

# The cancer epidemiology of radiation

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**Ionizing radiation has been the subject of intense epidemiological investigation. Studies have demonstrated that exposure to moderate-to-high levels can cause most forms of cancer, leukaemia and cancers of the breast, lung and thyroid being particularly sensitive to induction by radiation, especially at young ages at exposure. Predominant among these studies is the Life Span Study of the cohort of survivors of the atomic bombings of Japan in 1945, but substantial evidence is derived from groups exposed for medical reasons, occupationally or environmentally. Notable among these other groups are underground hard rock miners who inhaled radioactive radon gas and its decay products, large numbers of patients irradiated therapeutically and workers who received high doses in the nuclear weapons programme of the former USSR. The degree of carcinogenic risk arising from low levels of exposure is more contentious, but the available evidence points to an increased risk that is approximately proportional to the dose received. Epidemiological investigations of nonionizing radiation have established ultraviolet radiation as a cause of skin cancer. However, the evidence for a carcinogenic effect of other forms of nonionizing radiation, such as those associated with mobile telephones or electricity transmission lines, is not convincing, although the possibility of a link between childhood leukaemia and extremely low-frequency electromagnetic fields cannot be dismissed entirely.**

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## Introduction

Radiation is a generic term describing a flux of elementary particles, such as photons of light or electrons. When radiation interacts with biological matter, the resulting effect depends on the nature of the radiation, and this leads to two fundamental categories: *ionizing radiation* and *nonionizing radiation*. The energy of particles of ionizing radiation (e.g. X-rays and  $\alpha$ -particles) is sufficiently high that an electron can be removed from an atom or molecule with which the particle collides, creating an electrically charged ion

pair. This ionization can damage cellular DNA, either through a direct interaction between radiation and DNA or via the creation of chemically reactive free radicals. Such damage can lead to cell death, or to nonlethal DNA modification that is unrepaired or misrepaired. It is this nonlethal cell modification that can eventually lead to malignant disease. Nonionizing radiation (e.g. microwaves and extremely low-frequency electric and magnetic fields (ELF-EMF)) does not have enough energy to break chemical bonds and produce ionization. Optical radiation (ultraviolet, visible and infrared radiation) has sufficient energy to generate photoelectric excitation in biological media and consequent effects. The absorption of lower energy electromagnetic radiation in tissue results in the generation of heat and possibly other biological effects such as those related to resonant absorption frequencies and the enhanced passage of ions through cell membranes. However, with the exception of ultraviolet radiation (UVR) for which photochemical damage that may lead to skin cancer is established, any carcinogenic effect of nonionizing radiation has not been reliably demonstrated.

## Ionizing radiation

### Preamble

A nuclide (having an atomic nucleus composed of specific numbers of protons and neutrons in a particular configuration) is *radioactive* if it is unstable and transmutes in some characteristic period into a different nuclide with the emission of ionizing radiation. The *activity* of a radionuclide is the rate of radioactive decay and is measured in *becquerel* (*Bq*), where 1 Bq = 1 nuclear disintegration per second. The *absorbed dose* of ionizing radiation is the quantity of energy deposited by the radiation in a unit mass of matter and is measured in *gray* (*Gy*), where 1 Gy = 1 J/kg. Different types of ionizing radiation produce different ionization densities, ranging from sparsely ionizing radiations (e.g. X-rays,  $\gamma$ -rays and  $\beta$ -particles) to densely ionizing radiations (e.g.  $\alpha$ -particles and neutrons). The biological damage at the microscopic level relevant to the risk of subsequent development of cancer in humans is dependent on the ionization density of the specific type of radiation when it passes through tissue. Within the framework of radiological protection, ionization density is taken into

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account through the radiation weighting factor, which increases with the density of the ionization produced by the passage of a particle. The *equivalent dose* to an organ or tissue is the sum of each absorbed dose of a specific type of radiation (averaged over the organ or tissue) multiplied by the relevant radiation weighting factor, and is measured in *sievert (Sv)*. The radiation weighting factor for sparsely ionizing radiations is taken to be 1 so that, for these radiations, 1 Gy = 1 Sv, but this is not the case for densely ionizing radiations: e.g.  $\alpha$ -particles ( $^4\text{He}^{2+}$  nuclei) have a radiation weighting factor of 20, so 1 Gy = 20 Sv. The equivalent dose, therefore, is a measure of the risk of cancer developing in the human tissue in which the energy of the particular radiation is deposited.

Some tissues are more sensitive to the long-term effects of exposure to ionizing radiation than others. In radiological protection, this sensitivity is taken into account through the tissue weighting factor. The *effective dose* is the sum of all the tissue equivalent doses received by an individual each multiplied by the appropriate tissue weighting factor, and is measured in Sv. The tissue weighting factors are chosen so that the effective dose is equal in overall long-term risk to human health to a uniform whole body equivalent dose. The effective dose allows the appropriate addition and comparison of different radiations delivered to different parts of the body so that, for example, the adverse health impact of a dose to the lung delivered from the inhalation of  $\alpha$ -particle-emitting radon and its decay products may be directly compared with that of an X-ray computed tomography (CT) scan. Finally, some radiations (e.g.  $\gamma$ -rays and neutrons) penetrate deep into the body, so sources of these radiations external to the body pose a risk to internal organs and tissues. On the other hand,  $\alpha$ -particles travel only a very short distance in biological media and external fixed sources of this radiation present essentially no risk to health;  $\alpha$ -particle-emitting materials are of concern only if taken into the body (usually through inhalation or ingestion). Further information may be found in Publication 60 of the International Commission on Radiological Protection (ICRP, 1991a).

### Introduction

No other environmental carcinogen, with the possible exception of tobacco smoke, has been studied as extensively as ionizing radiation (Harvard Center for Cancer Prevention, 1996). It is beyond rational dispute that exposure to moderate and high levels of ionizing radiation can cause cancer, the epidemiological and experimental evidence for this being overwhelming (NRC, 1990; NCRP, 1993; NRPB, 1993, 1995; UNSCEAR, 1994, 2000; IARC, 2000, 2001; ICRP, 1991a, b). Studies have demonstrated that radiation can cause most forms of cancer, although it is a relatively weak carcinogen, partly due to the efficiency of radiation in killing cells – hence the effectiveness of radiotherapy. By way of illustration, the nominal excess lifetime risk coefficient for fatal cancer in a typical human population uniformly exposed to an acute high

dose of sparsely ionizing penetrating radiation is 10%/Gy (i.e. an average 10% additional probability of an individual in the exposed population developing fatal cancer over their lifetime after a homogeneous whole body dose of 1 Sv received at a high dose-rate) (ICRP, 1991a). This excess risk should be compared with the background lifetime risk of fatal cancer in a developed country such as the UK of around 25%. However, a whole body acute dose of 4 Gy of sparsely ionizing radiation will kill about half of the exposed individuals in a healthy adult human population within 60 days, so a substantial proportional increase in the risk of cancer from whole body acute exposure to radiation is precluded by early death from red bone marrow failure. Nonetheless, reasonable excess risks of cancer can occur if, for example, radioactive material that concentrates in certain tissues delivers a localized dose that is high but not sufficiently high to fatally compromise the function of that tissue through major cell-killing. Further, the excess relative risk (ERR) of certain cancers (e.g. leukaemia and thyroid cancer) after irradiation in childhood is high, but the background absolute risk is low so that the excess absolute risk (EAR) is comparatively small.

Exposure to ionizing radiation is ubiquitous. We are all constantly exposed to cosmic radiation and to  $\gamma$ -rays from naturally occurring radionuclides in the ground and building materials. Naturally occurring radioactivity is also present in food and drink. In general, the largest component of natural exposure arises from the inhalation of radon gas and its decay products. Natural background radiation delivers an average individual effective dose of about 2–3 mSv/annum and variations around the world of a factor of three are frequent, but it is not difficult to find areas with doses 10 times greater or more, mainly due to high levels of radon. To this natural background source must be added radiation from man-made sources. By far the largest component of anthropogenic radiation exposure comes from medical uses, with much smaller contributions from other sources such as nuclear weapons testing fallout, discharges from nuclear installations and miscellaneous uses of radiation (e.g. industrial radiography). Further information may be found in the 2000 Report of the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR, 2000).

*The Japanese atomic bomb survivors* Much of the detailed quantitative information on the risk of cancer arising from exposure to ionizing radiation is derived from the extensive studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in August 1945. Although the principal concern in the immediate aftermath of the bombings was the potential for a high level of heritable genetic effects in the offspring of these survivors, it is the excess risk of cancer among the survivors themselves that has proved to be the main long-term health effect resulting from radiation exposure during the bombings. It was in 1948 that a notable excess of leukaemia among the survivors was

first observed by alert clinicians (Folley *et al.*, 1952) and this was instrumental in the establishment of the Life Span Study (LSS). The Japanese national census of October 1950 allowed the identification of those individuals present in Hiroshima or Nagasaki (or, in a few unfortunate instances, both) during the atomic bombings. In this manner, a cohort study of Japanese survivors who were still alive in October 1950 was constructed and these survivors have been followed ever since in the LSS. The study consists of just over 93 000 persons, including almost all those survivors who were closest to the detonations. The responsibility for collecting, collating and analysing the data on the survivors and their children falls to a cooperative Japanese–US research organization based in Hiroshima and Nagasaki, originally called the Atomic Bomb Casualty Commission (ABCC), but since 1975 named the Radiation Effects Research Foundation (RERF).

The Japanese atomic bomb survivors are a large cohort of individuals of both sexes and all ages (although the number of healthy men in the age range of military service will have been reduced from the normal proportion) receiving a wide range of doses, which has been followed prospectively since 1950. The results from the LSS are of particular value because the individuals were not selected for exposure for a specific reason (e.g. a medical condition) – they just happened to be in the wrong place at the wrong time during a wartime attack on two cities using atomic weapons.

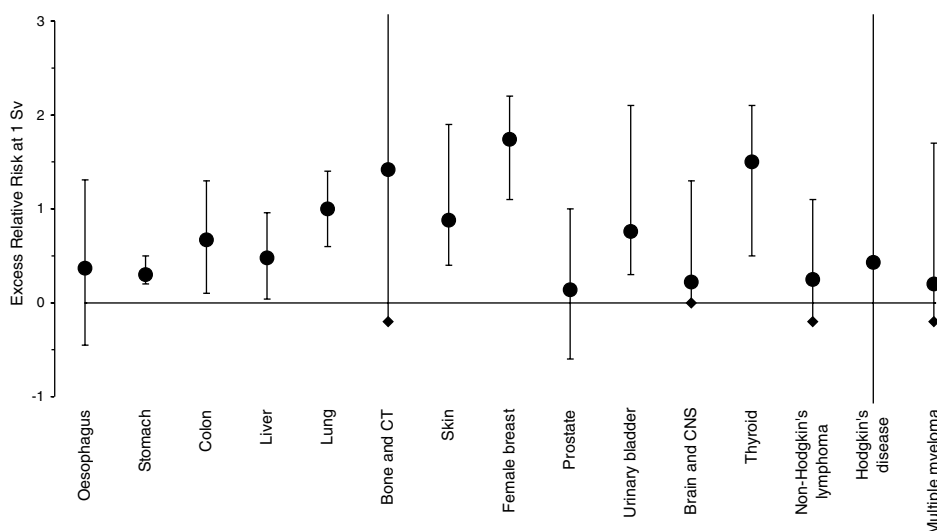
An important aspect of the Japanese studies is the effort that has been expended in reconstructing the doses received during the bombings. Each survivor was interviewed or responded to a questionnaire to determine his or her location during the explosions. Radiation source data from weapons tests in combination with sophisticated computational techniques for radiation transport and shielding, together with measurements of induced long-lived radioactivity in the environment, were used to determine the radiation dose to each organ of each survivor. The dosimetry system has undergone revision over the years and the latest revision has just been completed although it is not anticipated that substantial changes from the last, 1986, version (DS86) will occur (Straume *et al.*, 2003). The findings presented in this paper are based on the DS86 dosimetry system. Just over 86 500 survivors have DS86 doses assigned in the latest studies with an average dose of 0.28 Sv, and around 50 000 survivors have doses in excess of 5 mSv. It is commonly believed that the LSS is a study of the effects of high doses, and just over 2000 individuals did receive doses greater than 1 Sv, but the majority (~75%) of the nontrivially exposed survivors received doses less than 200 mSv (Pierce and Preston, 2000) – that is, less than the effective dose received by many people from natural background radiation over their lifetime.

The Japanese family registration (*koseki*) system permits effectively complete coverage of the vital status of LSS members, and underlying cause of death is obtained from death certificates. These mortality data are supplemented by cancer registration data obtained

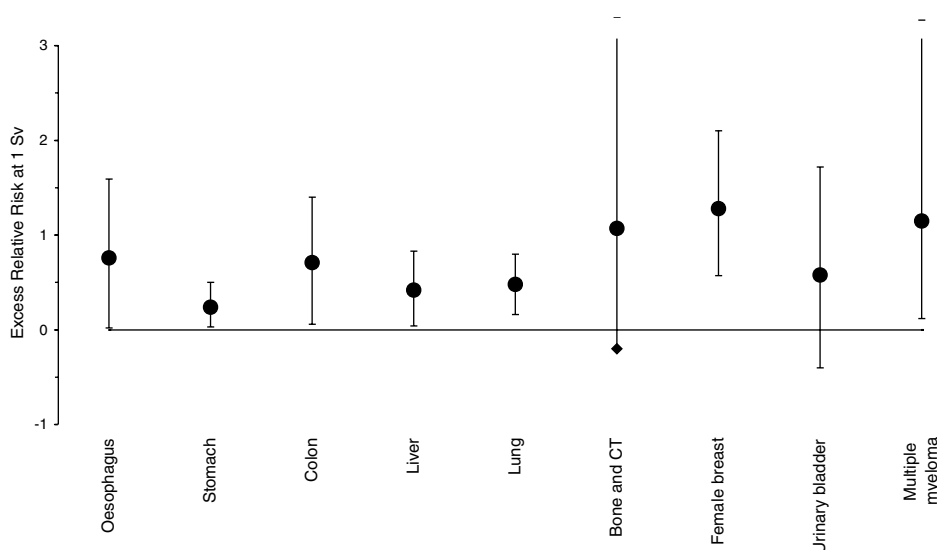
from specialist registries in Hiroshima and Nagasaki that allow cancer incidence to be studied for residents of the two cities from either 1950 (for leukaemia, lymphoma and multiple myeloma) or 1958 (for other cancers). The findings for cancer mortality and incidence are complementary and broadly consistent (Ron *et al.*, 1994). Pierce *et al.* (1996) studied mortality during the period up to 1990, while Preston *et al.* (1994) and Thompson *et al.* (1994) considered cancer incidence in the period up to 1987. The findings of these studies have been summarized in the 2000 Report of UNSCEAR. At the end of 1990, 56% of the survivors included in the LSS were still alive, so substantial information is still to flow from this cohort study, particularly for those exposed at young ages.

Figures 1 and 2 show the ERR at 1 Sv of, respectively, the incidence of, and mortality from, certain sites of cancer other than leukaemia for the LSS presented in the UNSCEAR (2000) report. These ERR values are summary statistics representing the average for all survivors (all ages and, in general, both sexes) over the entire periods of follow-up. Significantly elevated ERR are apparent for a variety of cancer sites, and the raised risks for female breast, thyroid and lung are particularly notable. Other sites of cancer, such as pancreas, rectum and uterus, show little indication of a raised risk at present; this may be due to a lower intrinsic sensitivity to radiation induction in combination with limited data. Leukaemia has been excluded from these figures because the ERR is materially greater than that for other cancers: the ERR at 1 Sv for leukaemia incidence is 4.4 (90% confidence interval (CI): 3.2, 5.6). It must be appreciated that the extraction of these risk estimates from the survivor data by the RERF scientists represents a considerable triumph for epidemiological analysis: of about 4700 cancer deaths that have occurred among the survivors during 1950–1990, only around 420 were in excess of expectation of which approximately 85 were due to leukaemia. Although the excess of leukaemia was readily apparent (because it was an ~50% excess that primarily occurred soon after the bombings), the <10% excess of other cancers has been spread out over the follow-up (many of the excess deaths occurring quite recently) and would not have been detected without sophisticated study design and data analysis, particularly the derivation of the trend in the increase of risk with dose. The Japanese survivor data have revealed a number of other features of the excess cancer risk resulting from exposure to radiation, and these will be considered for the main sites of radio-sensitive cancers below.

Most types of leukaemia were in excess, with the notable exception of chronic lymphoid leukaemia (CLL), which is rare in the Japanese population. The ERR of leukaemia is greater for females than males, and is especially pronounced at young ages at exposure. The most notable aspect of the pattern of excess risk concerns its expression with time since exposure – the excess risk is manifested as a wave that peaks within about 10 years of exposure and then subsides. For the survivors exposed as young children, the ERR



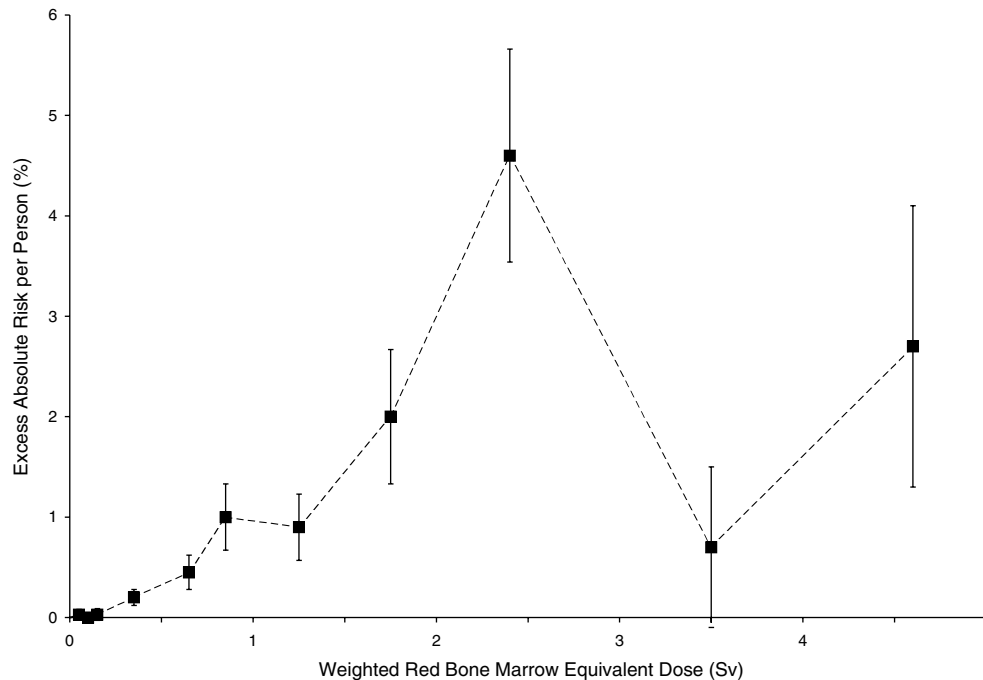
**Figure 1** The ERR at 1 Sv, and 90% CI, for the incidence up to 1987 of certain sites of cancer among the Japanese atomic bomb survivors (UNSCEAR, 2000) (◆ indicates that the lower 90% confidence limit is less than this value)



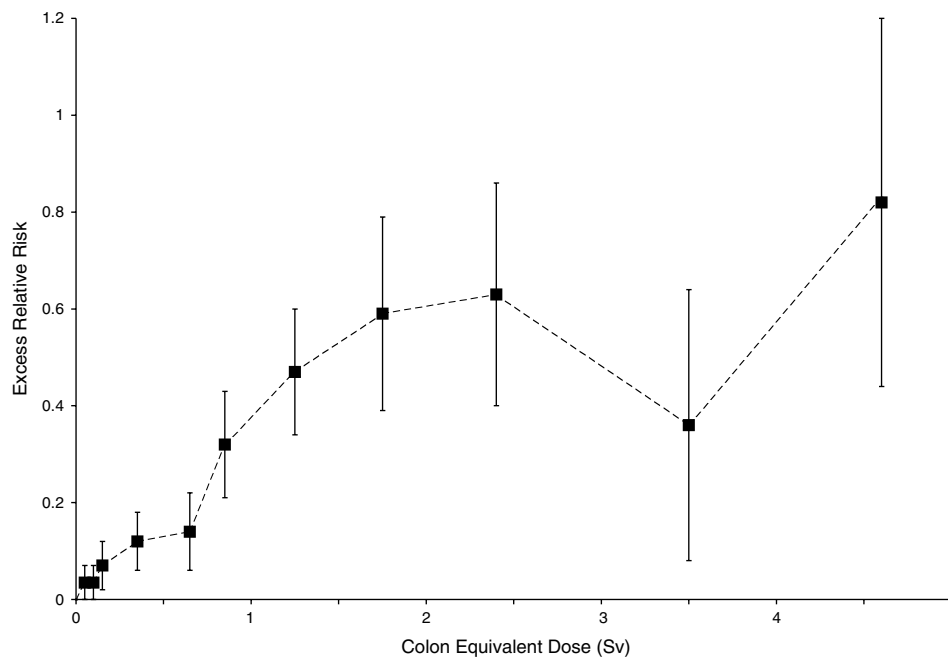
**Figure 2** The ERR at 1 Sv, and 90% CI, for the mortality during 1950–1990 from certain sites of cancer among the Japanese atomic bomb survivors (UNSCEAR, 2000) (◆ indicates that the lower 90% confidence limit is less than this value)

coefficient approached 100/Sv within the subsequent decade. Little *et al.* (1999) made a detailed analysis of excess risk by leukaemia type making use of the LSS and two large medical studies, and the results of this study will be discussed below. It must be borne in mind that the LSS was only established in 1950, so although there is ample evidence of an excess of leukaemia occurring before this date (Folley *et al.*, 1952) its magnitude cannot be calculated reliably. From other studies, the minimum latency for leukaemia would appear to be about 2 years (UNSCEAR, 2000). The dose–response for leukaemia mortality is shown in Figure 3. At high doses a significant downturn of risk occurs due to cell killing, but in the moderate-to-high dose region the curve is significantly sublinear (the slope increases with dose).

For cancers other than leukaemia considered as a whole (all solid tumours), the ERR after an initial latent period of 5–10 years has generally remained more or less constant over the period of follow-up, although an attenuation with time since exposure is apparent for those exposed at the youngest ages. The consequence of this approximately constant ERR is, of course, that the EAR reflects the large increase with age in the background absolute risk of cancer, and for those exposed at young ages most of the excess cases have only occurred recently in the follow-up, almost a half a century after the bombings. The ERR is higher for females than males, and greater for young ages at exposure. For solid tumour incidence during 1958–1987 the ERR at 1 Sv is 0.63 (95% CI: 0.52, 0.74) (Thompson *et al.*, 1994), and



**Figure 3** The variation of the EAR of leukaemia mortality per exposed person with the red bone marrow equivalent dose for Japanese atomic bomb survivors during 1950–1990 (Pierce *et al.*, 1996). Error bars show the standard error for each dose group

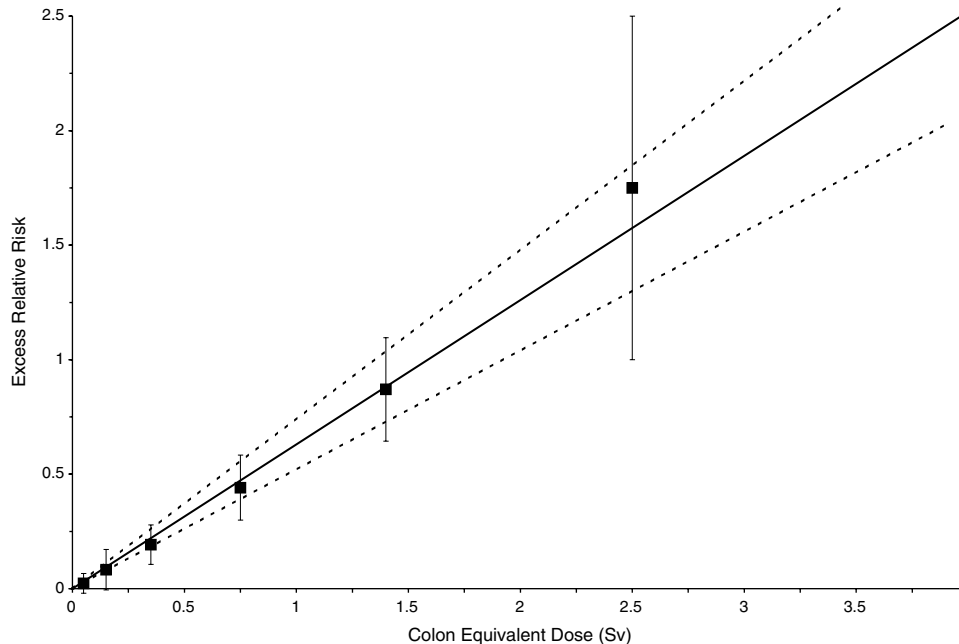


**Figure 4** The variation of the ERR of solid tumour mortality with the colon equivalent dose for Japanese atomic bomb survivors during 1950–1990, adjusted to males aged 30 years at exposure (Pierce *et al.*, 1996). Error bars show the standard error for each dose group

for mortality during 1950–1990 it is 0.40 (90% CI: 0.31, 0.51) (Pierce *et al.*, 1996). The dose–response for all solid tumours mortality (Figure 4) shows a marginally significant downturn of risk at high doses that is less pronounced than that for leukaemia. At moderate-to-

high doses (up to 4 Sv), the dose–response for the incidence of all cancers other than leukaemia is strikingly linear (Figure 5).

The latest study of solid tumour mortality in the LSS, covering 9335 solid tumour deaths during 1950–1997,



**Figure 5** The variation of the ERR of solid tumour incidence with the colon equivalent dose for Japanese atomic bomb survivors during 1958–1987 for the dose range 0–4 Sv (UNSCEAR, 1994). Error bars show the 95% CI for each dose group. The solid line is a linear fit to the data, with 95% confidence limits on the slope shown as dashed lines

has just been published (Preston *et al.*, 2003). Of the participants, 52% have now died, and it is estimated that 440 (5%) of the solid tumour deaths are due to radiation exposure during the atomic bombings, almost one-fifth of these occurring in the most recent 7 years of the 47-year follow-up. There is now a significant decrease of the ERR with increasing attained age for all ages combined, which has implications for lifetime risk estimates. The summary ERR at 1 Sv is now 0.47 (90% CI: 0.37, 0.57) for all solid tumours mortality.

For many of the specific sites of cancer other than leukaemia, the data from the LSS are insufficient to allow the derivation of a detailed picture of the variation of the excess risk with factors such as age at exposure and time since exposure. Certain solid tumours have been, however, the subject of particular investigations. Thyroid cancer was the first solid tumour to show a statistically discernible excess among the atomic bomb survivors (Hollingsworth *et al.*, 1963). The excess risk is most marked among, and almost wholly confined to, those exposed under the age of 20 years, the ERR at 1 Sv for this age at exposure group being 6.3 (90% CI: 5.1, 10.1) for incidence during 1958–1987 (UNSCEAR, 2000). Ron *et al.* (1995) conducted a comprehensive analysis of thyroid cancer incidence among a number of irradiated groups, including the LSS, and the results of this study will be considered below.

A radiation-related risk of lung cancer was also recognized early in the follow-up of the survivors and all the major types of lung cancer are now in excess (Thompson *et al.*, 1994). The principal challenge for RERF scientists is to disentangle the effect of cigarette smoking from that of radiation (and to explore their

possible interaction), particularly given the scarcity of cigarettes during the war and the marked increase in smoking among Japanese men in the post-war years. Recently, Pierce *et al.* (2003) reported the results of a study of 592 lung cancer cases during 1958–1994 among 45 113 survivors for whom information on smoking was available. They concluded that the joint effect of radiation and smoking was consistent with additivity, but not with multiplicativity, although the data are compatible with some submultiplicative interaction. The previously very low smoking relative risk is now at a level similar to that seen in the West. After adjusting for smoking, the average ERR coefficient is about 0.9/Sv, where the comparison is made with unexposed non-smokers. Adjustment for smoking removed a surprisingly high radiation ERR for females, and a puzzling positive trend of risk with increasing age at exposure, that is, in the opposite direction to that found for other solid tumours. Consequently, appropriate adjustment for smoking has produced a pattern of radiation-induced risk for lung cancer that is not greatly different from that of most other solid tumours.

Female breast cancer was also shown to be in excess early in the follow-up of the LSS. Tokunaga *et al.* (1994) studied breast cancer incidence during 1950–1985 and found a markedly increased risk among those exposed at a young age, the ERR at 1 Sv for ages at exposure <20 years being 2.41 (90% CI: 1.63, 3.44), which compares with that for ages at exposure >40 years of 0.48 (90% CI: 0.002, 1.28). For those exposed while under 20 years of age, there was a striking ERR at 1 Sv of 13.5 (90% CI: 4.4, 63.9) for early-onset breast cancer (an attained age of <35 years), leading Land *et al.* (1993) to suggest

the possible existence of a genetically susceptible subgroup. Land *et al.* (1994) noted that, among those exposed at a young age, a first full-term pregnancy at an early age subsequent to the exposure appeared to reduce the radiation-induced risk. Land *et al.* (2003) extended the study of Tokunaga *et al.* (1994) to cover 1059 incident cases of breast cancer (34 of them double primaries) diagnosed during 1950–1990. They demonstrated the importance of both age at exposure and attained age as modifiers of the excess risk, the risk declining with increasing attained age, by far the largest drop occurring at an attained age of around 35 years. Recently, Preston *et al.* (2002) have conducted a pooled analysis of breast cancer risk among eight cohorts, including the LSS, and the results of this study will be considered below.

Of other solid tumours, nonmelanoma skin cancer (NMSC) is of interest because the increased incidence has only been reported in the LSS comparatively recently (Thompson *et al.*, 1994), and because of the suggestion of substantial nonlinearity in the dose–response (Little and Charles, 1997). Ron *et al.* (1998) made a detailed study of skin cancer incidence among the bomb survivors during 1958–1987 and found a radiation-related risk of basal cell carcinoma that was most pronounced among those exposed as children. There was some suggestion of a departure from linearity in the dose–response, but no evidence of an interaction between ionizing and UVR.

The cohort of Japanese atomic bomb survivors has a number of desirable aspects as far as epidemiological inference is concerned and is considered to be the ‘gold standard’ in the generation of radiation risk estimates. However, the LSS consists of a malnourished wartime Japanese population, acutely and (in general) uniformly exposed to an external source of penetrating (mainly  $\gamma$ -ray) radiation and who survived the difficult first 5 years after the bombings. It has been suggested (e.g. Stewart and Kneale, 2000) that a ‘healthy survivor effect’ might lead to an underestimation of the risk to a general population, but there is little evidence for a large selection bias operating for late effects (Little and Charles, 1990; Little, 2002a). Nonetheless, it is pertinent to ask how risk estimates obtained from the Japanese survivors might be applied to, say, North American miners chronically exposed to radon and its decay products, a heterogeneous internal source of densely ionizing  $\alpha$ -particle radiation. To address the issues inherent in this question, such as the transfer of radiation-induced excess risks between populations with differing background risks, consideration must be given to the findings of the many other epidemiological studies of exposure to radiation under a variety of conditions that have been conducted.

*Medically irradiated groups* One such set of studies complementing the LSS concerns patients irradiated for therapeutic or diagnostic purposes. The results of these studies must be treated with care because the individuals were selected for exposure due to known or suspected

illnesses, often serious, and may not be representative of the population as a whole in their carcinogenic response to radiation. Further, therapeutic irradiation is designed to deliver high doses that kill the target cells, and the doses to other tissues are often not very well characterized and frequently distributed very heterogeneously within the body. Nonetheless, medical irradiation studies provide a valuable support to the findings of the Japanese survivor studies.

Two large medical irradiation studies are those of about 14000 ankylosing spondylitis patients treated with X-rays (Weiss *et al.*, 1994, 1995) and just over 80000 women treated for cervical cancer with X-rays and brachytherapy (Boice *et al.*, 1985, 1987, 1988). For the ankylosing spondylitis study doses were estimated for each case of leukaemia and a sample of the cohort, while in the cervical cancer study typical doses were assessed for the whole cohort and individual dose estimates obtained for a nested case–control study. Follow-up was long for both studies, although the patients were adults when treated and clearly were only women in the cervical cancer study. The results from these two studies are supplemented by those of a number of other medical irradiation studies, and 65 of these studies have been considered by Little (2001) in a comprehensive comparison of ERR coefficients derived from published information with the equivalent coefficients obtained from the Japanese atomic bomb survivor data. Relative risks tend to be lower in the medical series than in the bomb survivors, especially for leukaemia, but the cell sterilization effects of high doses can largely explain this difference (AGIR, 2000; Little, 2001).

Little *et al.* (1999) conducted a detailed pooled analysis of leukaemia data from the Japanese atomic bomb survivors, the ankylosing spondylitis patients and the cervical cancer patients. They found that distinct risk models were required for acute myeloid leukaemia (AML), chronic myeloid leukaemia (CML) and acute lymphoid leukaemia (ALL), but, importantly, that no significant differences between the three data sets existed when these leukaemia types were considered separately. For each model, the dose–response was best described by a quadratic curve in combination with an exponential term to account for cell killing at high doses. The models for the myeloid leukaemias (AML and CML) exhibit a reduction in the ERR with increasing time since exposure, while in the model for ALL the ERR decreases with increasing attained age, implying a decreasing ERR of ALL with increasing time since exposure and with increasing age at exposure. It must be recognized that data for exposure at young ages are confined to the atomic bomb survivors, which limits the analysis as far as age at exposure is concerned. Little *et al.* (1999) also found an absence of significantly elevated risks of CLL in the two medical series, a finding that is confirmed by other studies (UNSCEAR, 2000), indicating that CLL has low sensitivity to radiation induction.

A number of the medical irradiation studies are of specific interest because of features that shed light on particular aspects of radiation exposure. Ron *et al.*

(1995) conducted a pooled analysis of seven studies of thyroid cancer after external exposure to radiation (the LSS and six medical irradiation studies), including almost 60 000 irradiated individuals. They found the excess risk to be greatest for those exposed before the age of 15 years, the ERR coefficient being 7.7/Sv (95% CI: 2.1, 28.7), one of the highest risk estimates for any tissue. The raised risk of thyroid cancer reduced notably with increasing age at exposure, and effectively disappeared beyond an exposure age of 20 years. The excess risk among those exposed in childhood started to decline about 30 years after exposure.

North American studies of lung and breast cancer after multiple fluoroscopic examinations of the chest during pneumothorax therapy for tuberculosis (TB) are of interest because the dose was highly fractionated, so that the overall moderate-to-high dose consisted of many doses  $\sim 10$  mSv from each examination. These studies permit the investigation of the effect of different numbers of exposures (and, hence, overall doses) and the comparison with the effect of a single or limited number of acute exposures (Davis *et al.*, 1989; Boice *et al.*, 1991; Howe, 1995; Howe and McLaughlin, 1996; Little and Boice, 1999). No excess risk of lung cancer was detected in these patients, in contrast to the raised risk found in other medical irradiation studies and in the LSS, although the possible influence of the severity of TB must be borne in mind, both from the disease itself and its impact on smoking habits. For breast cancer, Little and Boice (1999) found scant evidence for a difference in radiation-induced risk estimates between the Japanese atomic bomb survivors and the Massachusetts TB fluoroscopy patients, noting that the difference in baseline risk between the two populations must be properly taken into account.

Recently, Preston *et al.* (2002) conducted a pooled analysis of breast cancer among eight large cohorts (the LSS and seven medical irradiation studies), including 1502 cases among about 35 000 exposed women. They found a linear dose-response with a downturn at high doses, and confirmed the importance of age at exposure and attained age in the determination of the risk of radiation-induced breast cancer. The authors concluded that EAR estimates are the best means of comparing radiation risks between populations having different background rates of breast cancer, implying additivity of radiation and important background risks. The excess risk was similar for acute and fractionated high dose-rate exposures, but that for low dose-rate exposures (the Swedish cohorts of individuals irradiated in childhood for skin haemangioma) appeared to be much smaller. Travis *et al.* (2003b), in their study of breast cancer after treatment for Hodgkin's disease at young ages, found that hormonal stimulation seems to be an important factor in the risk of radiation-induced breast cancer, and that the risk did not diminish at the highest doses or longest follow-up.

The stomach cancer mortality ERR coefficient of 0.20/Sv (95% CI: 0, 0.73) obtained by Carr *et al.* (2002) from a study of US patients irradiated for peptic ulcer to control gastric secretion is compatible with the estimate

of 0.24/Sv (95% CI: 0.10, 0.40) derived from the LSS. This finding is of particular interest given the 10-fold greater background rate of stomach cancer in Japan, and suggests a multiplicative interaction of risks. In a recent report of a study of skin cancer after irradiation in childhood for ringworm of the scalp, Shore *et al.* (2002) confirmed a strong association between basal cell carcinoma and exposure in childhood. However, unlike the findings of Ron *et al.* (1998) for skin cancer in the LSS, Shore *et al.* (2002) suggested that exposure to UVR was important as a cofactor because of the relatively low level of skin cancer among irradiated black patients. Studies of thyroid cancer following the medical administration of  $^{131}\text{I}$  have not discerned a prominent raised risk (e.g. Hahn *et al.*, 2001), but the great majority of the patients included in these studies are adults and the heightened sensitivity of the thyroid in children to radiation-induced cancer may not have been apparent in these studies (IARC, 2001; Dickman *et al.*, 2003).

Studies of those exposed for medical reasons have permitted the investigation of potentially increased carcinogenic radiosensitivity among certain subgroups. It is known that a few rare cancer-prone, human recessive genetic disorders (e.g. ataxia-telangiectasia) confer profound increases in radiosensitivity, but an important question is how great is the variation in radiation-induced risk among the general population. The relevant studies have been reviewed by ICRP (1998) and an enhanced carcinogenic radiosensitivity is apparent among those with a wider range of recognized genetic conditions, for example, an approximately fivefold excess of second primary cancers among irradiated bilateral (heritable) retinoblastoma patients relative to irradiated unilateral (nonheritable) retinoblastoma patients (Eng *et al.*, 1993). Particular attention has been paid to radiation-induced breast cancer risk among carriers of the ATM gene (ataxia-telangiectasia heterozygotes), given  $\sim \frac{1}{2}\%$  of ATM gene carriers in the population and reports of spontaneous breast cancer susceptibility among these individuals. However, there are uncertainties both in the strength of the association between ATM and spontaneous breast cancer and in the findings of those studies that have apparently indicated an increased radiosensitivity, although some enhanced risk cannot be discounted (ICRP, 1998). ICRP (1998) concluded that the increased carcinogenic radiosensitivity associated with familial cancer is likely to be around 10-fold as a summary statistic, but with a fairly wide range of uncertainty. While individual raised risks could be substantial, ICRP (1998) judged that materially elevated radiation-induced cancer risks would be experienced by only  $\sim 1\%$  of the general population.

Therapeutic irradiation studies also have the potential of investigating any interaction between radiation and chemicals since many patients are treated with a combination of radiotherapy and chemotherapy. In general, the combined carcinogenic risk has been found to be greater than additive (Travis *et al.*, 1996; de Vathaire *et al.*, 1999; Garwicz *et al.*, 2000), although this

is not always the case (Travis *et al.*, 2002) and complex combined effects (e.g. the effect of chemotherapy on ovarian hormones and the subsequent impact on radiation-induced breast cancer risk; Travis *et al.*, 2003b; van Leeuwen *et al.*, 2003) must be taken into account.

The diagnostic contrast medium Thorotrast is a thorium dioxide colloid that was injected intravenously for the purpose of angiography during the second quarter of the last century. The thorium is retained in cells of the reticuloendothelial system in the liver, spleen and bone marrow, which leads to long-term irradiation by densely ionizing  $\alpha$ -particles. The dosimetry of Thorotrast is complex, but organ-specific doses are high (typically 5–8 Sv/annum to the liver from  $\alpha$ -particles). About 5500 patients, mostly from Germany, have been followed and over 90% of them have died. A dramatic elevation (up to 100-fold or more) of liver cancer has been found and leukaemia is also in excess (IARC, 2001; NCRP, 2001a), and the excesses persist half a century after administration (Travis *et al.*, 2001, 2003a).

The carcinogenic risk from densely ionizing  $\alpha$ -particles may also be assessed from studies of two groups of German patients injected with  $^{224}\text{Ra}$  for the treatment of TB and ankylosing spondylitis during the 1940s and 1950s (Wick *et al.*, 1999; Nekolla *et al.*, 2000).  $^{224}\text{Ra}$  is a short-lived radionuclide that concentrates on the surface of the bone and although exact doses to the cells sensitive to the induction of bone cancers are difficult to calculate, the doses received were high (at around 600 and 100 Sv of  $\alpha$ -particle dose to the bone surface in the two groups, respectively). A clear excess (more than 100-fold) of bone cancer has been found in the higher dose group, which peaked about a decade after exposure and was greatest for young patients, with a smaller excess in the lower dose group. There are indications of much smaller increased risks of leukaemia (notably in the lower dose group), breast cancer and other solid tumours (IARC, 2001).

Finally, case-control studies of childhood cancer and obstetric X-ray examinations are of interest because the fetal doses ( $\sim 10\text{ mSv}$ ), received for diagnostic purposes, are appreciably lower than the doses received in most other studies of medical exposures. Childhood cancer is uncommon, affecting 1 in 600 children in the UK, but the ERR per unit dose is high potentially allowing large case-control studies to detect the effect of these acute low doses. By far the largest of these studies is the Oxford Survey of Childhood Cancers (OSCC; Bithell and Stewart, 1975) and this study shows a proportional increase in the risk of childhood cancer following an antenatal dose of 10 mSv of around 50%, this ERR being approximately equal for childhood leukaemia and other childhood cancers. This association is supported by other case-control studies conducted around the world (Doll and Wakeford, 1997). Interpretation of relative risks below two is always difficult because of the problems in accounting adequately for the influence of bias and confounding, but Doll and Wakeford (1997) concluded that the available evidence provides strong grounds for a causal explanation of the association.

**Occupational exposure** Those exposed to radiation in the course of their work provide another category of epidemiological evidence on radiation-induced cancer risk. Radiologists, radiographers and other medical staff are exposed as a result of their employment and medical workers provided one of the first pieces of reliable evidence that radiation increases the risk of leukaemia when in 1944 it was shown by March (1944) that there was an excess of leukaemia among early radiologists – evidence that predated the atomic bombings of Japan in 1945. The results of studies of medical personnel have been summarized by Carpenter (1990). Recently, Berrington *et al.* (2001) presented the results of 100 years of observation of British radiologists, which showed a significant 41% increase in the cancer mortality rate over that for all medical practitioners combined for radiologists registered with a radiological society for more than 40 years, and a significant trend of this rate with time since first registration. In a study of radiological technologists conducted in the USA, Mohan *et al.* (2003) found a marginally significant 28% increase in the rate of cancer mortality among those employed before 1940 relative to the rate for those employed after 1959, and a significant decreasing trend of the rate with later date of first employment. A similar pattern of breast cancer mortality was found for female technologists (Mohan *et al.*, 2002), and Sigurdson *et al.* (2003) have recently reported an excess of breast cancer incidence in this group. Wang *et al.* (2002a) examined cancer incidence among medical X-ray workers in China during 1950–1995 and found a significant 20% excess of cases in comparison with other medical specialists. A dose reconstruction exercise was carried out for workers employed in earlier years, which assessed the average dose accumulated by those employed before 1970 to be in excess of 0.5 Sv. The raised rate of cancer incidence was concentrated in these early workers receiving high occupational doses. Although the number of individuals occupationally exposed in a medical setting is large, doses were generally highest in earlier years when there was no monitoring of radiation dose at an individual level, requiring dose reconstruction from a knowledge of working practices over many years with its inevitable uncertainties. The absence of individual dose records is a major obstacle in deriving accurate risk coefficients from studies of medical workers who received the highest exposures.

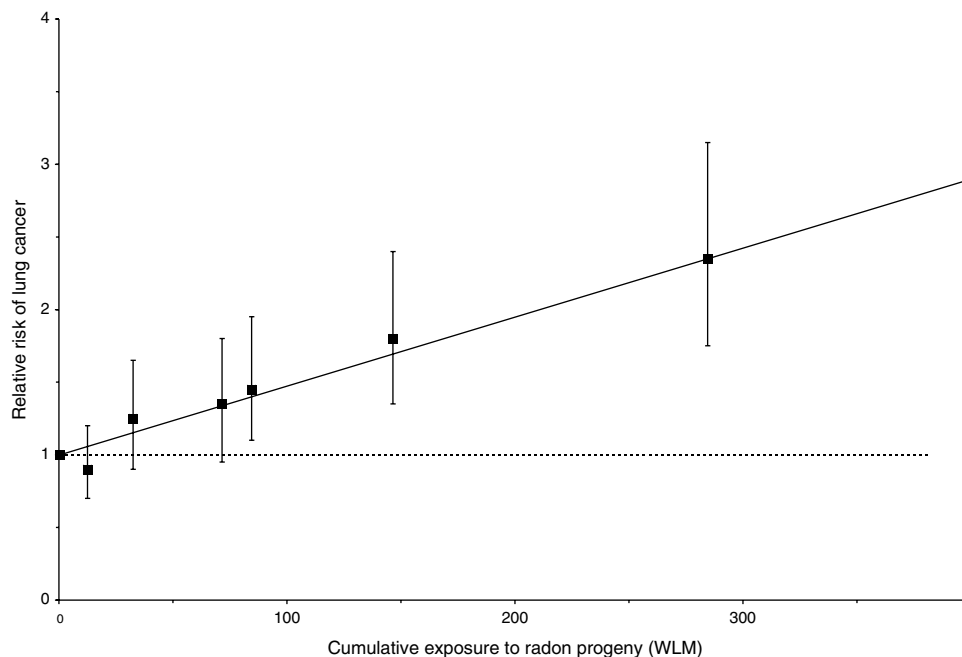
People, mainly women, employed in the first half of the 20th century to apply luminous paint to watch and instrument dials inadvertently ingested the radium-based paint. Radium (in this instance,  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$ ) concentrates in the bone and there is a large excess (approaching 100-fold) of bone cancer deaths among around 4800 luminizers in the USA with high intakes of radium (UNSCEAR, 1994; Fry, 1998). There are difficulties in deriving accurate doses from  $^{226}\text{Ra}$  and  $^{228}\text{Ra}$  to the cells sensitive to the induction of bone tumours, so risk estimates can only be crude. Radium exposures experienced by luminizers in the UK were much lower and just one bone cancer death was observed among these women, although only 0.17 death

was expected (Baverstock and Papworth, 1989). The US luminizers also experienced an large excess of cancer of the paranasal sinuses and mastoid air cells, which is attributed to exposure to radon and its radioactive progeny liberated during the decay of  $^{226}\text{Ra}$  deposited in the bone (UNSCEAR, 1994). There is also some evidence of an excess risk of breast cancer in the luminizers (Adams and Brues, 1980; Baverstock and Papworth, 1989), which may be due to enhanced external irradiation from the pots of paint situated in front of the women (UNSCEAR, 1994).

Underground hard rock miners (e.g. uranium, tin and iron ore miners) are exposed to raised levels of radon and its decay products, and in earlier years the  $\alpha$ -particle dose to the bronchial epithelium of some of these miners was very high. Epidemiological studies of underground hard rock miners around the world have demonstrated an unequivocal and marked radon-related risk of lung cancer. The excess risk of lung cancer broadly increases linearly with cumulative radon exposure (Figure 6) and it is notable that the doses received at low occupational exposures approach those experienced residentially in high background radon areas. Sophisticated analyses of the combined data from these miner studies have allowed detailed risk models for radon-induced lung cancer to be derived, which take into account factors such as time since exposure and exposure rate (Lubin *et al.*, 1995, 1997; NRC, 1999). The analysis of pooled data from 11 cohorts of underground hard rock miners includes around 2700 lung cancer deaths among about 68 000 miners (Lubin *et al.*, 1995). Lubin *et al.* (1997) focused on miners with low occupational radon exposures, comparable to high domestic exposures,

and found an overall ERR of 0.012/WLM (95% CI: 0.002, 0.025) (where WLM, working level month, is a measure of cumulative radon exposure in mines). The Committee on Health Risks of Exposure to Radon (NRC, 1999) found that the radon-induced lung cancer risk decreases with increasing time since exposure, decreases with increasing attained age and increases with decreasing exposure rate (although this last modifying factor only applied to higher cumulative exposures among the miners). The influence of cigarette smoking, the dominant risk factor for lung cancer, on the risk of exposure to radon has been difficult to determine because of the high prevalence of smoking among miners; however, it would appear that the risk from smoking and that from radon produce a combined risk that is more than additive and somewhat less than multiplicative (NRC, 1999). The seemingly stronger interaction between smoking and radiation among the miners than that found among the Japanese atomic bomb survivors may be due to the different conditions of irradiation (Pierce *et al.*, 2003). In a study of lung cancer among nonsmoking uranium miners, Gilliland *et al.* (2000) found the same general pattern of risk as that obtained from broader miner studies. Little (2002b) has shown that the patterns in the ERR of lung cancer are similar if the (male) Colorado Plateau uranium miners are compared with male Japanese atomic bomb survivors. The studies of underground hard rock miners have not revealed an excess risk of cancers other than lung cancer (Darby *et al.*, 1995).

Air crew and air couriers receive enhanced doses due to their increased exposure to cosmic radiation at high altitudes, although the increase amounts to just a few



**Figure 6** Relative risk of lung cancer mortality by cumulative exposure to radon decay products (in WLM), and fitted adjusted linear ERR model, from the combined data from 11 cohorts of underground hard rock miners with the exposure limited to <400 WLM (Lubin *et al.*, 1995). Error bars show the 95% CI for each exposure group

millisieverts per annum and it is very unlikely that the consequent increased risk could be detected (Boice *et al.*, 2000). Nonetheless, there have been reports of raised levels of cancer in air crew (e.g. Gundestrup and Storm 1999), which has led to larger studies being carried out (e.g. Band *et al.*, 1996; Nicholas *et al.*, 1998). Reasonably accurate individual doses may be computed from a knowledge of flight histories and cosmic radiation measurements. The results of these studies are not straightforward in interpretation since extraneous factors related to the unconventional lifestyle of air crews must be taken into account (Boice *et al.*, 2000). Those large studies that have been reported recently (Blettner *et al.*, 2003; Zeeb *et al.*, 2003; Langner *et al.*, 2004) have not found unexpected radiation-related risks. (It is of interest that enhanced levels of cosmic radiation are of particular concern for extended space flights, and considerable work has been carried out in assessing the doses likely to be received in a manned expedition to Mars (e.g. Simonsen *et al.*, 2000).)

The large numbers of workers who are, or have been, employed in the nuclear energy and weapons industries are an especially suitable group for the epidemiological study of protracted exposure to radiation at low dose-rates. It is usually the case that dose records exist for nuclear industry workers, and that personal information is sufficiently detailed to allow unambiguous follow-up to identify cause of death and, in some instances, cancer registration. At the predicted low levels of excess cancer risk, it is necessary to follow large numbers of nuclear industry workers for long periods to achieve risk estimates that are sufficiently accurate to allow a meaningful comparison with predictions based on the risk models underlying radiological protection. To date, most large studies of nuclear industry workers have been carried out in the USA, Canada and the UK, and most information may be extracted from studies that combine data from a number of workforces, maximizing the statistical power of a study. The study based on the UK National Registry for Radiation Workers (NRRW) (Muirhead *et al.*, 1999) considered just over 3500 cancer deaths among almost 125 000 radiation workers receiving an average lifetime occupational dose of 30 mSv. The trend of leukaemia (excluding CLL) mortality with dose was marginally significant – the ERR coefficient is 2.55/Sv (90% CI: –0.03, 7.16) – while no significant variation with dose of mortality from all other cancers combined was found – the ERR coefficient is 0.09/Sv (90% CI: –0.28, 0.52). These ERR coefficients are compatible with the equivalent coefficients derived from the Japanese atomic bomb survivors – 2.15/Sv (90% CI: 0.43, 4.68) for leukaemia (except CLL) and 0.24/Sv (90% CI: 0.12, 0.37) for other cancers. The International Agency for Research on Cancer (IARC) study of combined nuclear industry workforces in the USA, Canada and the UK (Cardis *et al.*, 1995) is the largest study of nuclear industry workers to date, and includes almost 4000 cancer deaths among just over 95 000 radiation workers receiving an average cumulative dose of 40 mSv. These authors found an ERR coefficient for leukaemia (except CLL) mortality of 2.18/Sv (90% CI:

0.13, 5.7) and for solid tumours mortality of –0.07/Sv (90% CI: –0.39, 0.30), again compatible with the equivalent estimates from the Japanese data although there was some overlap with the data included in the NRRW study. A large international study of radiation workers coordinated by IARC is currently underway, which should improve the precision of these risk estimates.

Nuclear industry workers also provide an opportunity to investigate any effect of internally deposited radionuclides. Carpenter *et al.* (1998) examined a large cohort of British nuclear industry workers who had been monitored for internal exposures and found that certain patterns of monitoring may be associated with particular cancers; however, the measures of exposure were relatively crude. Omar *et al.* (1999) studied the group of workers exposed to plutonium at the Sellafield nuclear installation in Britain for whom assessed organ-specific doses due to plutonium were available, and concluded that the plutonium workers were not at an increased risk of cancer when compared with other radiation workers. Following the finding of a statistically significant association between prostatic cancer mortality and external radiation dose among UK Atomic Energy Authority workers, which was stronger for those monitored for internally deposited radionuclides (Beral *et al.*, 1985), Rooney *et al.* (1993) conducted a nested case-control study of prostate cancer among these workers. They found that prostate cancer was associated with monitoring for exposure to either tritium ( $^3\text{H}$ ) or one of four fission or neutron activation product radionuclides, and they drew particular attention to the possible role of exposure to  $^{65}\text{Zn}$ . Whether potential exposure to  $^{65}\text{Zn}$  is directly related to the risk of prostate cancer was questioned by Atkinson *et al.* (1994), and Atkinson *et al.* (2002) have recently reported that an extended cohort of UKAEA workers does not confirm the prostate cancer associations when an analysis is made of data independent of those used in the earlier studies. As a result of concern over the possible health effects of exposure to depleted uranium munitions (that use uranium with a proportional  $^{235}\text{U}$  content lower than the 0.72% that occurs naturally), Beral and Darby (2001) reviewed the results of studies of uranium workers and concluded that these did not indicate a raised risk of cancer in these workers. Recently, Harrison and Muirhead (2003) have compared risk estimates derived from studies of people exposed to internal sources of radiation with estimates of the risk from external radiation. They found that the risk coefficients were broadly compatible, although the current radiation weighting factor of 20 for  $\alpha$ -particles may overestimate the risks of leukaemia and bone cancer from internal sources of this radiation.

There has been concern that those who participated in atmospheric nuclear weapons tests could experience a raised risk of cancer as a consequence, although radiation exposures were, in general, low. Studies of UK (Muirhead *et al.*, 2003), New Zealand (Pearce *et al.*, 1997) and US (Dalager *et al.*, 2000; Institute of Medicine, 2000) participants found little evidence for a

raised level of cancer generally, but there was some evidence for a raised risk of leukaemia among those who had taken part in the weapons tests.

An increasingly important source of information on occupational exposure is workers in the former USSR. Many of the approximately half a million workers involved in recovery operations after the Chernobyl accident in 1986 received doses of 100–200 mSv and studies of these workers may be capable of detecting increased risks if the numbers included are sufficiently large (Ivanov *et al.*, 2001; Kesminiene *et al.*, 2002). However, length of follow-up is currently limited, so interest should be focused on leukaemia with its shorter minimum latency. One study of Russian recovery workers did report an excess of leukaemia when compared with Russian national rates (Ivanov *et al.*, 1997a), but this may be due largely to underascertainment among the Russian general population since a subsequent nested case–control study did not find evidence of an excess risk related to radiation exposure (Ivanov *et al.*, 1997b). A highly significant excess of thyroid cancer incidence was found among the Russian recovery workers when compared with the rate for Russian men, but the cases displayed a (nonsignificant) negative trend with external dose, suggesting that enhanced detection at the routine follow-up medical examinations could be responsible (Ivanov *et al.*, 2002). No significant excess of cases of solid tumours has been found among the Russian workers whether the comparison group is the general Russian population or an internal control group (Ivanov *et al.*, 2004).

Possibly of significance to radiation epidemiology potentially ranking only just below the Japanese atomic bomb survivors are the workers of the Mayak nuclear complex in the southern Urals, who received high doses of radiation at a low dose-rate over a protracted period. Mayak was established in the late 1940s to produce plutonium for the weapons programme of the former USSR and the urgency placed by Stalin upon atomic weapons production led to workers receiving surprisingly high doses of radiation. During 1948–1951, many workers were exposed to a level whereby they suffered from early deterministic effects, but conditions improved after 1958. Of the original 19 000 workers (25% women), the vital status is known for 90%. Remarkably, the average individual dose received by these workers from external sources is almost 1 Sv (the highest doses exceeded 10 Sv), and to this must be added the substantial internal doses received from intakes of plutonium. Estimates of historical doses are being improved, especially the organ-specific doses from plutonium, but external doses are sufficiently accurate to allow approximate risk estimates to be generated. Clear and large excesses of lung, liver and bone cancers (sites where plutonium will accumulate) were found to be related to assessed plutonium exposure (Gilbert *et al.*, 2000; Koshurnikova *et al.*, 2000; Kreisheimer *et al.*, 2003). These cancers were also associated with external exposure and, as a grouping, the ERR coefficient was found to be 0.30/Sv external radiation (90% CI: 0.18, 0.46), after adjustment for exposure to plutonium

(Shilnikova *et al.*, 2003). Other solid tumours were less strongly associated with external exposure, the ERR coefficient for this grouping of cancers being 0.08/Sv external radiation (90% CI: 0.03, 0.14), after adjustment for plutonium exposure (Shilnikova *et al.*, 2003). A strong association of leukaemia with exposure to external radiation (but not with plutonium exposure) was found, which was markedly concentrated in the period 3–5 years after the dose was received when the ERR coefficient is 6.9/Sv (90% CI: 2.9, 15), reducing to 0.45/Sv (90% CI: 0.1, 1.1) for the period more than 5 years after exposure (Shilnikova *et al.*, 2003). The risk estimates derived by Shilnikova *et al.* (2003) are broadly compatible with those expected from the experience of the Japanese atomic bomb survivors, although the remaining dosimetric uncertainties need to be borne in mind. With the refinement of the data available from the Mayak workforce, material advancement of knowledge from radiation epidemiology should be possible.

*Environmental exposure* The final category of epidemiological studies concerns doses received from environmental sources of radiation. These studies are often difficult to interpret reliably because they frequently deal with low doses that are not well determined. Extracting meaningful information from such studies when the predicted excess risk exists against fluctuations in a much greater background risk presents substantial problems. For example, a large study of the high natural background radiation area of Yangjiang in China did not reveal excess cancers (Wei and Sugahara, 2000), but the average effective dose in the high background area was only about three times greater than in the control area; so any effect of this small difference in dose could easily be hidden by statistical and systematic variations in the rates (Boice, 2002). Current models of radiation-induced cancer predict that about one-fifth of childhood leukaemia cases in Britain could be due to natural background radiation, but in a nation-wide case–control study of childhood cancer in Britain, no association was found with any type of cancer and exposure to penetrating external (mainly  $\gamma$ -ray) radiation (UK Childhood Cancer Study Investigators, 2002b).

The largest component of exposure to natural background radiation is residential exposure to radon and its decay products, the inhalation of which delivers a dose almost entirely to the bronchial epithelium. In some high radon areas (such as southwest England), the dose to the lung can be comparable to the lower end of the range of doses experienced by underground hard rock miners. Nonetheless, extracting a radon-related excess risk of lung cancer in high radon areas presents a considerable challenge to epidemiologists given the dominance of cigarette smoking in the overall risk of lung cancer. A number of case–control studies have been conducted in high radon areas, which take account of individual radon exposures and smoking histories. Appropriately combining the results of these studies in meta-analyses produces a trend of lung cancer risk with

radon exposure that is just discernible statistically – the ERR is 0.14 (95% CI: 0.0, 0.3) at a radon concentration of 150 Bq/m<sup>3</sup> (Lubin and Boice, 1997) – and of a magnitude that is compatible with that obtained from the moderate-to-high exposures experienced in underground hard rock mines (Lubin and Boice, 1997; NRC, 1999; Little and Wakeford, 2001; Darby and Hill, 2003; Lubin, 2003). Lagarde *et al.* (2001) conducted a case-control study of lung cancer among nonsmokers in Sweden to examine the effect of residential radon exposure and found an ERR coefficient that was similar to the overall risk estimate obtained from the meta-analyses of domestic radon studies. Recently, Wang *et al.* (2002b) have reported the results of a case-control study of lung cancer incidence during January 1994 to April 1998 in a high residential radon area of Gansu Province in China. This is a predominantly rural area with low population mobility, and 99% of the study subjects had lived for some time in underground dwellings. Radon measurements were made in residences covering just over three-quarters of the exposure time. The ERR of lung cancer was 0.19 (95% CI: 0.05, 0.47) at a radon concentration of 100 Bq/m<sup>3</sup>, consistent with the findings of meta-analyses of residential studies and of underground miners. Pooling the data from this case-control study and another from China produced 1050 lung cancer cases and an ERR at 100 Bq/m<sup>3</sup> of 0.13 (95% CI: 0.01, 0.36) (Lubin *et al.*, 2004). Large investigations using the pooled data of case-control studies in North America (Lubin, 2003) and Europe (Darby and Hill, 2003) are due to report soon, which should further improve risk estimates.

Some geographical correlation studies (e.g. Henshaw *et al.*, 1990; Gilman and Knox, 1998) have found positive associations between average radon exposure and leukaemia, some solid tumours and childhood cancer. However, such correlation studies need to be interpreted with caution (NRC, 1999; Laurier *et al.*, 2001). These ‘ecological’ associations have not been confirmed by large case-control studies of childhood cancer (UK Childhood Cancer Study Investigators, 2002a) and childhood leukaemia (Lubin *et al.*, 1998).

Atmospheric nuclear weapons testing in the late 1950s and early 1960s led to widespread exposure to radioactive fallout. The resulting doses were low (generally less than those received from natural background radiation), but concentrated in time, and although a general increase of cancer due to fallout was very unlikely to be detected, there is a possibility of finding a fallout-related excess of childhood leukaemia. It is known from the experience of the Japanese atomic bomb survivors that the radiation-induced excess risk of leukaemia peaks a few years after exposure and is greatest in those exposed as children; so any effect of fallout would most likely be found through examining childhood leukaemia just after the period of peak testing. Investigations are complicated, however, by the background temporal pattern of childhood leukaemia during the mid-1960s: a steady fourfold rise in childhood leukaemia mortality from 1920, which was apparent in England and Wales, was halted at this time

by increasing treatment success, but the registration of incident cases was only just becoming reliable (Doll, 1989). Nonetheless, a study of childhood leukaemia incidence and fallout in the Nordic countries, where accurate nation-wide registries were available earlier than most other places, found a marginally significant rise in childhood leukaemia incidence that was compatible with the level predicted by risk models based principally on the atomic bomb survivor data (Darby *et al.*, 1992). A case-control study of leukaemia mortality in southwest Utah, an area that experienced fallout from the neighbouring Nevada Test Site, found a significant trend with assessed fallout dose for those dying of acute leukaemia at a young age in the period after maximum above-ground testing (Stevens *et al.*, 1990). Individual doses from fallout were assessed for this study from environmental measurements of radioactivity. Again, the observed excess of childhood leukaemia was comparable with that anticipated from standard radiation risk models.

The radioactive cloud from the Chernobyl nuclear reactor accident in 1986 contaminated surrounding areas in the former USSR and, to a lesser extent, the rest of Europe. Doses were generally low, although contamination was heavy in the immediate vicinity of Chernobyl in Ukraine, Belarus and Russia. Of particular importance are the doses to the thyroid from the short-lived radioisotopes of iodine, notably <sup>131</sup>I (with a half-life of 8 days), which reached levels of a sievert or more in certain parts of the former USSR, but rapidly attenuated with time as the cloud spread westwards across Europe. The most marked consequence of the exposure to radioiodine was a swift and pronounced increase in the incidence of childhood thyroid cancer in the most heavily contaminated areas of the former USSR, the number of excess cases being approximately 2000 to date (UNSCEAR, 2000; Williams, 2002). There is a strong relationship between childhood thyroid cancer and the estimated dose from radioiodine (Astakhova *et al.*, 1998; UNSCEAR, 2000). Evidence for an increase in thyroid cancer among those exposed as adults is much less clear (Ivanov *et al.*, 2003), but the notable sensitivity of the thyroid of children to radiation-induced cancer is apparent in studies of those exposed to external sources of radiation (Ron *et al.*, 1995). The role of iodine deficiency (Shakhtarin *et al.*, 2003), intense screening for thyroid cancer (Moysich *et al.*, 2002) and short-lived radioisotopes other than <sup>131</sup>I complicate the derivation of risk estimates from the Chernobyl data (UNSCEAR, 2000), but the ERR coefficient for childhood thyroid cancer that may be derived from the children exposed to radioiodine in the former USSR is compatible with that obtained from external irradiation (Jacob *et al.*, 2000). Little evidence has been found for an increased risk of childhood leukaemia associated with Chernobyl contamination (Parkin *et al.*, 1996). There is, however, some suggestive evidence of a raised incidence of infant (<1 year of age) leukaemia after the Chernobyl accident in Greece (Petridou *et al.*, 1996), West Germany (Steiner *et al.*, 1998), Belarus (Ivanov *et al.*, 1998) and Scotland

(Gibson *et al.*, 1988) that might be related to exposure to fallout, although the findings of these geographical correlation studies should be viewed with caution until the results of individual-based studies are available. Studies of adult cancers have not found excesses associated with the Chernobyl accident (UNSCEAR, 2000; Moysich *et al.*, 2002; Williams, 2002).

Owing to an unexpected change in wind direction following the BRAVO hydrogen bomb test at Bikini atoll in 1954, the Marshall Islands were contaminated with fallout, especially short-lived radioisotopes of iodine, leading to doses to the thyroids of infants that are assessed to approach 50 Sv. The number of Marshall Islanders who were heavily exposed was limited at around 250, but nine thyroid cancers were observed in this group over the following 32 years, although interpretation is complicated by the high occurrence of surgery and hormonal therapy (UNSCEAR, 1994; Howard *et al.*, 1997). Broader studies of thyroid cancer in the Marshall Islands have found evidence of a general excess risk among the Marshall Islanders potentially exposed after the BRAVO test (Hamilton *et al.*, 1987; Takahashi *et al.*, 2003). A cohort study of around 2500 individuals exposed to radioiodine from the Nevada Test Site in the 1950s while attending schools in the general vicinity of the test site, and who were still resident in the area in the mid-1980s, found a marginally significant association ( $P \sim 0.1$ ) between thyroid cancer and assessed thyroid dose (Kerber *et al.*, 1993). A few people received thyroid doses in excess of 1 Sv, but the mean dose was comparatively small at around 100 mSv. Gilbert *et al.* (1998) examined thyroid cancer rates at the county level across the continental USA in relation to weapons testing at the Nevada Test Site during the 1950s, making use of thyroid dose estimates for counties. No evidence for a general excess of thyroid cancer associated with fallout was found, but indications of a raised risk among infants and in the 1950–1959 birth cohort were observed. As the authors remark, it is not particularly surprising that this geographical correlation study did not find strong evidence for an elevated risk of thyroid cancer associated with fallout given the generally low doses and the limitations of the study. Atmospheric releases from the reprocessing of short-cooled irradiated uranium fuel at the Hanford nuclear facility, Washington State, in the mid-1940s during the production of weapons-grade plutonium led to environmental exposure to  $^{131}\text{I}$ . A dose reconstruction programme was conducted for the study of thyroid disease among over 3000 individuals who were born in the vicinity of Hanford during the mid-1940s and were still alive at the time of the study, and some assessed doses to the thyroids of infants exceeded 1 Sv. This study did not detect a radioiodine-related excess risk of thyroid cancer (Davis *et al.*, 2002), although the trend with dose was (nonsignificantly) positive. The relatively small average thyroid dose of 174 mSv suggests that this absence of association is not incompatible with the findings of other studies of exposure to radioiodine.

Epidemiological investigations of populations exposed as a result of nuclear weapons production and

testing in the former USSR have the potential to produce informative risk estimates because of relatively high environmental doses received by comparatively large numbers of people. Of particular interest are those exposed to fallout from the early weapons tests at Semipalatinsk in Kazakhstan (Grosche *et al.*, 2002) and residents of communities neighbouring the Techa River (Kossenko *et al.*, 2002). The Techa River received large quantities of highly radioactive effluent from the Mayak nuclear complex in the early years of weapons plutonium production, especially during 1950–1952, leading to heavy contamination of the river and its environs. Current efforts centre on the generation of reliable cancer incidence and mortality data and the reconstruction of doses, projects that present considerable challenges to researchers, but these studies could be significant sources of knowledge of the risks posed by protracted environmental exposure to radiation.

Reports during the 1980s and 1990s of excesses of childhood leukaemia near certain nuclear installations – in particular, at Seascale near Sellafield in England (COMARE, 1996), in west Thurso near Dounreay in Scotland (COMARE, 1988) and around La Hague in France (Guizard *et al.*, 2001) – led to suggestions that discharged radioactive material was responsible. Detailed radiological assessments demonstrated, however, that radiation doses from environmental exposure to discharged radioactivity were generally less than the doses received from natural background radiation and much too low to account for these excesses (e.g. COMARE, 1996), and no serious deficiencies in these assessments have been discovered despite extensive searches (e.g. Wheldon, 1989). A case-control study indicated that occupational exposure to radiation of fathers before the conception of their children might increase the risk of childhood leukaemia and could explain the Seascale cluster of cases (Gardner *et al.*, 1990). However, this novel association has not been confirmed among the offspring of the Japanese atomic bomb survivors (Yoshimoto *et al.*, 1990; Izumi *et al.*, 2003) or by any other study of the children of radiation workers (COMARE, 1996, 2002), and the notion that paternal preconceptional irradiation materially increases the risk of childhood leukaemia has now effectively been abandoned (Doll *et al.*, 1994). The most plausible explanation for these clusters is that childhood leukaemia is a rare response to a common infection and that population mixing between infected and susceptible individuals in these secluded areas produces localized epidemics of the relevant infection and a consequent increased risk of childhood leukaemia (Kinlen, 2000). Such an explanation would also account for the increased levels of childhood leukaemia that have been found after other instances of pronounced urban-rural population mixing in areas with no enhanced exposure to radiation (Doll, 1999; Kinlen, 2000).

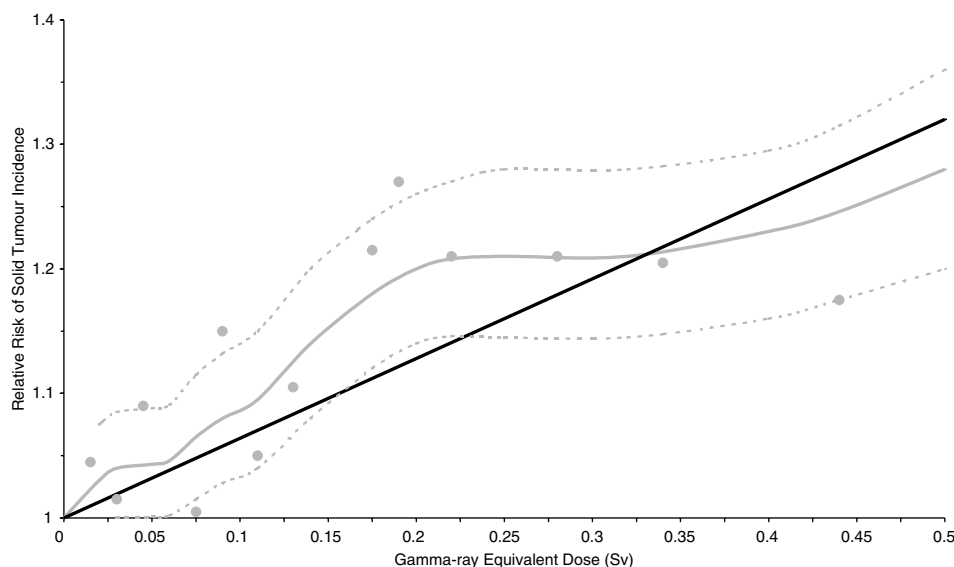
*Risk at low doses* Reliable estimates of the risk of cancer following exposure to ionizing radiation are derived from epidemiological studies of moderate-to-

high doses because these studies have sufficient statistical power to generate reasonably precise values. The statistical uncertainties associated with the small excess risks at low doses are such that direct estimates from low-dose studies are compatible with a wide range of underlying risks, often including no risk at all, and the problem is compounded by the presence of systematic errors. However, radiological protection is primarily concerned with risks at low doses, so some means of interpolating between the moderate-to-high dose region and no additional dose needs to be determined. The dose–response derived for this purpose by the International Commission on Radiological Protection (ICRP, 1991a) is a linear no-threshold (LNT) relationship with a slope at low doses or low dose-rates, which (for sparsely ionizing radiations, but not for densely ionizing radiations) is reduced to half of the slope at high doses delivered at high dose-rates. This curve is based on the statistical fit to data at moderate-to-high doses and an (inexact) knowledge of pertinent radiobiological mechanisms at low doses. The resultant nominal lifetime EAR coefficient for fatal cancer in a typical general population after radiation exposure at low doses or low dose-rates is 5%/Sv effective dose. This position has been challenged from one wing by those who argue for a threshold or even a beneficial (hormetic) effect at low doses (see, for example, Calabrese and Baldwin, 2003), and from the opposite wing by those who consider that the LNT model could seriously underestimate the risk (e.g. through the bystander effect; see Brenner *et al.*, 2001). Although epidemiological data from the low-dose region are of limited accuracy, they can, nonetheless, provide an envelope for possible dose–response curves.

Pierce and Preston (2000) made a detailed examination of the shape of the dose–response at low doses using the incidence data for solid tumours during 1958–1994 among the Japanese atomic bomb survivors. A statis-

tically significant elevation of risk was found for the dose group 0–100 mSv, and an effective upper bound for a putative threshold was determined from these data to be 60 mSv. The authors concluded that the Japanese data provide useful risk estimates for doses in the range 50–100 mSv, and that linear risk estimates from the wider dose ranges of 0–2 or 0–4 Sv provide an appropriate description of the risk at low doses (see Figure 7). Hence, this comprehensive study did not find evidence for a material deviation from linearity for the dose–response at low doses. This conclusion is supported by studies of those who have undergone medical irradiation, notably the pooled analysis of thyroid cancer by Ron *et al.* (1995), who found convincing evidence for an excess risk after exposure in childhood down to 100 mSv and a linear dose–response at moderate-to-high doses. Of particular interest are the studies of multiple fluoroscopic examinations of the chest during pneumothorax therapy for TB, since overall moderate-to-high doses are delivered over a protracted period in small fractions ( $\sim 10$  mSv). For breast cancer, the risk appeared to be directly proportional to the cumulative dose, suggesting that the excess risk is composed of the sum of the risks from the individual small component doses (Little and Boice, 1999; NCRP, 2001b). This was not the case, however, for lung cancer, for which no excess risk was detected, although the influence of factors such as the severity of the original TB and its impact on smoking habits must be taken into account (UNSCEAR, 2000; NCRP, 2001b).

Consistent evidence exists from case–control studies for a raised risk of childhood cancer following antenatal exposure to diagnostic X-rays, indicating that acute doses of around 10 mSv can induce cancer. A causal explanation of this association is not universally accepted (Boice and Miller, 1999), but Doll and

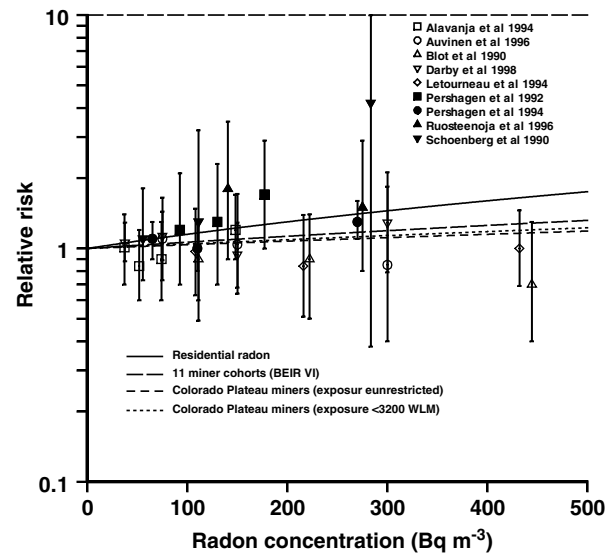


**Figure 7** The relative risk of solid tumour incidence among the Japanese atomic bomb survivors during 1958–1994 for an age at exposure of 30 years, showing a smoothed fitted curve through the low-dose data plus a 95% confidence band. The straight line is a linear fit to the data for the 0–2 Sv dose range (Pierce and Preston, 2000)

Wakeford (1997) concluded that the evidence strongly suggests an underlying cause-and-effect relationship. Recently, Wakeford and Little (2003) showed that the ERR coefficient that may be derived from the largest case-control study of childhood cancer and obstetric radiographic examinations (the OSCC) is consistent with the estimate obtained from the Japanese atomic bomb survivors irradiated *in utero* who received, on average, doses an order of magnitude higher, although the uncertainties associated with this comparison imply that any inference of linearity can only be tentative.

Studies of childhood leukaemia and radioactive fallout from nuclear weapons testing provide evidence that protracted, low dose and low dose-rate exposure does increase the risk of childhood leukaemia to a level that is consistent with the predictions of models derived from the findings of moderate-to-high dose studies (Stevens *et al.*, 1990; Darby *et al.*, 1992). The low-dose risk estimates are also supported by large studies of workers in the nuclear industry, the ERR coefficients derived from these studies being compatible with standard models, and for leukaemia the raised risk is of marginal statistical significance. This suggests that chronic exposure at low dose-rates increases the risk of cancer to a level that is not too far from that found after acute exposure to the cumulative dose.

Case-control studies of lung cancer and residential exposure to radon and its decay products allow a direct investigation of the effect of low doses of  $\alpha$ -particle radiation, and a comparison with the findings of those heavily exposed in underground hard rock mines. Meta-analyses of the residential studies show a significantly increasing lung cancer risk with increasing radon concentration, with a slope that is comparable with the interpolation from the miner studies (see Figure 8) (Lubin and Boice, 1997; NRC, 1999; Little and Wakeford, 2001; Brenner and Sachs, 2003). Given this, the results of a geographical correlation study of lung cancer mortality and residential radon exposure in the USA, which shows a strong *negative* association (Cohen, 1995), are surprising. This study compares the lung cancer mortality rate for US counties with the average radon exposures by county. However, the principal doubt surrounding this study is whether it is possible in an analysis of summary statistics for large groups of people to adjust for the predominant effect of smoking on the risk of lung cancer in a manner that can produce results that are reliable. This seems unlikely, although Cohen (1995) strongly maintains that the results can be taken at their face value. That the findings of this correlation study are heavily influenced by smoking habits has recently been convincingly demonstrated by Puskin (2003), who showed that negative associations with radon are also obtained for smoking-related cancers other than lung cancer (but not for cancers that are unrelated to smoking), even though these other cancers have not been linked to radon exposure in miner studies (Darby *et al.*, 1995). This example illustrates the dangers of overinterpreting the findings of correlation studies, especially when a dominant risk factor is present. A further example, from the opposite view-



**Figure 8** The relative risk of lung cancer by residential radon concentration from nine case-control studies. The solid line is the fit obtained from a meta-analysis of these studies, and the broken lines are the fits obtained from the analysis of various sets of data for underground hard rock miners. Further details can be found in Little and Wakeford (2001)

point, is the contention of Wing *et al.* (1997), based on the findings of a geographical correlation study of cancer incidence in the vicinity of the Three Mile Island nuclear power station, that releases of radioactivity following an accident at one of the reactors led to a discernible increase in the number of cases of lung cancer. As pointed out by Hatch *et al.* (1990), there are substantial problems in attributing the statistical association with lung cancer to radioactive releases and, as with the negative association with radon reported by Cohen (1995), there are more plausible explanations.

In summary, epidemiological studies of low-level exposures to ionizing radiation indicate that a radiation-induced excess risk of cancer does exist, although the uncertainties are such that accurate quantification of this excess risk is not possible. Risk estimates are compatible, however, with the predictions of standard models based on studies of moderate-to-high doses that the excess risk is approximately directly proportional to dose (NRPB, 1995; NCRP, 2001b; Preston, 2003). This inference is supported by a recent review by Brenner *et al.* (2003), who concluded that linearity of the dose-response at low doses was the most appropriate assumption, although the shape of the relationship could vary between different types of cancer.

### Nonionizing radiation

In this section, epidemiological studies involving exposure to electromagnetic radiation of an energy below that capable of producing ionization will be considered. Apart from exposure to UVR, these studies are

controversial because the epidemiological findings are not conclusive and no biological mechanisms of carcinogenesis have been established.

### Ultraviolet Radiation

UVR is that part of the electromagnetic spectrum lying between X-rays and visible violet light. Ultraviolet photons have energies just below the level that can produce ionization (although there is inevitably some overlap between 'soft' X-ray and 'hard' UVR), and UVR is conventionally divided into UVA, UVB and UVC radiation according to the increasing energy of the photon. DNA has an energy absorption maximum in the UVC region with a tail extending into the UVB region, and direct absorption of UVC and UVB leads to damage to DNA through excitation and the production of free radicals. In contrast, UVA radiation leads to potentially mutagenic base damage via oxidative pathways. UVA and UVB radiation, when incident upon the skin, can penetrate to the sensitive basal layer and pose a risk of skin cancer, but UVC radiation is mainly absorbed by the outer layers of the skin and does not readily reach the basal layer. For most people, the primary source of UVR is the sun, although cosmetic sunbeds, arc welding and UVR therapy can contribute to exposure for some individuals.

Epidemiological studies of cancer and exposure to UVR have been reviewed in detail by IARC (1992), WHO (1994), Scotto *et al.* (1996) and, more recently, AGNIR (2002). The evidence presented below summarizes the findings of these comprehensive reviews and some more recent studies.

Solar UVR appears to be the main cause of NMSC in the UK – both basal cell carcinoma (BCC, accounting for ~75% of cases of NMSC) and squamous cell carcinoma (SCC, accounting for almost all of the remaining cases) – and NMSC represents around one-sixth to one-fifth of cancers registered in the UK (AGNIR, 2002). The epidemiological study of NMSC is problematical due to the variable quality of registration data for a common cancer that is relatively easy to treat and has a low rate of mortality, and substantial under-reporting of NMSC exists. It is clear, however, that this cancer is much more frequent in white populations than in non-white populations, and the risk is particularly raised in albinos. For white populations, those of a fair complexion and those with sun-sensitive skins have a higher risk of NMSC. Among white populations, NMSC is more common in men and exhibits a steep rise in incidence with increasing attained age. Comparing registration data sets with equivalent assessed levels of ascertainment reveals a trend of increasing incidence among white populations of similar ethnicity with decreasing latitude. Rates in Australia are particularly notable, with north Queensland having the highest recorded rate of skin cancer in the world. It is of interest that British immigrants to Australia experience half the incidence rate of the native white populations and that the risk increases with earlier ages at immigration. The anatomical distribution of NMSC

site shows a disproportionate number of cancers on the head and neck, which experience the highest cumulative exposure to the sun, although there are differences between the distributions of BCC and SCC with a larger fraction of SCC than BCC occurring on skin usually exposed to solar UVR. Time trends for NMSC are difficult to interpret because of variable data quality, but there are compelling indications of large increases in incidence. Evidence exists for a greater risk of NMSC among those employed in outdoor work, although the findings are not wholly consistent, possibly due to self-selection by those choosing such employment. Studies that have assessed the individual level of exposure to the sun suggest that the risk of SCC is directly related to cumulative exposure to solar UVR whereas BCC is more associated with intense periods of exposure (e.g. sunbathing). A recent trial in Queensland of sunscreen application indicated that such use may reduce the risk of SCC. For artificial sources of UVR, dermatological patients treated with phototherapy consisting of oral 8-methoxypsoralen plus UVA irradiation (PUVA) show a strong dose–response relationship for the risk of SCC, while that for BCC is less persuasive. A recent study of NMSC and artificial tanning devices found an association for both SCC and BCC (Karagas *et al.*, 2002). Epidemiological studies of SCC of the lip provide evidence for a causal role for the cumulative exposure to UVR, although account must be taken of tobacco smoking (especially in pipes), which acts in synergy with UVR.

Malignant melanoma of the skin is less than one-tenth as common as NMSC, but its lethality is much greater so that melanoma accounts for about 80% of skin cancer mortality in the UK, and solar radiation is likely to be the main cause of these deaths (AGNIR, 2002). The incidence of melanoma is much greater in white populations than non-white populations and especially among red heads and those of a fair complexion with a tendency to freckle or, in particular, with many and atypical melanocytic naevi ('moles'). In white populations, melanoma incidence tends to be greater in men than in women under the age of about 50–60 years, but the difference narrows, or even reverses, at older ages. The rise with attained age is less steep than that for NMSC at older ages. The incidence of cutaneous melanoma in white populations tends to increase with closeness of residence to the equator, the highest recorded rate being in Queensland; however, within Europe, rates are higher in Scandinavia than in Mediterranean regions, which could be related to fair skinned people taking more holidays in sunny locations. A recent study of Finnish twins (Milan *et al.*, 2002) found a distinct lack of concordance for skin cancer (both melanoma and NMSC), suggesting the importance of environmental rather than hereditary factors. As with NMSC, the incidence of melanoma among white populations migrating to sunnier countries is less than that of the native white populations, and the reduction is greatest for those who migrated later in life.

Melanoma incidence rates in the UK have increased markedly, and more than for any other major cancer in

recent decades so that melanoma is now the third most common cancer in young adults. This increasing incidence is also found in other white populations, but some levelling off is now apparent in Australia where there is an intensive sun protection programme. It is of interest that the increase in incidence has been greatest for tumours of the trunk for men and of the lower limbs for women, areas of the body that might experience an intermittent rather than a prolonged exposure to sunlight. The rise in incidence has, in general, followed year of birth so that later generations tend to experience a greater risk of melanoma throughout their lives. Studies of the role of occupational exposure to sunlight are inconclusive, although (with the notable exception of head and neck melanoma) the risk is broadly greater among those with indoor occupations. That the risk of melanoma may be more related to the pattern of exposure to the sun than to cumulative exposure is supported by case-control studies that point to the importance of intermittent exposures such as sunbathing on holiday. The interpretation of these studies, however, is difficult due to, for example, recall bias and the differing behaviour of individuals in response to bright sunshine, although recent studies (Veierod *et al.*, 2003; Bataille *et al.*, 2004) have supported the importance of a history of sunburn. Fears *et al.* (2002) have reported the results of a case-control study that assessed lifetime exposure to UVR through residential histories, time spent outdoors and measurements of UVB flux. They found that melanoma risk is associated with both cumulative and average annual UVB exposure, the association being stronger for the latter; those who tan easily are at less risk. Interpretational problems are also encountered with case-control studies examining the variation of risk with age at exposure, although the findings tend to concur with the migrant study results that indicate a heightened carcinogenic sensitivity at young ages (Whiteman *et al.*, 2001). Epidemiological studies of melanoma and sunscreen use have not produced consistent results, and recent meta-analyses by Huncharek and Kupelnick (2002) and Dennis *et al.* (2003) found no overall association. Studies of sunbed use have also tended to generate inconclusive findings. However, the recent marked rise in the use of sunbeds and the similarity of the exposure to solar UVR are both a cause for concern and a potential source of additional epidemiological information in future, and evidence is mounting that sunbed use by the young may increase the risk of melanoma (Veierod *et al.*, 2003; Bataille *et al.*, 2004). Studies of those receiving PUVA therapy have not consistently indicated a raised risk of melanoma. Recent studies of UVR and melanoma have been reviewed by Tucker and Goldstein (2003).

An interesting development is the growing evidence suggesting a dual pathway for the development of melanoma. Whiteman *et al.* (2003) studied the anatomical distribution of melanoma on patients from Queensland and found a markedly different pattern of naevi for those with melanomas on the chronically exposed head and neck compared with those with melanomas on the intermittently exposed trunk: the

former patients were about threefold less likely to have large numbers of naevi than the latter group, the difference being highly statistically significant. The inference that one pathway is related to chronic sunlight exposure and the other to melanocyte instability induced by brief intense exposure is supported by a genetic study by Maldonado *et al.* (2003). They found that BRAF mutations were significantly more frequent in melanomas occurring on intermittently exposed skin than elsewhere, and that these mutations were rare in melanomas on chronically exposed skin.

In summary, there is strong evidence to link the risk of SCC of the skin and lip to cumulative exposure to solar UVR. Further, there is good evidence to link the risk of BCC and melanoma of the skin to exposure to sunlight, although it is unclear whether intermittent rather than cumulative exposure may play a more important role in these skin cancers. As for other cancers, there is some evidence for an association between UVR and ocular melanoma (e.g. Vajdic *et al.*, 2003), and an indication of a possible minor role for UVR exposure and the risk of a particular subtype of non-Hodgkin's lymphoma. Recently, in an exploratory study, Freedman *et al.* (2002) reported negative associations between mortality from female breast and colon cancer and residential and occupational exposure to sunlight, and suggested that further research in this area is required.

#### *Electromagnetic radiation at lower energies*

Whether electromagnetic radiation composed of photons having energies lower than quanta of UVR can cause cancer is a subject of some scientific debate. Biological mechanisms of carcinogenesis at these low energies have not been established, but various epidemiological reports of excess cancers following exposures to these nonionizing radiations have been published and have received considerable publicity. As a consequence, the epidemiological evidence relating to these radiations will be reviewed below. Given the absence of known biological mechanisms, the concept of dose has not been developed for these radiations and studies have been conducted in terms of general measures of exposure to the particular radiation.

*Microwave radiation* Current concern over the possible carcinogenic effects of exposure to nonionizing radiation in the microwave region of the radiofrequency electromagnetic spectrum centres on the use of cellular mobile and cordless telephones that utilize these frequencies for wireless communication. The energy of the radiation is far below that capable of breaking molecular bonds, but localized heating and increased molecular movement can be induced, although it is unclear how these effects could be related to an increased risk of cancer (IEGMP, 2000). Owing to the proximity to the head of mobile telephones when in use, it has been brain cancer that has been the focus of attention. The limited epidemiological studies have recently been comprehensively reviewed by Boice and

McLaughlin (2002) for the Swedish Radiation Protection Authority. When these authors examined those studies for which they considered the results reliable, they found no evidence for an increased risk of cancer associated with the use of mobile telephones. The IARC is coordinating a large study of brain cancers and mobile telephone use (the INTERPHONE study) that will collate the data of common-protocol case-control studies in 13 countries. Preliminary results should be available soon.

The relatively recent widespread use of mobile telephones does, of course, pose problems for epidemiological studies if, as anticipated, the latent period for any induced cancers is long (Rothman, 2000; Cox, 2003). Of interest in this context is the study by Morgan *et al.* (2000) of almost 200 000 Motorola workers engaged in the testing and manufacturing of mobile telephones during 1976–1996, for whom exposures were assessed by job. They found no indication of a raised risk of brain cancer, or of leukaemia or lymphoma. A recent study by Groves *et al.* (2002) considered cancer mortality among just over 40 000 US Navy veterans of the Korean War (1950–1954) who had the potential of being exposed to high-intensity radar (which is of an energy that encompasses that of the radiation utilized by mobile telephones), and about 20 000 sailors were judged to have had high potential for exposure based on their jobs. No evidence was found for an increased risk of brain cancer in this cohort. A slight increase in myeloid leukaemias was reported, but this was due to just one of the three high potential exposure occupational categories.

*Other radiofrequency radiations* Hocking *et al.* (1996) conducted a geographical correlation study of cancer incidence and mortality during 1972–1990 around three television transmitters in Australia and reported a raised rate of childhood leukaemia in areas near these transmitters. McKenzie *et al.* (1998) re-examined the childhood leukaemia data and estimated the levels of exposure to radiofrequency radiation in the areas. They found that this association was the result of one influential observation and concluded that the overall pattern of childhood leukaemia did not support an association. Dolk *et al.* (1997a) investigated a reported cluster of leukaemias and lymphomas near the TV and FM radio transmitter at Sutton Coldfield, England, and found an excess of adult leukaemia, which decreased with increasing distance from the mast. The incidence of skin and bladder cancer also decreased with distance. Given these findings, Dolk *et al.* (1997b) extended their study to cancer incidence during 1974–1986 around 20 similar transmitters in Great Britain. Adult leukaemia showed a marginally significant elevation within 10 km of transmitters and a marginally significant decrease with increasing distance, but, unlike at Sutton Coldfield, there was no increase within 2 km of transmitters. No other unusual pattern of cancer with distance from the transmitters was reported. The authors concluded that the results give no more than weak support to the

original Sutton Coldfield report. Elwood (1999) has reviewed these geographical correlation studies and inferred that the findings are inconsistent and the evidence for any association weak.

Recently, Michelozzi *et al.* (2002) examined adult leukaemia mortality during 1987–1998 and childhood leukaemia incidence during 1987–1999 in the area in Rome within 10 km of the powerful Vatican Radio transmitter. They reported marginally significant declines of leukaemia in adult men and in children with distance from the transmitter. The authors were cautious in their conclusions due to the limitations of geographical correlation studies, the small numbers of cases and the lack of exposure information.

AGNIR (2003) have reviewed the epidemiological evidence concerning cancer and exposure to radio-frequency electromagnetic fields, particularly that which has become available since the publication of the review of IEGMP (2000). The group concluded, 'Overall, none of the categories of epidemiological data gives persuasive evidence that RF field exposure causes cancer.' However, they added that 'although the studies do not suggest a raised risk of cancer, they do not rule one out, especially in relation to large cumulative exposures to mobile phones and possible effects occurring many years after their use'.

#### *Extremely low-frequency electric and magnetic fields*

Electrical power is, in general, transmitted and distributed as an alternating current at a frequency of 50/60 Hz and this leads to the generation of ELF-EMF by power lines, household wiring and electrical appliances. The wavelength of ELF-EMF is around 5000 km, so it is not reasonable to consider any interaction between this electromagnetic energy and biological media in terms of photons, rather effects are related to the component electric and magnetic fields of ELF-EMF as specific exposures. Electric fields induce electric currents but are readily shielded, whereas magnetic fields induce circulating currents and easily penetrate buildings and people. However, the induced currents under normal conditions of exposure are substantially below those that occur naturally in the body. It is difficult to envisage how ELF-EMF could present any hazard to human health, but this subject has produced a substantial volume of scientific research over the past two decades.

Interest in whether exposure to ELF-EML might raise the risk of cancer was initiated by the study of Wertheimer and Leeper (1979), who suggested from a study of childhood cancer in Colorado that an association could exist with residence near power lines, particularly for childhood leukaemia. However, the exposure assessment for this study was based on 'wire codes' as an indication of the degree of exposure to ELF-EMF, and it was unclear how accurate this assessment might be. The study of Wertheimer and Leeper (1979) might have been dismissed as an oddity had the association of childhood leukaemia with wire codes not been confirmed by studies using independent

data; however, interpretation remained equivocal due to methodological problems and the tendency for the association to be unconfirmed by measured fields (AGNIR, 1992). Later studies overcame these problems. Large studies in the Nordic countries utilized the long-standing nation-wide cancer registries, and considered calculated historical fields around power lines (AGNIR, 1992, 2001). These studies tended to support an association between childhood leukaemia and high calculated magnetic fields, although the evidence remained weak (AGNIR, 1994). Large prospective case-control studies using measured fields have been conducted in a number of countries. In the USA, Linet *et al.* (1997) found little evidence that residential exposure to magnetic fields increases the risk of childhood ALL (see also Kleinerman *et al.*, 2000), and this was also the conclusion of a similar study carried out in Great Britain for both childhood leukaemia and other childhood cancers (UK Childhood Cancer Study Investigators, 1999). The UK study also failed to detect any association with proximity to a power line (UK Childhood Cancer Study Investigators, 2000) or with measured electric fields (Skinner *et al.*, 2000).

Ahlbom *et al.* (2000) conducted a pooled analysis of data concerning magnetic fields and childhood leukaemia from nine studies that met specified quality criteria: the four Nordic studies, the large studies from the USA and UK, and studies from Canada, Germany and New Zealand. A total of about 3200 children affected with leukaemia and just over 10000 controls were included in the analysis. The authors found little evidence for an elevated risk associated with residential exposure to magnetic fields, with the exception of high residential exposures with a 48 h average  $\geq 0.4 \mu\text{T}$  for which the RR is 2.00 (95% CI: 1.27–3.13). These high exposures are rare, affecting <1% of children. Ahlbom *et al.* (2000) concluded that this association was unlikely to be due to chance and, while the explanation is unknown, considered that selection bias may have been responsible for some of the increase, although this could not be quantified (see, for example, Hatch *et al.*, 2000).

A number of studies of occupational exposure to ELF-EMF that have variously reported excesses of leukaemia, brain and breast cancer have been published. Early studies were difficult to interpret (AGNIR, 1992), but more recent studies are more reliable in their

structure. Overall, the evidence for an increased risk of cancer in workers exposed to ELF-EMF is unconvincing (AGNIR, 2001). Not surprisingly, given the generally lower levels of exposure experienced by adults in an environmental rather than occupational setting, the evidence for a risk of cancer in adults associated with residential exposure to ELF-EMF is also unconvincing (AGNIR, 2001).

Ahlbom *et al.* (2001), constituting the Standing Committee on Epidemiology of the International Commission for Non-Ionizing Radiation Protection (ICNIRP), comprehensively reviewed the epidemiological literature on ELF-EMF and health. They highlighted the association between childhood leukaemia and high magnetic field strengths as worthy of attention, but the evidence for associations with other cancers was less clear. The IARC (2002) has recently evaluated the possible carcinogenic hazards of ELF-EMF. The association between childhood leukaemia and high residential magnetic fields was judged to provide 'limited evidence' for an excess risk, whereas the epidemiological evidence for an excess risk of other childhood cancers or adult cancers was considered 'inadequate'. The 'inadequate' evidence for an excess risk from experimental animal studies together with the lack of any plausible biological mechanism led IARC to conclude that ELF-EMF is 'possibly carcinogenic to humans'.

## Ultrasound

Finally, a brief mention should be made of exposure to ultrasound. Ultrasound differs from the other forms of radiation considered above in that it is a longitudinal pressure wave travelling through a medium, which causes the constituent particles to oscillate at a high frequency. There have been some suggestions that ultrasound could increase the risk of cancer (see Naumburg *et al.*, 2000), and the high occurrence of obstetric ultrasound examinations implies that any increased risk might not be trivial in its collective impact. Recent studies, however, have not found any association between the use of ultrasound during pregnancy and the subsequent risk of childhood cancer (Sorahan *et al.*, 1995; Naumburg *et al.*, 2000; Shu *et al.*, 2002).

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