally, and selected tissues were examined histologically. Tumours were found in 24% of controls, 75% at 4.4 Gy, 88% at 8.8–10.6 Gy and 56% at 11.5–14.1 Gy. The tumours included four osteosarcomas of the jaw, five fibrosarcomas of the dermis and six basal-cell tumours of the skin (Hulse, 1980).

3.1.5 *Dogs*

Groups of 120 male and female beagle dogs, aged 2 or 70 days, were exposed by whole-body irradiation to 0.88 or 0.83 Gy of ^{60}Co γ-rays, and a further group of 240 dogs received 0.81 Gy at 365 days of age; 360 controls were available. The animals were allowed to die naturally or were killed because of terminal illness. In 1343 dogs allowed to live out their life span, heritable lymphocytic thyroiditis with hypothyroidism was a major contributor to mortality. Of 86 dogs irradiated at 70 days of age, 25/86 had thyroid follicular adenomas and 10/86 had carcinomas, which represented a significant increase ($p < 0.01$) over the 40/231 controls with adenomas and 16/231 with carcinomas. No significant increase in the incidence of thyroid tumours was found in dogs irradiated at 2 or 365 days of age. The irradiated dogs showed a consistent trend for a lower incidence of hypothyroidism when compared with controls. Hypothyroidal dogs had a significantly increased risk for thyroid neoplasia, including a greater risk for carcinomas, but no evidence was found in this group of a greater sensitivity to radiation-induced tumours (Benjamin *et al*., 1991, 1997).

3.1.6 *Rhesus monkeys*

Twenty rhesus monkeys (*Macaca mulatta*), three years of age, were exposed by whole-body irradiation to doses of 4–8.6 Gy of X-rays (300 kVp; half-value layer, 3 mm Cu) at a dose rate of 0.3 Gy min^{-1}. A few hours after irradiation, most of the animals received intravenous grafts of $2–4 \times 10^8$ autologous bone-marrow cells. Between 7.5 and 15.5 years later, eight animals developed malignant tumours, comprising five adenocarcinomas of the kidney, two follicular carcinomas of the thyroid, two osteocarcinomas and one glomus tumour of the subcutaneous tissues. No malignant tumours occurred in 21 controls within 18 years (Broerse *et al*., 1981).

3.2 Prenatal exposure

3.2.1 *Mice*

C57BL/6 female mice, 10–14 weeks of age, were mated with WHT/Ht males of the same age overnight and removed next morning for timed pregnancies. Subsequently, 19 pregnant females were irradiated with approximately 2 Gy of X-rays (180 kVp, 20 mA with a filter of 0.7 mm Cu) at a dose rate of ~0.86 Gy min^{-1} on days 12 or 16–18 *post coitum*. A total of 573 male and female offspring were delivered and observed for life, and all suspected lesions or tumours were examined histopathologically. The control group consisted of 141 unirradiated C57BL/6 × WHT/Ht offspring of 19 mice. Significant increases were found in the incidences of tumours of the lung (both sexes), the pituitary gland (females) and the ovary of the offspring that had been irradiated on days 16–18 *post coitum* [statistical methods not given], whereas X-irradiation at day 12 *post coitum* did not increase the incidence of tumours in the offspring (Sasaki *et al*., 1978a). In a study of 167 $B6WF_1$ (C57BL/6 × WHT/Ht) female mice irradiated 17 days *post coitum* with approximately 1.5 or 3 Gy of X-rays (200 kVp, 20 mA with a filter of 0.5 mm Al + 0.5 mm Cu) at a dose rate of 0.5–0.6 Gy min^{-1}, the offspring were allowed to die naturally. Significant increases were observed in the incidences of hepatocellular tumours in both male and female offspring in a dose-dependent manner (Table 33) [statistical method not given] (Sasaki *et al*., 1978b).

A total of 410 C57BL/6 female × DBA/2 male fetuses were exposed to 0.2, 0.5, 1.0 or 2.0 Gy of ^{60}Co γ-rays on day 18 of gestation and were killed and autopsied when moribund or at two years of age. Tissues showing macroscopic alterations were submitted to histopathological examination. A group of 1009 historical controls was available. Tumours were found mainly in the lung, uterus and lymphoid tissues, and the total tumour incidence was significantly increased at 0.5, 1.0 and 2.0 Gy (Pearson's χ^2 test) (Lumniczky *et al*., 1998).

In order to mimic human exposure to various carcinogenic and promoting agents in the diet and the environment, carcinogenic and/or promoting agents were given in some experiments postnatally after prenatal exposure to radiation. A total of 79 pregnant ICR mice, 9–11 weeks of age, were irradiated with 0.36 Gy of X-rays (180 kVp, 20 mA with a filter of 0.5 mm Cu) at the dose rate of 0.72 Gy min^{-1} on days 0, 2, 4, 6, 8, 10, 12, 14 or 16 of gestation. Then, 496 live offspring were treated with 5 μmol $(g\ bw)^{-1}$ of urethane, while 237 received distilled water, at 21 days of age. The mice were killed five months after the postnatal treatment, and tumour nodules in the lung were counted. As controls, 78 and 181 offspring of 26 unirradiated mice were similarly treated with urethane and water, respectively. No increase in the incidence of tumours was observed after prenatal X-irradiation alone, but both the incidence and the number of lung tumours per mouse were significantly increased when prenatal irradiation was coupled with postnatal urethane treatment on days 0–14 (except day 6) of gestation (χ^2 and Student's *t* test) (Nomura, 1984).

Table 33. Incidences of tumours in B6WF$_1$ (C57BL/6 × WHT/Ht) mice after prenatal exposure to X-radiation

Treated stage (dpc)	Sex	Dose (Gy)	No. of mice	Incidence (%)					Reference
				Total incidence	Lung tumour	Liver tumour	Ovarian tumour	Pituitary tumour	
12	Male	2	44	11**	5*	0	–	0	Sasaki *et al.* (1978a)
	Female		53	15**	4	0	0	0	
16–18	Male	2	126	73**	56**	17	–	1	
	Female		140	77	39**	10	14*	9*	
Control	Male	0	55	46	24	7	–	0	
	Female		77	65	17	7	1	1	
17	Male	3	22	–	–	46**	–	–	Sasaki *et al.* (1978b)
	Female		53	–	–	13*	–	–	
17	Male	1.5	39	–	–	28**	–	–	
	Female		53	–	–	8	–	–	
Control	Male		84	–	–	7	–	–	
	Female		129	–	–	1	–	–	

dpc, days *post coitum*. Significantly different from controls at *$p < 0.05$ and **$p < 0.01$

In a further study from the same laboratory, 289 fetuses of coat colour-mutant strains of PT and HT mice were exposed to 0, 0.3 or 1.03 Gy of X-rays at a dose rate of 0.54 Gy min^{-1} on day 10.5 of gestation. Offspring were examined for somatic mutations at six weeks of age, and then 139 offspring were treated with 12-*O*-tetradecanoylphorbol 13-acetate (TPA) and 150 with the acetone solvent. The mice were killed at 12 months of age, and the induced tumours were diagnosed histopathologically. Although a significant, linear dose-dependent increase in the incidence of somatic mutations was detected, no increase in tumour frequency was observed after prenatal irradiation alone. The incidences of skin tumours and hepatomas were increased in male offspring after prenatal irradiation and postnatal treatment with TPA (Table 34). When 59 $PTHTF_1$ fetuses were exposed to 1.03 Gy of X-rays at the low dose rate of 4.3 mGy min^{-1}, the mutant spot sizes and tumour incidences were about one-fifth of those produced by the dose rate of 0.54 Gy min^{-1} (Nomura *et al*., 1990).

Table 34. Induction of tumours in $PTHTF_1$ mice after irradiation *in utero* and postnatal treatment with TPA

Dose (Gy)	TPA	Tumour-bearing mice		Skin tumour[a]		Hepatoma in males		
		Incidence	%	Incidence	%	Incidence	%	Tumours per liver
1.03	+	14/47	29.8**	5/47	10.6*	8/23	34.8*	0.57
	–	3/49	6.1	0/49	0.0	1/25	4.0	0.04
0.3	+	6/38	15.8	1/38	2.6	4/20	20.0	0.20
	–	2/51	3.9	0/51	0.0	1/26	3.8	0.04
0	+	4/54	7.4	0/54	0.0	1/29	3.4	0.03
	–	3/50	6.0	0/50	0.0	1/22	4.5	0.05

From Nomura *et al.* (1990). TPA, 12-*O*-tetradecanoylphorbol 13-acetate

[a] Four squamous-cell carcinomas and two pigmented basal-cell carcinomas

*$p < 0.05$, **$p < 0.01$ when compared with untreated controls

In a separate study, 2241 male and female NMRI mouse fetuses were irradiated *in utero* with 0.2, 0.4, 0.8 or 1.6 Gy of X-rays (180 kVp, 10 mA with a filter of 0.3 mm Cu) at a dose rate of 0.6 Gy min^{-1} on day 15 of gestation. After birth, one subgroup at each dose received 45 mg (kg bw)$^{-1}$ *N*-ethyl-*N*-nitrosourea (ENU) at 21 days of age while another did not. All surviving animals were killed at 22 months. No significant increase in the incidence of tumours was observed in the offspring exposed to 0.2 or 0.8 Gy of X-radiation alone [0.4 and 1.6 Gy not tested], but significantly increased incidences of tumours of the liver, intestine, uterus and ovary were observed after prenatal exposure to 0.2, 0.4 or 0.8 Gy of X-rays in combination with postnatal treatment with ENU ($p < 0.05$–0.001; χ^2 test) when compared with ENU

alone. In mice at 1.6 Gy in combination with ENU, the tumour incidences were often reduced (Schmahl, 1988).

3.2.2 *Dogs*

Groups of 60 male and 60 female beagles received mean doses of 0.16 or 0.83 Gy of ^{60}Co γ-radiation on day 8 (preimplantation), 28 (embryonic) or 55 (late fetal) *post coitum*. The offspring were allowed to die naturally, when they were examined histopathologically. As controls, 360 dogs were sham-irradiated. The tumours found predominantly in the offspring of irradiated and unirradiated bitches up to 16 years of age were malignant lymphoma, haemangiosarcoma and mammary carcinoma. Analysis of trends with increasing dose indicated that the incidences of both fatal malignancies and all neoplasms were significantly increased in the offspring of bitches irradiated on day 55 *post coitum*, while no significant increase was observed after exposure *in utero* at day 28 *post coitum*; however, the incidence of fatal haemangiosarcomas was significantly increased in the offspring of bitches exposed on day 8 *post coitum* (Peto's test) (Benjamin *et al*., 1991).

3.3 Parental exposure

Male and female ICR mice were treated with X-rays (180 kVp, 20 mA with a filter of 0.5 mm Al + 0.5 mm Cu) at 0.36, 1.08, 2.16, 3.6 or 5.04 Gy at a dose rate of 0.72 Gy min^{-1} and mated with untreated mice at various intervals of days to examine the sensitivity of germ cells at different stages. About half of the pregnant mice were killed just before delivery (day 18 of gestation), and the others were allowed to deliver live offspring. Significant increases in the frequencies of dominant lethal mutations and congenital malformations were observed in a dose-dependent manner after exposure of the spermatozoa and spermatid stages to X-rays. Groups of 1529 and 1155 live offspring of male and female exposed parental mice were killed at eight months of age, and suspected tumours were diagnosed histopathologically. The control group consisted of 548 offspring of unirradiated mice. Significant increases in the incidences of total tumours were reported after paternal (153/1529, 10.0%) and maternal exposure (101/1155, 8.7%), when compared with controls (29/548, 5.3%; $p < 0.01$–0.005; χ^2 test). About 87% of the induced tumours were in the lung. At both germ-cell stages, the tumour incidence in the offspring increased in a nearly linear, dose-dependent mode after paternal exposure, and the increase was statistically significant at the high doses (χ^2 and *t* test). The sensitivity at the spermatogonial stage was about half that at the spermatid stage. No increase in the incidence of tumours was observed in offspring after maternal exposure to up to 1.08 Gy, but the incidence increased significantly at higher doses. When male and female parental mice were treated with doses of 0.36 Gy of X-rays at 2-h intervals, fractionation significantly reduced the carcinogenic effects of irradiation in offspring exposed at the spermatogonial and mature

oocyte stages; however, no such reduction was observed when postmeiotic stages were treated. In another study, F_1 offspring of X-irradiated male mice were mated and their progeny were examined. Significantly higher incidences of tumours were observed in the F_2 generation of F_1 progeny that had tumours. The author suggested that germ-line alterations that caused tumours were transmitted to the next generation (Nomura, 1982).

In order to confirm these results, male mice of the N5 and LT strains were similarly treated with 5.04 Gy of X-rays at the spermatogonial or postmeiotic stage, respectively, and 229 irradiated and 244 unirradiated N5 offspring and 75 irradiated and 411 unirradiated LT offspring were killed at 12 months of age. A significant increase in the incidence of lymphocytic leukaemias was observed: N5 strain, 3.9% versus 0.4% in controls and LT strain, 5.3% versus 1.0% in controls ($p < 0.05$; χ^2 test) (Nomura, 1986, 1989).

Cattanach *et al.* (1995) used the experimental protocol of Nomura (1982) but a different strain of mice. Male BALB/cJ mice were treated with 2.5 or 5.0 Gy of X-rays (250 kVp, 14 mA, filter of 0.25 cm Cu) at a dose rate of 0.76 Gy min^{-1} and were mated with females of the same strain for one week and then new ones for a further week. All of the progeny obtained were therefore derived from irradiated spermatozoa and late spermatids. The study was carried out as a series of 21 replicate experiments over a one-year period in order to accommodate the maximum capacity of the histological laboratory (approximately 45 animals per week). The offspring of about 600 male mice at each dose were retained for examination for lung tumours at eight months of age, and offspring of 70 animals at each dose were retained for examination at 12 months. The total incidences of lung tumours were not significantly different in offspring from irradiated and unirradiated male parents. Nevertheless, the incidence of lung tumours changed significantly in all treated groups during the one-year study: adenocarcinomas were found only in the later experiments, while the incidence of benign adenomas declined over the first 8–10 replicates and then rose to yet higher rates than observed in the early series. The authors ascribed this effect to a seasonal change in the incidence of tumours in these mice.

The same group carried out a study in a different strain of mice, C3H/HeH. In a series of replicate studies over two years, male mice were exposed to 0, 2.5 or 5.0 Gy of X-rays and mated with untreated females in the same protocol as in the previous study. In 1381 offspring killed at 12 months of age, no significant increase in the incidence of lung tumours was observed. Again, a seasonal variation in tumour incidence was observed (Cattanach *et al.*, 1998).

Groups of 27–28 male N5 mice were irradiated under conditions similar to those used by Nomura (1982, 1986) with 0 (control) or 5 Gy of X-rays (160 kVp, 18 mA, with a filter of 0.5 mm Cu + 10 mm Al) [dose rate not given] and mated 3, 7, 10 or 17 days after irradiation; 312 irradiated and 305 unirradiated offspring were observed until they were killed at one year of age. All tumours were examined histopathologically. The probability of dying from leukaemia (Kaplan-Meyer product-limit

procedure) and overall survival (Cox–Mantel log-rank one-tailed test) were statistically significantly different ($p < 0.05$) in the offspring of X-ray-treated males and unirradiated controls. The incidences of leukaemia at one year of age were 11/165 (6.7%) in those exposed to X-rays and 10/305 (3.3%) in controls ($p = 0.07$, Fisher's exact test) (Daher *et al*., 1998).

A lifetime experiment in CBA/J NCrj mice was carried out to examine whether paternal exposure to X-rays increases the risk for tumours. Male mice were exposed to 1 or 2 Gy of X-rays (100 kVp, 8 mA, with a filter of 1.7 mm Al + 0.2 mm Cu) at a dose rate of about 0.65 Gy min^{-1} and mated with unirradiated females one, three or nine weeks later. The 282 and 206 offspring of mice at 1 and 2 Gy were allowed to die naturally. A group of 631 unirradiated control offspring was available. The female offspring of males that had been exposed to 2 Gy of X-radiation one week before mating (spermatozoal stage) showed a trend towards a higher incidence of tumours of the haematopoietic system when compared with unirradiated offspring, and male offspring of these males had a somewhat higher incidence of broncho-alveolar adenocarcinomas. No increase in tumour incidence was observed in the offspring of males irradiated three or nine weeks before conception (Mohr *et al*., 1999).

Further studies were carried out in which the offspring of irradiated parents were treated with chemical carcinogens or promoting agents. Significant increases in the frequencies of lung tumour nodules per mouse were observed in the offspring of X-irradiated ICR mice given urethane by subcutaneous injection postnatally (Nomura, 1983), and similar results were obtained with outbred Swiss mice given urethane intraperitoneally (Vorobtsova & Kitaev, 1988). The incidence of skin tumours was significantly increased in the offspring of parentally X-irradiated outbred SHR mice treated postnatally with TPA by dermal application (Vorobtsova *et al.*, 1993). Similar enhancing effects were not, however, observed when CBA/J male mice were irradiated and their offspring were treated postnatally with urethane by subcutaneous injection (Mohr *et al.*, 1999).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Radiation syndromes: Early effects of whole-body irradiation

A hierarchy of health effects that appear sequentially after high doses of whole-body irradiation consists of the haematopoietic, gastrointestinal and central nervous syndromes, which are collectively referred to as the 'acute radiation syndromes' and have been extensively reviewed (Bond *et al*., 1965; Young, 1987; UNSCEAR, 1988). The dose range over which these syndromes occur is shown in Table 35. The cutaneous radiation syndrome and the chronic radiation syndrome are now considered sufficiently distinct to be included in the list of radiation syndromes. The more severe

Table 35. Effects and outcomes after exposure to ionizing radiation

Dose range (Gy)	Prodromal effects	Tissue effects	Survival
0.5–1.0	Mild	Small decrease in blood cell count	$LD_{0/60}$ (normal subject)
2.0–3.5	Moderate	Moderate-to-severe damage (bone marrow)	$LD_{5/60}$–$LD_{50/60}$
3.5–5.5	Severe	Severe damage (bone marrow)	$LD_{90/60}$–$LD_{99/60}$[a] (death, 3.5–6 weeks)
5.5–7.5	Severe	Ablation (bone marrow)	Death, 2–3 weeks[a]
10–20	Severe	Severe damage (gastrointestinal)	Death, 5–12 days
100	Severe	Cerebrovascular damage	Death, within 2 days

Adapted from Young (1987)

[a] Treatment may increase survival by raising the dose that is lethal by 50% but to a lesser extent in the case of the gastrointestinal syndrome.

effects are preceded by a prodromal phase, which is mediated by a poorly understood effect on the autonomic system. Apart from the signs and the symptoms of the prodromal phase and the central nervous syndrome, the early effects of radiation are due to cell killing in tissues with rapid cell turnover such as the bone marrow and the gut. Cell killing is also the major determinant in tissues such as lung and skin that incur early deterministic effects, but later. The relative radiosensitivity of the clonogenic cells in various solid tissues is shown in Table 36.

Table 36. Radiosensitivity of clonogenic cells in solid tissues, as indicated by the D_0

Tissue	D_0 (Gy)	Reference
Jejunum	1.30	Withers & Elkind (1970)
Testis	1.36	Withers *et al*. (1974)
Kidney	1.53	Withers *et al*. (1986)
Skin	1.35	Withers (1967)
Colony-forming units (haematopoietic)	0.95	McCulloch & Till (1962)
Breast	1.22	Gould & Clifton (1979)
Thyroid	2.0	Mulcahy *et al.* (1980)

D_0, reciprocal of the final slope of the curve of survival as a function of dose, representing cell killing due to multiple events

Death from bone-marrow damage occurs at lower doses than death from damage to the gut and longer after exposure. This reflects differences in the cell kinetics and design of the two cell renewal systems and to some extent the inherent radiosensitivity of the stem cells. In the haematopoietic system, the lifespan of the functional cells varies with cell type: the megakaryocyte–platelet and leukocyte populations are at highest risk because of their short lifespan.

Two main types of cell death are induced by radiation: (1) death associated with mitosis because of DNA damage, in many cases causing chromosomal alterations that make the first or subsequent post-irradiation cell division lethal, and (2) death through apoptosis in interphase, in some cases before the irradiated cells reach mitosis and in other cases after they have undergone mitosis. The probability that a cell will die through apoptosis depends largely on the type of cell. For example, in some types of lymphocytes, damage to the cell membrane can trigger a cascade of enzymatic events that ultimately result in scission of the DNA strands. In contrast, apoptosis is not frequently induced in fibroblasts. While apoptosis may occur in non-cycling cells, most such cells remain functional even though they carry DNA damage that is lethal when the cell attempts division.

Individual cell loss may be random, but it is the overall effect of killing a critical number of cells that causes the deterministic effect, which may be expressed either early or late. In lung and especially skin, some effects, such as erythema, occur relatively soon after exposure, but others, such as fibrosis, are observed many months later.

4.2 Late deterministic effects of ionizing radiation

The late effects of radiation are not fully explained, and the relative importance of depletion of parenchymal cells, which directly affects the functional and proliferative capacity of tissues, and of damage to the microvasculature, which indirectly affects the parenchymal cells, is a matter of discussion. The initial model of late effects was based on radiation-induced changes in the microvasculature of organs. Endothelial cells can be lost as a result of interphase death or death associated with mitosis as the slowly cycling cells come into division. The loss of vascular integrity in turn leads to fibrosis and loss of parenchymal cells (Rubin & Casarett, 1968; Casarett, 1980). An alternative model (Withers, 1989) stresses the importance of the loss of functional subunits, the architectural arrangement of organs and their stem cells. For example, the nephron in the kidney consists of epithelial cells; if a sufficient number are killed, the functional unit is lost because it cannot be repopulated from neighbouring nephrons. The function of the kidney is critically compromised as the loss of functional subunits increases. Similarly, in the spinal cord, the functional subunit essential for myelination and therefore for the function of the neurons is the minimum number of glial cells required for maintaining the integrity of the myelin. It is clear that not only radiosensitivity but also the volume of tissue irradiated is important. Withers (1989) contended that the severity of a radiation-induced late effect in an organ is

determined by the radiosensitivity of the stem cells and the arrangement into functional subunits. In those organs for which it has been determined, the radiosensitivity of the stem cells is fairly similar, with the exception of the more radiosensitive haematopoietic system. The most useful characteristic of the dose–response relationship is the α:β ratio (see section 5.1, Overall introduction), which is generally lower for late effects than for early effects and reflects the proportion of the damage repaired. The current approach to radiotherapy has gained from the idea that the quantal responses of tissues could be considered in terms of tissue-rescuing units (Hendry & Thames, 1986). It seems likely that damage to both the parenchymal cells and the microvasculature plays a role in the late deterministic effects, one being more important in some organs and less in others.

Most of the information about late effects comes from studies of patients undergoing radiotherapy. The success of radiotherapy comes at the risk of potential late effects, and dose fractionation is used to exploit the differential of repair and recovery between normal and cancerous tissues (see Thames & Hendry, 1987).

Atomic bomb survivors constitute the largest population that has been exposed to whole-body irradiation; they have been monitored for almost five decades (Shimuzu *et al*., 1999). During the period 1950–90, some 27 000 deaths occurred from causes other than cancer. The emphasis of the follow-up has been on diseases of the respiratory, cardiovascular and digestive systems, the rates of which increased 5–15% among people who received a dose of 1 Sv at these organs. This is a smaller increase than that for cancer. The most frequent causes of these deaths were stroke and heart disease, which accounted for about 54% of the total. It is not possible to distinguish statistically between a linear dose–response curve, a curvilinear response or the presence of a threshold. Late effects in the eye have also been studied, and the incidence of cataracts is discussed below.

The other relatively large population that has received whole-body irradiation is composed of patients who were exposed preparatory to bone-marrow transplantation. Late deterministic effects have been found in a number of tissues, including the lens of the eye, but no information is available on dose–response relationships, and the findings are confounded by prior chemotherapy in many patients. Future reviews of more homogeneous populations may provide more useful data.

The effects of radiation on organs for which some evidence of effects exists are described below.

4.2.1 *Skin*

The first reports of radiation-induced deterministic effects—erythema and radiodermatitis—in the X-ray technicians and physicians involved in the early days of what would become radiology appeared within months of Röntgen's discovery of X-rays. The ease with which the effects of radiation on the skin could be detected made it the obvious indicator of exposure for the purposes of radiation protection.

In 1925, the concept of the ‘tolerance dose’ was introduced for use in setting limits on exposure to radiation, and was expressed as 1% of the threshold dose for inducing erythema per month for whole-body exposure to X-rays (Taylor, 1981). The ease with which effects could be detected in the skin proved to be of no advantage when it was realized that cancer could be induced by doses of penetrating radiation below those that induce deterministic effects in the skin. The classification of early and late deterministic effects in the skin is shown in Table 37.

Table 37. Radiation-induced deterministic effects in skin and time of appearance after exposure

Effect	Time of appearance after exposure
Early transient erythema	Hours
Main erythematous reaction	About 2 weeks
Dry desquamation	3–6 weeks
Moist desquamation	4 weeks
Late erythema	8–20 weeks
Secondary ulceration	10 weeks
Dermal necrosis	10 weeks
Dermal atrophy	26 weeks
Telangiectasia	52 weeks

From ICRP (1991c)

The tolerance of the skin depends on the area of the exposed field, the total dose, the fraction size and the interval between fractions. Unless the fields are large, erythema occurs only after exposure to 5–6 Gy or to about 12 Gy if the dose is fractionated; transient loss of hair may also occur. Moist desquamation may occur after a single dose of 18 Gy or after 40–50 Gy in about 25 fractions over about five weeks. The skin has a remarkably large capacity to recover from the damage induced by large total doses (tens of grays) if the dose is spread over a number of fractions, which allows time for repair of sublethal damage and for repopulation.

The early or acute effects of radiation on the skin include erythema, which occurs in varous phases. Erythema may be seen within hours of exposure of large fields to doses in the range used in radiotherapy, about 2 Gy, reflecting increased permeability of the capillaries and the early onset of inflammation. This phase is transient, and the erythema disappears within 24–48 h. The more significant phase, known as the main erythematous reaction, usually appears during the third week of a fractionated regimen. This phase is due to the inflammatory reaction that follows the death of cells in the basal layer of the epithelium. A few days after irradiation, cell proliferation may

have stopped. Although the number of basal cells decreases, the integrity of the skin is maintained; however, dry desquamation may occur. With higher doses—about 30–40 Gy in multiple fractions—moist desquamation occurs. Desquamation is caused by inactivation of a critical number of clonogenic cells in the basal layer and follows within four to six weeks of exposure. Severe desquamation can lead to ulceration of the dermis. If the damage to the dermal vasculature is extensive, dermal necrosis may ensue within 10 or more weeks.

The responses to fractionated dose regimens are complex. In experimental studies of fractionated and prolonged irradiation of mouse skin, greater skin sensitivity was observed when 3-Gy fractions were given at an interval of 48 h than at either 6- or 24-h intervals. This effect was interpreted as the consequence of the increased radiosensitivity seen during the proliferative response induced by the radiation (Ruifrok *et al*., 1994).

A different form of acute ulceration is found after exposure of extremely small areas of skin (and other epithelial surfaces) to very high doses, as occurs when 'hot' particles, such as the very small fragments of steel activated by neutron irradiation in a reactor, stick to the skin or in the nose, where they can remain unnoticed long enough to deliver an appreciable dose of β-particles and γ-rays. Within about two weeks of exposure, a pale, circular area surrounded by a halo of erythema is seen, which is quite distinct from other skin lesions induced by radiation. Ulceration follows when the overlying epidermis separates to reveal a small area of necrotic dermis. The evidence suggests that endothelial cells and fibroblasts in the superficial dermis are killed in interphase. The dosimetry for this type of radiation damage was established in experiments on pig skin *in vivo*. The median effective doses for the induction of moist desquamation by exposure to circular sources of ^{90}Sr (a high-energy β emitter) of various diameters were 27.5 Gy for a 22.5-mm source up to 75 Gy for a 5-mm source; the 2-mm and 1-mm sources induced acute necrosis within three weeks, at median effective doses of 125 and 275 Gy, respectively (Hopewell *et al*., 1986).

Acute epithelial necrosis is induced by very-low-energy β-particles which cause interphase death in the suprabasal layer of the epidermis about 10 days after exposure. Radiation-induced lesions were studied in 56 workers, in particular firemen, at the Chernobyl facility who had incurred doses estimated to have been > 30 Gy at a depth of 150 mg cm^{-2} and over 200 Gy at about 70 mg cm^{-2}. The workers were exposed to high-activity fission products with a β-particle to γ-ray ratio of 10 to 30. Skin desquamation and subsequent infection in victims who received damage over 50% of their body surface area contributed to their deaths. All of these persons also had damage to their haematopoietic systems (UNSCEAR, 1988; Barabanova & Osanov, 1990).

Burns are induced by fall-out after detonation of nuclear weapons. For example, the doses to the skin received by Japanese fishermen exposed to the fall-out from one test were estimated to be 1.7–6.0 Gy. Erythema and necrosis were found in a few of the exposed men, and late effects were noted subsequently.

A late phase of erythema that gives the skin a dusky appearance is sometimes seen 8–20 weeks after exposure. It is seldom seen in patients receiving fractionated radiotherapy but was observed in victims of the Chernobyl accident who had received high doses 1.5 mm below the surface of the skin, where the deep dermal plexus of blood vessels is found. Loss of endothelial cells appears to be a major causal factor.

The other late effects of concern are dermal atrophy, telangiectasia and necrotic ulcer. The severity and the incidence of these lesions increase as the dose exceeds 30–40 Gy when given in fractions of 2 Gy. Dermal atrophy appears to develop in two phases, beginning 14–20 weeks after exposure and after about one year. The first phase is thought to be due to loss of endothelial cells, as in dermal necrosis (Hamlet & Hopewell, 1988), and to loss of fibroblasts (Withers *et al*., 1980), a significant loss of endothelial cells sometimes preceding that of fibroblasts. The second phase involves degeneration of the smooth muscle of arterioles.

Telangiectasia may occur in patients treated with fractionated doses about one year or more after therapy. The incidence and the severity increase with time in a dose-dependent manner.

4.2.2 *Lung*

Radiation pneumonitis and fibrosis are the main deterministic effects in the lung. Three types of pulmonary cell are involved in the responses to radiation: type-1 and type-2 alveolar cells and endothelial cells; the last two undergo renewal and are targets for radiation-induced damage (see review by Travis, 1987). Radiation pneumonitis occurs in experimental animals and in humans about 80–180 days after exposure and, depending on the dose, may be fatal. The human lung is slightly more sensitive than that of mice, with estimated LD_{50} values of 9–10 Gy of external irradiation for humans and 12–15 Gy for mice. Radiation pneumonitis is characterized by interstitial oedema, infiltration of inflammatory cells and desquamation of alveolar epithelial cells. At high doses, an exudate is found in alveolar air spaces. An alveolar infiltrate can be detected radiologically, and opacification is detected by computerized tomography in a high percentage of patients within about 16 weeks of receiving fractionated doses. Dyspnoea is a symptom of pneumonitis in both humans and mice.

The effects of total dose, the number of fractions and the total period of treatment on the incidence of radiation-induced pneumonitis in patients undergoing radiotherapy are shown in Table 38.

Fibrosis, the main long-term effect of radiation on the lung, may occur in patients in whom pneumonitis has not been detected. The loss of volume and of diffusing capacity depend, as in other tissues, on the size of the radiation field. The histological changes include an increased amount of collagen which replaces the alveolar septa, a decrease in the number of functioning capillaries, atypical alveolar epithelial cells and loss of alveoli due to fibrotic changes which may lead to atelectasis. Lung fibrosis

Table 38. Incidence of radiation pneumonitis in patients undergoing radiotherapy, according to dose regimen

Total dose (Gy)	No. of fractions	Length of treatment (weeks)	Incidence of pneumonitis (%)
6–7	1		0 (threshold)
10	1		84
26.5	20	4	5
20	10	2–4	5
30.5	20	4	5
30.0	10	2	100

Data from Mah *et al.* (1987); UNSCEAR (1988)

may appear about one year after irradiation, and the changes are usually irreversible (Travis, 1987).

4.2.3 *Gonads*

(*a*) *Ovary*

The ovary is a radiosensitive organ, but its radiosensitivity to the induction of sterility is age-dependent (Table 39). Radiation-induced ovarian failure gives rise not only to reduced fertility or sterility but also to reduction or cessation of hormone production, which may lead to premature menopause in younger women (Meistrich *et al*., 1997). Amenorrhoea has been reported in 10% of patients exposed during childhood to 0.5 Gy to the ovaries and in about 66% exposed to 3.0 Gy (UNSCEAR, 1993). A dose of 1.0–1.5 Gy appears to be the threshold for an effect on fertility. Ovarian failure occurs in 40% of 20-year-old women and in 90% of 35-year-old women receiving a dose of 4.5 Gy. The effect is reduced by dose fractionation and protraction of radiotherapy (Meistrich *et al*., 1997).

(*b*) *Testis*

The germinative cells of the seminiferous tubules are highly radiosensitive, whereas the Sertoli cells, which provide support and nutrition for the spermatogonia, and the Leydig cells, the source of testicular hormones, are considerably more resistant. Irradiation may reduce fertility or induce temporary or permanent sterility but has little effect on libido. The response of the testis has been studied in patients undergoing radiotherapy, radiation workers, volunteers in state penitentiaries, victims of nuclear accidents and atomic bomb survivors (see Meistrich & Van Beek, 1990). The sperm count remains within the normal range for about eight weeks after irra-

Table 39. Minimum fractionated doses to the ovary that induce sterility

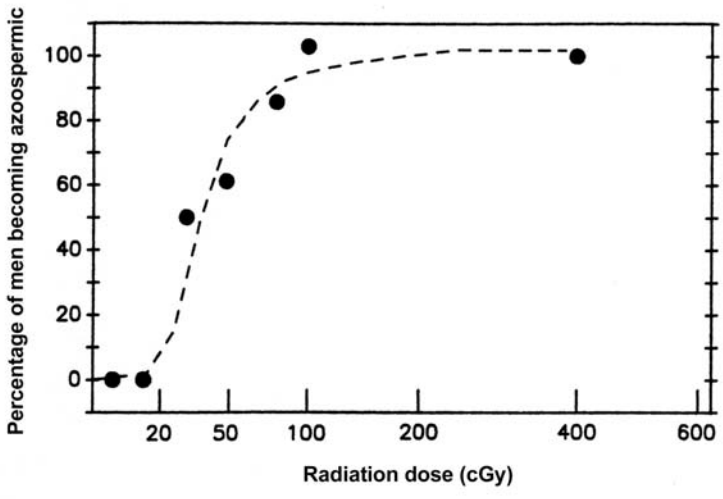
Dose (Gy)	Ovarian failure (%)	
	15–40 years of age	> 40 years of age
0.6	None	None
1.5	No risk	Small risk
2.5–5.0	60	100
5.0–8.0	60–70	NR
> 8.0	100	100

From Ash (1980) and Damewood & Grochow (1986);
NR, not reported

diation, but falls to its lowest level over the next three to eight months; aspermia may occur temporarily after a dose of about 0.2 Gy. The reduction in spermatogenesis is dose-dependent (Figure 13). A dose of 1.0 Gy causes aspermia in 90% of men. Fractionation does not reduce the effect and may increase it. The onset of recovery is also dose-dependent, occurring within about six months after a dose of 0.2 Gy but not until two years after a dose of 5 Gy. An analysis by Meistrich and Van Beek (1990) of the data obtained by Rowley *et al*. (1974) in a study of volunteers showed that type Ap and type B spermatogonia and early spermatocytes were the most radiosensitive cells and that late spermatocytes, spermatids and type Ad spermatogonia, considered to be the reserve stem cells, were somewhat less sensitive. It is difficult to estimate a threshold dose for temporary sterility, which depends on the time after exposure that fertility is assessed. A dose as low as 0.1 Gy has detectable effects in the young, and 0.15 Gy may cause oligospermia and temporary infertility in adults (UNSCEAR, 1993).

Two parameters have been used to assess the effect of radiation on the testis: loss of testicular weight and regeneration of the spermatogenic epithelium. The curve for loss of testicular weight as a function of dose has two components, and the logarithm of the loss of the radiosensitive component is linearly related to dose, with a D_0 of 0.9–1.0 Gy in mice, where D_0 represents cell killing due to multiple events (Kohn & Kallman, 1954; Alpen & Powers-Risius, 1981). The percentage of tubules that showed foci of repopulation by spermatogonial cells at 35–42 days after irradiation was used as a measure of stem-cell survival. At doses > 8 Gy, an exponential survival curve with a D_0 of 1.8 Gy was obtained (Withers *et al*., 1974). It is not clear why the values for D_0 vary by a factor of two. A detailed assessment of the sensitivity of cells in the development stages of spermatogenesis in mice showed that the range of sensitivities is broad, but in general the sensitivity decreases from the intermediate spermatogonial stage to the mature sperm (see Table 40; Oakberg & Clark, 1964).

Figure 13. Percentages of men developing azoospermia after various single doses of radiation



From Meistrich & Van Beek (1990). Doses are plotted after square-root transformation.

Table 40. Sensitivity of mouse spermatogenic cells to radiation

Cell type	LD_{50} (Gy)
Spermatogonia (types A_s, A_1–A_4)	2.0
Intermediate spermatogonia	0.2
Type B spermatogonia	1.0
Meiotic stages	2.0–9.0
Secondary spermatocytes	10.0
Spermatids	15.0
Spermatozoa	500.0

From Oakberg & Clark (1964); LD_{50}, median lethal dose

Although Leydig cells are generally considered to be relatively radioresistant, transient increases in serum follicular hormone concentrations were reported after exposure to doses as low as 0.2 Gy, while at 2.0 Gy the serum concentration of luteinizing hormone was increased. Both parameters are indicators of Leydig-cell dysfunction (Kinsella, 1989).

The outstanding features of the effects of radiation on the testis are the exquisite sensitivity of some testicular cells, the lack of sparing with fractionation and the long recovery time.

4.2.4 *Kidney*

Opinions about the relative radiosensitivity of the kidney vary (UNSCEAR, 1982). The importance of radiation-induced nephropathy and questions about whether the kidney should be shielded during whole-body irradiation before bone-marrow transplantation have renewed interest in the subject. The cells at risk in the three major components of the kidney, the renal tubules, the glomeruli and the complex, abundant vasculature, are mainly post-mitotic cells. This influences the response of the kidney to radiation and the sequelae. The late effects—nephritis, nephrosclerosis, tissue necrosis and fibrosis with subsequent hypertension and loss of renal function—are the main concerns (UNSCEAR, 1993).

Tests of renal function provide no evidence of renal damage during the first six months after radiotherapy with fractionated regimens of total doses < 23 Gy, but nephritis with signs and symptoms of renal damage may occur 6–12 months after treatment. Albuminuria and increased urea nitrogen in blood are common features. Renal failure and hypertension are later, more serious sequelae. The tolerance dose is about 23 Gy given in fractions over about five weeks to both kidneys. Doses of 20–24 Gy given over about four weeks may result in a 10–60% reduction in renal plasma flow and glomerular filtration rate.

The tolerance dose is lower in children than in adults, and radiation-induced nephropathy has been observed after bone-marrow transplantation in children. Anaemia, increased urinary creatinine concentrations and other signs of renal insufficiency have been observed after exposure to 12–14 Gy given in six to eight fractions. The precise contribution of radiation is difficult to assess because many such patients have had prior chemotherapy. It is also difficult to determine how much of the reduced tolerance, i.e. the delay before renal failure, is due to age or to chemotherapy. Experimental evidence in rats indicates that age is important and that tolerance increases with age at irradiation, within limits (Moulder & Fish, 1997).

The early histological changes seen in the kidneys after irradiation include hyperaemia, increased capillary permeability and interstitial oedema. The fine vasculature shows evidence of damaged endothelial cells and repopulation, which tends to occlude the lumen of the vessels. The glomerular arterioles are affected and blocked. The vascular occlusion and narrowing cause ischaemia in the cortex, and secondary degeneration of the tubular epithelium may follow. Damage to the tubules is the primary lesion, and dose–survival relationships have been determined in mice for the cells responsible for regeneration of the tubular epithelium. When regenerating tubules were scored in mice 60 weeks after irradiation, the D_0 was 1.53 Gy, which is comparable with that recorded for clonogenic cells in other tissues. The doses used in

the assay (11–16 Gy) may, however, have damaged the vasculature (Withers *et al*., 1986).

4.2.5 *Gastrointestinal tract*

The effects of radiation on the gastrointestinal tract have been the subject of extensive reviews (see e.g. Bond *et al*., 1965; Becciolini, 1987; Potten & Hendry, 1995), from which the following descriptions are derived. Because the structure and the kinetics of cell turnover differ in the various regions of the gastrointestinal tract, the response to radiation also varies from one site to another.

(a) *Oral cavity*

Effects on the oral mucosa provide a somewhat more sensitive indicator of radiation-induced damage than effects on the skin, and mucositis is widely used to assess the radiosensitivity of the oral cavity. The early changes are similar to those in the skin but occur sooner after exposure. In the second week of fractionated radiotherapy, dryness of the mouth and even dysphagia may occur. An interesting early effect is an alteration in sensitivity to taste, which appears to affect the taste of salt and bitter differentially from that of sour and sweet.

The late changes in the oral cavity are fibrosis in the submucosa, telangiectasia and fibrosis involving the mucous glands. Chronic ulcers of the mucosa can follow fibrosis in the vasculature. The environment of the oral cavity can be changed by exposure to radiation because the saliva from irradiated salivary glands is more acidic than normal, and dental caries may develop.

(*b*) *Oesophagus*

Fractionated doses of 20–30 Gy can cause transient oesophagitis. Stricture may occur four to eight months after radiotherapy with doses of 30–65 Gy, depending on the fractionation regimen.

(*c*) *Stomach*

Fractionated doses up to approximately 20 Gy have been used in the treatment of peptic ulcer. Irradiation suppressed gastric acidity for six months to many years and was well tolerated, but the risk for cancer increased subsequently. With conventional fractionated radiotherapy, the stomach can tolerate a dose of about 40 Gy, but the likelihood of ulceration and perforation increases rapidly above this dose. The delayed effects include dyspepsia, impaired gastric motility and chronic atrophic gastritis, due to fibrosis.

(*d*) *Small intestine*

The small intestine is radiosensitive because the functional cells undergo rapid renewal and have a short lifespan. Studies in experimental animals indicate that

damage to the intestinal epithelium occurs at doses > 1 Gy and that the degenerative changes are increasingly severe at doses of 5–10 Gy. Recovery depends on the survival of a sufficient number of clonogenic cells in the crypts before the villi and their vasculature lose their integrity. The acute radiation syndrome that occurs in humans after a single, high, whole-body irradiation is discussed in section 4.1. With fractionated radiotherapy, the probability of nausea, vomiting and diarrhoea is dependent on the dose per fraction and the frequency and number of fractions. Patients irradiated in the epigastric and abdominal regions experience nausea and vomiting, and when a dose of 25–30 Gy has been accumulated in radiation fields including the mid- and lower abdomen, loss of appetite, fatigue and diarrhoea are not uncommon. The malabsorption syndrome, involving reduced uptake of nutrients, may start during treatment and increase after therapy is completed. Patients vary in their sensitivity. Complications affecting the bowel after large-field abdominal radiotherapy have been reported to occur in 1% of patients receiving 35 Gy and in about 3% receiving higher doses. The late effects consist of excess collagen deposition in the submucosa and the typical radiation-induced changes in small vessels, such as intimal fibrosis (Becciolini, 1987).

(*e*) *Large intestine*

Because the cell turnover rate is lower in the large intestine than in the small intestine, the former is less radiosensitive. Acute transient changes in the mucosal epithelium of both the colon and the rectum may occur with doses > 30–40 Gy. The rectum is relatively radioresistant, but rectal bleeding may occur 6–12 months after irradiation with fractionated doses totalling 60 Gy. The late changes include fibrosis, shortening of the colon and strictures. As in other tissues, late changes in the vasculature, such as endarteritis and fibrosis, are characteristic (Becciolini, 1987).

The survival curves for clonogenic cells of the jejunum and colon after irradiation have been determined by the method introduced by Withers and Elkind (1970), which is based on the number of regenerating clones of crypt cells per cross-section of tissue three to four days after exposure to graded doses. The D_0 of the single-dose survival curve is about 1.3 Gy of 250-kVp X-rays. When the single-dose and the multiple-dose survival curves are separated, the 'shoulder' (see Figure 16, Overall introduction), assumed to indicate the amount of repair, is characterized by a D_q value between 4 and 4.5 Gy. Dose–survival curves for clonogenic cells in solid tissues can be determined experimentally only over a range of high doses, for example about 12–16 Gy in the jejunum. The survival curves for low doses must be obtained by reconstruction from data on fractionated doses.

4.2.6 *Haematopoietic system*

Death due to the acute radiation syndrome in the bone marrow is discussed in section 4.1. Depending on the dose, the prodromal stage is followed by the gastro-

intestinal syndrome; if the victim survives, the haematopoietic syndrome follows in the second week, and death may occur within two to three weeks after exposure to doses of 5.4–7.5 Gy and within four to six weeks after exposure to lower doses in the lethal range. The probability of death from bone-marrow damage depends on the treatment that is provided, more so than in any of the other syndromes. The prudent use of cytokines and growth factors has markedly improved the prospect of survival, although a fatal outcome becomes highly probable at doses ≥ 5.5 Gy. Survival of 10% of the haematopoietic progenitor cells is usually sufficient to prevent death.

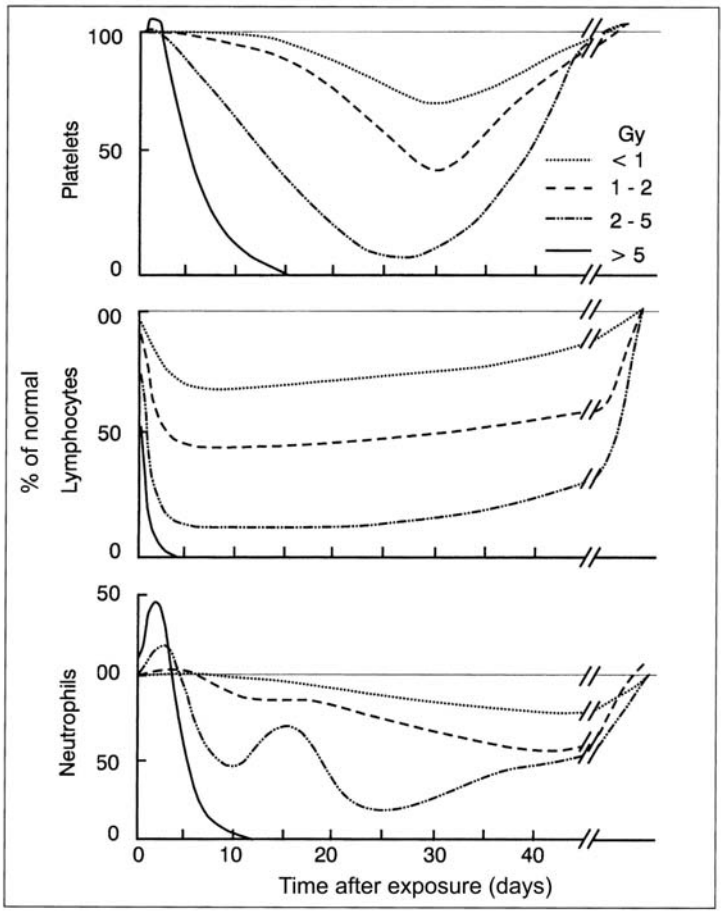
The radiation-induced loss of the functional elements of the blood and the subsequent response depend on the cell type and the cell kinetics. The short lifespan of the neutrophils and platelets is reflected in the decreases in their number before that of the long-lived red cells. The radiosensitive subpopulations of lymphocytes are also affected shortly after exposure. Within 8–10 days, the decreases in granulocytes and platelets become critical, and, at doses in excess of 5 Gy, pancytopenia may follow (Figure 14). Haemorrhage and infection may exacerbate the condition (Wald, 1971).

The bone marrow can withstand higher total doses of radiation when the dose rate is lower, the dose is fractionated or the size of the radiation field is reduced. For example, patients irradiated with single doses < 10 Gy on either the upper or the lower half of the body can recover within about eight weeks. The effect is more severe after irradiation of the upper half of the body, where about 60% of the active bone marrow is found.

McCulloch and Till (1960) developed a technique for determining survival curves of colony-forming units that contain progenitor cells capable of producing erythrocytes, myelocytic elements and platelets. Erythrocytes predominated in the colonies that grew in the spleens of irradiated mice transplanted with bone marrow. When the bone-marrow cells were irradiated *in vivo*, the D_0 was 0.95 Gy, with a small shoulder on the survival curve (extrapolation number (*n*), 1.5; see Figure 16, Overall introduction). Both the D_0 and *n* were higher when the cells were exposed *in vitro*. The survival curves of colony-forming units in humans and mice are similar.

Information about the late effects of radiation on the bone marrow comes mainly from studies of patients undergoing radiotherapy and, to a lesser extent, from reports of accidental exposure. The decrease in progenitor cells may persist, and the duration of depletion is dose-dependent; the counts of circulating blood cells, especially lymphocytes, may be depressed for months. In general, accidental exposure to high but sublethal doses is followed by recovery of the bone marrow, as was also observed in the survivors of the atomic bombings. In the case of localized exposures to high total doses, aplasia is followed by replacement of the bone marrow with fat cells and fibrosis.

Figure 14. Counts (percentage of normal) of platelets, lymphocytes and neutrophils as a function of time after exposure to and dose of radiation during accidents



From Wald (1971)

4.2.7 *Central nervous system*

The developing brain is most sensitive to radiation during gestation. As early as 1929, recognition of the fact that proliferating cells are more radiosensitive than differentiated cells led Goldstein and Murphy (1929) to study children born to women exposed to pelvic irradiation during pregnancy. They found some effects on the central nervous system. Miller and Mulvihill (1956) reported that children exposed *in utero* to atomic bomb radiation had small head sizes, an indication of damage to the central nervous system.

Observation of severe mental retardation and reduced intelligence quotients in children exposed to radiation *in utero* indicated that the most sensitive periods are 8–15 and 16–25 weeks after fertilization (Otake & Schull, 1984, 1998). The number of neurons increases rapidly during weeks 8–15 of gestation, and proliferation of the neurons of the cerebral cortex is virtually complete by 16 weeks; by 26 weeks, the neurons are differentiated. Accordingly, no cases of severe mental retardation have been found among individuals exposed to radiation before 8 weeks or after 26 weeks of gestation. Some cell proliferation continues in the brain, particularly in the cerebellum, during the first two years of life, and the proliferating neurons are radiosensitive. Glial cells, which proliferate actively during the early years of life, retain the ability to divide. Loss of glial cells can lead to demyelinization. In the developing brain, neurons not only proliferate but also migrate to specific sites. This migration occurs mainly between weeks 7 and 10 and 13–15 of gestation and is virtually complete at 16 weeks. Exposure to radiation during weeks 8–16 of gestation is thus likely to interfere with this process. In a study with explants of the cerebral cortex from rat embryos at day 16 of gestation, a dose as low as 0.1 Gy affected neuronal migration (Fushiki *et al*., 1993).

Most of the information on the effects of radiation on the brain postnatally comes from studies of patients—in particular, children treated for acute leukaemia. The degree of radiosensitivity depends on the effect and the age at exposure. In the adult brain, radiation-induced damage to the microvasculature is the major concern (for a review, see Gutin *et al*., 1991). The acute central nervous syndrome (see section 4.1) occurs with doses of 20–100 Gy, and the survival time is about two days or less, but damage to the membranes and the vasculature rather than neuronal cell killing is involved. In contrast, neurons can be induced to fire (as detected by electroencephalography) by doses as low as 0.01 Gy.

Four types of late effect of radiation in the central nervous system have been described: leukoencephalopathy, mineralizing microangiopathy, cortical atrophy and cerebral necrosis. Leukoencephalopathy is not strictly an effect of radiation as it is the result of an interaction between radiation and methotrexate. It gives rise to demyelinization, multifocal necrosis and gliosis, but the grey matter and the basal ganglia are spared. The histological changes are reflected by reduced mental ability, ataxia, dementia and even death. Radiation doses of ≥ 20 Gy plus methotrexate will cause these lesions, but fractionated radiotherapy with 18–24 Gy alone does not. Mineralizing microangiopathy affects the cerebral grey matter and less frequently the cerebellum. It is assumed to be due to damage to the microvasculature, which leads to calcification, obstruction of the vessels and necrosis. Headaches, seizures, ataxia and defective muscle control have been noted. The condition is seen in children treated with a total dose of at least 20 Gy. Cortical atrophy, caused by focal necrosis with a loss of neurons from all layers, occurs in about 50% of patients receiving more than 30 Gy of fractionated radiotherapy to the entire brain. Cerebral necrosis, which involves an amorphous fibrin exudate, often in the junctional tissues between the

white and grey matter, may appear 1–10 years after treatment. The incidence of cerebral necrosis increases rapidly at fractionated doses > 45 Gy (UNSCEAR, 1993).

The tolerance doses for brain damage are thus not known, but it is clear that the higher the dose per fraction the greater the probability of severe damage. In adults, a dose of 50 Gy to the brain in 2-Gy fractions over six weeks is considered to be critical, whereas the critical dose in children of three to five years of age is about 20% lower and that for younger children is even lower.

4.2.8 *Thyroid*

Hypothyroidism is the commonest late deterministic effect of radiation on the thyroid gland. It may be due to direct damage or, secondarily, to damage to the hypothalamic–pituitary axis (see UNSCEAR, 1993). Doses that are sufficient to affect function are more likely to be received during internal exposure from radionuclides such as ^{123}I, ^{125}I and ^{131}I for therapeutic treatment or as a result of a radiation accident.

Although there is conflicting evidence about the effect of age at the time of exposure, it is likely that the very young are more radiosensitive, as is the case for the induction of thyroid cancer (Ron, 1996). The activity of thyroid-stimulating hormone is frequently increased in children who have been irradiated for Hodgkin disease or brain tumours if the dose to the thyroid reaches about 24 Gy (Oberfield *et al*., 1986), but no increase was found after exposure to 15 Gy (Glatstein *et al*., 1971). Hypothyroidism was found in 20% of long-term survivors among children with acute leukaemia who received cranial or craniospinal irradiation with fractionated doses of a total of 18–25 Gy, the dose to the thyroid being about 3–8% of the total dose. No evidence of hypothyroidism has been found in children exposed to < 1 Gy (UNSCEAR, 1993). A study by DeGroot *et al*. (1983) indicated that chronic lymphocytic thyroiditis is relatively common in patients who received external irradiation in childhood. Hypothyroidism with increased serum levels of thyroid-stimulating hormone was found in 15% of patients who received < 30 Gy and in 68% of those who received higher doses (Kaplan *et al*., 1983).

4.2.9 *Eye*

The ocular lens and the skin are the two tissues for which specific dose limits have been set for the prevention of deterministic effects of radiation. The occupational dose limits are 150 mSv year^{-1} and 500 mSv year^{-1}, respectively. The effects of radiation on these tissues were recognized soon after the discovery of X-rays. Much of the early literature on radiogenic cataracts was reviewed by Bendel *et al*. (1978), and the responses of the human eye were detailed by Merriam *et al*. (1972).

The lens is the most important radiosensitive structure in the eye, but it is not the only tissue affected. Keratitis and oedema of the cornea can occur after exposure to

single doses of about 10 Gy, and damage to the lachrymal gland, the retina and the conjunctiva can be induced by higher doses (Merriam *et al*., 1972).

The development and progression of the effects of radiation on the ocular lens can be studied by non-invasive techniques. While the mechanism of cataract induction by radiation is not known, the evidence indicates that cataracts are caused by damage of cells in the germinative zone, resulting in abnormal differentiation of the developing lens fibres. The latent period from the time of exposure to the appearance of opacities is consistent with the time required for the differentiation and migration of abnormal fibres. The long-held hypothesis that cell killing is central to the formation of lens opacities is being questioned, and damage to the genome of the epithelial cells has been proposed as an underlying principle (Worgul *et al*., 1991). If this is so, cataract induction is probably a stochastic process with a threshold for a clinically significant lesion, and therefore differs from other deterministic effects. Like other deterministic effects, its incidence and severity increase with the dose of radiation.

The early stage of radiation-induced cataract is marked by changes in the posterior capsular area; subsequently, the anterior part of the lens is involved, and the posterior lesion expands. Opacities of the lens may develop and then cease to progress, and anecdotal accounts suggest that regression can occur. The latent period between exposure and detection of a cataract is dose-dependent but ranges from six months to several decades, with an average of two to three years (UNSCEAR, 1993).

Patients receiving radiotherapy are the main source of data for estimating the threshold dose for cataract induction and the increase in incidence with dose (Merriam *et al*., 1972). The threshold single dose was estimated to be about 2 Gy, and the threshold for a dose fractionated over 3–13 weeks was estimated to be about 5.5 Gy. Further evidence of an effect of fractionation comes from studies of patients irradiated before bone-marrow transplantation: the incidence of cataract after a single dose of 10 Gy was 80%, while only 19% of patients who had received fractions of 2–4 Gy over six or seven days (total dose, 12–15 Gy) developed cataracts (Deeg *et al*., 1984). At low doses above the threshold, the opacities are minimal and become static. The threshold dose for a progressive cataract is probably between 2.0 and 5.0 Gy.

In the survivors of the atomic bombings, the threshold dose for minimal opacities was reported to be 0.6–1.5 Gy, although the results are confounded by exposure of the survivors in Hiroshima not only to γ-rays but also to neutrons (see separate monograph; Otake & Schull, 1990). The data on radiation-induced cataracts in children treated for cancer are also confounded because in many cases the treatment consisted of a combination of radiotherapy and chemotherapy. Nevertheless, children appear to be more susceptible than adults. The data for the atomic bomb survivors also indicate age-dependency, the risk for cataract being two to three times higher in children under the age of 15 at the time of exposure than in older persons (UNSCEAR, 1993).

4.3 Radiation-sensitive disorders

Individuals who might be at enhanced risk for cancer caused by ionizing radiation include patients suffering from disorders that are associated with increased sensitivity to radiation at the cellular level. A paradigm of such disorders is xeroderma pigmentosum, in which enhanced sensitivity to the toxic effects of ultraviolet radiation (UV) parallels an enhanced risk for skin cancer after exposure to UV. The molecular mechanism underlying this phenomenon is reduced or absent repair of UV-induced DNA lesions, resulting in an increased frequency of mutations in the genome of cells from exposed parts of the body. These mutations can ultimately lead to cancer (see e.g. IARC, 1992). On the basis of this example, an enhanced risk for cancer induced by ionizing radiation might be expected in patients with a reduced capacity for repair of DNA damage and a smaller risk in those with conditions that result in disturbances in progression of the cell cycle. A further group of individuals who might be expected to show enhanced susceptibility to radiogenic cancer are those who have mutations of dominant tumour suppressor genes which are responsible for preventing the expansion of potentially malignant (initiated) cells. If radiation were to increase the number of these initiated cells, there would be an increased probability of their progression to frank tumours (for discussion, see National Radiological Protection Board, 1996).

4.3.1 *Ataxia telangiectasia*

The human genetic disorder ataxia telangiectasia is characterized by immunodeficiency, neurodegeneration, radiosensitivity and increased risks for developing a number of leukaemias and lymphomas and solid tumours (Boder, 1985; Sedgwick & Boder, 1991).

(*a*) *ATM gene and gene product*

The *ATM* gene (‘mutated in ataxia telangiectasia’) was identified by Savitsky *et al.* (1995). Full-length *ATM* cDNA was eventually cloned in two laboratories and shown to be capable of correcting aspects of the radiosensitivity of cells from patients with the disease as well as the defective cell-cycle checkpoints (Zhang *et al.*, 1997; Ziv *et al.*, 1997). Analysis of the *ATM* gene in patients with ataxia telangiectasia throughout the world showed over 300 mutations (see ataxia telangiectasia mutation database—http://www.vmmc.org/vmrc/atm.htm; P. Concannon and R. Gatti).

The ATM gene product is a highly phosphorylated nucleoprotein of about 370 kDa, which has a phosphatidylinositol 3-kinase (PI3) domain close to the C-terminus, through which it is related to a family of proteins involved in DNA damage recognition and/or cell cycle control (Hartley *et al.*, 1995; Anderson & Carter, 1996; Bentley *et al.*, 1996; Cimprich *et al.*, 1996). These proteins phosphorylate one or more substrates in response to DNA damage to activate signal transduction pathways and/or recruit

proteins to sites of DNA repair. In the case of ATM, substrates such as TP53, c-Abl, RPA, mdm2 and PHAS-1 have been identified (Banin *et al.*, 1998; Canman *et al.*, 1998; Khanna *et al*., 1998; Tibbetts *et al*., 1999).

Immunoblotting studies showed that the ATM protein is located predominantly in the nucleus in proliferating cells (Chen & Lee, 1996; Keegan *et al.*, 1996; Lakin *et al.*, 1996; Brown *et al.*, 1997; Jung *et al.*, 1997; Watters *et al.*, 1997), although cell fractionation followed by immunoblotting revealed that 5–20% of ATM is in a microsomal fraction (Lakin *et al.*, 1996; Brown *et al.*, 1997; Watters *et al.*, 1997). Immunofluorescence studies confirmed that ATM is predominantly nuclear in fibroblasts, with relatively uniform distribution throughout the nucleus, except for nucleoli (Watters *et al.*, 1997). A distinct pattern of punctate labelling was seen in the cytoplasm, and immunoelectron microscopy showed that the protein is localized in 60–250-nm vesicles (Watters *et al.*, 1997) and co-localizes with β-adaptin to endosomes (Lim *et al.*, 1998).

(*b*) *ATM and cell-cycle checkpoint control*

Cells from patients with ataxia telangiectasia are defective in activating both G_1/S and G_2/M phase checkpoints after irradiation, and DNA synthesis is inhibited to a lesser extent than in controls (Houldsworth & Lavin, 1980; Painter & Young, 1980; Scott & Zampetti-Bosseler, 1982; Nagasawa & Little, 1983; Beamish & Lavin, 1994).

Kastan *et al.* (1992) demonstrated that the response of the TP53 tumour suppressor protein in activating the G_1/S checkpoint after irradiation was defective in cells from patients with ataxia telangiectasia, and the induction of a number of *p53* effector genes was subsequently found to be reduced and/or delayed after irradiation (Canman *et al.*, 1994; Dulic *et al.*, 1994; Artuso *et al.*, 1995; Khanna *et al.*, 1995). Thus, *ATM* is initially activated in response to DNA damage by an unknown mechanism, which in turn activates *p53* (Shieh *et al.*, 1997; Siliciano *et al.*, 1997).

Cells from patients with ataxia telangiectasia are also characterized by radioresistant DNA synthesis (Houldsworth & Lavin, 1980; Painter & Young, 1980) and a defective G_2/M checkpoint after irradiation (Nagasawa & Little, 1983; Ford *et al.*, 1984; Rudolph *et al.*, 1989). The reduced inhibition of DNA synthesis appears to be due to the failure of these cells to recognize and respond to the damage. Hyperphosphorylation of replication protein A is induced after irradiation in normal cells but is significantly delayed in cell lines from patients with ataxia telangiectasia (Liu & Weaver, 1993). When cells from patients with ataxia telangiectasia are irradiated in G_2 phase, they progress into mitosis with less delay than normal cells (Zampetti-Bosseler & Scott, 1981), but when they are irradiated in G_1 or S phase they progress through these phases unhindered and block irreversibly in the subsequent G_2/M phase (Beamish & Lavin, 1994).

(*c*) *Sensitivity to ionizing radiation*

Clinical radiosensitivity in patients with ataxia telangiectasia was revealed when adverse reactions were observed during treatment with X-rays and other agents (Gotoff *et al.*, 1967; Morgan *et al.*, 1968; Feigin *et al.*, 1970). Increased sensitivity to radiation and radiomimetic agents was also demonstrated *in vitro* as reduced cell survival (Taylor *et al*., 1975; Shiloh *et al.*, 1982a; Morris *et al.*, 1983; Shiloh *et al.*, 1983) and an increased frequency of chromosomal aberrations in cells from such patients after exposure to ionizing radiation (Higurashi & Cohen, 1973; Cohen *et al*., 1975; Rary *et al.*, 1975). Defects in DNA repair in response to radiation damage were not found in early studies (Vincent *et al.*, 1975; Taylor *et al.*, 1976; Fornace & Little, 1980; Lavin & Davidson, 1981; Shiloh *et al*., 1983), but a defect in potentially lethal damage repair was observed (Weichselbaum *et al.*, 1978; Cox *et al.*, 1981; Arlett & Priestley, 1983). Evidence was subsequently provided for a defect in DNA strand-break repair in cells from patients with ataxia telangiectasia. Cornforth and Bedford (1985) reported the existence of residual breaks in these cells, as demonstrated by premature chromatin condensation 24 h after irradiation. Foray *et al.* (1997) demonstrated that approximately 10% of double-strand breaks in such cells remained unrepaired for up to 72 h after irradiation. The exact nature of the lesion recognized by the ATM protein has not been identified, but it is likely to be some form of strand interruption (Taylor *et al.*, 1975; Chen *et al.*, 1978; Shiloh *et al.*, 1982b).

Since cells from patients with ataxia telangiectasia are defective in all cell-cycle checkpoints after irradiation and since they eventually accumulate and die in G_2/M, it was suggested that these cell-cycle anomalies could account for the radiosensitivity of these cells (Beamish & Lavin, 1994). The sensitivity is more likely to be due to a defect in the recognition and repair of specific lesions in DNA, with consequent effects on the cell cycle. Since radiosensitivity is observed in non-dividing cells from patients with ataxia telangiectasia, a repair defect is probably involved, rather than defective cell-cycle control (Jeggo *et al.*, 1998). Lack of correlation between *P53* status, G_1/S phase arrest and radiosensitivity in a variety of human cells and the fact that cells from *p53*$^{-/-}$ mice are more resistant to radiation (Lotem & Sachs, 1993; Lowe *et al.*, 1993; Clarke *et al*., 1994) would appear to eliminate defective cell-cycle checkpoints as an explanation for sensitivy to radiation.

(*d*) *Cancers in patients with ataxia telangiectasia*

A major hallmark of patients with ataxia telangiectasia is a predisposition to develop a range of lymphoid malignancies (Boder & Sedgwick, 1963). Around 10% of all such patients develop cancer, most of which are of the lymphoid type (Morrell *et al.*, 1986, 1990). The association between a defective thymus, immunodeficiency and the high frequency of lymphoid malignancies initially suggested that these tumours arose as a consequence of the immunodeficiency (Peterson *et al.*, 1964; Lévêque *et al.*, 1966; Miller & Chatten, 1967), but the observations that the spectrum

of malignancies was not confined to those resulting from immunodeficiency and that chromosomal instability accompanied leukaemia in this syndrome provided an alternative explanation. Chromosomal rearrangements with specific breakpoints involving primarily chromosomes 7 and 14 are observed in up to 10% of T-lymphocytes from all patients with ataxia telangiectasia (Taylor *et al*., 1996). The breakpoints are largely located in the vicinity of immunoglobulin heavy chain and *TCR* (T-cell receptor) genes, preferentially involving four regions, 7p13, 7q33-35, 14q11-12 and 14q32 (Hecht & Hecht, 1985). Clones capable of proliferation can be generated from translocations involving *TCR* genes and non-immune genes or inversions of chromosome 14, and these clones have been shown to develop into leukaemias (Taylor & Butterworth, 1986; Baer *et al*., 1987; Davey *et al.*, 1988; Taylor *et al*., 1992).

The lymphoid malignancies in patients with ataxia telangiectasia are of both B-cell and T-cell origin and include non-Hodgkin lymphoma, Hodgkin disease and several forms of leukaemia (Spector *et al.*, 1982; Hecht & Hecht, 1990). In a series of 119 patients with ataxia telangiectasia with neoplasms, 41% had non-Hodgkin lymphoma, 23% had leukaemia of any kind (usually acute lymphoblastic) and 10% had Hodgkin disease (Hecht & Hecht, 1990). In a smaller study in the United Kingdom of 17 children with ataxia telangiectasia, seven had leukaemias and 10 had lymphomas. The leukaemias were five T-cell acute lymphocytic leukaemias, a prolymphocytic leukaemia and a T-cell chronic lymphocytic leukaemia (Taylor *et al.*, 1996). In contrast, young adult patients with ataxia telangiectasia developed abnormal lymphocyte clones that converted with a high frequency into T-cell prolymphocytic leukaemia (Matutes *et al.*, 1991). Since the clonal expansions that give rise to lymphoid tumours in patients with ataxia telangiectasia are characterized by specific chromosomal breakpoints and rearrangements, it was considered likely that alterations in genes and/or their expression would contribute to the malignant phenotype. The breakpoints in chromosome 14 in patients with and without ataxia telangiectasia with T-prolymphocytic leukaemia occur in the vicinity of the *TCL-1* (T-cell leukaemia) locus (Baer *et al.*, 1987; Davey *et al.*, 1988; Mengle-Gaw *et al.*, 1988; Russo *et al.*, 1989; Virgilio *et al*., 1993). *TCL-1* is expressed at high levels in leukaemia cells characterized by rearrangements of chromosome 14, suggesting that it is deregulated as a consequence of these changes (Virgilio *et al.*, 1994). Transcriptional activation of the *Tcl-1* proto-oncogene in transgenic mice caused the appearance of proleukaemic T-cell expansion expressing *Tcl-1*, and leukaemia developed after a long latency (Virgilio *et al.*, 1998). These results suggest that *TCL-1* plays an important role in the initiation of T-cell prolymphocytic leukaemia.

Overall, therefore, patients who are homozygous for *ATM* are cancer-prone, and their cells are hypersensitive to the induction of chromosomal damage and death by radiation, but they are not hypersensitive to other end-points such as inhibition of DNA synthesis and induction of *HPRT* mutations. There is no evidence that they are prone to radiogenic cancer.

(*e*) *ATM mutations in cancers in patients without ataxia telangiectasia*

Clearly, the spectrum of leukaemias and lymphomas observed in patients with ataxia telangiectasia also occurs in the general population, albeit at low frequency. Since a higher incidence of these neoplasms is associated with loss of functional *ATM*, it was thought possible that sporadic cases of leukaemia, such as the rare T-cell prolymphocytic leukaemia, might show mutations in the *ATM* gene. Vorechovsky *et al.* (1997) used exon-scanning single-strand conformation polymorphism and described *ATM* mutations in 17/37 patients with T-cell prolymphocytic leukaemia. The pattern of mutations was complex, but most were missense mutations clustered in a region corresponding to the PI3-kinase domain of *ATM*. The mutations were predicted to interfere with either ATP binding or the catalytic activity of the ATM molecule. The pattern of mutations differed from those in patients with ataxia telangiectasia, the majority of which are predicted to give rise to truncated and unstable proteins (Gatti, 1998), and they did not tend to accumulate in specific regions of the molecule. Stilgenbauer *et al.* (1997) demonstrated loss of the q21–23 region of chromosome 11 (11q21–23) in 13/24 patients with T-cell prolymphocytic leukaemia. In six cases in which deletion of one *ATM* allele was shown, the second allele was also mutated and predicted to cause either absence, premature truncation or alteration of the ATM gene product. DNA fibre hybridization revealed structural lesions in both alleles of four T-cell prolymphocytic leukaemia samples (Yuille *et al.*, 1998). In a study of paired leukaemic and non-leukaemic cells, loss of heterozygosity at 11q22–23, including the *ATM* gene region, was detected in 10 of 15 cases. In cells from five T-cell prolymphocytic leukaemias with loss of heterozygosity, immunoblotting revealed that the ATM protein was either absent or decreased in amount. These changes in ATM protein were reflected in nonsense, aberrant splicing and missense mutations in the second allele (Stoppa-Lyonnet *et al.*, 1998). These studies suggest that *ATM* is a tumour suppressor gene which, when inactivated, leads to the development of T-cell prolymphocytic leukaemia.

A second leukaemia seen frequently in patients with ataxia telangiectasia is B-cell chronic lymphocytic leukaemia (Taylor *et al.*, 1996). Loss of heterozygosity in the *ATM* gene was found in five of 36 cases (Starostik *et al.*, 1998), and reduced ATM protein (> 50%) was seen in 34% (38/111) of cases of this cancer. Patients with this deficiency had shorter survival times and more aggressive disease. Stankovic *et al.* (1999) detected mutations in the *ATM* gene in six of 32 patients and reduced or absent protein expression in eight of 20 tumours. There was no evidence of loss of heterozygosity in the region of the *ATM* gene, suggesting that the effect on ATM protein was due to a mutation within the gene. Germ-line mutations were detected in two of the six patients, indicating their *ATM* carrier status, whereas the frequency of *ATM* heterozygosity in the general population is 0.5–1% (Swift *et al.*, 1991; Easton, 1994). DNA sequence analysis revealed a mutated *ATM* gene in four of six patients with B-cell

chronic lymphocytic leukaemia and an increased frequency of germ-line mutations (Bullrich *et al.*, 1999).

Loss of heterozygosity (loss of the wild-type allele leading to allelic imbalance) in the region of 11q23 has been reported in tumours of the cervix (Hampton *et al.*, 1994; Bethwaite *et al.*, 1995; Skomedal *et al.*, 1999), ovary (Gabra *et al.*, 1996), breast (Kerangueven *et al.*, 1997; Laake *et al.*, 1997; Rio *et al.*, 1998; Waha *et al.*, 1998), colon/rectum (Gustafson *et al.*, 1994; Uhrhammer *et al.*, 1998) and skin (melanoma) (Herbst *et al.*, 1995). While loss of heterozygosity in the 11q22–23 region is observed in T-cell acute lymphocytic leukaemia and ovarian cancer, no mutations in *ATM* have been reported in such cases (Takeuchi *et al.*, 1998; Koike *et al.*, 1999). These results suggest that epigenetic regulation of the *ATM* gene may play an important role in tumour development in some tissues. *ATM* is thus often mutated in some tumours that occur frequently in patients with ataxia telangiectasia but not in all.

(*f*) *Radiosensitivity,* ATM *mutations and cancer risk in people heterozygous for* ATM

Since ataxia telangiectasia is an autosomal recessive disorder, the *ATM* phenotype would not be expected to appear in gene carriers. Nevertheless, some penetrance does appear in carriers, namely intermediate sensitivity of their cells to ionizing radiation and increased risks for developing cancer and in particular breast cancer. Radiosensitivity of people heterozygous for *ATM* was first described by Chen *et al.* (1978), who used agar gel cloning and trypan blue exclusion to show that the radiosensitivity of six *ATM* heterozygous lymphoblastoid cell lines was intermediate between that of normal people and *ATM* homozygotes. Paterson and Smith (1979) subsequently described enhanced radiosensitivity, as determined by colony forming ability, and intermediate sensitivity to γ-radiation-induced DNA repair replication in fibroblasts from *ATM* heterozygotes. Such persons were subsequently reported to have greater radiosensitivity when taken as a group (Cole *et al.*, 1988). Dahlberg and Little (1995) demonstrated that the mean surviving fraction of irradiated control fibroblasts was significantly greater than that of *ATM* heterozygotes. Intermediate sensitivity in *ATM* heterozygotes has been shown in a number of other assays, including induction of chromosomal aberrations (Waghray *et al.*, 1990), production of micronuclei (Rosin & Ochs, 1986), flow cytometric analysis (Rudolph *et al.*, 1989; Lavin *et al.*, 1992) and by a cumulative labelling index (Nagasawa *et al.*, 1987). Heterozygotes as a group have been distinguished from controls by the radiosensitivity and accumulation of cells in the G_2 phase of the cell cycle (Shiloh *et al.*, 1986; Sanford & Parshad, 1990). A variety of measures of radiosensitivity distinguish *ATM* heterozygotes from controls, but there is considerable variation among heterozygotes and significant differences were found only when comparison was made between groups. None of the assays was specific for the detection of *ATM* heterozygotes.

Swift *et al*. (1991) concluded that diagnostic or occupational exposure to ionizing radiation probably increases the risk for breast cancer in women heterozygous for *ATM*. High doses of ionizing radiation, particularly before puberty, are known to increase the risk for breast cancer, but it is not yet known whether mammography leads to an increased risk for *ATM* carriers. A well-conducted mammographic examination involves an absorbed dose of about 0.3 cGy per breast, which, if applied annually over 35 years (between 40 and 75 years of age), would give rise to a lifetime radiation dose of 10.5 cGy—approximately the same as background radiation (Norman & Withers, 1992). An exposure of this order at the age of 40 would be estimated to increase the number of deaths from breast cancer by approximately 1/2000 women, which is insignificant when compared with the normal lifetime risk of 1/9 for breast cancer. If the increased sensitivity of *ATM* heterozygotes to radiogenic cancer were to parallel the hypersensitivity of their cells to radiation killing and the induction of chromosomal aberrations, i.e. an increase of 1.5–2-fold, a total dose of 10.5 cGy would not be expected to increase the lifetime risk for breast cancer in this group significantly. While the epidemiological studies point to a three- to fourfold increase in the risk for breast cancer, it is uncertain whether this is associated with mutation of the *ATM* gene.

(*g*) *Cancer risk in* Atm$^{-/-}$ *mice*

Several murine models for ataxia telangiectasia have been developed by disrupting the mouse homologue, *Atm*, by gene targeting (Barlow *et al.*, 1996; Elson *et al.*, 1996; Xu *et al.*, 1996; Herzog *et al.*, 1998). Targeting led to loss of Atm protein, since truncated forms are highly unstable. In another model, deletion of nine nucleotides gave rise to a relatively stable, near full-length protein. Mice with a disturbed *Atm* gene showed disease characteristics similar in many respects to those of its human counterpart: growth retardation, mild neurological dysfunction, male and female infertility, immunodeficiency, sensitivity to cell killing by radiation and a predisposition to develop thymic lymphomas (Barlow *et al.*, 1996; Elson *et al.*, 1996; Xu *et al.*, 1996). In none of these studies in *Atm*$^{-/-}$ mice were the neurodegenerative changes seen in patients with ataxia telangiectasia reproduced, nor the ataxia and other abnormalities resulting from cerebellar changes. Kuljis *et al.* (1997) used electron microscopy to demonstrate the degeneration of several types of neuron in the cerebellar cortex of two-month-old *Atm*$^{-/-}$ mice. This process was accompanied by glial activation, deterioration of neutrophil structure and both presynaptic and postsynaptic degeneration, similar to observations made in patients with ataxia telangiectasia. Most *Atm*$^{-/-}$ mice also develop thymic lymphomas by three months of age (Barlow *et al.*, 1996; Elson *et al.*, 1996). These lymphomas grow rapidly, metastasize and lead to organ failure and death.

4.3.2 *Nijmegen breakage syndrome*

A number of syndromes have been described that overlap with ataxia telangiectasia in some of their clinical, cellular or molecular features (Byrne *et al.*, 1984; Lange *et al.*, 1993). Nijmegen breakage syndrome is an autosomal recessive condition characterized by immunodeficiency, chromosomal instability, sensitivity to cell killing by radiation and predisposition to cancer (Weemaes *et al.*, 1981; Shiloh, 1997). Documented cases of malignancy have been reported in 42 patients, including 12 lymphomas, one glioma, one rhabdomyosarcoma and one medulloblastoma (Van der Burgt *et al.*, 1996), and a significantly increased incidence of malignant neoplasms has been observed among persons heterozygous for the *NBS* (Nijmegen breakage syndrome) gene (Seemanová, 1990). The clinical presentation of this syndrome includes microcephaly, distinctive facial appearance, growth retardation and normal serum α fetoprotein, with none of the neurocutaneous manifestations seen in patients with ataxia telangiectasia (Chrzanowska *et al.*, 1995; Shiloh, 1997). The overwhelming majority of the 42 patients in the registry in Nijmegen in 1996 were detected in eastern Europe, particularly in Poland and the Czech Republic (Van der Burgt *et al.*, 1996).

Mapping of the *NBS* gene to chromosome 8q21 confirmed that the disease is genetically distinct from ataxia telangiectasia (Stumm *et al.*, 1995; Komatsu *et al.*, 1996; Matsuura *et al.*, 1997; Saar *et al.*, 1997; Cerosaletti *et al.*, 1998). The *NBS1* gene was cloned, and positional cloning showed a truncating mutation in patients with the syndrome (Matsuura *et al.*, 1998; Varon *et al.*, 1998). The gene product was designated 'nibrin' or p95 (Carney *et al.*, 1998).

Prior to its identification, nibrin/p95 was identified as part of a complex with four other components: hMre11 (Petrini *et al.*, 1995), hRad50 (Dolganov *et al.*, 1996) and two unidentified proteins of higher relative molecular mass. hMre11 and hRad50 are highly conserved between yeast and humans; in yeast, the phenotype of mutants includes hyper-recombination, sensitivity to DNA-damaging agents and DNA repair deficiency (Ajimura *et al.*, 1993; Game, 1993). This phenotype closely resembles that seen in Nijmegen breakage syndrome, suggesting that these patients have a defect in double-strand break repair. The hypothesis that hMre11 and hRad50 are involved in double-strand break repair is supported by the co-localization of these proteins in nuclear foci in response to breaks in DNA (Petrini *et al.*, 1995; Dolganov *et al.*, 1996). While Mre11, Rad50 and p95 co-immunoprecipitate as part of the same complex, Mre11 and Rad50 maintain a complex in the absence of p95 in cell extracts from patients with Nijmegen breakage syndrome, although radiation-induced foci are not evident.

These findings suggest that p95 is required for localization of the complex to damaged DNA. The hMre11–hRad50–p95 complex has magnesium-dependent single-strand DNA endonuclease and 5′→3′ exonuclease activities, which could be important in recombination, repair and genetic instability (Lieber, 1997). Since the homologue

of hMre11 in *Saccharomyces cerevisiae* has nuclease activity, it is likely that the corresponding human protein is responsible for these cleavages (Cao *et al.*, 1990).

Radiosensitivity is a uniform feature of Nijmegen breakage syndrome. The results of cytogenetic analyses by Conley *et al.* (1986), Taalman *et al.* (1989), Barbi *et al.* (1991) and Stoppa-Lyonnet *et al.* (1992), reviewed by Weemaes *et al*. (1994), showed that the percentage of chromosome 7 and 14 rearrangements was significantly higher in patients with this syndrome than in patients with ataxia telangiectasia. The hypersensitivity of cells from patients with Nijmegen breakage syndrome to X-rays and bleomycin was demonstrated by Taalman *et al*. (1983) and Jaspers *et al*. (1988). The D_0 values of the survival curves were of the same order as those reported for cells from patients with ataxia telangiectasia, and reduced inhibition of DNA synthesis after irradiation was noted. The basis for the radiosensitivy appeared to be distinct from that in cells from patients with ataxia telangiectasia, as fusion of these cells with cells from patients with Nijmegen breakage syndrome fully abolished the X-ray hypersensitivy of the former to cell killing (Jaspers *et al.*, 1988).

A defect in the S phase checkpoint in cells from patients with Nijmegen breakage syndrome was first described by Taalman *et al.* (1983), who showed that suppression of DNA synthesis by ionizing radiation was less effective in these cells than in control cells.

Abnormalities in the activation of the *p53*-inducible response to ionizing radiation have been documented in Nijmegen breakage syndrome cells, with a reduced response in fibroblast and lymphoblastoid lines after exposure to 5 Gy (Jongmans *et al.*, 1997). Studies of G_1–S cell-cycle progression in Nijmegen breakage syndrome cells after exposure to ionizing radiation produced conflicting results (Antoccia *et al.*, 1997; Jongmans *et al.*, 1997; Sullivan *et al.*, 1997; Tupler *et al.*, 1997; Yamazaki *et al.*, 1998), which may be due in part to differences in the cell types being studied. Increased accumulation in G_2 phase after exposure to ionizing radiation has also been reported (Seyschab *et al.*, 1992; Antoccia *et al.*, 1997; Jongmans *et al.*, 1997).

4.3.3 *Human severe combined immunodeficiency syndromes*

Bosma *et al.* (1983) first described a mouse mutant which had no detectable B or T lymphocytes. This severe combined immunodeficient (SCID) mouse was defective in recombination of the immunoglobulin heavy chain and *Tcr* genes and hypersensitive to ionizing radiation (Kim *et al.*, 1988; Biedermann *et al.*, 1991; Budach *et al.*, 1992), due to defective repair of double-strand breaks in DNA (Biedermann *et al.*, 1991), in which DNA protein kinase is involved (Blunt *et al.*, 1995; Araki *et al.*, 1997). To date, no human mutant in the catalytic subunit of DNA protein kinase has been described, but cell lines deficient in this protein and sensitive to radiation have been isolated from human tumours, including gliomas (Allalunis-Turner *et al.*, 1995). An extremely low level of ATM protein in these cells could also contribute to their radiosensitivity (Chan *et al.*, 1998), as dominant negative and anti-sense *ATM*

constructs led to sensitization of normal control cells as a consequence of decreasing endogenous levels of ATM (Morgan *et al.*, 1997; Zhang *et al.*, 1998).

Human SCID includes a spectrum of X-linked and autosomal recessive disorders characterized by abnormalities in cellular and humoral immunity (Rosen *et al.*, 1984; Puck, 1994). These syndromes include X-linked SCID, adenosine deaminase deficiency, Swiss-type agammaglobulinaemia and atypical syndromes, Omenn syndrome, purine nucleoside phosphorylase deficiency and immunodeficiency with short limb dwarfism. SCID is usually classified into two general groups according to the presence (B^+ SCID) or absence (B^- SCID) of B cells (Fischer, 1992). Some 70% of patients represent the former group. The incidence of classical SCID is between one in 5×10^4 and one in 7.5×10^4 births; the disease is detected by the occurrence of severe bacterial, viral and fungal infections and is fatal unless treated by bone-marrow transplantation. Some rare cases of SCID have been reported in which pre-B and mature B cells are absent (Ichihara *et al.*, 1988).

Little information has been reported on human SCID. Cavazzana-Calvo *et al.* (1993) described increased sensitivity to radiation of granulocyte macrophage colony-forming units in three patients without mature T or B cells and a twofold sensitization of the cells to X-rays. The D_0 value of the survival curve for fibroblasts from one of these patients was the same as that observed for granulocyte macrophages, indicating that the basis for the radiosensitivity overlapped with the immune defect. In the same study, increased sensitivity to radiation was also observed for granulocyte macrophages in a patient with Omenn syndrome, which includes a restricted T-cell repertoire and no B cells, but cell survival was normal in a patient with X-linked SCID who lacked only T cells. In a follow-up study, Nicolas *et al.* (1998) demonstrated increased sensitivity to ionizing radiation in fibroblasts and bone-marrow precursor cells in T^- B^- SCID patients. Sproston *et al.* (1997) described variable radiosensitivity of fibroblasts in a variety of SCID disorders. SCID strains were significantly more sensitive to radiation at both low- and high-dose rates. The cells most sensitive to radiation were from patients with T^- B^- SCID (D_0, 0.60 Gy), at a dose comparable to that reported by Cavazzano-Calvo *et al.* (1993). Lymphoblastoid cells from two patients with X-linked agammaglobulinaemia showed radiosensitivity equivalent to that of cells from patients with ataxia telangiectasia (Huo *et al.* 1994). Overall, SCID patients with no detectable B cells (30% of patients) are the most severely affected and have abnormalities in immunoglobulin gene rearrangements (Schwarz *et al.*, 1991; Abe *et al.*, 1994). These irregular rearrangements were subsequently shown to be due to mutations in the V(D)J recombinases RAG1, RAG2 or both in approximately 50% of B^- SCID patients (McBlane *et al.*, 1995; Akamatsu & Oettinger, 1998).

4.3.4 *Adverse responses to radiotherapy*

Severe chemosensitivity and acute radiation reactions were observed in a patient being treated for acute lymphoblastic leukaemia (Plowman *et al.*, 1990). Fibroblasts

from this individual were found to be indistinguishable from cells from patients with ataxia telangiectasia when exposed to ionizing radiation and were defective in repair of double-strand breaks in DNA (Plowman *et al.*, 1990; Badie *et al.*, 1995, 1997). The enhanced radiosensitivity was suggested to be due to a mutation in DNA ligase IV (Riballo *et al.*, 1999), as a patient was identified in whom DNA ligase was mutated in a conserved motif encompassing the active site. The defective protein was severely compromised in its ability to form a stable enzyme–adenylate complex. This individual, who appeared to be immunologically normal, had pronounced radiosensitivity, indicating that apparently normal individuals exist in the population who are radiosensitive due to a DNA-repair deficiency and may therefore be predisposed to leukaemia.

Individuals vary considerably in their ability to respond to radiation, as evidenced by the range of severity of the reactions of normal tissues of cancer patients exposed to radiotherapy; approximately 5% of patients show severe reactions (Norman *et al*., 1988; Ribeiro *et al*., 1993). Data on the survival of fibroblasts in culture have not predicted tissue sensitivity (West & Hendry, 1992; Budach *et al*., 1998); only the adverse effects of radiotherapy in patients with ataxia telangiectasia (Gotoff *et al*., 1967) were reflected in the hypersensitivity of the cells in culture to ionizing radiation (Taylor *et al*., 1975; Chen *et al*., 1978).

Chromosomal radiosensitivity has been observed in a number of syndromes characterized by a predisposition to cancer. Scott *et al*. (1998) drew attention to the importance of this characteristic as a biomarker for cancer, although sensitivity in these syndromes to various agents, including ionizing radiation, may not be the mechanism for cancer development. Using an assay to detect radiation-induced chromosomal damage in lymphocytes in G_2 phase, Scott *et al*. (1996) found that approximately 40% of an unselected series of breast cancer patients had elevated chromosomal radiosensitivity. Parshad *et al*. (1996) suggested that deficient DNA repair is a predisposing factor in breast cancer. When G_2/M cell-cycle arrest was determined 18–24 h after irradiation, lymphoblastoid cell lines from 22 of 108 breast cancer patients were shown to be radiation-sensitive (Lavin *et al*., 1994), and in a rapid assay for micronucleus formation in lymphocytes exposed to γ-rays with delayed mitogenic stimulation, 12 of 39 breast cancer patients and 2 of 42 controls were found to be hypersensitive to radiation (Scott *et al*., 1998). Thus, a substantial proportion of breast cancer patients showed cells that were sensitive to radiation *in vitro*. Severe clinical radiosensitivity, however, is observed in a considerably smaller proportion, approximately 5%, of breast cancer patients. Some of these patients may harbour a mutation in the *ATM* gene, particularly since there is substantial evidence that the sensitivity of at least some *ATM* heterozygotes to radiation is intermediate (Chen *et al*., 1978; Shiloh *et al*., 1986; Rudolph *et al*., 1989; Waghray *et al*., 1990; Lavin *et al*., 1992). No mutations were found in the *ATM* gene in 16 breast cancer patients with severe acute reactions to radiotherapy (Appleby *et al*., 1997) or in 15 patients who had developed severe late reactions to a standard radiotherapy schedule (Ramsay *et al*., 1998),

although the method used in the latter study would have missed up to 30% of non-truncating mutations, including missense mutations (Gatti, 1998). About 10% of *ATM* mutations are missense mutations. In this respect, it is of considerable interest that several rare allelic substitutions in *ATM* were observed in patients with various cancers but not ataxia telangiectasia (Vorechovsky *et al*., 1997). It is unclear whether these changes affect the function of the ATM protein in such a way as to influence either radiation sensitivity or cancer susceptibility.

4.3.5 *Tumour suppressor gene disorders*

(*a*) *Humans*

The term 'tumour suppressor gene' has been used to describe genes involved in growth control, differentiation and apoptosis, which undergo loss of function in the development of cancer (Stanbridge, 1990). Mutation in these genes would be expected to lead to a predisposition to cancer and a propensity to develop tumours in response to radiotherapy, but not necessarily to increased sensitivity of cells in culture.

(i) *Retinoblastoma*

Retinoblastoma is the most common intraocular malignancy in children and has served as the prototypic example of genetic predisposition to cancer (see Knudson, 1984; Newsham *et al*., 1998). Loss of one germ-line copy of *RB1* from all somatic cells predisposes to cancer in a dominant fashion because of the high probability of the loss of the remaining wild-type gene from a critical cell. It is estimated that 60% of cases are non-hereditary and unilateral, 15% are hereditary and unilateral, and 25% are hereditary and bilateral.

A significant proportion of children with the heritable bilateral form of retinoblastoma develop second cancers, most frequently bone and soft-tissue sarcoma. In an analysis of the treatment of 151 patients who developed a second neoplasm more than 12 months after the first, the second malignancy was considered to be associated with radiation in 61% of cases (Kingston *et al*., 1987). A dose–response relationship for the induction of bone and soft-tissue sarcomas in patients with the heritable form of the disease who were treated by radiotherapy has been documented. The relative risks for soft-tissue sarcomas showed a step-wise increase for all dose categories and were statistically significant at 10–29.9 Gy and 30–59.9 Gy. An increased risk for all sarcomas combined was evident at doses > 5 Gy, rising to 10.7-fold at doses ≥ 60 Gy ($p < 0.05$) (Wong *et al*., 1997). In a retrospective cohort study of mortality from second tumours among 1603 long-term survivors of retinoblastoma, follow-up was complete for 91% of the patients for a median of 17 years after diagnosis of the retinoblastoma. Of the 305 deaths, 167 were from retinoblastoma and 96 were from second primary tumours (relative risk, 30), with statistically significant excess mortality from second primary cancers of bone, connective tissue and malignant melanoma and benign and

malignant neoplasms of the brain and meninges. Radiotherapy for retinoblastoma further increased the risk of dying from a second neoplasm (Eng *et al*., 1993).

(ii) *Li–Fraumeni syndrome*

Li–Fraumeni syndrome is a rare disorder with a high penetrance in respect of a range of tumour types. It is often associated with a germ-line mutation in the *p53* tumour suppressor gene (Malkin *et al.*, 1990; Malkin, 1998). Patients with Li–Fraumeni syndrome or with a similar familial pattern of cancer are at increased risk for second cancers after irradiation, many of the neoplasms occurring in the irradiated field. Patients with familial patterns of cancer similar to those of the syndrome are found to form a significant fraction of those who develop bone sarcoma or acute leukaemia after radiotherapy for rhabdomyosarcoma (Heyn *et al*., 1993).

(iii) *Naevoid basal-cell carcinoma syndrome*

The carcinogenic effects of ionizing radiation in patients with naevoid basal-cell carcinoma syndrome were recognized more than 50 years ago when a five-year-old boy was reported to have developed more than 1000 pigmented basal-cell lesions in the irradiated field after radiotherapy for thyroid enlargement. DNA synthesis is abnormally rapid in X-irradiated cells from such patients, and it has been suggested that this might be related to the susceptibility to cancer after exposure to X-rays (Fujii *et al*., 1997). Taylor *et al*. (1975) and Stacey *et al*. (1989) reported no difference in survival between normal cells and those from patients with naevoid basal-cell carcinoma syndrome after exposure to γ-rays. Children with this syndrome who were treated for medulloblastoma developed multiple basal-cell carcinomas on irradiated skin (Atahan *et al.*, 1998; and see section 2.7).

(iv) *BRCA1 and BRCA2*

Mutations in a small number of highly penetrant autosomal dominant genes are responsible for approximately 5% of breast and ovarian cancers (Szabo & King, 1995; Stratton & Wooster, 1996; Easton, 1997). Mutations in two of these genes, *BRCA1* and *BRCA2*, lead to early-onset breast cancer (Futreal *et al*., 1994; Miki *et al*., 1994). In families with multiple cases of both breast and ovarian cancer, *BRCA1* mutations are primarily responsible for the disposition, while they make a smaller contribution in families with breast cancer only (Easton *et al*., 1993; Peto *et al*., 1996). The prevalence of *BRCA1* mutations has been estimated to be 1/800 in western populations and that of *BRCA2* to be less (Peto *et al*., 1996), although the prevalence can be as high as 1/100 in some inbred populations (Friend, 1996). The BRCA1 protein co-localizes in S-phase nuclei of human fibroblasts with Rad51 and interacts with this protein through a region encoded by exon 11 of *BCRA1* (Scully *et al*., 1997). It shares this property with BRCA2 (Sharan *et al*., 1997), which suggests that both proteins are involved in DNA repair and maintenance of genome integrity. In support of such a role, Gowen *et al*. (1998) demonstrated that *Brca1*$^{-/-}$ embryonic stem cells are defective in transcription-coupled repair of oxidative DNA damage and are hyper-

sensitive to ionizing radiation and hydrogen peroxide. Whether the sensitivity to ionizing radiation arises as a consequence of a defect in transcription-coupled repair or is due to defective strand-break repair through the Rad51 pathway or to a combination of the two remains unclear. Further evidence for a role of the BRCA1 protein in DNA damage repair was reported by Husain *et al*. (1998), who showed that *BRCA1* is overexpressed in a cisplatin-resistant breast cancer cell line (MCF-7) and that inhibition of *BRCA1* with antisense vectors increased the sensitivity, decreased the efficiency of DNA repair and enhanced the rate of apoptosis. Ramus *et al*. (1999) showed that *p53* mutations are significantly more frequent in ovarian tumours with mutations in either *BRCA1* or *BRCA2* than in controls. These results support a model of BRCA-induced tumorigenesis in which loss of cell-cycle checkpoint control coupled with inefficient DNA repair is necessary for tumour development.

(v) *Second tumours arising in response to radiotherapy*

Second malignant neoplasms occur at a higher frequency than expected after prior treatment with radiotherapy, particularly of childhood cancer (Tucker *et al.*, 1984; Hawkins *et al.*, 1987; de Vathaire *et al.*, 1989, 1999b). The studies of children with naevoid basal-cell carcinoma syndrome after being treated for medulloblastoma, discussed above, and other studies show that genetic background can influence the process of carcinogenesis in response to radiation. A case–control study has been reported in which 25 children from a cohort of 649 developed a second malignant neoplasm in response to radiotherapy during the period 1953–85. Children with one or more family relatives who had cancer had an odds ratio of 4.7 (95% CI, 1.3–17.1; $p = 0.02$) for a second malignant neoplasm when compared with children who had no family history of early-onset cancer. Thus, it is important to monitor children treated with radiotherapy, especially when there is a family history of early-onset cancer (Kony *et al.*, 1997).

(*b*) *Experimental models*

Several animal models have been used to mimic cancer-predisposing conditions in humans in which radiation is implicated as a tumorigenic agent. These include inbred strains susceptible to the development of tumours (Storer *et al.*, 1988) and animals with mutations in known tumour suppressor genes (Friedberg *et al*., 1998). In general, strains with a high spontaneous frequency of solid tumours also show an increased frequency of radiation-induced tumours (Storer *et al.*, 1988; Kemp *et al.*, 1994).

(i) pr53 *gene*

Mutation of the *p53* gene is among the most frequent genetic alterations in human tumours (Hainaut *et al.*, 1998). The TP53 protein is important in maintenance of a normal cellular phenotype owing to its involvement in cell-cycle control, as a promoter of DNA repair and programmed cell death (Ko & Prives, 1996). *pr53* knock-out mice provide a dramatic demonstration of the role of *pr53* in experimental

carcinogenesis: mice homozygous for a null *pr53* allele develop tumours at very high rates early in life, and the latent period for spontaneous tumours in *pr53* heterozygotes lies between that of the nulls and the wild types. The latent period for tumours in such mice can be significantly reduced by exposure to ionizing radiation (Kemp *et al.*, 1994), and the mice develop lymphoid tumours. The principal effect of *pr53* deficiency in the haematopoietic system of mice appears to be a constitutive abnormality that gives rise to an approximately 20-fold increase in the frequency of stable aberrations in *pr53* null mice and a 13-fold increase in *pr53* heterozygotes. The induction of stable aberrations was not increased by γ-rays, but *pr53* deficiency resulted in excess radiation-induced hyperploidy (> 10-fold the wild-type frequency) (Bouffler *et al.*, 1995).

(ii) *Murine adenomatous polyposis coli gene*

Min (multiple intestinal neoplasia) is a mutant allele of the murine *Apc* (adenomatous polyposis coli) locus that contains an *N*-ethyl-*N*-nitrosourea-induced nonsense mutation at codon 850 (Su *et al.*, 1992; Moser *et al.*, 1995). Heterozygosity for this mutation in the Min mouse is analogous to the genetic condition of familial adenomatous polyposis in humans (Joslyn *et al.*, 1991; Nishisho *et al.*, 1991), in that it predisposes to intestinal neoplasia. γ-Irradiation has been shown to increase the number of intestinal adenomas per mouse (Luongo & Dove, 1996; Ellender *et al.*, 1997). While these tumours were not observed in irradiated or untreated wild-type animals, the adenomas in the irradiated Min mice depended on the *Min* mutation, and the exposure caused chromosomal deletions involving loss of the *Apc* gene (Luongo & Dove, 1996).

(iii) *Eker rat*

The Eker rat strain is characterized by heterozygosity for a germ-line mutation in the *Tsc* 2 tumour suppressor gene, which predisposes this animal to spontaneous renal-cell carcinoma (Eker & Mossige, 1961). The corresponding mutation in humans is associated with tuberous sclerosis syndrome and leads to an increased incidence of renal cancers and of blastomas of the skin, heart and nervous system (Al-Saleem *et al.*, 1998). Exposure of Eker rats to 9 Gy of radiation caused an 11–12-fold increase in the incidence of renal tumours. When comparison was made with wild-type rats, the relative risk for developing renal-cell carcinomas after irradiation was 100-fold greater in the mutant animals (Hino *et al.*, 1993). This study has some deficiencies, however, because the wild-type animals were monitored for only 11 months, a short period for estimating life-time risk.

(iv) *Brca2*

Although disruption of the *Brca2* gene in mice led to embryonic lethality, it was possible to establish that *Brca2* expression is transient and largely embryo-specific, with transcripts particularly prevalent in tissues with a high mitotic index. Evidence that the Brca2 protein might be involved in repair of damage to DNA stems from its

ability to bind to the MmRad51 protein, a key component in the repair of double-strand breaks in DNA. Furthermore, homozygous mutants in these genes show developmental arrest at a similar stage, and their expression patterns are similar (Sharan *et al.*, 1997). In keeping with the radiosensitivity of *MmRad51*$^{-/-}$ embryos (Lim & Hasty, 1996), exposure of blastocysts from *Brca2*$^{-/-}$ embryos to 4 Gy of γ-rays led to complete ablation of the inner cell mass. It was not possible to distinguish between *Brca2*$^{+/-}$ and wild-type embryos. Because of the involvement of *Brca2* in DNA repair and the sensitivity to irradiation of *Brca2*$^{-/-}$ embryos, it will be of interest to determine whether heterozygous animals are susceptible to tumours.

4.4 Genetic and related effects

4.4.1 *Humans*

Evaluation of the hereditary effects associated with exposure of human populations to ionizing radiation has been a major concern of UNSCEAR. Many approaches have been used to formulate optimal predictions of the extent to which a given dose of ionizing radiation will increase the naturally occurring rate of mutation of germ cells in humans and how such an increase would affect the health of future generations.

(*a*) *Background radiation*

The cytogenetic effects of chronic exposure to ionizing radiation have been studied among populations in areas with high background levels of natural radiation (see section 2.5.1). A group of 100 women aged 50–65 years living in Yangjiang County, China, with an annual whole-body dose of 0.18–0.28 cGy were compared with a control group of 100 women living in an area where the annual whole-body dose was 0.06–0.09 cGy. Peripheral blood lymphocytes were collected from all of the women and analysed for the presence of chromosomal aberrations. Overall and for each category of stable and unstable chromosomal aberrations, women in the area with high background radiation had more detectable abnormalities. The increase was statistically significant for unstable aberrations (dicentrics and rings; $p < 0.04$) and for the combination of stable and unstable aberrations ($p < 0.02$) (Wang *et al.*, 1990b).

Similar results were obtained in another study in the same region among people in a wider age group (15–65 years). The frequencies of dicentrics and rings were significantly higher in lymphocytes of inhabitants of the area with high background radiation than those from the area with low background exposure ($p < 0.05$). A higher frequency of stable aberrations was also reported among students aged 15–16 years ($p < 0.01$), and higher frequencies of stable and unstable aberrations were again found among women aged 50–65 years ($p < 0.05$ for both categories) (Chen & Wei, 1991).

(*b*) *Survivors of the atomic bombings*

The data on the survivors of the atomic bombings of Hiroshima and Nagasaki indicate that acute irradiation at moderate doses has a negligible adverse effect on the health of subsequent generations. Any minor effect that may be produced is so small that it is lost in the background noise of naturally occurring mutational effects: an increase above this background has not been demonstrated even by the refined epidemiological methods that have been used over the last five decades (Neel *et al*., 1988; Neel, 1991; UNSCEAR, 1993). Information on the following types of adverse effect has been accumulated: untoward pregnancy outcome (congenital malformations, stillbirths and neonatal deaths); deaths among children before reproductive age (exclusive of those resulting from a malignant tumour); cancer before the age of 20; increased frequencies of certain types of chromosomal abnormalities (balanced structural rearrangements, abnormalities in sex chromosomes); increased frequencies of mutations affecting certain characteristics of proteins; altered sex ratios and impaired physical development of children.

Although some changes in these effects were noted in comparison with a control group, no statistically significant effect of parental irradiation has been found. The average combined dose of acute ionizing radiation to the gonads received by the parents was approximately 0.4 Sv (Neel *et al*., 1988, 1990), which is similar to the dose that has been estimated to double the frequency of genetic effects in mice. This suggests that humans may be less sensitive to the genetic effects of radiation than mice. When it was assumed that some of the mutations did indeed result from the exposure to radiation from the atomic bombings, a doubling dose of 1.7–2.2 Sv was calculated (Neel *et al*., 1990; Sankaranarayanan, 1996), whereas the doubling dose for severe genetic effects after long-term exposure was estimated to be approximately 4 Sv. The notion that ionizing radiation must have some genetic effect was strengthened by the observation of an increase in the frequency of chromosomal damage in the lymphocytes of atomic bomb survivors (Awa, 1997).

(*c*) *Chernobyl accident*

(i) *Effects in somatic cells*

The accident in 1986 at the Chernobyl nuclear power station in the Ukraine resulted in acute irradiation from external and internal exposure to ^{131}I, with a half-life of eight days, and then to more stable isotopes, mainly ^{137}Cs. Between 1986 and 1992, peripheral blood samples were obtained from 102 workers who were on the site during the Chernobyl emergency or arrived there shortly thereafter to assist in the clean-up of radioactive contaminants and to isolate the damaged reactor. Blood was also taken from 13 unexposed individuals. The samples were analysed by flow cytometry with the allele-loss somatic mutation assay for glycophorin A (see Langlois *et al*., 1986). The frequency of N/O variant red cells increased in proportion to the estimated exposure to radiation of each individual. The dose–response function derived for this

population closely resembled that determined previously for atomic bomb survivors whose blood samples were obtained and analysed 40 years after exposure (Langlois *et al*., 1993), which suggests comparable mutation induction per unit dose in these two populations and long-term persistence of the mutational damage. Measurements on multiple blood samples from each of 10 donors taken over seven years showed no significant change in N/O variant cell frequency, confirming the persistence of radiation-induced somatic mutations in long-lived bone-marrow stem cells (Jensen *et al*., 1995).

A group of children exposed to the ionizing radiation released during the Chernobyl accident had an appreciable number of chromosomal breaks and rearrangements several years later, reflecting the persistence of the radiation-induced damage. The results suggested that the children were still being exposed to radioactive contamination from foods and other sources (Padovani *et al*., 1993). In a follow-up study, 31 exposed children were compared with a control group of 11 children. All underwent measurements with whole-body counters and conventional cytogenetic analysis. The frequency of chromosomal aberrations in the exposed children was significantly greater than that in the control group, confirming the earlier report that a persistently abnormal cytogenetic pattern was still present many years after the accident (Padovani *et al*., 1997).

A group of 125 workers involved in the initial clean-up operation (called 'liquidators', exposed mainly in 1986) and 42 people recovering from acute radiation sickness of second- and third-degree severity were examined in 1992–93 for cytogenetic effects. Increased frequencies of unstable and stable markers of exposure to radiation were found in all groups, showing a positive correlation with the initial exposure even as long as six to seven years after the accident. In a study of the mutagenic effects of long-term exposure to low levels of radiation, cytogenetic monitoring was also conducted among children, tractor drivers and foresters living in areas of the Ukraine contaminated by radionuclides released after the Chernobyl accident. All groups showed significantly increased frequencies of aberrant metaphases, chromosomal aberrations (both unstable and stable) and chromatid aberrations, and the number of aberrations in the children's cells correlated to the duration of exposure (Pilinskaya, 1996; see also section 2).

(ii) *Heritable effects*

After the Chernobyl accident, germ-line mutations at human minisatellite loci were studied among children born in heavily polluted areas of the Mogilev district of Belarus (Dubrova *et al*., 1996, 1997, 1998a,b). Many tandem-repeat minisatellite loci have a high spontaneous germ-line mutation rate, which allows detection of induced mutations in relatively small populations. Blood samples were collected from 79 families (father, mother, child) of children born between February and September 1994 whose parents had both lived in the Mogilev district since the time of the Chernobyl accident. The control sample consisted of 105 unirradiated white families

in the United Kingdom, the children being matched by sex to the exposed group of offspring. The mutation frequency was found to be twice as high in the exposed families as in the control group. When the exposed families were divided into those that lived in an area with less than the median level of ^{137}Cs surface contamination and those that lived in more contaminated areas, the mutation rate in people in more contaminated areas was 1.5 times higher than that in those in the less contaminated areas. Since the blood samples for the control group were collected in the United Kingdom, it is conceivable that the increased mutation rate in the group in Mogilev might reflect intrinsic differences in minisatellite instability between these two white populations. It is also possible that the group in Mogilev was exposed to relatively high levels of other environmental contaminants, such as heavy metals, in addition to radioactive contamination.

(*d*) *Accident at Goiânia (Brazil)*

A ^{137}Cs radiotherapy source (51×10^{12} Bq) was abandoned at a private hospital and picked up by a scrap dealer in Goiânia, Brazil, who destroyed the source capsule, thus releasing the radioactive material. The highest individual dose from internally deposited ^{137}Cs was accumulated at an initial rate of 0.25 Gy h^{-1}. The most highly exposed group received doses of 4–7 Sv, one receiving up to 10 Sv. The collective external dose amounted to 56 person–Sv and the internal dose to 4 person–Sv. Four people died within six weeks; of 112 000 people monitored, 249 showed detectable contamination, and 129 of them were found to have internal contamination and were referred for medical care. In order to estimate the absorbed radiation dose, the initial frequencies of chromosomal aberrations (dicentrics and rings) were determined in 110 exposed persons (Natarajan *et al.*, 1991a,b; Ramalho & Nascimento, 1991; Ramalho *et al.*, 1991; Straume *et al.*, 1991), and some were followed cytogenetically in a search for parameters that could be used for retrospective radiation dosimetry. The frequencies of translocations detected years after the accident by fluorescence *in situ* hybridization were two to three times lower than the initial frequencies of dicentrics, the differences being larger at higher doses (> 1 Gy) (Ramalho *et al.*, 1995; Natarajan *et al.*, 1998; Ramalho *et al.*, 1998). *HPRT* mutant frequencies were also monitored in T lymphocytes of this population, but no convincing increase in the mutation rate was detected (da-Cruz *et al.*, 1996; Saddi *et al.*, 1996; da-Cruz & Glickman, 1997; Skandalis *et al.*, 1997).

4.4.2 *Experimental systems*

(a) Mutations in vivo

Mice have been the main source of information on the genetic effects of ionizing radiation in mammals. Estimates of the spontaneous mutation rates for various genetic end-points are listed in Table 41, and those of induced mutation rates per centigray for the same end-points are given in Table 42, for both high and low dose rates of low-

LET radiation. The results for visible recessive mutations (specific locus test) indicate a conversion factor of 3 for acute to chronic irradiation (Russell & Kelly, 1982). This is the factor that has often been used to account for the difference between acute and protracted doses in humans, although a factor of 5–10 could equally well be proposed in view of the data shown in Table 42. The main results given in the tables are summarized in the text below.

Table 41. Estimated spontaneous mutation rates (mouse, unless otherwise indicated)

Genetic end-point and sex	Spontaneous rate
Dominant lethal mutations	
Both sexes	2×10^{-2}–10×10^{-2} per gamete
Recessive lethal mutations	
Both sexes	3×10^{-3} per gamete
Dominant visible mutations	
Male	
Skeletal	3×10^{-4} per gamete
Cataract	2×10^{-5} per gamete
Other	8×10^{-6} per gamete
Female	8×10^{-6} per gamete
Recessive visible mutations (seven-locus tester stock)	
Male	8×10^{-6} per locus
Female	2×10^{-6}–6×10^{-6} per locus
Reciprocal translocations (observed in meiotic cells)	
Male	
Mouse	2×10^{-4}–5×10^{-4} per cell
Rhesus monkey	8×10^{-4} per cell
Heritable translocations	
Male	1×10^{-4}–10×10^{-4} per gamete
Female	2×10^{-4} per gamete
Congenital malformations (observed *in utero* in late gestation)	
Both sexes	1×10^{-3}–5×10^{-3} per gamete
Aneuploidy (hyperhaploids)	
Female	
Preovulatory oocyte	2×10^{-3}–15×10^{-3} per cell
Less mature oocyte	3×10^{-3}–8×10^{-3} per cell

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

Table 42. Estimated induced mutation rates per cGy (mouse, unless otherwise indicated)

Genetic end-point, cell stage and sex	Low-LET radiation (dose rate)	
	High	Low
Dominant lethal mutations		
Postgonial, male	10×10^{-4} per gamete	5×10^{-4} per gamete
Gonial, male	10×10^{-5} per gamete	2×10^{-5} per gamete
Recessive lethal mutations		
Postgonial, male	1×10^{-4} per gamete	
Gonial, male	1×10^{-4} per gamete	
Dominant visible mutations		
Gonial, male	2×10^{-5} per gamete	
Skeletal	5×10^{-7} per gamete	
Cataract	$5–10 \times 10^{-7}$ per gamete	
Other	$5–10 \times 10^{-7}$ per gamete	1×10^{-7} per gamete
Postgonial, female	$5–10 \times 10^{-7}$ per gamete	
Recessive visible mutations (specific locus test)		
Postgonial, male	65×10^{-8} per locus	
Postgonial, female	40×10^{-8} per locus	$1–3 \times 10^{-8}$ per locus
Gonial, male	22×10^{-8} per locus	7×10^{-8} per locus
Reciprocal translocations		
Gonial, male		
Mouse	$1–2 \times 10^{-4}$ per cell	$1–2 \times 10^{-5}$ per cell
Rhesus monkey	2×10^{-4} per cell	
Marmoset	7×10^{-4} per cell	
Human	3×10^{-4} per cell	
Postgonial, female		
Mouse	$2–6 \times 10^{-4}$ per cell	
Heritable translocations		
Gonial, male	4×10^{-5} per gamete	
Postgonial, female	2×10^{-5} per gamete	
Congenital malformations		
Postgonial, female	2×10^{-4} per gamete	
Postgonial, male	4×10^{-5} per gamete	
Gonial, male	$2–6 \times 10^{-5}$ per gamete	
Aneuploidy (trisomy)		
Postgonial, female		
Preovulatory oocyte	6×10^{-4} per cell	
Less mature oocyte	6×10^{-5} per cell	

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

(i) *Visible dominant mutations*

The mutations detected in the F_1 progeny of the irradiated generation comprise skeletal abnormalities, abnormalities of the lens (cataracts) and other dominant mutations.

The mutation rates for skeletal abnormalities in mice after single doses of X-rays were estimated to be 1×10^{-5} per gamete per cGy for spermatogonia and 3×10^{-5} per gamete per cGy for the post-spermatogonial cell stages (corrected for unirradiated controls) (Ehling, 1965, 1966). Another study showed a mutation rate in mouse spermatogonial cells of 2.3×10^{-5} per gamete per cGy induced by ^{137}Cs γ-rays (Selby & Selby, 1977) when the radiation was given in doses of 1–5 Gy separated by an interval of 24 h. This procedure is often used to increase the mutation yield while avoiding excessive cell killing (Russell, 1962).

In X- and γ-irradiated spermatogonia, the mutation rate for abnormalities of the lens was $3–13 \times 10^{-7}$ per gamete per cGy (Ehling, 1985; Graw *et al*., 1986). No difference was observed between single and split-dose exposure. The mutation rate in post-spermatogonial stages appeared to be two- to fivefold higher than that in spermatogonia.

Other dominant mutations include those that result in changes in growth rate, coat colour, limb and tail structure, eye and ear size, hair texture and histocompatibility. No significant increase in mutation frequency at histocompatibility loci was detected in irradiated sperm or spermatogonia (Kohn & Melvold, 1976; Dunn & Kohn, 1981). This result could indicate reduced mutability of these loci or a greater susceptibility for lethal mutations than expected on the basis of known mutation rates for visible recessive mutations in mice.

The spontaneous rate of visible dominant mutations other than skeletal abnormalities and cataracts is approximately 8×10^{-6} per gamete per generation (see Table 41). Protracted treatment with ^{60}Co γ-rays yielded a spermatogonial mutation rate of 1.3×10^{-7} per gamete per cGy (Batchelor *et al*., 1966). In X-irradiated female mice, the induced rates were between 5×10^{-7} and 10×10^{-7} per gamete per cGy for single doses of 2, 4 and 6 Gy (Lyon *et al*., 1979). Studies with a different marker stock suggested a mutation rate as high as 3×10^{-6} per gamete per cGy, after two doses of 5 Gy of X-rays at a 24-h interval (Searle & Beechey, 1985, 1986).

(ii) *Dominant lethal mutations*

Dominant lethal mutations are scored, essentially by their absence, in the F_1 progeny of an irradiated generation. Thus, a deficiency in the number of offspring is measured from conception to the time of weaning, i.e. as pre-implant or post-implant losses and reductions in litter size. Dominant lethal mutations are attributed to the induction of chromosomal aberrations that interfere with cell and tissue differentiation during fetal growth. These aberrations are generally eliminated during mitotic cell division and do not persist in stem-cell populations.

Post-gonial stage: In many studies, male mice were exposed to low-LET radiation at a high dose rate and mated during the first four to five weeks after exposure in order

to obtain offspring derived from germ cells exposed at the postgonial stage. In general, mutation rates of about 10×10^{-4} per gamete per cGy were reported (Ehling, 1971; Schröder, 1971; Grahn *et al*., 1979, 1984; Kirk & Lyon, 1984), while the control value was $0.025–0.1 \times 10^{-4}$ per gamete per cGy. At low dose rates of radiation, mutation rates of 5×10^{-4} per gamete per cGy were observed (Grahn *et al.* 1979).

Few data are available on the induction of dominant lethal mutations in irradiated female mice. In one study, the average mutation rate 1–28 days after irradiation was similar to that seen in the male mice, 10×10^{-4} per gamete per cGy (Kirk & Lyon, 1982). In guinea-pigs, rabbits and hamsters, the rate of dominant lethal mutations in males appeared to be lower than that in male mice, but those in females were similar (Lyon, 1970; Cox & Lyon, 1975).

Stem-cell stage: Dominant lethal mutations generally do not persist in stem-cell populations because of chromosomal imbalance; however, balanced chromosomal translocations can be transmitted during the proliferative phase of gametogenesis, and such gametes behave like dominant lethal mutations. The average rate of mutations induced in spermatogonia by low-LET ionizing radiation at a high dose rate was reported to be 9×10^{-5} per gamete per cGy (Lüning & Searle, 1971). The dose-rate effect for γ-rays is significant, as the mutation rate fell to 3×10^{-5} per gamete per cGy with weekly exposures from 1.4×10^{-4} per gamete per cGy with continuous low-intensity exposure (Grahn *et al.*, 1979).

(iii) *Recessive autosomal and sex-linked lethal mutations*

Reviews of the rates of recessive autosomal lethal mutations in mice showed an average of 1×10^{-4} per gamete per cGy (Searle, 1974; Lüning & Eiche, 1976), but no information was available on the effects of dose rate.

The rate of sex-linked lethal mutations was first determined after the detection of a large inversion of the X chromosome. Two doses of 5 Gy of X-rays at a 24-h interval to the spermatogonia of mice gave a mutation rate of 3.7×10^{-6} per X chromosome per cGy (Lyon *et al*., 1982).

(iv) *Visible recessive mutations*

Visible recessive mutations have been studied in the specific locus test (Russell, 1951) with seven stocks of mice bearing six coat-colour mutants and one structural (ears) mutant. Irradiated wild-type male or female mice are crossed with stock bearing these mutations, and new mutations at any of the marker loci are observed in the F_1 progeny. The spontaneous mutation rate in the tester stock is $8–8.5 \times 10^{-6}$ per locus, based on pooled data from the three principal laboratories where this test is conducted, for > 800 000 control F_1 mice. Most of the radiation-induced mutations examined at the molecular level appeared to be deletions (Bultman *et al*., 1991; Russell & Rinchik, 1993; Rinchik *et al*., 1994; Johnson *et al.*, 1995; Shin *et al*., 1997).

The mutation rates induced in spermatogonia when male mice were exposed to low-LET radiation at a high dose rate was $21.9 \pm 1.9 \times 10^{-8}$ per locus per cGy with

single doses of 3–7 Gy and $7.3 \pm 0.8 \times 10^{-8}$ per locus per cGy with 0.35–9 Gy of low dose-rate radiation (Russell & Kelly, 1982). In post-spermatogonial stages, the mutation rate reached $65–70 \times 10^{-8}$ per locus per cGy in progeny conceived four weeks after exposure of the male parent to 3 Gy of low dose-rate X-rays (Sega *et al*., 1978). The mutation rate was increased by fractionation of 1 Gy into two equal doses at a 24-h interval, but not by a larger number of fractions or a shorter interval (Russell, 1962).

The spontaneous rate of recessive visible mutations in female mice was estimated to be 1.4 or 5.6×10^{-6} per locus, depending on whether two or eight spontaneous events had been observed, as six events that occurred in one cluster could have been treated as one event (Russell, 1977). Exposure of mature oocytes to single doses of 0.5–6 Gy of X-rays at 0.5 Gy min^{-1} gave a mutation rate of 39×10^{-8} per locus per cGy in progeny conceived during the first week of exposure, whereas at lower dose rates values of $1–3 \times 10^{-8}$ per locus per cGy were observed. From these results it is clear that the dose-rate factor—the ratio of the mutation rates at high and low dose rates—for females is at least 10, whereas it is 3 for males (Lyon *et al*., 1979; Russell 1977; see Table 42).

(v) *Somatic mutations*

Mouse spot assay: X-Radiation induced somatic coat colour mutations in C57BL × NB mice in a pioneering study by Russell and Major (1957). In a somewhat more recent system, somatic mutations were induced when embryos heterozygous for five recessive coat-colour genes from the cross C57BL/6 J Han × T-stock were X-irradiated with 1 Gy (Fahrig, 1975). The controls consisted of irradiated embryos resulting from wild-type C57BL × C57BL matings, which are homozygous for the genes under study, and untreated offspring of both matings. The colours of the spots on the adult fur were due either to expression of the recessive genes or were white because of cell killing. Irradiated offspring of the C57BL matings had only white spots, which were always midventral. No spots were seen in untreated offspring of either mating. After correction for the white midventral spots observed in C57BL matings, the frequency of expression of a recessive colour gene after C57BL/6 J Han × T-stock matings was about 11% for embryos irradiated 11 days after conception and about 1% for embryos irradiated 9 days after conception.

Loss of heterozygosity: Genetic alterations that result in loss of heterozygosity play an important role in the development of cancer. The underlying mechanisms are mitotic recombination, mitotic non-disjunction, gene conversion and deletion (Smith & Grosovsky, 1993). Such events occur not only in genetically unstable cancer cells but also in normal human and mouse somatic cells (Hakoda *et al*., 1991a,b). The mechanisms of loss of heterozygosity have been studied in mice rendered heterozygous for the autosomal *Aprt* gene by gene targeting (Van Sloun *et al*., 1998), which allows the study of mutations in both the *Aprt* and X-chromosomal *Hprt* loci *in vivo*. $Aprt^{+/-}$ mice received up to 3 Gy whole-body irradiation with X-rays, and seven weeks later the *Hprt* and *Aprt* mutant frequencies were determined in the same splenic T-lym-

phocyte cell population. A dose-dependent increase was observed in *Hprt* mutant frequency, but that for *Aprt* was no different from that of controls, even though clear induction of mutations at the *Aprt* locus was observed after treatment with chemical carcinogens. Molecular analysis indicated that 70% of these mutations were caused by loss of heterozygosity. The hemizygous *Hprt* locus appeared to be a better target for the recovery of X-ray-induced mutants than the heterozygous *Aprt* locus. This result is unexpected, as X-rays induce predominantly multilocus deletions (Hutchinson, 1995), and deletion of an essential flanking gene from a hemizygous locus would be more detrimental for the cell. The results also suggest that loss of heterozygosity might not occur after ionizing irradiation, at least at the *Aprt* locus in mice (Wijnhoven *et al*., 1998).

(vi) *Minisatellite mutations*

Tandem repeat minisatellite loci in mice frequently have a high rate of germ-line mutations, and exposure to radiation increases the germ-line rate at a doubling dose comparable to that for other genetic end-points. The rate of induction cannot be explained by the occurrence of initial radiation damage within the minisatellite sequence, and suggests an unexpected mechanism involving radiation-induced damage elsewhere in the genome (Dubrova *et al.*, 1998a,b; Sadamoto *et al.*, 1994). Such minisatellite mutations have no known phenotypic effect or any direct relation to carcinogenesis. Their importance is that they illustrate the amplification of radiation-induced damage which results in the occurrence of mutation in a remote DNA sequence (Morgan *et al*., 1996; Little *et al*., 1997; see also section (c), below).

(vii) *Transgenic animals*

The development of transgenic mutagenesis systems has made it possible to study the mutagenic effects of ionizing radiation at both the molecular and the chromosomal level in the same animal. The responses of Big Blue® *LacI* transgenic mice to ionizing radiation were measured as induction of *LacI* mutations in the spleen. C57BL/6 Big Blue® transgenic mice were exposed to ^{137}Cs γ-rays at doses of 0.1–14 Gy and then allowed expression times of 2–14 days. Mutant plaques were analysed by restriction enzyme digestion. Of 34 mutations analysed, four were large-scale rearrangements, three of which were deletions within the *LacI* gene, while the fourth was a deletion that extended from within the α *LacZ* gene into downstream sequences. The other mutants did not involve major deletions (Winegar *et al*., 1994).

The Big Blue® *LacI* transgenic mouse reporter system was also used to investigate mutation induction in the testis, spleen and liver after whole-body irradiation of the mice with ^{60}Co γ-rays. The spontaneous mutation frequencies were $6–17 \times 10^{-6}$. No statistically significant induction of mutation was observed in testis or spleen 35 days after exposure, although the mutation frequencies tended to be increased by approximately 1.5-fold. In the liver, however, the mutation frequencies were elevated approximately 4.5-fold after exposure to 1 Gy of ^{60}Co γ-rays. When the data for all

organs were pooled, the mutation frequency was doubled, but no other significant increase was observed (Hoyes *et al*., 1998).

[The Working Group noted that neither of these systems would detect the large, multilocus deletions that constitute the predominant radiation-induced mutations in mammalian cells.]

(*b*) *Studies* in vivo/in vitro

The dynamics of the process of carcinogenesis and of the contribution of the initial carcinogenic insult to initiation and progression are difficult to study in intact animals and virtually impossible to study in humans. The main obstacles to understanding the fundamental processes involved in radiation-induced cancer in animal models until recently included the long latency and the complexity of the neoplastic process. In an effort to overcome these problems, animal models have been developed for the identification, isolation and characterization of radiation-altered or radiation-initiated cells from irradiated tissues shortly after exposure (Ethier & Ullrich, 1982; Clifton *et al*., 1986; Adams *et al*., 1987; Gould *et al*., 1987). These 'in-vivo/in-vitro' systems have been used to show that initiation of cells by ionizing radiation is a frequent event, of the order of 10^{-2}, which is much greater than would be expected if initiation were the result of a simple mutation. Subsequent analysis of initiated cells and detailed study of their progression led to the hypothesis that a critical early event in radiation-induced carcinogenesis is the induction of widespread genomic instability, which is apparent from increased cytogenetic damage and increased mutation rates in the progeny of irradiated cells many cell doublings after exposure (Ullrich & Ponnaiya, 1998). Support for this hypothesis comes from a number of observations.

In one model involving transplantation of mammary tissue or mammary cells into syngeneic hosts (DeOme *et al*., 1978; Medina, 1979), a differential effect of ionizing radiation was demonstrated on the growth of transplanted normal and hyperplastic mammary tissue (Faulkin *et al*., 1983).

In an assay to determine the effects of exposure to γ-radiation at 0.5 or 1 Gy and of the time that the cells remained *in situ* after the treatment, mammary epithelial cells were isolated from BALB/cAnNBd mice at various times between 24 h and 52 weeks after irradiation *in vivo* and assayed for the growth of epithelial foci *in vitro*. The cell populations that emerged had increased growth potential *in vitro* and enhanced tumorigenic potential with increasing time *in situ* (Adams *et al*., 1987).

In order to determine the radiation-induced transformation frequencies in sensitive BALB/C mice, in resistant C57BL mice and in resistant hybrid B6CF1 mice, independently of the host environment, ductal dysplasia was determined 10 or 16 weeks after injection of mammary epithelial cells from γ-irradiated (1 Gy from a ^{137}Cs source) donor mice into gland-free fat pads of recipient mice. The variations in radiation sensitivity of these mouse strains were shown to result from inherent differences in the sensitivity of the mammary epithelium to radiation-induced cell transformation (Ullrich *et al*., 1996).

Cells of the EF42 cell line, derived from the mammary tissue of a female BALB/C mouse four weeks after γ-irradiation (1 Gy from a ^{137}Cs source), become neoplastic with time *in vitro* and *in vivo*. Before acquisition of the neoplastic phenotype, however, multiple mutations occur in *p53*. This finding suggests that the mutations are not caused directly by the radiation treatment but arise several cell generations later as a consequence of radiation-induced genomic instability (Selvanayagam *et al*., 1995).

(*c*) *Cellular systems*

(i) *Genomic instability*

A characteristic of cancer cells is the presence of multiple mutations and chromosomal alterations. Although a single dose of ionizing radiation may induce a tumour, there is virtually no possibility that the changes needed to result in a malignant cell can be caused directly by a single exposure to the radiation. Nowell (1976) suggested that the chromosomal aberrations in cancer cells are associated with genomic instability. Loeb (1998) proposed that the acquisition of a mutator phenotype is central to cancer induction, in particular the genomic changes in tumour progression.

Radiation has been shown to induce genomic instability, a characteristic of which is the delay between exposure and the appearance of the effect, despite a number of mitotic divisions. Early observations of delayed heritable effects included small colony size of irradiated cells *in vitro* and a persistent reduction in the size of the cells that continued to grow *in vitro* (Sinclair, 1964).

The first report of delayed development of chromosomal aberrations was that of Weissenborn and Streffer (1988, 1989), who found that new aberrations were expressed in the second and third mitoses after exposure of one-cell mouse embryos to X-rays or neutrons. Pampfer and Streffer (1989) showed that irradiation of an embryo at the zygote stage induced genomic instability that later became apparent as chromatid and chromosome fragments in fibroblasts of fetal skin. In addition, delayed reduction in plating efficiency (Seymour *et al.*, 1986; Chang & Little, 1992) and delayed chromosomal alterations (Kadhim *et al.*, 1992, 1994, 1995; Marder & Morgan, 1993; Sabatier *et al.*, 1994) have been reported. Kadhim *et al.* (1992) found that α-particles were markedly more effective than X-rays in inducing delayed chromosomal aberrations in murine and human haematopoietic cells. In these experiments, 40–60% of the cells had chromosomal aberrations although only 10% of the surviving cells had been traversed by α-particles, indicating some indirect or 'bystander' effect. Marder and Morgan (1993) concluded that radiation-induced genomic instability probably results from deletion of a gene or genes responsible for genomic integrity.

Ponnaiya *et al.* (1997) showed that chromatid-type gaps and breaks appear in human epithelial MCF-10A cells as a delayed effect of irradiation. The aberrations were not found until about 20–35 cell population doublings after exposure to γ-rays.

The large number of cell doublings required to reveal genomic instability after exposure to X- or γ-rays may explain the reports of an absence of delayed chromosomal changes after exposure to low-LET radiation. There appears to be a LET-dependent difference in the time course of expression of radiation-induced genomic instability.

In mice, an association has been found between the probability of radiation-induced chromatid-type aberrations and susceptibility for induction of mammary cancer. Ullrich and Ponnaiya (1998) showed that BALB/c mice were more sensitive than C57BL/6 mice to induction of mammary cancer by radiation and also to the induction of delayed chromatid-type aberrations.

A possible role of genomic imprinting in the development of genomic instability and radiation-induced mutations was discussed by Schofield (1998). Genomic imprinting usually depends on post-replication modification of DNA, such as methylation, which regulates which of the two alleles of a gene is expressed or suppressed, depending on the gamete from which it was inherited. Thus, a cell becomes hemizygous for the expression of certain key genes. For example, in radiosensitive mice that are predisposed to gastroschisis, its induction is closely linked to a region on chromosome 7 in which a number of genes for imprinting are located. Genomic instability is thus apparently associated with the development of the malformation: it occurs only in the predisposed mouse strain and is transmitted to the next generation. Genomic instability therefore contributes to radiation-induced carcinogenesis and to other effects such as malformations.

The evidence for the induction by radiation of chromosomal instability is compelling, but the susceptibility of cell lines is clearly influenced by their genetic background. Neither the target, which appears to be large, nor the mechanism(s) of induction has been identified unequivocally. The probability of induction depends on the LET of the radiation; dose-dependence has been reported (Limoli *et al.*, 1999). Delayed appearance of *hprt* mutations has also been demonstrated after exposure to low-LET radiation *in vitro* in several systems (Little *et al.*, 1990; Harper *et al.*, 1997; Loucas & Cornforth, 1998).

The possibility that radiation-induced genomic instability contributes to radiation-induced carcinogenesis has important mechanistic implications. The characteristic delay between the event that initiates genomic instability and its expression is consistent with the long latent period between exposure to radiation and the appearance of a tumour. Better understanding of this phenomenon will be required before the implications of genomic instability for extrapolation of epidemiological findings to low-level exposures are fully understood.

(ii) *Cell transformation*

Ionizing radiation was one of the first agents to be used in cell transformation systems (Borek & Sachs, 1966), and there is now an extensive literature (reviewed by Hall & Hei, 1985; Kakunaga & Yamasaki, 1985; Hall & Hei, 1990; Suzuki, 1997). The initial studies were carried out with primary Syrian hamster embryo cells, a fibroblast

cell system that has the advantage that the effects of radiation on initial immortalization (or transformation) and the other changes required for neoplastic transformation can be studied. Because of technical problems with these primary cells, the C3H/10T½ cell line developed by Reznikoff *et al.* (1973a,b) has been used more extensively. Very high transformation frequencies were obtained in C3H/10T½ and C3H/3T3 cells when the frequencies were expressed per initial number of cells plated (Terzaghi & Little, 1976), indicating that even dishes with very few cells would eventually yield a neoplastically transformed clone. The actual neoplastic transformation process appears to be delayed and a change occurs in a large proportion of cells even after very low doses, so that there is a finite probability that one of their descendants will have a transformed phenotype (Kennedy *et al.*, 1980). This may be an expression of induced genetic instability, and its mechanism is still obscure.

Human primary cells have proven very difficult to transform neoplastically. Human keratinocytes (Rhim *et al.*, 1990, 1993) and bronchial cells (Hei *et al*., 1994) immortalized by SV40 and papilloma virus, respectively, have been used to study neoplastic transformation. These systems have the advantage that the cells are human and epithelial, but they are immortalized and therefore do not allow study of the initial change in the carcinogenic process.

In a human hybrid cell system, HeLa × skin fibroblasts, the appearance of transformed foci is associated with apoptosis which begins about eight days after irradiation. The authors suggested that the instability process has two relevant outcomes: induction of apoptotic death and neoplastic transformation of a small subset of survivors. These survivors were shown to have lost fibroblast chromosomes 11 and 14, and the authors suggested that tumour suppressor gene loci might be located on these chromosomes. The yield of transformants was found to be modulated by serum batch and this was correlated with the extent of delayed death, possibly reflecting altered expression of the induced genetic instability (Mendonca *et al.*, 1995, 1998a,b).

The results obtained with the human hybrid system can be as difficult to understand as those from earlier systems. For example, cells exposed to a dose of 1 cGy (which is too low to induce either cell killing or neoplastic transformation) and held for 24 h at 37 °C before plating, showed fewer transformants on subsequent incubation than unirradiated cells (Redpath & Antoniono, 1998). This confirmed an earlier result with a specific clone of C3H/10T½ cells (Azzam *et al.*, 1996).

Little work has been done to elucidate the type of initial radiation damage that leads ultimately to cell transformation. Obe *et al*. (1992) argued that double-strand DNA breaks are the critical lesion, citing the results of Zajac-Kaye and Ts'o (1984), who showed that application of DNase I in liposomes to Syrian hamster embryo cells led to foci of transformed cells that gave rise to tumours when injected into newborn hamsters, and the work of Bryant and Riches (1989) who treated C3H/10T½ cells with the restriction enzyme *Pvu*II in the presence of inactivated Sendai virus and observed that the cells became morphologically altered.

While cell transformation systems may be useful for revealing the potential of radiation to induce changes that may be associated with carcinogenesis, it is not clear how some of the observations obtained *in vitro* should be extrapolated to the situation *in vivo*.

(iii) *Chromosomal damage*

Three classes of chromosomal aberration are known to occur in somatic and germ cells: numerical aberrations, chromosomal breaks and structural rearrangements (Savage, 1976, 1979). Numerical and structural aberrations are associated with congenital abnormalities and neoplasia in humans. Numerical aberrations in germ cells occur as a result of nondisjunction during female gametogenesis. In normal somatic cells, the frequency of changes in chromosome number is low and difficult to estimate, but in cancer cells such changes are rather common (Holliday, 1989). A single-strand break induced before DNA replication gives rise to a chromosomal break at the following mitosis. When breakage occurs after the S phase or during G_2, it will be observed as a chromatid break, but many such breaks rejoin rapidly and go unnoticed. Single-strand breaks, both chromosomal and chromatid, are readily induced by ionizing radiation, and their number increases linearly with dose. Unrepaired breaks generally result in cell death in normal (as opposed to transformed) cells.

Structural chromosomal rearrangements are the result of inappropriate joining of radiation-induced breaks at one or more sites. They comprise simple unstable forms such as rings and dicentrics, simple stable forms including inversions, interstitial deletions and translocations, and also more complex combinations. The conventional assumption has been that two sites of radiation damage are necessary to produce simple exchange aberrations, either linearly with dose by a single track or proportional to the square of the dose by pairs of tracks (ICRP, 1991a; see also section 3.4, Overall introduction). Alternatively, some evidence suggests that simple chromosomal exchanges result from single tracks, due to recombination with undamaged DNA, and that multiple-track damage can lead to more complex chromosomal aberrations (Goodhead *et al.*, 1993; Chadwick & Leenhouts, 1998; Griffin *et al.*, 1998). The ability of X- and γ-radiation to induce all types of chromosomal damage has been documented extensively (see UNSCEAR, 1988; Committee on the Biological Effects of Ionizing Radiations (BEIR V), 1990; UNSCEAR, 1993). Dose–response curves for dicentrics, the most useful aberration for dosimetric purposes, were reported by Lloyd and Purrott (1981).

Although ionizing radiation induces more DNA single-strand breaks than double-strand breaks, several observations indicate that double-strand breaks of variable complexity are the major lesions responsible for the induction of chromosomal aberrations. Direct evidence that simple double-strand breaks can lead to chromosomal aberrations comes from experiments in which restriction endonucleases were introduced into cells. Although restriction enzymes produce only simple double-strand breaks (with blunt or cohesive ends), the induction of chromosomal aberrations was

efficient and the observed aberration patterns were similar to those induced by ionizing radiation (Bryant, 1984; Natarajan & Obe, 1984). The structural chromosomal aberrations seen at metaphase are of two types: chromosome-type aberrations and chromatid-type aberrations. Ionizing radiation induces chromosome-type aberrations in cells exposed in G_0 or G_1 phase of the cell cycle and chromatid-type aberrations in cells exposed in the S or G_2 phase (Savage, 1976).

Since human T lymphocytes have a long lifetime—a small proportion survive for decades—and the rate of replacement is rather slow, the frequency of structural chromosomal aberrations can serve as an indicator of the dose received by the exposed individual. In early work, the frequency of dicentric chromosomes at the first metaphase after stimulation of human T cells was determined. With the introduction of fluorescent *in situ* hybridization and chromosome-specific probes, it became possible to quantify the frequency of chromosomal translocations accurately (Natarajan *et al*., 1996), and these approaches were used to estimate past exposure during radiation accidents (see section 4.4.1; Natarajan *et al.*, 1991a,b; UNSCEAR, 1993; Natarajan *et al.*, 1998). The development of additional chromosome arm-specific probes as well as specific probes for telomeres allowed detailed analysis of the spectrum of ionizing radiation-induced chromosomal aberrations in humans cells *in vivo* as well as *in vitro* (Natarajan *et al.*, 1996; Boei *et al.*, 1997, 1998a,b).

(iv) *Mutagenicity*

Ionizing radiation has held a special place in mutation research ever since Muller (1927) demonstrated that X-rays induce hereditary effects in the fruit fly, *Drosophila melanogaster*. His was the first report on the induction of germ-cell mutations by a toxic, exogenous agent. Since that time, many studies have shown that ionizing radiation is mutagenic in essentially all experimental systems in which it has been examined (see extensive reviews of UNSCEAR, 1988; Committee on the Biological Effects of Ionizing Radiations (BEIR V), 1990; UNSCEAR, 1993).

In most mammalian systems, the predominant mutations induced by ionizing radiation are deletions, which range in size from extensive regions visible by microscopy to single nucleotides. Southern blotting, a technique used frequently for detecting deletions, is sensitive for deletions of more than about 100 nucleotides (Southern, 1975).

Base-pair substitution mutations have been shown to be induced by ionizing radiation in bacteria (Bridges *et al.*, 1967), mediated by the same SOS system that is involved in mutation induction by ultraviolet light and most other DNA damaging agents (Bridges *et al.*, 1968). The mutation rates at various loci ranged from 1.5×10^{-11} to 1.5×10^{-10} per cell per cGy. While such rates are readily measured in bacteria, mammalian cells are much more sensitive to the lethal effect of radiation; thus, a mutation rate of the order of 10^{-10} per cell per cGy would cause increases in the mutation frequency that are too small to be measured at doses at which cell survival is sufficiently good.

The first demonstration of the mutagenic action of ionizing radiation in mammalian cells was *Hprt* deficiency in Chinese hamster cells (Bridges *et al.*, 1970). The observation has since been confirmed and extended (for a review, see Thacker, 1992). Various mammalian somatic cell systems have been used to compare the spectrum of radiation-induced mutations with that of spontaneous mutations. The genetic loci most commonly used for mutation analysis in human cells are those encoding *HPRT* (Albertini *et al*., 1982), adenine-phosphoribosyltransferase (*APRT*; Grosovsky *et al*., 1986), a histocompatibility gene (*HLA-A*; Janatipour *et al*., 1988), thymidine kinase (*TK*; Yandell *et al*., 1990) and dihydrofolate reductase (*DHFR*; Urlaub & Chasin, 1980). Another method for detecting mutations in humans is an assay of loss of the allele for glycophorin A, a surface protein of erythrocytes (Langlois *et al*., 1986). Ionizing radiation does not significantly increase the frequency of ouabain-resistant mutants, which are believed to be due to base-pair substitutions (Thacker *et al*., 1978).

Depending on the test system used, 80–97% of the spontaneous *HPRT* and *APRT* mutations are base-pair changes. The percentages are only 50–60% at the *HLA-A* locus and 5–20% at the *TK* locus because mitotic recombination contributes substantially to the spontaneous mutation spectra at these loci. With a few exceptions, most radiation-induced mutations in cultured cells are deletions and other gross changes that are visible in Southern-blot patterns: at the *Hprt* or *HPRT* locus, mutations of this type constitute 70–90% of those in Chinese hamster ovary cells, 50–85% of those in TK6 human lymphoid cells and 50–75% of those in human T lymphocytes, and deletions constitute 60–80% of *TK* mutations in the TK6 cell line, 80% at the *HLA-A* locus in T lymphocytes and 100% at the *Dhfr* locus in Chinese hamster ovary cells. Of the radation-induced changes in *Aprt* in Chinese hamster ovary cells, only 16–20% consisted of deletions or other changes. Mutations that do not show aberrant Southern blot patterns may, of course, still be small deletions (Sankaranarayanan, 1991).

The results of a study in which *Hprt* and *Aprt* mutations were analysed after exposure of two Chinese hamster ovary cell lines ($Aprt^{+/-}$ and $Aprt^{+/0}$, respectively) to ionizing radiation strongly suggested that radiation-induced mutational events often consist of deletions of more than 40 kilobases (the length of the *Hprt* gene) and that the difference in the frequency at the two loci in the two types of cell lines was due to the presence of essential sequences close the respective target genes, a deletion of which would be lethal to the cell (Bradley *et al*., 1988).

Spontaneous and induced *Aprt* deficiencies were studied in the mouse P19H22 embryonal carcinoma cell line, which contains two distinct chromosome 8 homologues, one derived from *Mus domesticus* and the other from *M. musculus*. The cell line also contains a deletion for the *M. musculus Aprt* allele, which is located on chromosome 8. The large majority (> 95%) of the spontaneous and γ-radiation-induced mutants showed *Aprt* gene loss, indicating that relatively large deletions had occurred and that homozygosity for these regions is not a lethal event. Loss of heterozygosity for

adjacent markers was found to be a common event in cells with *Aprt* gene loss (Turker *et al.*, 1995).

In Chinese hamster ovary K1 cells and 10T5 cells, a K1 derivative containing the bacterial gene xanthine-guanine phosphoribosyl transferase *(Gpt)*, mutants were analysed at the *Gpt*, *Hprt* and *Tk* loci. After X-irradiation, the mutation rates at the *Tk* and *Gpt* loci were 8–10 times higher than that at the *Hprt* locus. The greater sensitivity of the *Tk* locus compared to that of the *Hprt* locus to mutation induction by ionizing radiation is likely to be due, at least in part, to the recovery of an additional class of mutants, possibly ones containing larger mutational events giving rise to small colonies. Approximately half of the X-ray-induced *Tk* mutants were small-colony mutants (Schwartz *et al.*, 1991).

Reduction of the radiation dose rate generally diminishes the severity of the biological effect per unit dose. The influence of dose rate on the mutagenicity of ionizing radiation has been investigated extensively in cultured cells. In his review, Thacker (1992) concluded that the results of studies in cells and animals indicated that a reduction in dose rate could reduce mutagenic effectiveness by a factor of 2–4, with some notable exceptions. Changing the dose rate of low-LET radiation had no effect in certain cell types, such as human TK6 cells and certain repair-deficient rodent cell lines or for certain types of mutation. Thacker (1992) concluded that, insofar as it was possible, there was no deviation from linearity in the dose–response relationship measured at low doses and low dose rates, but the errors were inevitably large in such measurements.

(v) *DNA damage*

Ionizing radiation may act directly on the cellular molecules or indirectly through water molecules. The high energy (typically megavolts) of an incident particle or electromagnetic wave ultimately results in a large number of small energy deposits (typically 60–100 eV), each of which provides energy for one or a small number of ionizations. As a result, electrons, charged and neutral radicals and non-radical species are generated. In aqueous media these are e_{aq}^-, $^\bullet H$, $^\bullet OH$, H_{aq}^+ and H_2O_2, and they react with nearby molecules in a very short time, leading to breakage of chemical bonds or oxidation of the affected molecules. The hydroxyl radical in particular is highly reactive and is also the most active mutagen generated by ionizing radiation.

The major effects of ionizing radiation on DNA are the induction of base damage, breaks of either single strands or both strands and more complex combinations. Double-strand breaks and damage of varying complexity are considered to be biologically more important because repair of this type of damage is much more difficult, and erroneous rejoining of broken ends may occur (see e.g. Sikpi *et al.*, 1992; Jenner *et al.*, 1993; Goodhead, 1994; Prise, 1994; Löbrich *et al.*, 1995, 1998). These so-called ‘misrepairs’ may result in mutations, chromosomal aberrations or cell death. The types, frequencies and extent of repair of these lesions depend on the dose, the dose rate and the LET of the radiation. Most cells can survive a dose of about 1.5 Gy low-

LET radiation, despite the fact that hundreds of DNA strand breaks are induced in each cell. This means that repair processes play an important role in the cellular response to radiation (see e.g. Cole *et al.*, 1988).

The active oxygen species produced when ionizing radiation interacts with water are comparable to those that are generated continuously by the metabolic processes of aerobic organisms. Double-stranded DNA breaks may be produced, but rarely, by the active oxygen species associated with metabolism. Instead, oxidative damage is induced in individual nucleotides. In some cases, this leads to the removal of a base, which results in an apurinic or apyrimidinic site. These sites, if not removed by the relevant endonuclease repair system, can be mutagenic because an incorrect nucleotide will be incorporated into the opposite strand (Schaaper *et al*., 1982).

Free radical-induced DNA damage associated with exposure to ionizing radiation may give rise to a number of oxidized purines, of which 7*H*-8-oxoguanine and 7*H*-8-oxoadenine predominate. In a detailed quantum-mechanical study to assess the tautomeric preferences of the bases in aqueous solution, the 6,8-diketo form of guanine and the 6-amino-8-keto form of adenine were the major species. The estimated free energies of hydration indicate that mutagenically significant amounts of minor tautomeric forms exist in the aqueous phase and may be responsible for induction of both transversion and transition mutations (Venkateswarlu & Leszczynski, 1998).

Minor oxidative lesions induced in DNA by exposure to ionizing radiation are 5-hydroperoxymethyl-2′-deoxyuridine and its decomposition products 5-hydroxymethyl-2′-deoxyuridine and 5-formyl-2′-deoxyuridine. The first compound was a more potent mutagen than the other two in *Salmonella typhimurium*, the TA100 strain being the most sensitive (Patel *et al*., 1992).

Because of the ubiquitous presence of nucleotide damage resulting from endogenously generated active oxygen species, living organisms have evolved a comprehensive array of DNA repair systems to deal with such damage (see Friedberg *et al.*, 1995). At low doses of radiation, the yield of active oxygen species would be small in comparison with those occurring spontaneously, and most of the resulting nucleotide damage (base damage and single-strand breaks) would be expected to be removed by repair processes. This is consistent with the accumulated evidence that multiple damaged sites, including double-strand breaks, are responsible for the effects of ionizing radiation on DNA (Goodhead, 1988; see also section 3.4, Overall introduction). Such damage presents a severe and often insurmountable challenge to the cellular repair systems. Because of the non-homogeneity of the energy deposition and the ensuing clustered damage, the effects of radiation are quite different from those induced by endogenously generated active oxygen species.

5. Summary of Data Reported and Evaluation

5.1 Exposure data

The greatest exposure of the general population to X-rays and γ-rays comes from natural terrestrial radiation. The next most significant source is the use of X-rays and radiopharmaceuticals in various diagnostic and therapeutic procedures. Exposures from the atmospheric testing of nuclear weapons have diminished, and only small contributions to the collective human dose are made by the generation of electrical energy by nuclear reactors, by accidental releases from nuclear facilities and radioactive devices and by occupational exposure during medical uses, commercial nuclear fuel cycles, nuclear industrial sources, military activities and the clean-up of nuclear or radiation accidents. The latter contributions are important, however, as they can result in significant exposure of groups of individuals.

The most important exposures to X- and γ-rays from the point of view of the determination of cancer risk in humans are from the past use of atomic weapons and from the medical uses of radiation.

With regard to the overall exposure of the population, the variation in individual doses over time, place and conditions of exposure makes it difficult to summarize mean individual doses accurately, although some indications are possible. Most exposures are measured in units of absorbed dose (Gy) in individual organs, but they are compared in units of effective dose (Sv) in order to account for effects in all the organs, which differ in radiosensitivity (and for differences in radiation quality when appropriate). The average annual effective dose from X- and γ-rays from natural sources is about 0.5 mSv, with elevated values up to about 5 mSv. Medical procedures in developed countries result in an annual effective dose of about 1–2 mSv, of which about two-thirds comes from diagnostic radiography. Possible exposures in medicine vary widely, however, ranging from several hundred millisieverts from frequent diagnostic procedures to several sieverts from therapeutic procedures. The annual effective doses to monitored workers are commonly in the range of 1–10 mSv.

5.2 Human carcinogenicity data

The carcinogenic effects of ionizing radiation in human populations have been studied extensively. Evidence for causal associations comes primarily from epidemiological studies of survivors of the atomic bombings in Japan and patients exposed to radiation for medical reasons. Epidemiological studies of populations exposed to lower doses of radiation were considered but were determined not to be informative for this evaluation.

In epidemiology, associations between exposure and disease are most often accepted as causal when there is consistency across many studies conducted by different investigators using different methods; when the association is strong; and when

there is evidence of a dose–response gradient, with risk increasing as the level of exposure increases. These three important causal criteria are satisfied for exposure to radiation and the induction of cancer.

Perhaps most important is that the association between radiation and cancer has been found consistently in many different populations exposed at different times and in different countries throughout the world. Among survivors of the atomic bombings in Hiroshima and Nagasaki, who were exposed primarily to γ-rays, excess numbers of cases of leukaemia and other cancers have been observed up to 45 years after exposure. Excess numbers of cases of leukaemia and other cancers have also been observed among patients treated with X-rays or γ-rays for malignant or benign diseases. Important evidence comes from studies of women in 15 countries who were irradiated for cervical cancer and persons who were irradiated for ankylosing spondylitis in the United Kingdom. Excess risks for cancer were also found among children irradiated for an enlarged thymus gland in the USA, for ringworm of the scalp in Israel and for skin haemangioma in Sweden. Increased numbers of breast cancers have been observed in patients in Canada and the USA who received frequent chest fluoroscopic X-rays for tuberculosis. There are well over 100 studies of patient populations in which excess numbers of cancers have been linked to radiotherapy. Pioneering medical radiologists practising shortly after the discovery of X-rays in 1895 had increased rates of leukaemia and other cancers in studies conducted in the United Kingdom, the USA and, later, in China.

Strong associations between exposure to radiation and several types of cancer have been reported. Exposure to radiation at sufficiently high doses has increased the risk of developing leukaemia by over fivefold. Even higher relative risks have been reported for thyroid cancer following irradiation during childhood. Greater than twofold increases in the risk for breast cancer have been seen after irradiation before the menopause.

Since in many studies the dose of radiation received by individuals was estimated with considerable accuracy, dose–response relationships could be evaluated. An increase in the risk for leukaemia with increasing dose was seen among atomic bomb survivors over a broad range of doses and among patients given radiotherapy for cervical cancer. Dose–response relationships for thyroid cancer have been demonstrated following irradiation in childhood for various conditions and among atomic bomb survivors. Dose–response relationships for breast cancer have been demonstrated among atomic bomb survivors, women treated for acute post-partum mastitis and benign breast conditions and patients who received many chest fluoroscopies. A dose–response relationship was also demonstrated for the combined category of all cancers among the survivors of the atomic bombings.

The level of cancer risk after exposure to X-rays or γ-rays is modified by a number of factors, in addition to radiation dose, including the age at which exposure occurs, the length of time over which the radiation is received and the sex of the exposed person. The level of cancer risk also varies with time since exposure. The sensitivity

of tissues to the carcinogenic effects of ionizing radiation differs widely. Cancers that appear to be readily inducible by X- and γ-rays include leukaemia, breast cancer in women exposed before the menopause, cancer of the thyroid gland among people exposed during childhood and some gastrointestinal tumours, including those of the stomach and colon. Some tissues in which cancer is induced only rarely or at relatively high doses include bone, soft tissue, uterus, skin and rectum. A number of cancers, such as chronic lymphocytic leukaemia, have not been linked to exposure to X- or γ-rays.

While there is some variation in the level of risk for specific cancers seen in epidemiological studies of populations exposed to X- and γ-rays, the consistency of the association, the strength of the association and the dose–response relationships all provide strong evidence that X-rays and γ-rays cause cancer in humans.

5.3 Animal carcinogenicity data

X-Rays and γ-rays have been tested for carcinogenicity at various doses and under various conditions in mice, rats, rabbits, dogs and rhesus monkeys. They have also been tested by exposure of mice and dogs *in utero* and by parental exposure of mice.

In adult animals, the incidences of leukaemia and of a variety of neoplasms including mammary, lung and thyroid tumours were increased in a dose-dependent manner with both types of radiation. When sufficient data were available over a range of doses and dose rates, the dose–response relationship was generally consistent with a linear–quadratic model, while lowering the dose rate resulted in a diminution of the quadratic portion of the curve. The effects of fractionation of the dose were highly dependent on fractionation size. Most importantly, low dose fractions were equivalent to low dose rates with respect to carcinogenic effectiveness.

Prenatal exposure of mice to X-rays in two studies and to ^{60}Co γ-rays in one study and of dogs to ^{60}Co γ-rays at late fetal stages resulted in significant increases in the incidences of lung and liver tumours in mice and malignant lymphoma, haemangiosarcoma and mammary carcinoma in dogs. Exposure at early fetal stages, however, did not increase the incidence of tumours in the offspring of either species. Parental effects in mice appear to depend on the strain tested. Parental exposure of mice of four strains to X-rays resulted in increased incidences of lung tumours and leukaemia in the offspring; however, studies with two other strains of mice showed no increase in the incidence of neoplasms.

5.4 Other relevant data

Exposure to radiation may result in effects on tissues and organs that are known as deterministic effects, which are distinct from cancer and genetic effects, known as stochastic effects. Deterministic effects increase in both incidence and severity with increasing dose and are not recognized below a threshold dose. The dose-dependent

increase in severity and the fact that the damage must reach a critical or threshold level to be detected distinguish deterministic effects from stochastic effects, for which, by convention for radiation protection purposes, there is no threshold and which do not increase in severity with increasing dose.

Deterministic effects, in general, result from cell killing. In the case of rapidly proliferating tissues, such as the gastrointestinal and haematopoietic systems, the effects may be early, occurring within a matter of days to a few weeks after high doses at high dose rates. Doses that kill critical numbers of clonogenic or stem cells may result in loss of the integrity of tissues and death. The loss of cells may be severe but not lethal, and in both cases the damage to these and other proliferating cell systems is reflected in clinical syndromes that result from impairment of organ function. Depending on the rates of cell renewal, radiation-induced damage is expressed at different times. In humans, death from damage to the gut may occur within about 10 days, whereas death from damage to the pulmonary system may occur only after six months. The information about deterministic effects comes from studies of humans exposed accidentally, to the atomic bombs or to radiotherapy. Much of the understanding of the underlying mechanisms and kinetics comes from studies in experimental animals. The need to understand deterministic effects led to studies of cell kinetics and the development of methods of studying cell survival and repair and the recovery of stem cells *in vivo* in the major tissues. Tissues affected early after exposure to radiation may also show late effects months or years after irradiation. Other tissues, such as those of the central nervous system and kidney, do not show effects until quite late after irradiation. Clinically, the former class of tissues is called ‘early responding’ and the latter, ‘late responding’.

The damage that appears late may result from lesions incurred at the time of exposure but which are not expressed for many months. If the cells are renewed slowly and die only when attempting mitosis, the timing of the critical damage reflects the cell renewal rate. The function of some cell populations is affected indirectly by damage to blood vessels and by the fibrosis that replaces damaged tissue.

The success of radiotherapy depends on the differential between the killing of cancer cells and of cells of normal tissues. Recovery of normal tissues depends on repair of sublethal damage and repopulation. Fractionation of the dose increases the probability of recovery of the normal tissue more than recovery of the cancer cells. The total dose, the dose per fraction and the interval between fractions influence the effect of fractionation. The probability of late effects is determined mainly by the dose per fraction. Lowering the dose rate also reduces the effect. The degree and time of expression of injury vary among tissues and organs, depending on the radiosensitivity of the stem cells, which varies by a factor of about 2, and cell renewal rates, which vary many-fold. Cell survival is influenced by many genes, especially those concerned with repair of sublethal damage and also by *p53*, a tumour suppressor gene. Data on cell survival are frequently fitted by the so-called linear–quadratic model.

In the two large populations that received total-body irradiation—the atomic bomb survivors and patients receiving bone-marrow transplantation—the rates of non-cancer adverse effects in a number of organs, including the lens, increased at about 1 Sv.

Radiation-induced deterministic effects were first reported in the skin, and effects such as erythema are still used as an indicator of individual patients' reponse to radiation.

When the radiation field is restricted, as in the case of radiotherapy, and the doses are fractionated, many tissues can maintain their integrity and function even when receiving total doses up to 20–30 Gy; however, the gonads, the lens of the eye and the developing brain are highly radiosensitive.

Cellular hypersensitivity to radiation is shown in several (primarily two) rare, heritable cancer-prone disorders of DNA processing, but evidence that such individuals are prone to radiogenic cancer is lacking. Some normal members of the general population, including persons heterozygous for the *ATM* gene, can be made more sensitive to cell killing and induction of chromosomal damage by exposure to radiation. There is no evidence that they are at increased risk for radiogenic cancer. Individuals heterozygous for tumour suppressor gene mutations would be expected to be hypersensitive to both radiogenic and spontaneous cancer, and this hypothesis is borne out by the results of several studies in humans and experimental animals.

The induction of chromosomal aberrations, particularly dicentrics, in human lymphocytes has been well established *in vitro* and has been used as a biological dosimeter in a variety of situations of exposure in which induction of aberrations has occurred. The persons exposed include inhabitants of areas with a high background level of natural radiation, survivors of the atomic bombings, workers involved in cleaning-up after the accident at the Chernobyl nuclear reactor in Chernobyl, Ukraine, and people accidentally exposed to a discarded source of ^{137}Cs in Goiânia, Brazil. An increase in the number of minisatellite mutations has been reported in the children of parents living in a region heavily polluted by the Chernobyl accident. The lack of availability of appropriate local controls and possible confounding by heavy metal pollution indicate that this result should be treated with some caution.

Most of the data available on effects in mammals come from experiments with mice. The effects of ionizing radiation can be divided into two categories: those in germ cells, which become visible in the offspring of exposed mice, and those in somatic cells, determined directly in the exposed animals. X- and γ-radiation induce dominant lethal mutations, recessive autosomal mutations and sex-linked recessive lethal mutations. The germ cells have been most extensively studied, and a clear picture is available of the sensitivity of the germ cells of male mice during the various stages of development. The rate of germ-cell minisatellite mutations in mice was increased after exposure to ionizing radiation, with a doubling dose comparable to that for other genetic end-points. Recessive coat-colour mutations were seen in mice when embryos were treated with X-rays *in utero* two and nine days after conception.

Mutations were also induced by ionizing radiation in somatic cells of exposed mice, both in endogenous genes (*Hprt* and *Aprt*) of T lympocytes isolated from the spleen and in transgenic mice carrying a marker gene in which mutation rates can be determined in all cells of the body, provided enough DNA can be isolated from the organ or cell type of interest. Ionizing radiation was reported not to induce loss of heterozygosity at the *Aprt* locus in mice.

A number of in-vivo/in-vitro systems have been developed in which mammary, thyroid and tracheal cells are isolated and examined after exposure of the whole animal or are exposed *in vitro* and introduced into the whole animal. Studies with these systems have shown that: (i) X- and γ-radiation initiate many more cells than tumours develop; (ii) strain differences in susceptibility for radiation-induced mammary cancers are related to the sensitivity of the cells more than to host factors; and (iii) the late changes in chromosomes and multiple mutations in the *p53* tumour suppressor gene associated with the development of neoplasms suggest that genomic instability is an early event induced by radiation.

Chromosomal aberrations, gene mutations and reduced plating efficiency have been shown to occur in various systems many cell generations after exposure to radiation, indicating the induction of persistent genomic instability.

Ionizing radiation induces neoplastic transformation *in vitro* in mammalian cells, including human cells. While this indicates a potential for carcinogenicity, it is not clear to what extent these observations made *in vitro* can be extrapolated to the situation *in vivo*.

Ionizing radiation induces gene mutations in a wide variety of cellular systems. The predominant mutations are deletions resulting in gene inactivation. Chromosomal aberrations are induced in all eukaryotic systems that have been examined.

Although ionizing radiation can give rise to many different types of nucleotide damage in DNA through the active oxygen species that it generates, double-stranded DNA breaks and more complex lesions are believed to be largely responsible for its biological effects.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of X-radiation and γ-radiation.

There is *sufficient evidence* in experimental animals for the carcinogenicity of X-radiation and γ-radiation.

Overall evaluation

X-radiation and γ-radiation are *carcinogenic to humans (Group 1)*.

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