

Radioprotectors

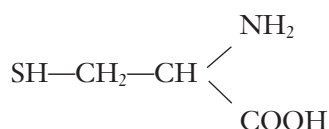
The Discovery of Radioprotectors
 Mechanism of Action
 Development of More Effective Compounds
 Amifostine (WR-2721) as a Radioprotector in
 Radiotherapy
 Radioprotectors and Chemotherapy

Amifostine as a Protector Against Cancer
 Dietary Supplements as Countermeasures to
 Radiation
 Summary of Pertinent Conclusions
 Bibliography

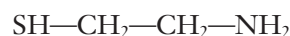
■ THE DISCOVERY OF RADIOPROTECTORS

Some substances, although they do not directly affect the radiosensitivity of cells, nevertheless, may protect whole animals because they cause vasoconstriction or, in some way, upset normal processes of metabolism to such an extent that the oxygen concentration in critical organs is reduced. Because cells are less sensitive to x-rays under hypoxia, this confers a measure of protection. Examples of such protective substances are sodium cyanide, carbon monoxide, epinephrine, histamine, and serotonin. Such compounds are not really radioprotectors per se and are not discussed further here.

The most remarkable group of true radioprotectors is the sulfhydryl (SH) compounds. The simplest is **cysteine**, an SH compound containing a natural amino acid, the structure of which is



In 1948, Patt discovered that cysteine could protect mice from the effects of total body exposure to x-rays if the drug was injected or ingested in large amounts before the radiation exposure. At about the same time, Bacq and his colleagues in Europe independently discovered that **cysteamine** could also protect animals from total body irradiation. This compound has a structure represented by



Animals injected with cysteamine to concentrations of about 150 mg/kg require doses of x-rays 1.8 times larger than control animals to produce the same mortality rate. This factor of 1.8 is called the **dose reduction factor (DRF)**, defined as

$$\text{DRF} = \frac{\text{Dose of radiation in the presence of the drug}}{\text{Dose of radiation in the absence of the drug}}$$

to produce a given level of lethality.

■ MECHANISM OF ACTION

Many similar SH compounds have been tested and found to be effective as radioprotectors. The most efficient SH compounds tend to have certain structural features in common: a free SH group (or potential SH group) at one end of the molecule and a strong basic function, such as amine or guanidine, at the other end, separated by a straight chain of two or three carbon atoms. SH compounds are efficient radioprotectors against sparsely ionizing radiations such as x- or γ -rays.

The mechanisms most implicated in SH-mediated cytoprotection include:

1. Free-radical *scavenging* that protects against oxygen-based free radical generation by ionizing radiations or chemotherapy agents such as alkylating agents
2. Hydrogen atom donation to facilitate direct chemical *repair* at sites of DNA damage

Chapter 1 includes a discussion of the chain of events between the absorption of a photon and the eventual biologic damage, which includes the

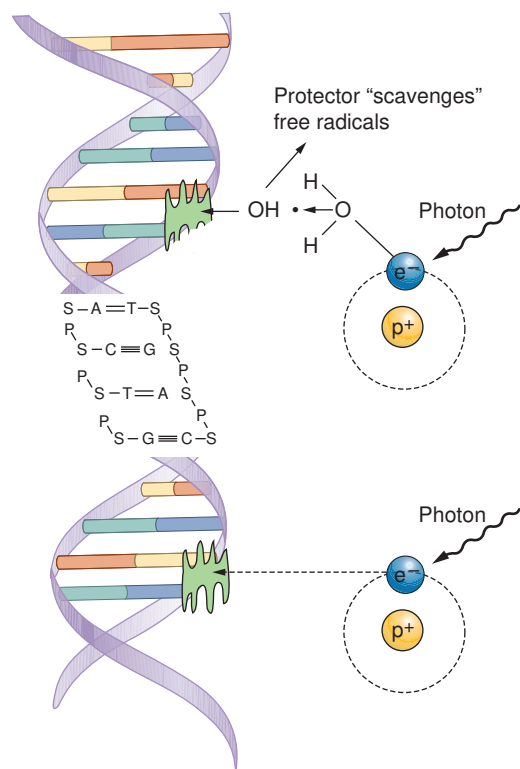


FIGURE 9.1 Radioprotectors containing a sulfhydryl group exert their effect by scavenging free radicals and by reducing free-radical damage to DNA. They are most effective for radiations characterized by low linear energy transfer (LET), becoming progressively less effective with increasing LET because the amount of local damage is so great.

production of free radicals, which are highly reactive species. If these free radicals are scavenged before they can interact with biologic molecules, the effect of the radiation is reduced. This process is illustrated in Figure 9.1.

The protective effect of SH compounds tends to parallel the oxygen effect, being maximal for sparsely ionizing radiations (e.g., x- or

γ-rays) and minimal for densely ionizing radiations (e.g., low-energy α-particles). It might be predicted that with effective scavenging of all free radicals, the largest possible value of *DRF* for sparsely ionizing radiations would equal the oxygen enhancement ratio, with a value of 2.5 to 3.0.

This simple description of the mechanism of action of SH radioprotectors is intellectually satisfying, but it is clearly not the whole story because radioprotectors of this class have more effect with densely ionizing radiations (such as neutrons) than would be expected based on this explanation alone. Other factors must be involved that are not fully understood.

■ DEVELOPMENT OF MORE EFFECTIVE COMPOUNDS

The discovery in 1948 of a compound that offered protection against radiation excited the interest of the U.S. Army because the memory of Nagasaki and Hiroshima was vivid in the years immediately after World War II. However, although cysteine is a radioprotector, it is also toxic and induces nausea and vomiting at the dose levels required for radioprotection. A development program was initiated in 1959 by the U.S. Army in studies conducted at the Walter Reed Institute of Research to identify and synthesize drugs capable of conferring protection to individuals in a radiation environment, but without the debilitating toxicity of cysteine or cysteamine. More than 4,000 compounds were synthesized and tested. At an early stage, the important discovery was made that the toxicity of the compound could be greatly reduced if the SH group was covered by a phosphate group. This is illustrated for cysteamine, otherwise known as mercaptoethylamine (MEA), in Table 9.1. The 50% lethal

TABLE 9.1 Effect of Adding a Phosphate-Covering Function on the Free Sulfhydryl of β-Mercaptoethylamine (MEA)

Drug	Formula	Mean 50% Lethal Dose (Range) in Mice	Dose Reduction Factor
MEA	NH ₂ —CH—CH ₂ —SH	343 (323–364)	1.6 at 200 mg/kg
MEA-PO ₃	NH ₂ —CH ₂ —CH—SH ₂ PO ₃	777 (700–864)	2.1 at 500 mg/kg

TABLE 9.2

Two Radioprotectors in Practical Use

Compound	Structure	Use
WR-638	$\text{NH}_2\text{CH}_2\text{CH}_2\text{SPO}_3\text{HNa}$	Carried in field pack by Russian army (cystaphos)
WR-2721	$\text{NH}_2(\text{CH}_2)_3\text{NHCH}_2\text{CH}_2\text{SPO}_3\text{H}_2$	Protector in radiotherapy and carried by US astronauts on lunar trips (amifostine)

Comparison of Gastrointestinal and Hematopoietic Dose Reduction Factors in Mice for these Radioprotectors (the Two Compounds Listed Previously)

Compound	Drug Dose, mg/kg	Dose Reduction Factor	
		7 Days (Gastrointestinal)	30 Days (Hematopoietic)
WR-638	500	1.6	2.1
WR-2721	900	1.8	2.7

dose of the compound in animals can be doubled and the protective effect in terms of the *DRF* can be greatly enhanced if the SH group is covered by a phosphate. This tends to reduce systemic toxicity. Once in the cell, the phosphate group is stripped and the SH group begins scavenging for free radicals.

The structures of two typical compounds of more than 4,000 synthesized in the Walter Reed series are shown in Table 9.2. The first compound, WR-638, called *cystaphos*, was said to be carried routinely in the field pack of Soviet infantry in Europe during the Cold War for use in the event of a nuclear conflict.

The second compound, WR-2721, now known as *amifostine*, is perhaps the most effective of those synthesized in the Walter Reed series. It gives good protection to the blood-forming organs, as can be seen by the *DRF* for 30-day death in mice, which approaches the theoretic maximum value of 3. It was probably the compound carried by US astronauts on their trips to the moon, to be used if a solar event occurred. On these missions, when the space vehicle left Earth's orbit and began coasting toward the moon, the astronauts were committed to a 14-day mission because they did not have sufficient fuel to turn around without first orbiting the moon and using its gravitational field. If there had been a major solar event in that

period, the astronauts would have been exposed to a shower of high-energy protons, resulting in an estimated total body dose of several grays. The availability of a radioprotector with a *DRF* of between 2 and 3 would have been very important in such a circumstance. As it turned out, no major solar event occurred during any manned lunar mission, thus the protectors were not used. The potential for this problem will be greatly magnified in future missions to Mars, which may take as long as 3 years.

■ AMIFOSTINE (WR-2721) AS A RADIOPROTECTOR IN RADIOTHERAPY

The only radioprotective drug approved by the U.S. Food and Drug Administration (FDA) for use in radiation therapy is amifostine (WR-2721), sold under the trade name Ethyol for use in the prevention of xerostomia in patients treated for head and neck cancer. The Radiotherapy Oncology Group (RTOG) conducted a phase III randomized clinical trial, which demonstrated the efficacy of amifostine in reducing xerostomia in patients with head and neck cancer receiving radiotherapy without prejudice to early tumor control. The drug was administered daily, 30 minutes before each dose fraction in a multifraction regimen. Three months posttreatment, the incidence of xerostomia was significantly reduced

in those patients treated with amifostine. There was an improvement in the patients' assessments of such symptoms as dry mouth and difficulty in eating or speaking and in the need for fluids and oral comfort aids. There was no difference in locoregional tumor control between patients who received the radioprotector and those who did not. Giving the amifostine only 30 minutes before each treatment was designed to exploit the slower rate at which the drug penetrates tumors relative to normal tissues.

Amifostine is a phosphorothioate that is non-reactive and does not readily permeate cells, primarily because of its terminal phosphorothioic acid group. It is therefore a "prodrug." When dephosphorylated by the enzyme alkaline phosphatase, which is present in high concentrations in normal tissues and capillaries, it is converted to the active metabolite designated WR-1065. This metabolite readily enters normal cells by facilitated diffusion and scavenges free radicals generated by ionizing radiations or by drugs used in chemotherapy such as alkylating agents.

It might have been expected that radioprotectors would enjoy a wider use in radiation therapy, but in practice, clinical use continues to be plagued by issues relating to possible tumor protection and loss of therapeutic gain. The potential use of such protectors is based on the observation from animal studies that amifostine quickly floods normal tissues but penetrates more slowly into tumors. Consequently, if the radiation dose is given within minutes after the administration of the radioprotector, there is a differential sparing of normal tissue compared with tumor cells. Because one can never be sure that the tumor is not protected to some extent, the use of radioprotectors is not "fail safe." For this reason, radioprotectors are not widely used in radiotherapy, indeed, in practice they are used only for the reduction of xerostomia.

■ RADIOPROTECTORS AND CHEMOTHERAPY

Although SH compounds were developed initially as radioprotectors against ionizing radiation, they also protect against the cytotoxic effects of several chemotherapeutic agents. The experimental clinical use of amifostine has shown that the compound offers significant protection against nephrotoxicity, ototoxicity,

and neuropathy from cisplatin and hematologic toxicity from cyclophosphamide. The same experimental studies indicated no obvious antitumor activity of the radioprotector, implying a differential uptake between normal and malignant tissues.

■ AMIFOSTINE AS A PROTECTOR AGAINST CANCER

Although the emphasis for the development of amifostine was to protect against cell killing, this compound also protects against radiation-induced mutagenesis and oncogenic transformation in cells in culture and against carcinogenesis in mouse model systems. Furthermore, although a dose of about 400 mg/kg is required to demonstrate optimal cytoprotection—a dose that carries with it significant side effects—its antimutagenic effect persists following prolonged exposure to a dose as low as 25 mg/kg, which is nontoxic. Of even greater interest is the observation that the effect occurs even when cells are exposed to amifostine up to 3 hours following irradiation. This has led to the speculation that the antioxidant properties of amifostine may not be the only mechanism by which it protects against cancer; it has been proposed that the polyamine-like properties of the phosphorothioates may result in a stabilization of DNA-damaged sites, facilitating a slower and more error-free repair of damage.

■ DIETARY SUPPLEMENTS AS COUNTERMEASURES TO RADIATION

Long-term exposure to nonlethal doses of ionizing radiation is known to result in an excess incidence of cancer and other deleterious biologic effects. To the extent that the mechanism involved may include oxidative stress, dietary supplements involving antioxidants have a potential role to play. Several possibilities have shown promise in cellular and animal systems. One such example is the soybean-derived serine protease inhibitor known as the Bowman-Birk inhibitor (BBI), which has long been proposed as a cancer chemopreventive agent. Another possibility is a cocktail of common antioxidants, including L-selenomethionine, ascorbic acid, N-acetyl cysteine, alpha-lipoic acid, vitamin E succinate, and coenzyme Q10.

Following the destruction of the World Trade Center on September 11, 2001, and the rise of a nuclear terrorism threat, there has been a revived interest in the development of novel, effective, and nontoxic radioprotectors for potential use in homeland defense as well as in medical applications. In addition, National Aeronautics and Space Administration (NASA) is interested in countermeasures to the exposure to protons and high-energy heavy ions that astronauts experience during long-term missions in space.

SUMMARY OF PERTINENT CONCLUSIONS

- Radioprotectors are chemicals that reduce the biologic effects of radiation.
- The SH compounds, cysteine and cysteamine, were discovered early but are toxic. If the SH group is covered by a phosphate group, toxicity is reduced.
- The mechanism of action is the scavenging of free radicals and restitution of free-radical damage, although this is not the whole story.
- The *DRF* is the ratio of radiation doses required to produce the same biologic effect in the absence and presence of the radioprotector.
- The best available radioprotectors can attain *DRF* values of 2.5 to 3.0 for bone marrow death in mice irradiated with x-rays.
- *DRF* values close to the oxygen enhancement ratio are possible for γ -rays, but the effectiveness of radioprotectors decreases with increasing linear energy transfer.
- During the Cold War, it is said that Soviet infantry in Europe carried radioprotectors for use in a possible nuclear war. Radioprotectors were carried to the moon by US astronauts to be used in the event of a solar flare.
- More than 4,000 compounds were synthesized by the U.S. Army in studies conducted at the Walter Reed Institute of Research. Amifostine (WR-2721) appears to be the best for use in conjunction with radiotherapy.
- Amifostine, sold under the trade name Ethiol, is the only radioprotective drug approved by the FDA for use in the prevention of xerostomia in patients treated for head and neck cancer.
- An RTOG phase III trial demonstrated the efficacy of amifostine in reducing xerostomia in patients with head and neck cancer receiving radiation therapy without affecting locoregional control. The radioprotector was administered 30 minutes before radiation.
- Amifostine is a “prodrug” that is unreactive and that penetrates poorly into cells until it is dephosphorylated by the enzyme alkaline phosphatase to the active metabolite WR-1065.
- The rationale for the use of phosphorothioate radioprotectors is that they flood normal tissues rapidly after administration but penetrate tumors much more slowly. The strategy is to begin irradiation soon after administration of the drug to exploit a differential effect.
- The clinical use of radioprotectors in radiation therapy continues to be plagued by issues relating to possible tumor protection and diminution of therapeutic gain.
- Amifostine is useful as a protector for chemotherapy as well as radiotherapy. It is reported to offer protection against nephrotoxicity, ototoxicity, and neuropathy from cisplatin and hematologic toxicity from cyclophosphamide, without reduction of tumor activity.
- A dose of 400 mg/kg is required for optimal cytoprotection, which is toxic with many side effects, but its antimutagenic effect persists at a low nontoxic dose of 25 mg/kg. Furthermore, its antimutagenic effect still occurs if the drug is added 3 hours following irradiation.
- Dietary supplements, including various antioxidants, have been suggested as countermeasures to the long-term biologic effects of radiation exposure.
- Following the destruction of the World Trade Center on September 11, 2001, and the rise of a nuclear terrorism threat, there has been a revived interest in the development of novel, effective, and nontoxic radioprotectors for potential use in homeland defense. In addition, NASA is interested in countermeasures to the radiation exposure that astronauts experience on long-term space missions.

■ BIBLIOGRAPHY

- Brizel DM, Overgaard J. Does amifostine have a role in chemoradiation treatment? *Lancet Oncol.* 2003;4(6):378–381.
- Brizel D, Sauer R, Wannenmacher M, et al. Randomized phase III trial of radiation \pm amifostine in patients with head and neck cancer [abstract 1487]. *Proceedings of ASCO* 17. 1998.
- Bump EA, Malaker K, eds. *Radioprotectors: chemical, biological, and clinical perspectives*. Boca Raton, FL: CRC Press; 1997.
- Grdina DJ, Kataoka Y, Basic I, et al. The radioprotector WR-2721 reduces neutron-induced mutations at the hypoxanthine-guanine phosphoribosyl transferase locus in mouse splenocytes when administered prior to or following irradiation. *Carcinogenesis*. 1992;13:811–814.
- Grdina DJ, Kataoka Y, Murley JS. Amifostine: mechanisms of action underlying cytoprotection and chemoprevention. *Drug Metabol Drug Inter.* 2000;16(4):237–279.
- Grdina DJ, Murley JS, Kataoka Y. Radioprotectants: current status and new directions. *Oncology*. 2002;63(suppl 2):2–10.
- Grdina DJ, Shigematsu N, Dale P, et al. Thiol and disulfide metabolites of the radiation protector and potential chemopreventive agent WR-2721 are linked to both its anti-cytotoxic and anti-mutagenic mechanisms of action. *Carcinogenesis*. 1995;16:767–774.
- Kennedy AR, Guan J, Ware JH. Countermeasures against space radiation induced oxidative stress in mice. *Radiat Environ Biophys.* 2007;46:201–203.
- Kennedy AR, Zhou Z, Donahue JJ, et al. Protection against adverse biologic effects induced by space radiation by the Bowman-Birk inhibitor and antioxidants. *Radiat Res.* 2006;166:327–332.
- Liu T, Liu Y, He S, et al. Use of radiation with or without WR-2721 in advanced rectal cancer. *Cancer*. 1992;69:2820–2825.
- Patt HM, Tyree B, Straube RL, et al. Cysteine protection against x-irradiation. *Science*. 1949;110:213–214.
- Rasey JS, Nelson NJ, Mahler P, et al. Radioprotection of normal tissues against gamma-rays and cyclotron neutrons with WR2721: LD50 studies and 35S-WR2721 biodistribution. *Radiat Res.* 1984;97:598–607.
- Sweeney TR. *A Survey of Compounds from the Antiradiations Drug Development Program of the US Army Medical Research and Development Command*. Washington, DC: Walter Reed Army Institute of Research, 1979.
- Utley JF, Marlowe C, Waddell WJ. Distribution of 35S-labeled WR-2721 in normal and malignant tissues of the mouse. *Radiat Res.* 1976;68:284–291.
- Yuhas JM. Active versus passive absorption kinetics as the basis for selective protection of normal tissues by S-2-(3-aminopropylamino)-ethyl-phosphorothioic acid. *Cancer Res.* 1980;40:1519–1524.
- Yuhas JM. Differential chemoprotection of normal and malignant tissues. *J Natl Cancer Inst.* 1969;42:331–335.

Radiation Carcinogenesis

Deterministic and Stochastic Effects
Carcinogenesis: The Human Experience
The Latent Period
Assessing the Risk
Committees Concerned with Risk Estimates and Radiation Protection
Radiation-Induced Cancer in Human Populations
 Leukemia
 Thyroid Cancer
 Breast Cancer
 Lung Cancer
 Bone Cancer
 Skin Cancer
Quantitative Risk Estimates for Radiation-Induced Cancer

Dose and Dose-Rate Effectiveness Factor
Summary of Risk Estimates
Second Malignancies in Radiotherapy Patients
 Second Cancers after Radiotherapy for Prostate Cancer
 Radiation Therapy for Carcinoma of the Cervix
 Second Cancers among Long-Term Survivors from Hodgkin Disease
Dose-Response Relationship for Radiation Carcinogenesis at High Doses
Cancer Risks in Nuclear Industry Workers
Mortality Patterns in Radiologists
Childhood Cancer after Radiation Exposure In Utero
Nonneoplastic Disease and Radiation
Summary of Pertinent Conclusions
Bibliography

■ DETERMINISTIC AND STOCHASTIC EFFECTS

If cellular damage occurs as a result of radiation and it is not adequately repaired, it may prevent the cell from surviving or reproducing or it may result in a viable cell that has been modified, that is, suffered a change or mutation that it retains as a legacy of the radiation exposure. The two outcomes have profoundly different implications for the person of whom the cell is a part.

Most organs or tissues of the body are unaffected by the loss of a few cells; but if the number of cells lost is sufficiently large, there is observable harm, reflecting the loss of tissue function. The probability of such harm is zero at small radiation doses, but above some level of dose, called the *threshold dose*, the probability increases rapidly with dose to 100%. Above the threshold, the severity of harm also increases with dose. Effects such as these are said to be *deterministic*. A deterministic effect has a threshold in dose, and the severity of the effect is dose related. Radiation-induced cataracts and late tissue fibrosis are examples of deterministic effects.

The outcome is very different if the irradiated cell is viable but modified. Carcinogenesis and heritable effects fall into this category. If somatic cells are exposed to radiation, the probability of cancer increases with dose, probably with no

threshold, but the severity of the cancer is not dose related. A cancer induced by 1 Gy is no worse than one induced by 0.1 Gy, but of course, the probability of its induction is increased. This category of effect is called *stochastic*, a word that has been given a special meaning in radiation protection but in general, just means “random.” If the radiation damage occurs in germ cells, mutations may occur that could cause deleterious effects in future generations. Again, there is probably no threshold and the severity of heritable effects is not dose related, although the probability of it occurring is.

The belief that stochastic effects have no dose threshold is based on the molecular mechanisms involved. There is reason to believe that even a single x-ray photon could result in a base change leading to a mutation that could cause cancer or a heritable defect. For this reason, it is considered prudent and conservative to assume that no dose is too small to be effective, although this can never be proved.

The two types of effects are summarized as follows:

Deterministic effect: severity increases with dose; practical threshold; probability of occurrence increases with dose (e.g., cataract).
 Stochastic effect: severity independent of dose; no threshold; probability of occurrence increases with dose (e.g., cancer).

■ CARCINOGENESIS: THE HUMAN EXPERIENCE

Cancer induction is the most important somatic effect of low-dose ionizing radiation. In sharp contrast to the case for the heritable effects of radiation (Chapter 11), risk estimates for leukemogenesis and carcinogenesis do not rely on animal data but can be based on experience in humans. There is a long history of a link between radiation exposure and an elevated incidence of cancer. Figure 10.1 is a beautiful photograph of Marie Curie and her daughter Irene, who are both thought to have died of leukemia as a result of the radiation exposure they received while conducting their experiments with radioactivity. Figure 10.2 is a photograph of the hand of a dentist in New York who held x-ray films in place in patients' mouths for many years and who suffered malignant changes as a result. Quantitative data on cancer induction by



FIGURE 10.1 Marie Curie (seated) at work with her daughter, Irene. Both are thought to have died of leukemia as a consequence of the radiation exposure they received during their experiments with radioactivity. (Courtesy of the Austrian Radium Institute and the International Atomic Energy Bulletin.)



FIGURE 10.2 Hand of a dentist who, for 35 years, held x-ray films in place in patients' mouths. The thumb has been partially amputated. Damaged skin on the fingers has been replaced by grafts. The lesion on the finger is a skin cancer subsequently removed. (Courtesy of Dr. Victor Bond, Brookhaven National Laboratory.)

radiation come from populations irradiated for medical purposes or exposed deliberately or inadvertently to nuclear weapons. Persons exposed therapeutically received comparatively high doses, and their susceptibility to the effects of radiation might have been influenced by the medical condition for which treatment was being given. Populations exposed to γ -rays and neutrons from nuclear weapons represent a wider cross section in terms of age and health and also include persons exposed to lower doses. In both cases, dose rates were high and exposure times brief.

There are a few groups of exposed persons to whom these generalizations do not apply. Examples include pitchblende and uranium miners who inhaled the radioactive gas radon and its progeny products over a prolonged period, patients injected with radium chloride or Thorotrast for medical purposes, and persons who ingested radionuclides while painting luminous dials on clocks and watches with paint containing radium. Hundreds of thousands of nuclear workers have been exposed occupationally, and useful cancer risk estimates have become available in recent years. Miners exposed to radon in the uranium mines are an excellent source of data on lung cancer.

The early human experience of radiation-induced cancer may be summarized as follows:

1. Skin cancer and leukemia were common in early x-ray workers, principally physicists and engineers who worked around accelerators before radiation safety standards were introduced.
2. Lung cancer was a frequent problem in pitchblende miners in Saxony, who dug out the ore from which radium was extracted. In the years following World War II, lung cancer also was noted in uranium miners in the central Colorado plateau. In both cases, the mines were poorly ventilated and there was a buildup of radon gas in the atmosphere of the mine; radon and its progeny were inhaled by the miners, depositing atoms of radioactive material in their lungs. The intense local α -radiation was responsible for inducing lung tumors. Bone tumors were observed in the radium dial painters. The painters were mostly young women who worked in factories in which the luminous dials on clocks and watches were painted with a special paint preparation containing radium. The workers dipped their brushes into the radium paint and used their tongues to shape the brushes into sharp points to paint the small dials on watches. As a result, some radium was ingested, which, because it is in the same group in the periodic table as calcium, was deposited in the tips of the growing bones. The intense α -radiation produced bone tumors. There is also history of bone tumors in people who, in the 1920s and 1930s, received injections of radium salts for the treatment of tuberculosis or ankylosing spondylitis.
3. An excess incidence of liver tumors was reported in patients in whom the contrast material Thorotrast was used. Thorotrast contains radioactive thorium, which, when deposited in the liver, produced a small incidence of liver tumors by α -radiation.

These early examples are interesting but largely anecdotal, although they did alert scientists to the danger of excessive radiation exposure. None of these examples involved situations that now constitute a public health hazard; these problems will never happen again, and the

dosimetry in each instance is so uncertain that it is rarely possible to deduce any quantitative relationship between the dose of radiation involved and the tumor incidence.

More recent examples of the human experience with radiation-induced cancer and leukemia include the following:

1. The Japanese survivors of the atomic bomb attacks on Hiroshima and Nagasaki are the most important single group studied because of their large number, the care with which they have been followed, and the fact that people of all ages and both sexes received a wide range of doses. About 120,000 people have been followed carefully, of whom about 50,000 received doses in excess of 0.005 Sv. By 1998, there had been more than 17,000 cases of cancer, of which about 853 were considered to be caused by radiation. The weapons used on the two cities were very different. The one used on Nagasaki was of a type that would be expected to emit gamma rays with few neutrons and had been previously tested, so dosimetry is based partly on measurements. The weapon used at Hiroshima was of a type never tested before or since, so that dose estimates are based largely on computer simulations. The radiation from this weapon was a mixture of neutrons and γ -rays. The dosimetry relating to the atomic bombs has been revised several times over the years, leading to changes in the cancer risk estimates. The most recent estimates were published in the *Biologic Effects of Ionizing Radiation* (BEIR) VII report in 2006 and will be discussed later in this chapter.
2. In Britain, from 1935 through 1944, some 14,000 patients suffering from ankylosing spondylitis were given radiotherapy to various regions of their spine to relieve pain. A small risk of leukemia mortality has been reported in these patients. Although the spondylitic series provides one of the largest bodies of data on leukemia in humans after exposure to x- or γ -radiation, and the dosimetry is quite good, it is far from ideal because it lacks a proper control, consisting of patients with the same disease who did not receive x-ray therapy but whose treatment was otherwise the same. A possible contribution

of carcinogenic drugs to the tumor incidence also has been suggested.

3. There is also documentation of an elevated incidence of leukemia in radiologists who joined learned societies before about 1922, before the introduction of radiation safety standards. This will be discussed later in the chapter.
4. Thyroid cancer has been observed in children who received radiotherapy for what was thought to be an enlarged thymus. The thyroid was included in the treatment field, and both malignant and benign thyroid tumors have been observed. Breast cancer is also elevated in these patients.
5. Until the 1950s, it was common practice to use x-rays to epilate children suffering from *tinea capitis* (ringworm of the scalp). An increased incidence of thyroid cancer from this practice was first reported by Modan and his colleagues in Israel, who treated more than 20,000 immigrant children from North Africa in whom ringworm of the scalp reached epidemic proportions. There was also a significantly increased risk of brain tumors (mostly meningiomas), salivary gland tumors, skin cancer, and leukemia mortality. A comparable group of children in New York for whom x-rays were used for epilation before treatment for *tinea capitis* show quite different results. There were only two malignant thyroid tumors in addition to some benign tumors. There is, however, an incidence of skin cancer around the face and scalp in those areas also subject to sunlight. The skin tumors arose only in white children and there were no tumors in black children in the New York series.
6. Patients with tuberculosis, who were fluoroscoped many times during artificial pneumothorax, have shown an elevated incidence of breast cancer. This was first reported in Nova Scotia, but the report was confirmed by a similar study in New England. The doses these patients received are uncertain but must have been about 0.8 to 0.9 Gy, because some of the women developed skin changes in the chest wall on the side frequently fluoroscoped. Patients who received radiotherapy for postpartum mastitis were also shown to have an excess incidence of breast cancer.

■ THE LATENT PERIOD

The time interval between irradiation and the appearance of a malignancy is known as the **latent period**.

Leukemia has the shortest latent period. Excess cases began to appear in the survivors of Hiroshima and Nagasaki a few years after irradiation and reached a peak in 5 to 7 years; most cases occurred in the first 15 years. Solid tumors show a longer latency than the leukemias, on the order of anything from 10 to 60 years or more. For example, an excess incidence of solid tumors is still evident in Japanese survivors exposed to radiation from the atomic bombs in 1945. Indeed, for solid cancers, the excess risk is apparently more like a lifelong elevation of the natural age-specific cancer risk.

As the Japanese data have matured, the concept of a fixed time interval between irradiation and the appearance of the malignancy has been replaced by or combination of “age at exposure” and “time since exposure.” Regardless of the age at the time of exposure, radiation-induced solid tumors tend to be expressed later in life, at the same time as spontaneous tumors of the same type. Breast cancer in women is the most striking example. This suggests that although radiation may initiate the carcinogenic process at a young age, additional steps are required later in life, some of which may well be hormone dependent.

■ ASSESSING THE RISK

To use the available human data to estimate risks as a function of dose, it is necessary to fit the data to a model. Several reasons for this are as follows:

1. Data obtained at relatively high doses must be extrapolated to the low doses of public health concern.
2. No large human population exposed to radiation has yet been studied for its full life span, and so estimates must be projected into the future. For example, in the year 2000, about half of the Japanese survivors irradiated in 1945 were still alive.
3. The best data pertain to the Japanese irradiated by the atomic bombs and risk estimates based on this must be transferred to other populations that have quite different characteristics, including their natural cancer incidence.

There are two types of models that are conceptually quite different: the absolute risk model and the relative risk model. The **absolute risk model** assumes that radiation induces a “crop” of cancers over and above the natural incidence unrelated to it. The **relative risk model** assumes that the effect of radiation is to increase the natural incidence *at all ages* subsequent to exposure by a given factor. Because the natural or spontaneous cancer incidence rises significantly in old age, the relative risk model predicts a large number of radiation-induced cancers in old age.

The model favored by recent BEIR committees, for the assessment of the cancer risks from the Japanese atomic bomb survivors is the **time-dependent relative risk model**. The excess incidence of cancer was assumed to be a function of dose, the square of the dose, age at exposure, and time since exposure. For some tumors, gender must be added as a variable—for example, in the case of breast cancer.

■ COMMITTEES CONCERNED WITH RISK ESTIMATES AND RADIATION PROTECTION

There are two series of reports that analyze available data and come up with risk estimates for radiation-induced cancer. The first is the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) reports. This committee reports to the General Assembly at regular intervals; the most recent report appeared in 2000. The second is the committee of the U.S. National Academy of Sciences known as the Biologic Effects of Ionizing Radiation (BEIR). Reports appear periodically, the most recent comprehensive report (BEIR VII) appearing in 2006. To a large extent, these are “scholarly” committees, inasmuch as they are under no compulsion to draw conclusions if data are not available.

On the other hand, there are committees involved with radiation protection that cannot afford to be scholarly because they must make recommendations whether or not adequate data are available. First, there is the International Commission on Radiological Protection (ICRP). This commission was originally set up and funded by the first International Congress of Radiology. Over the years, the funding base of this commission has broadened, and it

has assumed the role of an independent, self-propagating committee. At a national level in the United States, there is the National Council on Radiological Protection and Measurements (NCRP). This is an independent body chartered by Congress and is funded from industry, government grants, and professional societies. The NCRP formulates policies for radiation protection in the United States often, but not always, following the lead of the ICRP. The recommendations of the NCRP carry no weight in law but are usually adopted eventually and enforced by the regulatory agencies in the United States, although there can often be a long lag period. (See Chapter 17 on radiation protection for more regarding these committees.)

■ RADIATION-INDUCED CANCER IN HUMAN POPULATIONS

Under appropriate conditions, a malignancy can be induced in essentially all tissues of the body. Some of the most common are discussed below.

Leukemia

The incidence of chronic lymphocytic leukemia does not appear to be affected by radiation. Acute and chronic myeloid leukemia are the types chiefly responsible for the excess incidence observed in irradiated adults. Susceptibility to acute lymphatic or stem cell leukemia seems to be highest in childhood and to decrease sharply during maturation.

Two principal population groups provide data to determine risk estimates:

1. Survivors of the atomic bomb attacks on Hiroshima and Nagasaki
2. Patients treated for ankylosing spondylitis

Leukemia was the first malignancy to be linked with radiation exposure in the A-bomb survivors and has the highest relative risk of any malignancy. Leukemia risks increased with dose up to about 3 Sv, with evidence of upward curvature; that is, a linear-quadratic function of dose fits the data significantly better than a linear function. Because of this curvature, the risk per unit of dose at 1 Sv is about three times greater than at 0.1 Sv.

For those exposed younger than age about 30, nearly all of the excess deaths occurred before 1975, but for those exposed at older ages,

the excess risk appeared to persist throughout the follow-up period. Because of these complications, simple models cannot adequately summarize leukemia risks.

Thyroid Cancer

The thyroid gland is an organ of high sensitivity for radiation carcinogenesis, at least in children; in adults, radiation is much less efficient in inducing thyroid cancer. The malignant tumors that have been produced, however, consistently have been of a histologically well-differentiated type, which develops slowly and often can be removed completely by surgery or treated successfully with radioactive iodine if metastasized; consequently, these tumors show a low mortality rate. It is estimated that about 5% of those with radiation-induced thyroid cancer die as a result.

The following are the principal population groups available for deriving risk estimates for thyroid cancer:

1. Survivors of the atomic bomb attacks on Hiroshima and Nagasaki.
2. Residents of the Marshall Islands exposed to external radiation and ingested iodine-131 from fallout after the 1954 testing of a thermonuclear device, in whom there was a high incidence of nodule formation and some thyroid cancer (benign as well as malignant tumors).
3. Individuals who ingested radioactive iodine as a result of the Chernobyl accident (this experience shows how very sensitive children are and that adults are relatively resistant).
4. Children treated with x-rays for an enlarged thymus.
5. Children treated for diseases of the tonsils and nasopharynx.
6. Children epililated with x-rays for the treatment of tinea capitis.
7. Children treated for cancer.

Figure 10.3 shows the relative risk for thyroid cancer after exposure to external radiation, taken from a pooled analysis of seven different studies, which dramatically illustrates the importance of age at exposure.

Breast Cancer

Breast cancer may be induced with relatively high frequency by radiation. The cancer is of the type arising initially from duct cells but is commonly found to infiltrate breast tissue.

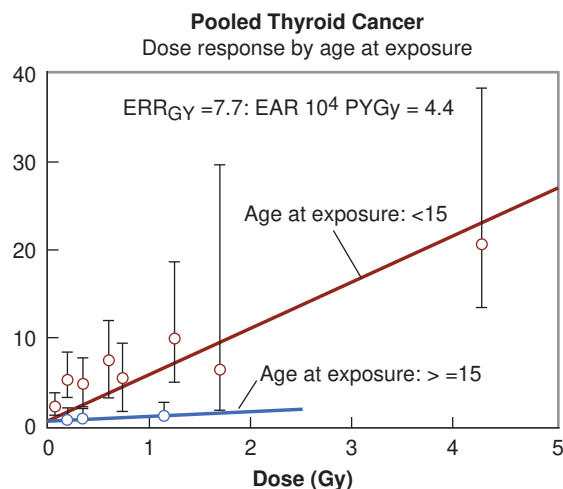


FIGURE 10.3 Relative risk of thyroid cancer after exposure to external radiation, taken from a pooled analysis of seven studies. The data clearly show the importance of age at exposure. (Figure prepared by Dr. Elaine Ron, based on the data from Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res.* 1995;141:259–277.)

There are three principal exposed populations from which the risk of breast cancer incidence may be derived:

1. Japanese female survivors of the atomic bomb attacks on Hiroshima and Nagasaki.
2. Female patients in a Nova Scotia sanatorium subjected to multiple fluoroscopies during artificial pneumothorax for pulmonary tuberculosis. There is doubt about the dosimetry, but the dose to breast tissue per fluoroscopy is estimated to have been 0.04 to 0.2 Gy. The number of examinations commonly exceeded 100, and in some instances, women received more than 500 fluoroscopies; three patients, in fact, developed radiation dermatitis. This group of exposed women probably constitutes the most convincing evidence of the production of cancer by fractionated x-rays used for diagnosis. This Canadian study also showed the importance of age at the time of exposure. The study was later confirmed by the follow-up of patients discharged from two tuberculosis sanatoria in Massachusetts. These patients were examined fluoroscopically at an average of 102 times over a period of years and, subsequently, were

found to be 80% more likely to develop breast cancer than a comparable unexposed population.

3. Females treated for postpartum mastitis and other benign conditions. Patients typically received 1 to 6 Gy and showed an excess incidence of breast cancer compared with the general female population of New York State. A legitimate objection to the use of these data for risk estimates is the uncertainty of whether postpartum mastitis predisposes to breast cancer.
4. The data for excess incidence of breast cancer in these populations are shown in Figure 10.4. Several interesting points are immediately apparent. First, the data from the New York series of postpartum

mastitis patients are so poor that they do not give any clue about the shape of the dose–response relationship. Second, there is a marked difference in the natural incidence of breast cancer in Japanese women in whom it is low, compared with American and Canadian women in whom it is high; nevertheless, in all cases, incidence rises with radiation dose. Third, the data for breast cancer are reasonably well fitted by a straight line.

Lung Cancer

Radiation is but one of a long list of carcinogens for lung cancer: Cigarette smoking, asbestos, chromium salts, mustard gas, hematite, and asphalt derivatives have also been implicated.

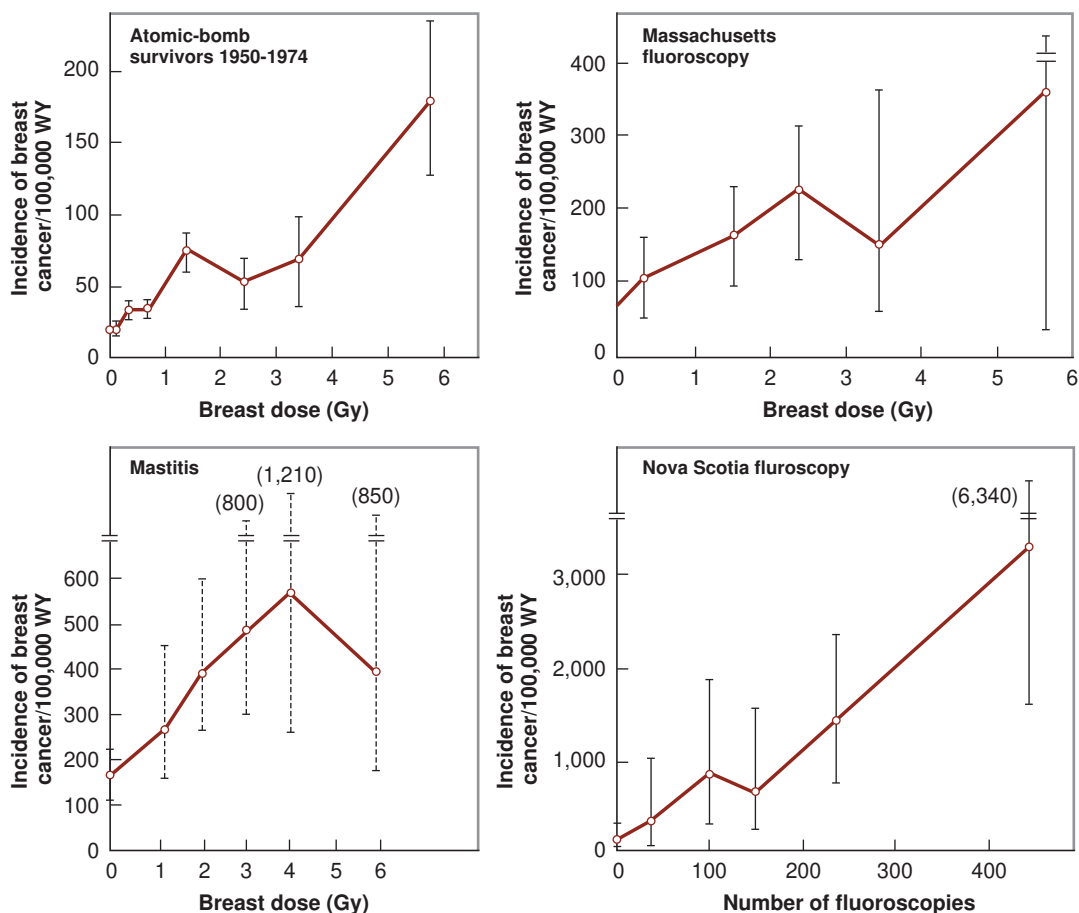


FIGURE 10.4 Incidence of breast cancer as a function of dose for four human populations that allow risk estimates to be made. The data are expressed in terms of the number of cases per 100,000 women-years (WY). Note that the natural incidence of breast cancer is low in Japanese women and high in American and Canadian women. (Adapted from Boice JD Jr, Land CE, Shore RE, et al. Risk of breast cancer following low-dose exposure. *Radiology*. 1979;131:589–597, with permission.)

Radiation risk estimates come from two principal sources:

1. Individuals exposed to external sources of radiation, including the Japanese survivors and those with ankylosing spondylitis. An excess was found even when smoking was taken into account.
2. Underground miners exposed to radon in the mine atmosphere. The naturally occurring deposits of radioactive materials in the rocks of the earth decay through a long series of steps until they reach a stable isotope of lead. One of these steps involves radon, which, unlike the other elements in the decay series, is a gas. In the closed environment of a mine, workers inhale radon gas and some radon atoms decay to the next solid member of the radioactive series, which consequently is deposited on the bronchial epithelium. Subsequent steps in the radioactive decay series take place in the lungs, causing intense α -irradiation of localized surrounding tissue.

There is a clear excess of lung cancer among workers in the uranium mines of the Colorado plateau in the United States, the uranium mines in Czechoslovakia, the nonuranium mines in Sweden, and the fluorspar mines in Newfoundland. It remains difficult to separate adequately the contributory effects of radon and cigarette smoking in causing the cancers, because there are too few nonsmoking miners to form an adequate control group. In addition, the average duration of exposure usually spans from 15 to 20 years, during which standards of safety and ventilation have changed substantially. In any case, it is no easy matter to estimate the dose to the critical cells in the basal layer of the epithelium of the lung from knowledge of the radon concentration in the air that is breathed. There is also some evidence, summarized in the BEIR VI report, of an excess of lung cancer from domestic radon exposure. It is estimated that 10% of the 150,000 lung cancer deaths annually in the United States are caused by radon.

Bone Cancer

There is some evidence of bone cancer induced by external x-irradiation in children epilated for the treatment of tinea capitis and

in patients treated for ankylosing spondylitis. The numbers are small and the risk estimates poor. The largest body of data comes from two populations, each of which ingested isotopes of radium that emit high linear energy transfer (LET) α -particles and that follow the metabolic pathways of calcium in the body to become deposited in the bone. The populations include the following:

1. Young persons, mostly women, employed as dial painters, who ingested radium as a result of licking their brushes into a sharp point for application of luminous paint to watches and clocks. In this group, there have been bone sarcomas and carcinomas of epithelial cells lining the paranasal sinuses and nasopharynx. None of these tumors occurred at doses below 5 Gy; above this level, the incidence rose sharply, particularly the sarcomas. The radium in these paints consisted of the isotopes radium-226 and radium-228, with half-lives of about 1,600 years and 6 years, respectively.
2. Patients given injections of radium-224 for the treatment of tuberculosis or ankylosing spondylitis.

There are three points that need to be emphasized. First, the dose is made up of α -particles, which have a short range and deposit their energy close to the site at which the isotope is deposited; α -particles are also more effective than x-rays by a factor of about 20. Second, osteosarcomas arise predominantly from endosteal cells, and the relevant dose for estimating the risk of sarcoma is the dose to these cells, which lie at a distance of up to 10 μm from the bone surface, rather than the mean dose throughout the bone. Radium-224 has a short half-life (3.6 days), and its radiation therefore is largely delivered while it is still present on the bone surface. This contrasts sharply with radium-226 and radium-228, which have long half-lives and, consequently, become distributed throughout the bone during their periods of radioactive decay. The dose to endosteal cells from radium-224 is about nine times larger than the dose averaged throughout bone, whereas it is about two-thirds of the mean bone value from radium-226. Consequently, it is difficult to compare data from the two groups of people who were exposed to these very different

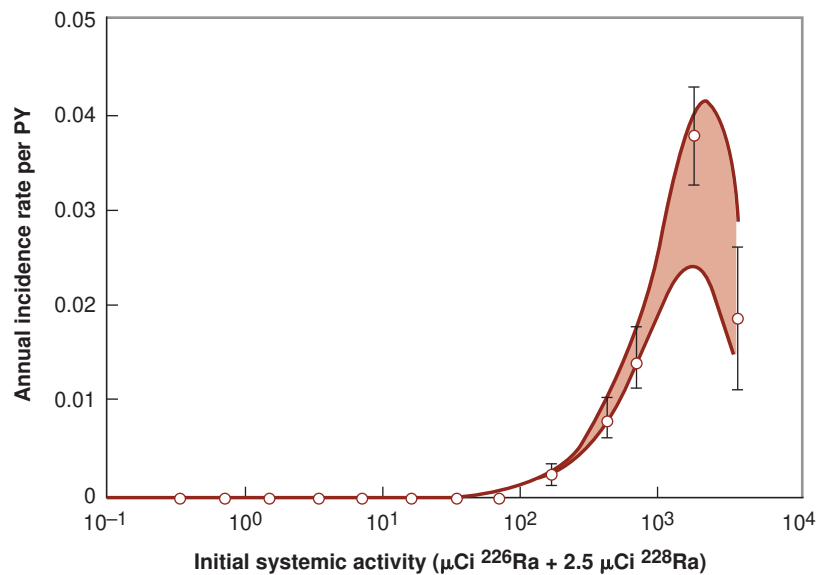


FIGURE 10.5 A semilogarithmic plot of bone sarcoma incidence rate as a function of systemic intake for female dial painters employed before 1950, showing a dose-squared exponential fit. The shaded band indicates the range covered by the fitted function if the coefficients are allowed to vary by ± 1 standard deviation. (Adapted from Rowland R, Stehner AF, Lucas HF. Dose-response relationships for radium-induced bone sarcomas. *Health Phys.* 1983;44:15–31, with permission.)

isotopes of radium. Third, age at the time of exposure is an important factor in the development of bone cancer. For young persons, and possibly for those exposed in utero, the rapid deposition of bone-seeking radioisotopes during active bone growth might confer a higher risk of cancer than in adults. There is, in general, poor agreement among the risk estimates derived from the various groups of persons showing an excess of bone cancer, so that risk estimates must be very crude. Figure 10.5 shows the incidence of bone sarcoma in female dial painters as a function of activity of radium ingested. These data imply that a linear extrapolation from high to low doses would overestimate risks at low doses. It appears that sarcomas are induced only after large doses that are sufficient to cause tissue damage and, therefore, to stimulate cell proliferation.

Skin Cancer

The first neoplasm attributed to x-rays was an epidermoid carcinoma on the hand of a radiologist, which was reported in 1902. In the years that followed, several hundred of such cases arose among physicians, dentists, physicists, and

x-ray technicians, in an era in which safety standards were virtually nonexistent. In most cases, the onset of neoplasms followed chronic radio-dermatitis and a long latent period. Squamous cell and basal cell carcinomas have been most frequently observed, and occasionally, a sarcoma of the subcutaneous tissues has been seen. Since the evolution of modern safety standards, epidermoid carcinoma has ceased to be an occupational disease of radiation workers.

Radiation-induced skin cancers are diagnosed readily and treated at an early stage of development, and there is a large difference between rates of incidence and mortality. There is a small excess incidence of skin cancer in the children epilated with x-rays for the treatment of tinea capitis.

■ QUANTITATIVE RISK ESTIMATES FOR RADIATION-INDUCED CANCER

Despite a diverse collection of data for cancer in humans from medical sources, both the BEIR and UNSCEAR reports elect to base their risk estimates almost entirely on the data from the survivors of the atomic bomb attacks on Hiroshima



RERF A-Bomb Cohorts

Cohort	Size
Life Span Study	120,000 Allows an estimate of cancer incidence and mortality
In-Utero Cohort	3,600 Allows estimates of mental retardation, microcephaly, etc.
Children of exposed individuals	77,000 Allows estimate of heritable effects

FIGURE 10.6 There are three cohorts of A-bomb survivors available at the RERF in Japan. The life span cohort includes 120,000 people that allow an estimate to be made of the cancer incidence and mortality that resulted from radiation exposure. The in utero cohort, consisting of 3,300 people who were irradiated in utero, allows an estimate to be made of mental retardation and microcephaly caused by radiation. The F1 generation (i.e., the children of exposed persons) allows a study of the heritable effects of radiation. (Reproduced with permission of RERF.)

and Nagasaki. Figure 10.6 summarizes the study groups available from the Radiation Effects Research Foundation (RERF).

1. The Life Span Study (LSS), comprising about 120,000 people, allows estimates to be made of the radiation-induced cancer incidence and cancer mortality.
2. The in utero cohort, comprising about 3,300 people who were exposed to radiation from the bombs while in utero, allows estimates to be made of the incidence of malformations, growth retardation, microcephaly, and mental retardation.
3. The children of the exposed persons, the so-called F1 generation, allows estimates to be made of heritable effects.

Figure 10.7 charts the incidence of radiation associated deaths following the A-bomb attacks in 1945. Leukemia was the first malignancy to be linked with radiation exposure in bomb survivors

and has the highest relative risk of any malignancy. Leukemia deaths reached a peak of 5 to 7 years after irradiation, subsequently falling rapidly. For those exposed younger than the age of about 30 years, nearly all of the excess deaths occurred within 30 years, but for those exposed at older ages, the excess risk appears to persist throughout the follow-up period. An excess of solid tumors did not appear at first, but once they did, excess deaths have continued up to the present time. There are about six solid cancers for each leukemia. Since about 1990, there is evidence for the induction of noncancer effects, particularly heart disease, stroke, digestive disorders, and respiratory disease, particularly at higher doses of around 1 Sv. For these noncancer end points, it is not possible to say with any certainty whether there is a threshold, nor is it clear what cellular or tissue mechanisms might underlie such a diverse set of disorders.

Table 10.1 shows a summary of the data for cancer incidence in the atomic bomb survivors

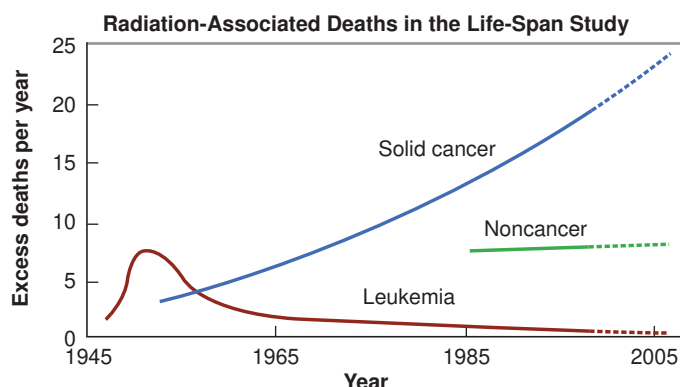


FIGURE 10.7 Illustrating the pattern of radiation-associated deaths in the life span study in the A-bomb survivors. Leukemia appeared first, reaching a peak by 5 to 7 years after irradiation, before falling off later. Solid cancers did not appear in excess for several years, but have continued to increase ever since. By about 1990, it was evident that there is also an excess of noncancer deaths, especially stroke and heart disease. (Courtesy of Dr. Mabuchi.)

up to 1998. The raw data are shown principally to emphasize the relative poverty of the data; only a few hundred excess cancer cases caused by radiation are involved, compared with many thousands of naturally occurring malignancies—and these must be allocated to different dose groups and different sites.

Figure 10.8 shows the data for cancer incidence in the A-bomb survivors for the years 1958–1994. The relative risk is a linear function of dose up to about 2 Sv. Over the lower dose range from 0 to 0.5 Sv, there is a suggestion that the risks are slightly higher than the linear extrapolation from higher doses. There is some uncertainty in the control group (i.e., the zero-dose group) used for comparison. There are in fact two zero-dose groups; N beyond 3,000 m and survivors within

3,000 m who, for one reason or another, were not exposed (e.g., they might have been out of the city at the time). The two groups have slightly different cancer rates, which is not surprising, because one is a rural and the other, an urban population.

■ DOSE AND DOSE-RATE EFFECTIVENESS FACTOR

The Japanese data relate only to high dose rates (HDR) because they are based on the atomic bomb survivors. Both the UNSCEAR and BEIR committees considered that there is a dose-rate effect for low LET radiations; that is, fewer malignancies are induced if a given dose is spread out over a period of time at low dose rate (LDR) than if it is delivered in an acute

TABLE 10.1 Solid Cancer 1958 through 1998

Dose, Gy	Subjects	Mean Dist, m	Cases	Excess
No in city	25,427	—	3,994	0
<0.005	35,545	3,969	5,603	3
0.005–	27,789	2,114	4,406	81
0.1–	5,527	1,608	968	75
0.2–	5,935	1,430	1,144	179
0.5–	3,173	1,260	688	206
1–	1,647	1,118	460	196
2–4	564	934	185	111
Total	105,427	—	17,448	853

Abbreviations: dist, distance; m, meter.

Source: Preston DL, Ron E, Tokuoka S, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res.* 2007;168:1–164.

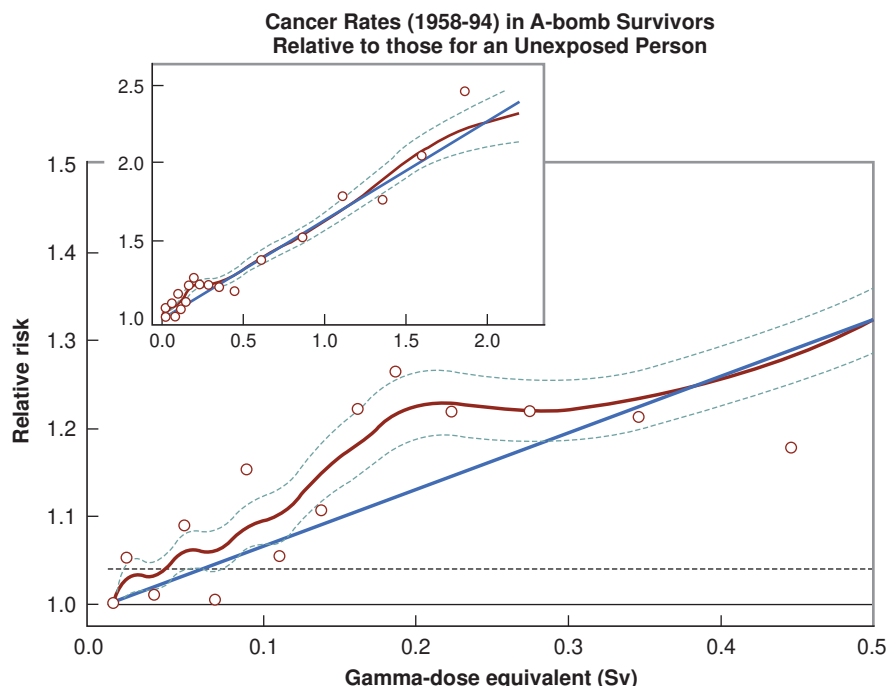


FIGURE 10.8 Estimated relative risks for cancer rates in the A-bomb survivors over the 1958–1994 follow-up period relative to unexposed persons. The dashed curve represents ± 1 standard error for the smoothed curve. The inset shows data over the whole dose range 0 to 2 Sv (0 to 200 rem), to which a straight line is fitted (i.e., relative risk is proportional to dose) with no threshold. The main figure is an expanded version of the low-dose region up to 0.5 Sv (500 rem). The straight line is taken from the inset data for the whole dose range. There is a suggestion that low-dose risks are above the line. (Adapted from Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiation Research*. 2000;154:178–186.)

exposure. The **dose and dose-rate effectiveness factor (DDREF)** is defined as the factor by which radiation cancer risks observed after large acute doses should be reduced when the radiation is delivered at LDR or in a series of small dose fractions. Animal data are equivocal on the subject with experiments suggesting a DDREF in the range of 2 to 10. For purposes of radiation protection, the ICRP recommends a DDREF of 2, which reflects their policy of being conservative. BEIR VII came up with an even lower value of 1.5 based on the possible slight curvature of the dose–response relationship for solid cancers.

■ SUMMARY OF RISK ESTIMATES

The population averaged cancer risk estimates from the BEIR VII committee are summarized in Table 10.2. As would be expected, the radiation-induced cancer incidence at 10.8% per Sv is approximately double the cancer mortality at

5.4% per Sv. It is also clear that the female cancer risks are significantly higher than the male cancer risks, not only because of breast cancer, but also because of lung and bladder cancers, which are affected by smoking. In Japan in 1945, smoking was common in males, but not in females.

These estimates from the BEIR committee are for all solid cancers lumped together and for

TABLE 10.2 Population Average Cancer Risk Percent per Sievert

	Incidence	Mortality
Male	8.6	4.6
Female	12.8	6.2
Combined	10.8	5.4

Source: Calculated from the Biologic Effects of Ionizing Radiation (BEIR) VII report.

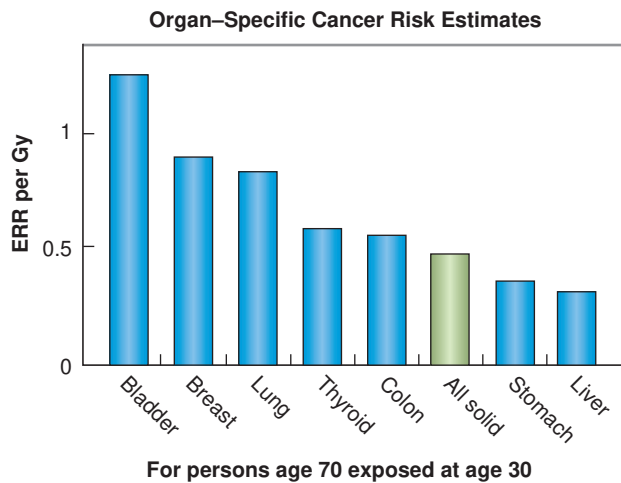


FIGURE 10.9 The study of the A-bomb survivors also makes it possible to calculate cancer risk estimates for some specific organs. In this figure, they are expressed in terms of the ERR/Sv. These figures are useful for estimating the possible risks from medical radiation where often only part of the body is exposed.

all age groups. The data from the A-bomb survivors also make it possible to calculate organ-specific risk estimates. These are summarized in Figure 10.9. It appears that the bladder, breast, lung, thyroid, and colon are more radiosensitive than the average, whereas the stomach and liver are less sensitive. These data are of enormous importance because they can be used, for example, to calculate cancer risks from diagnostic or therapeutic procedures where only a specific area of the body is irradiated.

As the data from Japan have matured and more detailed information has become available, it is evident that the risk of radiation-induced cancer also varies considerably with age at the time of exposure. In most cases, those exposed at an early age are much more susceptible than those exposed at later times. The difference is most dramatic for thyroid cancer; children are very radiosensitive,

whereas adults are quite resistant. It is also dramatic for breast cancer in females; females exposed before 15 years of age are most susceptible; women 50 years of age or older show little or no excess. Figure 10.10 shows the variation of cancer incidence as a function of age for males and females as calculated by the BEIR VII committee from the A-bomb data. There are exceptions to this general rule. Susceptibility to radiation-induced leukemia is relatively constant throughout life, and susceptibility to respiratory cancers increases in middle age. The overall risk, however, drops dramatically with age; children and young adults are much more susceptible to radiation-induced cancer than the middle- and old-aged.

An important question is the lowest dose at which there is epidemiologic evidence of a radiation-induced excess cancer incidence. There is a population of about 30,000 A-bomb survivors who

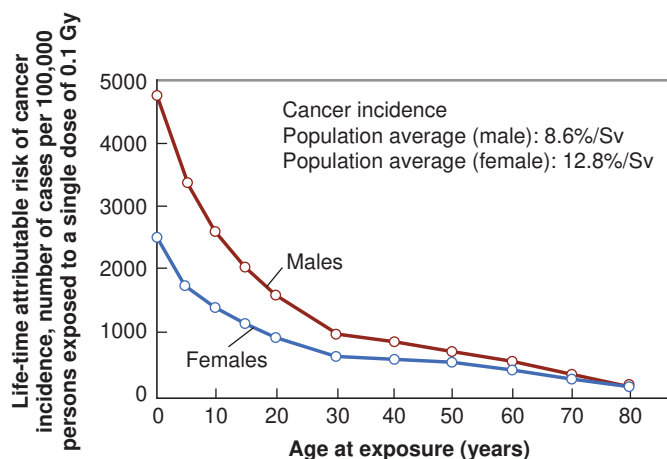


FIGURE 10.10 Illustrating how cancer incidence from radiation exposure falls dramatically with age. Children are 10 times more sensitive than older adults. It is also clear that females are more radiosensitive than males. Based on data from the BEIR VII report.

lived in the outskirts of the two cities and were exposed to doses in the range of 5 to 100 mSv. This low-dose sub population has been studied for more than 50 years, and shows a small, but statistically significant increased cancer risk.

■ SECOND MALIGNANCIES IN RADIOTHERAPY PATIENTS

The risk of second malignancies after radiotherapy is a subject not without controversy. One of the reasons for the uncertainty is that patients undergoing radiotherapy are often at high risk of a second cancer because of their lifestyles, and this factor is more dominant than the radiation risk.

There are many single institution studies in the literature involving radiotherapy from various sites that conclude that there is no increase in second malignancies, although a more accurate assessment would have been that the studies had limited statistical power to detect a relatively small increased incidence of second malignancies induced by the treatment.

Whenever large studies have been performed, radiotherapy has been shown to be associated with a statistically significant, although small, enhancement in the risk of second malignancies, particularly in long-term survivors. The three requirements for a study to be credible are as follows:

1. A sufficiently large number of patients.
2. A suitable comparison group; that is, patients with the same cancer treated by some means other than radiation.
3. A sufficiently long follow-up for radiation-induced solid tumors to manifest.

Only a few studies satisfy these criteria; these will be further discussed in details.

Second Cancers after Radiotherapy for Prostate Cancer

Brenner and colleagues described a study using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The SEER program is a set of geographically defined, population-based tumor registries, covering approximately 10% of the US population. The database contained information on 51,584 men with prostate cancer treated by radiotherapy and 70,539 men who underwent surgery. There was no evidence of a difference in the risk of leukemia for radiotherapy versus surgery

patients, but the risk of a second solid tumor at any time postdiagnosis was significantly greater after radiotherapy than after surgery. The relative risk increased with time posttreatment and reached 34% after 10 years or more. The most dramatic increases in relative risk were for the bladder (77%) and the rectum (105%) for 10 years or more following diagnosis. The relative risks are shown in Figure 10.11, together with the distribution of second cancers; note that even sites remote from the treatment area (e.g., lung) show an increased incidence. The absolute risk was about 1 in 70 by 10 years posttreatment. Figure 10.12 shows the relative risk of sarcomas in the heavily irradiated tissues in or near the treatment field. It can be seen that the relative risk increases to more than 200% at 10 years or more, compared with the surgical patients.

It is interesting to note that the increase in relative risk for carcinoma of the lung, which was exposed to a relatively low dose (about 0.5 Gy), is of the same order as that for carcinomas of the bladder, rectum, and colon, all of which were subject to much higher doses (typically more than 5 Gy). This pattern may reflect the fact that carcinomas, originating in actively dividing cells or cells under hormonal control, can be efficiently induced by relatively low doses of radiation as evidenced by the atomic bomb survivors, but the cancer risk at high doses decreases because of the effects of cell killing. In contrast to this pattern for radiation-induced carcinomas, radiation-induced sarcomas appear only in heavily irradiated sites, close to the treatment volume, because large radiation doses are needed to produce sufficient tissue damage to stimulate cellular renewal in mostly dormant cells. The sarcoma data in this study appear to follow this pattern, with significant radiation-related risks being exhibited for sites in and close to the treatment volume, but no significant increases being shown for sites that are more distant.

Radiation Therapy for Carcinoma of the Cervix

In the largest study of its kind, Boice and colleagues studied the risk of second malignancies in a wide range of organs and tissues as a consequence of the treatment by radiation of carcinoma of the uterine cervix. This huge international study was a tour de force. The paper had 42 authors from 38 institutions representing both

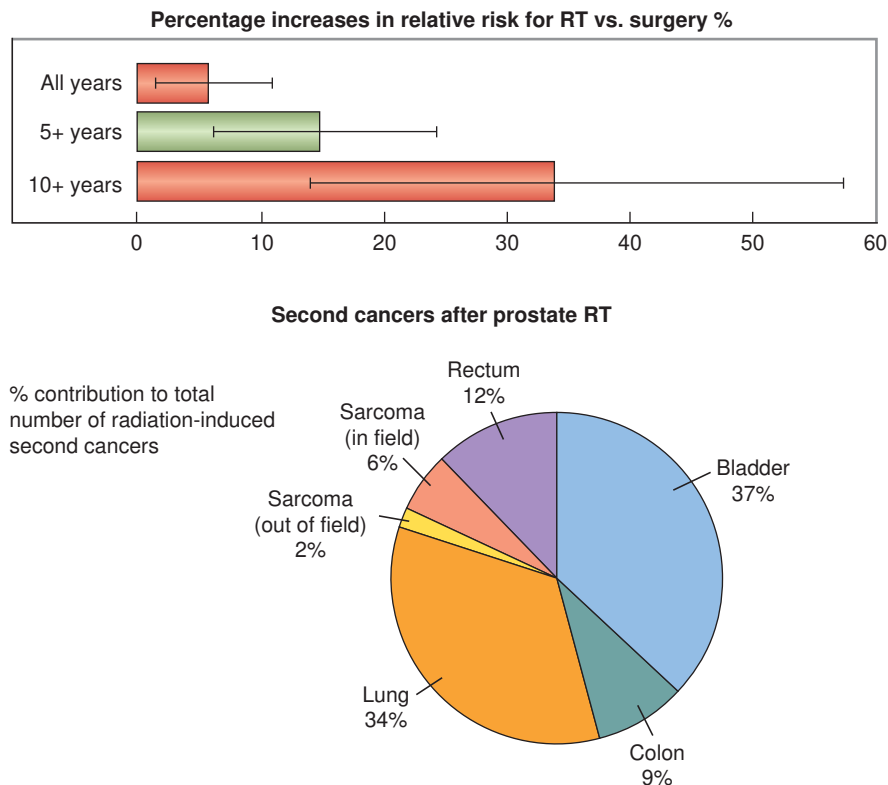


FIGURE 10.11 **Top panel:** Percentage increase in relative risk for all solid tumors (except prostate cancer) for patients who received radiotherapy for prostate cancer relative to the risk for patients who underwent surgery for prostate cancer. **Bottom panel:** Distribution of radiation-induced second cancer at 5+ years postradiotherapy. (Illustration prepared by Dr. David Brenner based on the data from Brenner DJ, Curtis RE, Hall EJ, et al. Second cancers after radiotherapy for prostate cancer. *Cancer*. 2000;88:398–406.)

sides of the Atlantic. Such collaboration allowed the accumulation of data from 150,000 patients to be studied. This study is strengthened enormously by the fact that an ideal control group is available for comparison. This malignancy is

equally well treated by radiation or surgery. The results can be summarized as follows:

1. Very high doses, on the order of several hundred gray, were found to increase the risk of

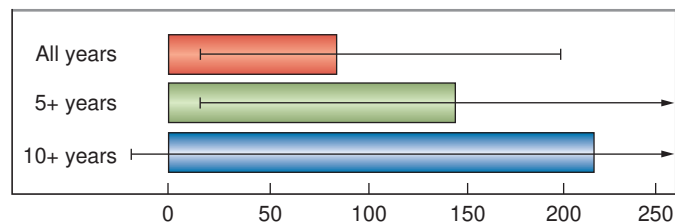


FIGURE 10.12 Percentage increase in relative risk for sarcomas in or near the treatment field for patients who received radiotherapy for prostate cancer relative to patients who underwent surgery. Although the number of tumors involved is much smaller than for all solid tumors (shown in Figure 10.9), the relative risks are extremely high. (Adapted from Brenner DJ, Curtis RE, Hall EJ, et al. Second cancers after radiotherapy for prostate cancer. *Cancer*. 2000;88:398–406, with permission.)

cancer of the bladder, rectum, vagina, and possibly bone, uterine corpus, and cecum as well as non-Hodgkin lymphoma. The risk ratios vary from a high of 4.0 for the bladder to a low of 1.3 for the bone. For all female genital cancers combined, a steep dose-response curve was observed, with a 5-fold excess at doses of more than 150 Gy.

2. Doses of several grays increased the risk of stomach cancer and leukemia.
3. Perhaps surprisingly, radiation was found not to increase the overall risk of cancers of the small intestine, colon, ovary, vulva, connective tissue, or breast or of Hodgkin disease, multiple myeloma, or chronic lymphocytic leukemia.

The overall conclusion of this study was that excess cancers certainly were associated with radiotherapy, as opposed to surgery, and that the risks were highest among long-term survivors and concentrated among women irradiated at relatively young ages.

Second Cancers among Long-Term Survivors from Hodgkin Disease

Second cancer represents the leading cause of death in long-term survivors of Hodgkin disease, with exceptionally high risks of breast cancer among women treated at a young age. Several studies have been reported. Bhatia and colleagues reported that 17 out of 483 girls in whom Hodgkin disease was diagnosed before the age of 16 years subsequently developed breast cancer, with radiotherapy implicated in most cases. The ratio of observed to expected cases is 75.3. Another study (by Sankila and colleagues) involved 1,641 patients treated for Hodgkin disease as children in five Nordic countries and reported a relative risk that was 17 times higher than the general population based on 16 cases of breast cancer. Travis and colleagues evaluated 3,869 women in population-based registries participating in the SEER program. All these women received radiotherapy as an initial treatment for Hodgkin disease. Breast cancer developed in 55 patients, who represents a ratio of observed to expected cases of 2.24. The risk of breast cancer, however, was 60.57% in women treated before the age of 16 years, with most tumors appearing 10 or more years later. This agrees with previous studies that have shown the female breast to be very radiosensitive to carcinogenesis at young ages. The risk of breast cancer decreased with in-

creasing age at the time of therapy and was only slightly elevated in women who were 30 years old or older when treated. In a later study, Travis and colleagues followed 3,817 female survivors of Hodgkin disease, diagnosed at age 30 years or younger, over a long period of time. A radiation dose of 4 Gy or more delivered to the breast was associated with a 3.2-fold increase in risk. Risk increased 8-fold with a dose of more than 40 Gy hormonal stimulation appears to be important for the development of radiation-induced breast cancer, as evidenced by the reduced risk in patients who received alkylating agents, as well as radiation, which caused ovarian damage.

These studies clearly show that if an adequate cohort can be studied, there is a clear excess of second cancers induced by radiotherapy. The data confirm previous studies that show that in the young, the breast is especially sensitive to the carcinogenic effects of radiation. In addition, excess cancers develop with a latency of 10 years or more and persist for decades after exposure.

■ DOSE-RESPONSE RELATIONSHIP FOR RADIATION CARCINOGENESIS AT HIGH DOSES

In the 1960s, Gray proposed that the dose-response relationship for radiation-induced malignancies would be bell-shaped, as illustrated in Figure 10.13; that is, the incidence would rise at low doses but fall at high doses. He explained this shape by the concurrent presence of two phenomena: (1) a “dose-related” *increase* in the proportion of normal cells that are transformed to a malignant state and (2) a dose-related *decrease* in the probability that transformed cells may survive the radiation exposure. Gray argued that whatever sequence of changes has taken place in the course of cell transformation, the changes must have been such as to leave the cell capable of indefinite proliferation; that is, with full reproductive integrity. The balance between transformation and cell killing leads to the overall shape, with cell killing becoming dominant at increasingly high doses. With Figure 10.13, Gray was specifically attempting to explain the shape of the dose-response relationship for the induction of leukemia in mice exposed to total body irradiation, which is why the dose goes up only to 5 Gy, but it has been tacitly assumed ever since that this bell-shaped curve applies to radiation-induced carcinogenesis in general. However, several recent studies challenge the validity of this assumption by

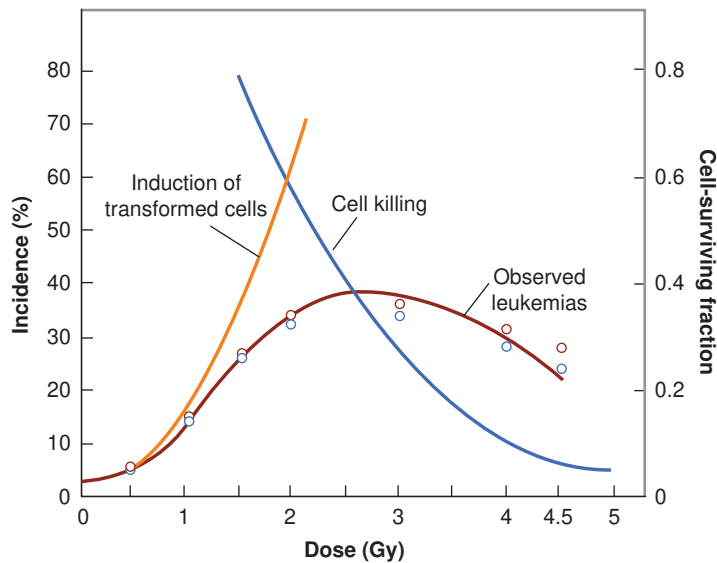


FIGURE 10.13 Illustrating the concept, introduced by Gray, that the incidence of radiation-induced leukemia in mice follows a “bell” shape because of the balance between the induction of transformed cells and cell killing. (Adapted from Gray LH: Radiation biology and cancer. In: *Cellular Radiation Biology: A Symposium Considering Radiation Effects in the Cell and Possible Implications for Cancer Therapy; A Collection of Papers*. Published for the University of Texas, MD Anderson Hospital and Tumor Institute. Baltimore, MD: Lippincott Williams & Wilkins; 1965:8–25.)

examining whether the linear dose response for radiation-induced cancer, evident in the A-bomb survivors at doses up to 2 Sv, extends to the higher dose ranges used for radiotherapy. Two studies involved the incidence of breast cancer in women treated for Hodgkin disease with a mantle field, which results in a large dose gradient across the breast (3 to 42 Gy). There was an increasing risk of breast cancer over this entire dose range. Some of the data from the Hodgkins patients, together with data from the A-bomb survivors, are shown in Figure 10.14, taken from a paper by Brenner and Sachs. It clearly shows that for the Excess Relative Risk (ERR) for high-fractionated doses is larger than at the low doses received by the A-bomb survivors. It certainly does not fall as would be predicted by the Gray model in Figure 10.13. Brenner and Sachs explained this difference by suggesting that cells initiated and transformed by radiation proliferate rapidly between daily dose fractions commonly used in radiotherapy.

Another study from St. Jude Children’s Research Hospital evaluated 1,612 patients with acute lymphoblastic leukemia, whose primary treatment was chemotherapy, but who also received prophylactic cranial irradiation because many chemotherapy agents do not effectively cross the blood–brain barrier (BBB). An excess of high-grade gliomas and meningiomas were evident during the first decade of follow-up, whereas an increased risk of low-grade brain tumors was observed at later follow-up intervals. The risk of brain tumors increased significantly with increasing radiation

dose, as shown in Figure 10.15, but there is no sign of the cancer incidence falling at high doses. There is some indication of a plateau, but no fall as would be predicted as cell killing takes over. As a consequence of these studies, prophylactic cranial radiotherapy (PCR) in children with leukemia has been largely replaced by intrathecal methotrexate.

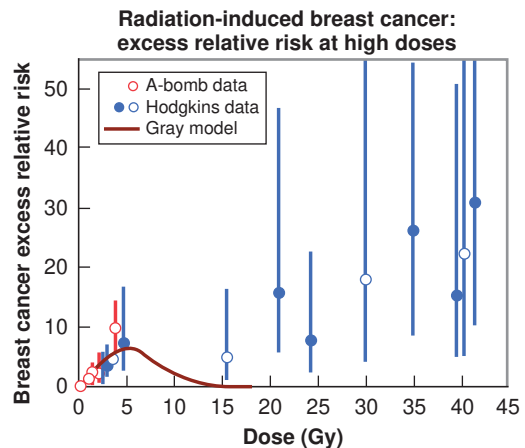
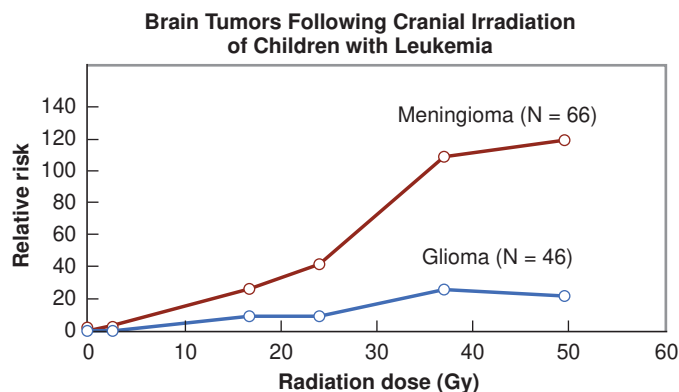


FIGURE 10.14 Excess relative risks for radiation-induced breast cancer. The low-dose data come from the A-bomb survivors, whereas the high-dose data are taken from patients treated for Hodgkin disease. The ERR does not fall at high doses as would be predicted by the Gray model, illustrated in Figure 10.11, but of course, the high doses were delivered in many small fractions over a period of time, not in a single exposure as in the Gray model. (Adapted from Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. *Proc. Natl Acad. Sci. USA* 2005;102:13040–13045, with permission).

FIGURE 10.15 Illustrating the incidence of brain tumors, meningiomas, and glioma as a function of dose in children receiving total brain irradiation during the treatment of leukemia with chemotherapy. Note how the incidence tends to plateau. (Adapted from Neglia JP, et al. New Primary Neoplasms of the Central Nervous System in Survivors of Childhood Cancer: a Report from the Childhood Cancer Survivor Study. *JNCI J Natl Cancer Inst* 2006;98[21]:1528-1537, with permission.)



These examples are further evidences that the incidence of radiation-induced solid cancers does not fall at the high-fractionated doses typically used therapeutically and accords with the clinical observation that second cancers often occur in or near the treatment field in high-dose areas, as well as in more remote locations.

■ CANCER RISKS IN NUCLEAR INDUSTRY WORKERS

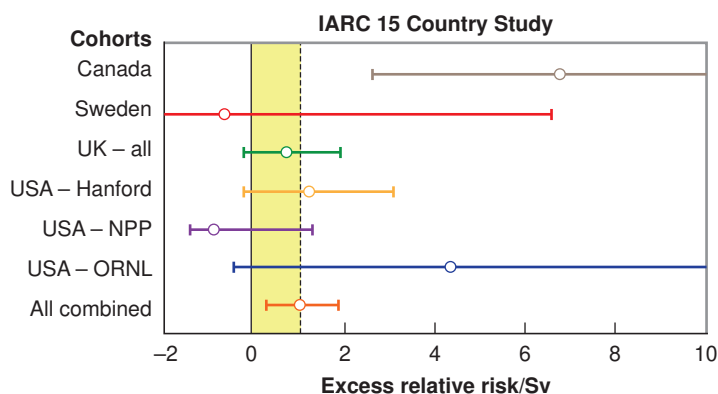
The International Agency for Research on Cancer (IARC), a branch of the World Health Organization (WHO), conducted an impressive epidemiologic study of cancer mortality among 400,000 nuclear workers from 15 countries. The importance of this study stems from the fact that nuclear workers receive protracted exposures to multiple low doses of radiation over many years, in contrast to the acute instantaneous dose

received by the Japanese A-bomb survivors. The surprising result was a statistically significant excess of solid cancers for a mean dose of only 19.4 mSv. The data are shown in Figure 10.16. Furthermore, the excess relative risk per sievert (ERR/Sv) was 0.97, more than three times larger than the corresponding quantity for the A-bomb survivors (see Table 10.3).

However, these results need to be viewed with caution for two reasons.

1. While data from 15 nations were pooled, the overall solid cancer risk is driven by the Canadian data, which is evident from Figure 10.16. Indeed, if the data from Canada are excluded, the excess of solid cancer deaths no longer has significance.
2. Lung cancer is prominent in the excess solid cancers, suggesting a confounding effect of smoking, a possibility recognized by the authors of the study.

FIGURE 10.16 Excess relative risk illustrating the data on cancer mortality from the 15-country study of nuclear workers by the IARC. With all countries combined, the ERR is statistically significant. However, the result is driven by the Canadian data, which makes a disproportionate contribution and casts some doubt on the validity of the study. In addition, there are a disproportionate number of cancers of the lung, which raise the possibility that the confounding effect of smoking has not been adequately accounted for. (Adapted from Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries *BMJ*. 2005;331:77, with permission.)



NPP = Nuclear power plants
ORNL = Oak Ridge National Laboratory

TABLE 10.3 Excess Relative Risk Per Sievert for Cancer Mortality

	Leukemia Excluding CLL	Solid Cancers
A-bomb survivors	1.4	0.26
15-nation study	1.93*	0.97
UK-NRRW analysis	1.7*	0.275

*Not Statistically Significant

Abbreviations: CLL, chronic lymphocytic leukemia; NRRW, National Registry of Radiation Workers.

Source: Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *BMJ*. 2005; doi:10.1136/bmj.38499.599861.EO. UK-NRRW analysis. Muirhead CR, O'Hagan JA, Haylock RGE, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer*. 2009;100:206–212.

The other important epidemiologic study of nuclear workers published recently was the third analysis of the data from the UK National Registry of Radiation Workers (NRRW). This study involved about 175,000 workers in the UK and showed the familiar “healthy worker effect,” in that, the rates of mortality from all causes (including cancer) was significantly lower than expected from national mortality rates, undoubtedly due to the higher socioeconomic status, better health care, and lower level of background risk factors among nuclear workers compared with the general population. Of greatest interest is that the cancer risk increases with cumulative dose and that the slope of this trend with dose (the ERR/Sv) is very similar to the corresponding figure for the A-bomb survivors (see Table 10.3). The positive trend of cancer mortality with dose is statistically significant and, unlike the 15-nation study, does not depend materially on lung cancer. The study clearly shows that there are harmful effects of low doses accumulated over a long period of time at LDR, although the increased risk is small. There is no evidence of a threshold, or of a hormetic (i.e., beneficial) effect of low doses. Furthermore, the similarity of the ERR/Sv values between the nuclear worker study and

the data from the A-bomb survivors, one involving a protracted exposure and the other one an acute instantaneous exposure, supports the low DDREF values suggested by both the ICRP and BEIR VII committees (i.e., a given dose appears to result in a similar cancer mortality whether delivered in an instantaneous acute exposure, or spread out over a protracted period of years).

■ MORTALITY PATTERNS IN RADIOLOGISTS

An extensive and interesting report was published by Sir Richard Doll and colleagues in 2003 that assessed 100 years of observations in terms of mortality from cancer and other causes in British radiologists entering the field from 1897 to 1997. Table 10.4 shows the trend in the Standard Mortality Ratio (SMR) over the years. There was a clear excess of cancer in the early radiologists in the years before the introduction of radiation safety standards. This is not surprising, in that, estimated annual doses to early radiologists were typically in the range of 1 Gy per year. What is surprising is that the SMR for the post-war period, 1955 to 1979 is much smaller than unity, due largely to a statistically significant lower rate of noncancer deaths. This attracted much interest, leading to speculation by some that low doses of radiation may be beneficial and may actually lead to a longer life!

A weakness of the British study is that the data for the control group, labeled “all-male medical practitioners” were in fact estimated indirectly from census data, with adjustments made

TABLE 10.4 Standard Mortality Ratios for All Causes of Death in British Radiologists, 1897–1997

Years	Standard Mortality Ratio
1897–1920	1.75
1921–1935	1.24
1936–1954	1.12
1955–1979	0.71
All post-920	1.04

Source: Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol*. 1997;70:130–139.

TABLE 10.5 Second Analysis of Post-World War II British Radiologists

	Berrington et al.	Carpenter et al.
Employment years	1955–1979	1962–1979
Controls	Based on census data	Other physicians
SMR for cancer mortality	0.71 n.s.	0.99 n.s.
SMR for overall mortality	0.68 s.s.	1.03 n.s.

Abbreviations: SMR, standard mortality ratio; n.s., not statistically significant; s.s., statistically significant.

Source: Berrington A, Darby SC, Weiss HA, et al. 100 years of observation on British radiologists: mortality from cancer and other causes 1897–1997. *Br J Radiol.* 2001;74:507–519 and Carpenter LM, Swerdlow AJ, Fear NT. Mortality of doctors in different specialties: findings from a cohort of 20,000 NHS hospital consultants. *Occup Environ Med.* 1997;54:388–395.

to account for socioeconomic status. This weakness was remedied in a later paper by Carpenter et al. in which a subset of British radiologists, entering the field in the postwar years were compared directly with other physicians. When this was done, the SMR for either cancer mortality or overall mortality is indistinguishable from unity (see Table 10.5).

In summary, in the early days before the establishment of radiation safety standards, radiation risks to radiologists were large and easily demonstrable. In more recent years, where annual occupational doses are more than a hundredfold lower, there is no sign of an excess mortality in radiologists, compared with other medical specialties, although the numbers involved are small. At the same time, there is no good evidence that low doses of radiation may be beneficial or can prolong life.

■ CHILDHOOD CANCER AFTER RADIATION EXPOSURE IN UTERO

In several widely publicized British studies in the 1950s and 1960s, Stewart and her colleagues reported an excess of leukemia and childhood cancer in children irradiated in utero as a consequence of diagnostic x-ray examinations involving the pelvis of the mother. An association between leukemia and x-rays in utero was confirmed in the United States by MacMahon.

This has been a highly controversial topic. It is discussed in more detail in Chapter 12. In a 1997 paper, Doll and Wakeford summarized all of the available data and came to the conclusion

that radiation was the causative agent. They concluded that:

- Low-dose irradiation of the fetus in utero, particularly in the last trimester, causes an increased risk of childhood malignancies.
- An obstetric x-ray examination, even though the dose is only about 10 mGy, increases the risk of childhood cancer by 40%.
- The excess absolute risk is about 6% per gray.

The relative risk of 40% is very high because, of course, cancer is relatively rare in children. The absolute risk works out to be about 6% per gray, which is not very different from the cancer risk calculated for the atomic bomb survivors following adult exposure.

■ NONNEOPLASTIC DISEASE AND RADIATION

A link between exposure to high doses of ionizing radiation and damage to the heart and coronary arteries has been well established for many years, based on the treatment of breast cancer during the era of cobalt-60 units, characterized by a large penumbra to the treatment field, which inevitably resulted in an appreciable dose to the heart. An association between lower doses of radiation and late occurring cardiovascular and other diseases emerged in the 1990s from a study of the A-bomb survivors (see Fig. 10.7). Statistically, significant associations were seen for the categories of heart disease, stroke, and diseases of the digestive, respiratory, and hematopoietic systems. However, the data are inadequate to distinguish between a linear dose

response, a quadratic dose response, or, indeed, a dose response with a threshold of about 0.5 Sv. What is clear is that dose of around 1 Sv or more result in an excess of late occurring diseases other than cancer. The biologic mechanism for these effects is not clear. One possibility is the damage to endothelial cells and the subsequent induction of an inflammatory response, although it is unlikely that this would extend to low doses and LDR.

SUMMARY OF PERTINENT CONCLUSIONS

- A deterministic effect has a threshold in dose, and the severity of the effect is dose related. A radiation-induced cataract is an example of a deterministic effect.
- Radiation carcinogenesis is a stochastic effect; that is, the probability of an effect increases with dose, with no dose threshold, but the severity of the effect is not dose related. Heritable effects are also stochastic.
- The human experience of radiation-induced carcinogenesis includes the survivors of the atomic bomb attacks on Hiroshima and Nagasaki, patients exposed to medical irradiation, and early workers exposed occupationally. Some examples include the following:
 1. Leukemia and solid tumors in Japanese survivors of the atomic bomb.
 2. Leukemia in patients irradiated for ankylosing spondylitis.
 3. Thyroid cancer in children irradiated for benign conditions of the head and neck, such as enlarged thymus or tonsils, and children epilated for tinea capitis. Benign and malignant tumors were seen in children exposed to radioactive iodine at Chernobyl.
 4. Breast cancer in patients treated with x-rays for postpartum mastitis and patients fluoroscoped repeatedly during the management of tuberculosis.
 5. Lung cancer in uranium miners.
 6. Bone cancer in dial painters who ingested radium and patients who had injections of radium for tuberculosis or ankylosing spondylitis.
- Latency refers to the time interval between irradiation and the appearance of the malignancy.
- The shortest latency is for leukemia, with a peak of 5 to 7 years. For solid tumors, the latency may extend for 60 years or more.
- Regardless of the age at exposure, radiation-induced malignancies tend to appear at the same age as spontaneous malignancies of the same type. Indeed, for solid cancers, the excess risk is apparently more like a lifelong elevation of the natural age-specific cancer risk.
- To determine risk estimates for radiation-induced cancer from observed data (the Japanese atomic bomb survivors), a model must be assumed because of the following:
 1. Data must be extrapolated from relatively high doses to the low doses of public health concern.
 2. Data must be projected out to a full life span, because large exposed populations, such as the A-bomb survivors, have not yet lived out their life span.
 3. Risks must be “transferred” from the Japanese population to, for example, a Western population with different natural cancer rates.
- There are two principal risk models: The absolute risk model assumes that radiation produces a discrete “crop” of cancers, over and above the spontaneous level and unrelated to the spontaneous level. The relative risk model assumes that radiation increases the spontaneous incidence by a factor. Because the natural cancer incidence increases with age, this model predicts excess cancers appearing late in life after irradiation.
- The assessment of radiation-induced cancer risks by both the BEIR and UNSCEAR committees is based on a time-related relative risk model. Excess cancer deaths were assumed to depend on dose, square of the dose, age at exposure, time since exposure, and, for some cancers, gender.
- For solid tumors, the A-bomb data show that both the excess cancer incidence and mortality are a linear function of dose up to about 2 Sv.
- Leukemia data were best fitted by a linear-quadratic function of dose (i.e., an upward curvature), so that the risk per unit of dose at 1 Sv is about three times that at 0.1 Sv.

- The Japanese atomic bomb data refer to acute exposure at an HDR. A DDREF is needed to convert risk estimates to the low dose and LDR encountered in radiation protection. From animal studies, this is anywhere from 2 to 10. The ICRP conservatively assumes a value of 2, whereas the BEIR VII committee assumes a value of 1.5.
- The BEIR VII committee suggests a risk estimate of excess cancer incidence of 10.8% per sievert and excess cancer mortality of 5.4% per sievert, including a DDREF of 1.5. These figures represent a population average, with risks for females slightly higher than for males.
- There is a marked reduction with age of the risk of both cancer incidence and cancer mortality. Children are so much more radiosensitive than adults.
- The ICRP estimates that, on average, 13 to 15 years of life are lost for each radiation-induced cancer and that death occurs at age 68 to 70 years.
- There is a clear excess of second cancers induced by radiation therapy, both in heavily irradiated tissue and in more remote organs. This is evident if a sufficiently large number of patients and an adequate control group are available for study and if there is a sufficiently long follow-up for solid tumors to manifest.
- Large studies show a clear excess of second cancers after radiotherapy for prostate cancer, carcinoma of the cervix, and Hodgkin lymphoma. An excess has also been shown following radiation therapy for breast cancer, carcinoma of the testes, and various childhood malignancies.
- The IARC studied 400,000 nuclear workers from 15 countries and found a statistically significant excess of solid cancers at a mean dose of 19.4 mSv. However, this result must be viewed with caution because the result is dominated by the Canadian data, and in addition, the large incidence of lung cancer suggests that smoking may be a confounding factor. The UK NRRW studied about 175,000 nuclear workers in the UK over a very long period of time. The study showed the usual “healthy worker effect,” in that, rates of mortality from all

causes were significantly lower than those expected from national mortality data, but the cancer risk increased with cumulative dose and the slope of this trend (ERR/Sv) is very similar to the corresponding figure for the A-bomb survivors.

- Early radiologists who practiced prior to the 1920s showed an excess of malignancies. No excess is evident in radiologists in recent years. The report that British radiologists live longer is not confirmed in later studies.
- Irradiation in utero by diagnostic x-rays appears to increase the spontaneous incidence of leukemia and childhood cancers by a factor of about 1.4. This is a high relative risk because malignancies in children are rare, but the absolute risk is about 6% per gray—not very different from the risk estimate calculated for the A-bomb survivors following adult exposure.
- From a study of both radiotherapy patients and the A-bomb survivors, it is evident that doses of more than about 0.5 Sv can also result in an excess of nonneoplastic diseases, including cardiovascular diseases.

■ BIBLIOGRAPHY

- Andersson M, Carstensen B, Storm HH. Mortality and cancer incidence after cerebral arteriography with or without Thorotrast. *Radiat Res.* 1995;142:305–320.
- Berrington A, Darby SC, Weiss HA, et al. 100 years of observation on British radiologists: mortality from cancer and other causes 1897–1997. *Br J Radiol.* 2001;74:507–519.
- Bhatia S, Robison LL, Oberlin O, et al. Breast cancer and other second neoplasms after childhood Hodgkin's disease. *N Engl J Med.* 1996;334:745–751.
- Boice JD Jr, Engholm G, Kleinman RA, et al. Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat Res.* 1988;116:3–55.
- Boice JD, Hutchison GB. Leukemia in women following radiotherapy for cervical cancer: ten-year follow-up of an international study. *J Natl Cancer Inst.* 1980;65:115–129.
- Boice JD Jr, Land CE, Shore RE, et al. Risk of breast cancer following low-dose exposure. *Radiology.* 1979;131:589–597.
- Boice JD Jr, Preston D, David FG, et al. Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts. *Radiat Res.* 1991;125:214–222.
- Brenner DJ, Curtis RE, Hall EJ, et al. Second malignancies in prostate patients after radiotherapy compared with surgery. *Cancer.* 2000;88:398–406.
- Brenner DJ, Doll R, Goodhead DT, et al. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. *PNAS.* 2003;100:13761–13766.
- Brenner DJ, Hall EJ. Mortality patterns in British and US radiologists: what can we really conclude? *Br J Radiol.* 2003;76:1–2.

- Cardis E, Vrijheid M, Blettner M, et al. Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *BMJ*. 2005; doi:10.1136/bmj.38499.599861.EO
- Carpenter LM, Swerdlow AJ, Fear NT. Mortality of doctors in different specialties: findings from a cohort of 20,000 NHS hospital consultants. *Occup Environ Med*. 1997;54:388–395.
- Coleman CN. Second malignancy after treatment of Hodgkin's disease: an evolving picture. *J Clin Oncol*. 1986;4:821–824.
- Committee on the Biological Effects of Ionizing Radiation. *The Effects on Populations of Exposure to Low Levels of Ionizing Radiations*. Washington, DC: National Academy of Sciences, National Research Council; 1972.
- Committee on the Biological Effects of Ionizing Radiation (BEIR III). *The Effects on Populations of Exposure to Low Levels of Ionizing Radiations*. Washington, DC: National Academy of Sciences, National Research Council; 1980.
- Committee on the Biological Effects of Ionizing Radiation (BEIR V). *Health Effects of Exposure of Low Levels of Ionizing Radiations*. Washington, DC: National Academy of Sciences, National Research Council; 1990.
- Committee on the Biological Effects of Ionizing Radiation (BEIR VII). *Health Effects of Exposure of Low Levels of Ionizing Radiations*. Washington, DC: National Academy of Sciences, National Research Council; 2006.
- Czesnin K, Wronkowski Z. Second malignancies of the irradiated area in patients treated for uterine cervix cancer. *Gynecol Oncol*. 1978;6:309–315.
- Darby SC, Reeves G, Key T, et al. Mortality in a cohort of women given x-ray therapy for metropathia haemorrhagica. *Int J Cancer*. 1994;56:793–801.
- Delongchamp RR, Mabuchi K, Yoshimoto Y, et al. Cancer mortality among atomic bomb survivors exposed in utero or as young children, October 1950–May 1992. *Radiat Res*. 1997;147:385–395.
- Doll R, Wakeford R. Risk of childhood cancer from fetal irradiation. *Br J Radiol*. 1997;70:130–139.
- Fry SA. Studies of US radium dial workers: an epidemiological classic. *Radiat Res*. 1998;150:S21–S29.
- Giles D, Hewitt D, Stewart A, et al. Malignant disease in childhood and diagnostic irradiation in utero. *Lancet*. 1956;271:447.
- Gray LH. Radiation biology and cancer. In: *Cellular Radiation Biology: A Symposium Considering Radiation Effects in the Cell and Possible Implications for Cancer Therapy; A Collection of Papers*. Published for the University of Texas MD Anderson Hospital and Tumor Institute. Baltimore, Md: Lippincott Williams & Wilkins; 1965:8–25.
- Hildreth NG, Shore RE, Hempelmann LH, et al. Risk of extrathyroid tumors following radiation treatments in infancy for thymic enlargement. *Radiat Res*. 1985;2:378–392.
- Howe GR, McLaughlin J. Breast cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian Fluoroscopic cohort study and a comparison with breast cancer mortality in the atomic bomb survivors study. *Radiat Res*. 1996;145:694–707.
- International Commission on Radiation Units and Measurements. *Radiation Quantities and Units*. Report 33. Washington, DC: ICRU; 1967.
- International Commission on Radiological Protection. *Recommendations of the ICRP. ICRP Publication 60*. Oxford, England: Pergamon Press; 1990.
- Kapp DS, Fisher D, Grady KJ, et al. Subsequent malignancies associated with carcinoma of uterine cervix, including an analysis of the effects of patient and treatment parameters on incidence and site metachronous malignancies. *Int J Radiat Oncol Biol Phys*. 1982;8:192–205.
- Kleinerman RA, Boice JD Jr, Storm HH, et al. Second primary cancer after treatment for cervical cancer. An international registries study. *Cancer*. 1995;76:442–452.
- Land CE. Studies of cancer and radiation dose among atomic bomb survivors. The example of breast cancer. *JAMA*. 1995;274:402–407.
- Land H, Parada LF, Weinberg RA. Tumorigenic conversion of primary embryo fibroblasts requires at least two cooperating oncogenes. *Nature*. 1983;304:596–602.
- Lee JY, Perez CA, Ettinger N, et al. The risk of second primaries subsequent to irradiation for cervix cancer. *Int J Radiat Oncol Biol Phys*. 1982;8:207–211.
- MacMahon B. Prenatal x-ray exposure and childhood cancer. *JNCI*. 1962;28:1173–1191.
- Matanoski GM. Risk of cancer associated with occupational exposure in radiologists and other radiation workers. In: Burchenal JH, Oettgen HF, eds. *Cancer—Achievements, Challenges and Prospects for the 1980s*. New York, NY: Grune and Stratton; 1981:241–254.
- Matanoski GM, Sternberg A, Elliott EA. Does radiation exposure produce a protective effect among radiologists? *Health Phys*. 1987;52:637–643.
- Modan B, Baidatz D, Mart H, et al. Radiation-induced head and neck tumors. *Lancet*. 1974;1:277–279.
- Mole RH. Endosteal sensitivity to tumor induction by radiation in different species: a partial answer to an unsolved question? In: Mays C, Jee W, Lloyd R, et al., eds. *Delayed Effects of Bone-Seeking Radionuclides*. Salt Lake City, UT: University of Utah Press; 1969:249–258.
- Muirhead CR, O'Hagan JA, Haylock RGE, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer*. 2009;100:206–212.
- Nekolla EA, Kellerer AM, Kuse-Isingschulte M, et al. Malignancies in patients treated with high doses of radium-224. *Radiat Res*. 1999;152:S3–S7.
- Nyandoto P, Muhonen T, Joensuu H. Second cancers among long-term survivors from Hodgkin's disease. *Int J Radiat Oncol Biol Phys*. 1998;42:373–378.
- Pederson BJ, Larson SD. Incidence of acute nonlymphocytic leukemia, preleukemia and acute myeloproliferative syndrome up to 10 years after treatment of Hodgkin's disease. *N Engl J Med*. 1982;307:965–975.
- Pierce DA, Preston DL. Radiation-related cancer risks at low doses among atomic bomb survivors. *Radiation Research*. 2003;154:178–186.
- Pierce DA, Shimizu Y, Preston DL, et al. Studies of the mortality of atomic bomb survivors: report 12, Part I. Cancer: 1950–1990. *Radiat Res*. 1996;146:1–27.
- Preston DL, Kumusumi S, Tomonaga M, et al. Cancer incidence in atomic bomb survivors. Part III: Leukemia lymphoma and multiple myeloma, 1950–1987. *Radiat Res*. 1994;137:S68–S97.
- Preston DL, Pierce DA. The effect of changes in dosimetry on cancer mortality risk estimates in the atomic bomb survivors. *Radiat Res*. 1988;114:437–466.
- Ron E, Lubin JH, Shore RE, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. *Radiat Res*. 1995;141:259–277.
- Rotblat J, Lindop P. Long-term effects of a single whole-body exposure of mice to ionizing radiations: II. Causes of death. *Proc R Soc Lond B Biol Sci*. 1961;154:350–368.
- Rowland RE, Stehney AF, Lucas HF. Dose-response relationships for radium-induced bone sarcomas. *Health Phys*. 1983;44:15–31.
- Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. *Proc Natl Acad Sci USA*. 2005;102:13040–13045.

- Saenger EL, Thoma BE, Tompkins EA. Leukemia after treatment of hyperthyroidism. *JAMA*. 1968;205:855–862.
- Sankila R, Garwicz S, Olsen JH, et al. Risk of subsequent malignant neoplasms among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence: a population-based cohort study in the five Nordic countries. *J Clin Oncol*. 1996;14:1442–1446.
- Shore RE, Hildreth N, Woodard E, et al. Breast cancer among women given x-ray therapy for acute postpartum mastitis. *J Natl Cancer Inst*. 1986;77:689–696.
- Shore RE, Woodard E, Hildreth N, et al. Thyroid tumors following thymus irradiation. *J Natl Cancer Inst*. 1985;74:1177–1184.
- Stewart A, Kneale GW. Changes in the cancer risk associated with obstetric radiography. *Lancet*. 1968;1:104–107.
- Stewart A, Webb J, Hewitt D. A survey of childhood malignancies. *Br Med J*. 1958;1:1495–1508.
- Tatsuo A, Takashi N, Fukushima K, et al. Second cancer after radiation therapy for cancer of the uterine cervix. *Cancer*. 1991;67:398–405.
- Thompson DE, Mabucchi K, Ron E, et al. Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat Res*. 1994;138:209–223.
- Tokunaga M, Land CE, Tokuoka S, et al. Incidence of female breast cancer among atomic bomb survivors, 1950–1985. *Radiat Res*. 1994;138:209–223.
- Travis LB, Curtis RE, Boice JD Jr. Late effects of treatment for childhood Hodgkin's disease. *N Engl J Med*. 1996;335:352–353.
- Travis LB, Hill DA, Doros GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin's disease. *JAMA*. 2003;290:465–475. Erratum in: *JAMA*. 2003;290:1318.
- United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Atomic Radiation: UNSCEAR 1994 Report to the General Assembly, with Scientific Annexes*. E 94 IXII. New York, NY: United Nations; 1994.
- United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation*. New York, NY: UNSCEAR; 1988.
- Upton AC. The dose–response relation in radiation-induced cancer. *Cancer Res*. 1961;21:717–729.
- van Kaick G, Dahlmeier A, Hornik S, et al. The German thorotrast study: recent results and assessment of risks. *Radiat Res*. 1999;152:S64–S71.
- van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy and hormonal factors in breast cancer following Hodgkin's disease. *J Natl Cancer Inst*. 2003;95:971–980.
- Wall PL, Clausen KP. Carcinoma of urinary bladder in patients receiving cyclophosphamide. *N Engl J Med*. 1975;293:271–273.
- Walter AW, Hancock ML, Pui CH, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St. Jude Children's Research Hospital. *J Clin Oncol*. 1998;16:3761–3767.
- Weiss HA, Darby SC, Doll R. Cancer mortality following x-ray treatment for ankylosing spondylitis. *Int J Cancer*. 1994;59:327–338.
- Yamamoto T, Kopecky KJ, Fujikura T, et al. Lung cancer incidence among Japanese A-bomb survivors, 1950–1980. *J Radiat Res*. 1987;28:156–171.

Heritable Effects of Radiation

Germ Cell Production and Radiation**Effects on Fertility****Review of Basic Genetics****Mutations**

Mendelian

Chromosomal Changes

Multifactorial

Radiation-Induced Heritable Effects in Fruit Flies**Radiation-Induced Heritable Effects in Mice****Radiation-Induced Heritable Effects in Humans****International Commission on Radiological****Protection Estimates of Heritable Risks****Mutations in the Children of the A-Bomb Survivors****Changing Concerns for Risks****Epigenetics**

Imprinted Genes

Summary of Pertinent Conclusions**Bibliography**

■ GERM CELL PRODUCTION AND RADIATION EFFECTS ON FERTILITY

In the male mammal, spermatozoa arise from the germinal epithelium in the seminiferous tubules of the testes, and their production is continuous from puberty to death. The spermatogonial (stem) cells consist of several different populations that vary in their sensitivity to radiation. The post-spermatogonial cells pass through several stages of development: primary spermatocytes, secondary spermatocytes, spermatids, and finally spermatozoa. The division of a spermatogonium to the development of mature sperm involves a period of 6 weeks in the mouse and 10 weeks in the human. The effect of radiation on fertility is not apparent immediately because the post-spermatogonial cells are relatively resistant compared with the sensitive stem cells. After exposure to a moderate dose of radiation, the person remains fertile as long as mature sperm cells are available, but decreased fertility or even temporary sterility follows if these are used up. The period of sterility lasts until the spermatogonia are able to repopulate by division.

Radiation doses as low as 0.15 Gy result in oligospermia (diminished sperm count) after a latent period of about 6 weeks. Doses greater than 0.5 Gy result in azoospermia (absence of living spermatozoa) and therefore temporary sterility. The duration of azoospermia is dose dependent; recovery can begin within 1 year after doses of less than 1 Gy but requires 2 to 3.5 years after a dose of 2 Gy. The original single-dose data came

from the irradiation of prisoners, which showed that a dose in excess of 6 Gy is needed to result in permanent sterility. In contrast to most organ systems where fractionation of dose results in sparing, fractionated courses cause more gonadal damage than a single dose. Studies of patients receiving radiation therapy indicate that permanent sterility can result from 2.5 to 3 Gy in a fractionated regime over 2 to 4 weeks. The induction of sterility by radiation in human males does not produce significant changes in hormone balance, libido, or physical capability.

Gonadal kinetics in women are opposite to those in men, as the germ cells are nonproliferative. All cells in the oogonial stages progress to the oocyte stage in the embryo. By 3 days after birth, in the mouse or human, all of the oocytes are in a resting phase and there is no cell division. Consequently, in the adult, there are no stem (oogonial) cells, but there are three types of follicles: immature, nearly mature, and mature. At birth, a woman has about 1 million oocytes, which are reduced to about 300,000 at puberty.

In women, radiation is highly effective at inducing permanent ovarian failure, but there is a marked age dependence in sensitivity. The dose required to induce permanent sterility varies from 12 Gy prepubertal to 2 Gy premenopausal. Pronounced hormonal changes, comparable to those associated with the natural menopause, accompany radiation-induced sterilization in females.

Overall, radiation sterility is very different between men and women, and these differences are compared and contrasted in Table 11.1.