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# Second Cancers Following Radiotherapy

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The introduction and widespread use of intensive combined modality cancer therapy regimens during the past 30 years have resulted in major improvements in cancer survival, particularly for cancers of childhood and early adulthood (1–4). However, the aggressive treatment regimens carry risks as well as benefits. Among the most serious of these risks is the potential for therapy-induced second primary tumors. The genotoxic agents used to kill cancer cells also can transform normal cells and give rise to new cancers years or decades later. Such risks typically are small relative to the more immediate risks posed by the initial tumor and, indeed, only become relevant because of the success of the treatments (5). Nonetheless, it is important to quantify treatment-related risks and identify patients at high risk of second primary cancers. In some cases, it may be possible to modify cancer treatments to minimize adverse effects with no loss of curative efficacy. Surveillance and counseling can be arranged, including for patients treated by methods no longer in use, to promote early detection of cancers and the avoidance of behaviors or exposures that act synergistically with therapeutic exposures. Prevention is particularly important in the context of therapy-induced second primaries that are refractory to treatment and almost invariably fatal, such as secondary acute nonlymphocytic leukemia (ANLL) and osteosarcoma (6–9).

This chapter reviews the role of radiation therapy for an initial malignancy in the increased incidence of subsequent malignancies. The roles of chemotherapy, genetic susceptibility, and other host factors are the subjects of other chapters and are addressed here only insofar as they may have a bearing on the effect of radiotherapy. This review is not intended to be comprehensive with respect to the literature on radiation-induced multiple primaries. Rather, attention is focused on large analytical studies, particularly those with the most detailed treatment information. Such studies provide the strongest basis for generalizations. Descriptions of case series of second or multiple primary cancers can provide etiologic clues, but do not provide the basis for quantitative estimates of risk (10) and are not emphasized here. The reader is referred to the monograph edited by Boice et al. (11) for a comprehensive overview of the occurrence of multiple primary cancers by type of first primary cancer, based on long-term data from high-quality cancer registries in Connecticut and Denmark. The Connecticut Tumor Registry includes information about first course of treatment (surgery, radiotherapy, chemotherapy) (12) and enables one to develop hypotheses about possible effects of treatments. However, treatment data recorded in such registries often are incomplete or incorrect, as many patients go on to have additional or other treatments (13). Studies that are able to classify exposure only at the level of

ever/never for radiotherapy and chemotherapy, or only on the basis of initial treatment, are of limited value in evaluating treatment-specific second cancer risks. What are needed are large, well-designed studies that collect and evaluate detailed information on the types, quantities, and timing of exposures to particular agents. There have been a number of such studies during the past 15 years, and they constitute the foundation of this chapter.

I begin with a brief review of some general principles that have emerged from epidemiologic studies of radiation carcinogenesis. These provide a broader context in which to consider findings concerning radiotherapy-induced multiple primary tumors.

### **BACKGROUND: EPIDEMIOLOGY OF RADIATION-INDUCED CANCER**

Awareness of the carcinogenic potential of ionizing radiation came very soon after the discovery of x-rays by Wilhelm Roentgen in 1895 (14,15), and studies during the last 50 years have provided extensive quantitative information about radiogenic cancer risks (16–18). While studies of therapeutically irradiated populations have contributed extensively to this understanding, investigations of many other populations have as well, and these data should be kept in mind when interpreting findings for populations given radiotherapy. The single most important source of information has been the long-term follow-up of survivors of the atomic bomb explosions in Japan (19,20).

Ionizing radiation can cause most types of human cancer, but different organs (and cell types within organs) vary widely in susceptibility (16–18). Cancers considered to be most easily caused by radiation include acute leukemia (AL); chronic myelocytic leukemia (CML); and cancers of the thyroid gland, female breast, and lung. Excesses of these cancers have been demonstrated clearly for doses less than 1 Gy (100 rad) and for populations irradiated in a variety of settings. Most radiation-induced thyroid cancers are well-differentiated papillary or follicular carcinomas and rarely are fatal (21). Cancers of the stomach, ovary, bladder, colon, liver, skin, and nervous system also were positively associated with exposure to radiation among atomic bomb survivors (20). Most radiogenic skin cancers are basal cell or squamous cell carcinomas, and there is little evidence that ionizing radiation causes melanoma (22,23). Tumors of the salivary glands can be caused by relatively low doses of radiation, but a large proportion of these are histologically benign (16,24). Susceptibility appears to be low for the kidney and pancreas. Radiogenic cancers of the bone, connective tissues, rectum, and uterine corpus typically are seen only following very high doses, of the order of 10 Gy or greater. A radiation etiology has not been demonstrated for cancers of the prostate gland, uterine cervix, small intestines, testis, or most childhood cancers, with the exception of acute leukemia (16,18). Chronic lymphocytic leukemia (CLL), Hodgkin's disease, and non-Hodgkin's lymphoma (NHL) also do not appear to be caused by ionizing radiation, at least not to any marked degree, and the role of radiation in the etiology of multiple myeloma remains unsettled (16,18,25). The apparent resistance of lymphocytes to radiation carcinogenesis may be due, in part, to their sensitivity to radiation-induced cell killing (26–28).

Although the experience of the Japanese atomic bomb survivors provides useful perspective, there are reasons for caution in extrapolating or generalizing findings for this population to patients receiving radiotherapy for cancer. Exposure to radiation from the atomic bomb explosions was brief and approximately uniform throughout the body; thus it differed from the high-dose, partial-body, and fractionated or protracted exposures typical of most cancer radiotherapy. Radiation doses for the majority of

survivors of the atomic bomb explosions were low (mean dose equivalent  $<0.3$  Sv) (20). Most persons receiving acute, whole-body doses greater than 5 Gy would not have survived the acute effects of radiation exposure (29). Local doses associated with cancer radiotherapy often are much higher than this, by a factor of ten or more, and dose drops off sharply outside of the irradiated field. Furthermore, radiation effects might be modified by concomitant exposure to chemotherapy agents, by treatment-induced immunosuppression, or by host susceptibility factors related to the development of the first primary cancer (30).

Cancers that rarely are induced at doses of the order of several grays or less may assume greater importance at the extremely high doses characteristic of radiotherapy; however, the opposite may be true as well. At low to moderate radiation doses, the incidence of most solid cancers increases approximately linearly with dose; at least, a linear model has not been shown to be statistically inferior to a dose-response model that allows for upward or downward curvature (20). However, rather than continuing to increase with increasing radiation dose, the risk of leukemia, and perhaps other cancers, levels off or even drops at high doses (16,18). This is believed to reflect the net outcome of competing processes of radiation-induced cell transformation and cell sterilization (31–33). Cells that have lost the ability to proliferate cannot give rise to cancer. Cell sterilization (also referred to as cell killing or cell inactivation) is thought to assume greater relative importance at higher doses. What qualifies as a “high” or “low” dose depends, of course, on one’s frame of reference. A local (partial-body) dose of 10 Gy is not high in the context of radiation oncology, where the killing of tumor cells is the objective, but it is high in the broader context of radiation exposures in general.

In addition to the total dose of radiation, radiation exposures also are characterized by the type and energy of radiation and the time course over which it is delivered. Ionizing radiation is classified as sparsely or densely ionizing, depending on the density of primary ionizing events produced (16). Sparsely ionizing radiation also is referred to as low-linear energy transfer (low-LET) radiation (e.g., x-rays and  $\gamma$  rays). Examples of densely ionizing (high-LET) radiation include  $\alpha$  particles and neutrons. For sparsely ionizing radiation, higher dose rates generally are associated with higher risks of cancer and other biological effects, although this generalization might not extend to cancer induction at very high doses (16). For high-LET radiation, the association can go in the other direction; that is, the higher the dose rate, the lower the level of biological effect (“reverse dose-rate” effect) (16,18,34).

Susceptibility to radiation-induced cancer depends strongly on the age at which exposure occurs. The risks of radiogenic cancers of the thyroid, breast, stomach, nervous system, skin, and AL are greater if exposure occurs early in life than if it occurs in middle or old age (18–20,23,35). The age dependence of radiogenic cancer risk presumably is related to age-related differences in levels of cell proliferation and differentiation in specific tissues. DNA damage in cells that are not cycling and cannot be induced to divide may be irrelevant from the standpoint of carcinogenesis.

Radiogenic leukemias first appear relatively soon after exposure, beginning after about 2 years (16,18,36). The relative risk (RR) commonly peaks between 4 and 8 years after irradiation and then drops back toward baseline levels. Some studies suggest a complete exhaustion of effect within 10 to 15 years, whereas others show risk remaining elevated even after 20 to 25 years (16, 18). Among atomic bomb survivors, the early peak was more pronounced among persons exposed during childhood, whereas the expression of excess risk over time was more delayed and prolonged

when exposure occurred in adulthood (19). This was especially true for acute myelocytic leukemia (AML); CML showed an early peak following exposure even among adults (19). In general, if there is going to be a detectable increase in the incidence rate of leukemia as a result of acute radiation exposure in a particular population, it will become apparent well before ten years have elapsed after exposure.

This is not the case for radiogenic solid cancers, which often are not detectable until at least 10 or 20 years after irradiation (16,17,36). The long latency is believed to reflect the multistep nature of carcinogenesis (36). It underscores the need for long-term surveillance of populations with appreciable radiation exposures. Studies that do not demonstrate an excess of solid tumors but have only short-term follow-up should not be interpreted as indicating an absence of long-term risk, and risk estimates for radiation-induced cancers must be interpreted in the context of the length of follow-up. An exception to the usual time-response pattern for solid cancers is the wavelike excess incidence of bone sarcomas among persons given radium ( $^{224}\text{Ra}$ ) to treat tuberculosis or ankylosing spondylitis (37,38).

Several factors influence the time to appearance or detection of radiation-induced cancers. To some extent, the apparent minimum induction period for a given type of radiogenic cancer depends on the dose and sample size; the greater the number of radiogenic cancers, the more likely that radiation-induced cancers of all latency periods, including short periods, will occur. More substantively, the induction period may depend on age at exposure, dose protraction or fractionation, exposure to other carcinogens (including chemotherapy agents), genetic susceptibility, and other host factors such as immunosuppression or hormonal stimulation. For example, a cancer might be initiated at a young age, but tumor growth might be arrested until later in life when hormonal or other changes stimulate cell proliferation. In such a situation, the apparent induction period probably would be greater for irradiation at a young age than at an older age. Hereditary or familial tumors tend to occur at a younger age than sporadic tumors, and the latency of radiation-induced tumors also might be shortened among the genetically susceptible. Thus, it is not appropriate to think of each tumor type as having a characteristic minimum latency time that applies to all situations.

Because it can take decades for the full scope of radiation-induced solid cancers to become apparent, currently we can only fully assess the effects of cancer treatments given many years ago. During the interim, not only have radiotherapy equipment and practice changed, but accompanying chemotherapy regimens have changed as well. Thus, in assessing risks of therapy-induced cancers, we are always running behind, using risks associated with past treatments to enlighten contemporary clinical practice and guide future research.

### TYPES OF RADIOTHERAPY AND CHANGES OVER TIME

The potential application of ionizing radiation to the treatment of cancer was recognized within a year after the discovery of x-rays (15,39), and radiation was used routinely in the treatment of certain types of cancer by the 1920s. With time, radiation oncologists became increasingly aware of both the acute and chronic side effects of radiotherapy and developed ways to minimize radiation dose to normal tissue while delivering an effective therapeutic dose to the cancer. These efforts continue today (40-43). Here, I briefly address general types of radiotherapy and some of the major changes that have occurred during the past several decades.

For a more detailed and informed discussion, the reader is referred to the recent chapter by Hellman (42).

The most common forms of radiotherapy are teletherapy and brachytherapy (42). Teletherapy (external beam therapy) is administered from an external source, such as an x-ray machine or cobalt 60 ( $^{60}\text{Co}$ ) source, whereas brachytherapy involves placement of the radiation source within body cavities or tissues, in direct proximity to the cancer. Brachytherapy often is used in the treatment of cancers of the female genital tract and oral cavity (42). Manufactured radioisotopes generally are used today, but radium ( $^{226}\text{Ra}$ ) or radon usually was used in previous decades (42). The radium delivered  $\gamma$ -radiation to the tumor and surrounding tissue. This was the modality of choice early in this century because  $\gamma$  radiation is more energetic and penetrating than what could be achieved with x-ray machines of the time and so was more effective in the treatment of deep tumors (15). Brachytherapy with  $^{226}\text{Ra}$  or other long-lived isotope irradiated tissue at a constant, low dose rate as long as it was left in place, which often was several days for gynecologic cancers. The use of pulsed, rather than continuous, brachytherapy is a recent development (44).

External beam therapy has been used for many years in the treatment of a variety of tumors, but there have been dramatic changes in the energy of the radiation used and in the ability to concentrate energy deposition in the tumor while sparing healthy tissue. Orthovoltage x-rays (125 to 400 KeV) were the usual type of external beam radiation before the 1940s or 1950s, but a switch then began to higher-energy external sources: first, to  $^{60}\text{Co}$   $\gamma$  rays, then to megavoltage betatron machines and, more recently, to linear accelerators (42). The higher the energy, the more penetrating the radiation (42), so megavoltage can deliver a higher dose to subsurface tumors while sparing the skin. Furthermore, unlike orthovoltage, megavoltage does not deliver a higher dose to bone than to the surrounding soft tissue, and megavoltage radiation is associated with less scatter (40,42). It has been hypothesized, but not demonstrated, that second cancer risks are lower for megavoltage treatments (45,46). Neutron therapy and proton beam therapy now are being used in the treatment of some types of cancer (47,48).

The protracted, low-dose-rate radiation exposure associated with brachytherapy contrasts with the fractionated external beam exposures, in which fractions of the order of 1.8 to 2.5 Gy were given 5 days per week over an interval of 6 to 8 weeks (42,44). Smaller fractions were used when larger volumes were irradiated, to lessen the acute effects of the radiotherapy (42). More recently, concern about late effects of radiotherapy contributed to decisions to use smaller fractions and less extensive fields in the treatment of some types of cancer, such as Hodgkin's disease (49). Other recent developments include the use of lower-dose fractions of 1.15 to 1.20 Gy, given twice per day over the same treatment period ("hyperfractionation") and of multiple low-dose fractions per day given over a shorter treatment period ("accelerated treatment") (50). Another trend has been toward organ preservation, in which limited surgery (rather than complete resection or amputation) is coupled with radiotherapy; examples include treatment for breast cancer, bone and soft tissue sarcomas, and rectal cancer (40,41).

The planning of radiation treatments has benefited greatly from advances in imaging technology and computer graphics software, which have made it possible to visualize tumors in three dimensions rather than two (41). Improved tumor localization makes it possible to concentrate energy deposition within the tumor and minimize irradiation of normal tissue (40). Modern equipment and techniques also allow for improved

collimation of the radiation beam, and shielding is more widely used than in the past (40,42).

Most radiotherapy is administered in high doses to restricted parts of the body. An extreme case is stereotactic radiotherapy, so-called radiosurgery, such as is used in the treatment of intracranial tumors (41). At the other extreme is the irradiation of lymph nodes throughout the body, as in the case of lymphoma (51). Whole-body irradiation is included as part of the conditioning regimen before bone marrow transplantation to treat metastatic cancer or high-risk disease that is likely to recur, but the high-dose regimens used in bone marrow transplantation are very different from the low-dose, whole-body radiation treatments used for NHL (42,52).

Internally administered, unsealed radionuclides have been used in the treatment of several cancers. For example, thyroid cancers commonly are treated with iodine 131 ( $^{131}\text{I}$ ), which is selectively taken up by thyroid tissue and has a short half-life; polycythemia vera is treated with phosphorus 32 ( $^{32}\text{P}$ ); several tumors are treated with radioactive colloidal gold ( $^{198}\text{Au}$ ); and strontium 89 ( $^{89}\text{Sr}$ ) has been used as a palliative measure in patients with widespread disease (41,53).

## SECOND PRIMARY CANCERS FOLLOWING RADIOTHERAPY

Historical treatment practices, cancer incidence rates, age at diagnosis and posttreatment survival all influence which types of first primary cancer have been most studied in the context of radiotherapy-induced multiple primary tumors. Radiation has, historically, been used much more in the treatment of some types of cancer than others. Based on cancers reported to the Connecticut Tumor Registry between 1935 and 1982 (11), radiation commonly was used to treat cancers of the oral cavity and esophagus, respiratory tract, female genital tract, testis, and brain, as well as lymphoma, but was used infrequently for most cancers of the gastrointestinal tract, prostate, and urinary tract, melanoma of the skin, and leukemia (Table 6-1). There have been changes in the use of radiotherapy for different types of cancer since that time (40), but late effects of recently introduced treatments are not yet described in the literature. Extent of irradiation also varied considerably among cancer sites (data not shown). Obviously, the more extensive the fields used, the greater the number of organs for which radiation-induced second cancers are of potential concern. Extended fields often were used for lymphomas and testicular cancer (51,54-56).

The average age at diagnosis of the first primary cancer was between 60 and 70 years for most sites, with several notable exceptions, including acute lymphoblastic (or lymphocytic) leukemia (ALL), cancers of the testis and bone, Hodgkin's disease, and cancers of the brain, thyroid gland, connective tissue, eye, and cervix (Table 6-1). Many cancers diagnosed among children, adolescents, or young adults can be treated effectively (3,4), and patients are potentially at risk for second cancers for seven or eight decades. For other cancers, including those of the esophagus, stomach, liver, pancreas, lung, and brain (in adults), survival is poor, and only a small percentage of patients survive for more than 5 years after diagnosis. Because radiation-induced solid cancers generally do not *begin* to appear until at least ten years after irradiation, second cancers following primary cancers of these sites have not been studied in detail. Even with improved treatments, death attributable to other causes would intercede among the many of the more elderly patients before the induction period for radiogenic solid cancers had elapsed. It is difficult to assemble a large series of long-term survivors

TABLE 6-1. Selected characteristics of patients with first primary cancers.

Site or type of first primary cancer	Incidence rate <sup>a</sup> (per 100,000 PY)	Percentage given radiotherapy <sup>b</sup>	Mean age at diagnosis (y)	Five-year relative survival (%) <sup>c</sup>
Lip		24.7	64	
Tongue		63.3	62	
Salivary gland	} 10.9	30.5	56	} 52.7
Mouth		56.2	63	
Pharynx		85.4	60	
Esophagus	3.9	61.3	64	8.5
Stomach	7.9	6.0	65	17.5
Small intestine		4.3	60	
Colon	35.0	2.3	66	58.8
Rectum	14.0	9.6	65	56.3
Hepatobiliary tract	2.9	9.0	66	6.0
Pancreas	9.1	10.5	65	3.3
Nasal cavities or sinuses		65.6	60	
Larynx	4.6	59.3	61	66.3
Lung and bronchus	57.8	55.6	62	13.3
Female breast	59.5	28.4	59	78.9
Uterine cervix	8.7	80.5	52	66.6
Uterine corpus	21.2	59.0	60	82.9
Ovary and fallopian tubes	14.3	40.6	56	39.2
Prostate	107.7	12.5	72	76.8
Testis	4.4	58.4	35	92.5
Kidney, renal pelvis, ureter	8.5	20.8	59	55.3
Bladder, other urinary tract	16.9	21.1	66	78.8
Melanoma of skin	10.9	3.3	52	84.1
Eye		10.2	50	
Brain and nervous system	6.2	62.8	45	26.6
Thyroid	4.5	21.1	46	94.0
Bone		41.7	39	
Connective tissue		24.9	49	
Non-Hodgkin's lymphoma	13.9	51.3	58	51.7
Hodgkin's disease	2.8	65.6	40	78.1
Multiple myeloma	4.3	38.1	65	27.2
Leukemia	9.9	18.7	53	37.6
Acute lymphocytic leukemia	1.5	28.5	19	51.5
Chronic lymphocytic leukemia	2.9	17.5	67	68.1

Data shown are a composite of SEER data (incidence rate and 5-year relative survival) from ref. 2 and a compilation of information for cancers reported to the Connecticut Tumor Registry for the years 1935 to 1982 (percentage given radiotherapy and mean age at diagnosis) from ref. 11. Note that the two sources refer to somewhat different populations and time periods.

<sup>a</sup>Rates for 1986–1990, standardized to 1970 U.S. population.

<sup>b</sup>As part of first course of therapy.

<sup>c</sup>For 1983–1987; all ages, all stages.

from any one center to study late effects, and multicenter collaborations usually are required.

In this review, particular attention is directed to second cancers following radiotherapy for childhood cancer, Hodgkin's disease, NHL, testicular cancer, breast cancer, and cancer of the female genital tract. These are the first primary cancers that have been most studied with respect to treatment-induced second cancer. Nonetheless, a review of findings from these studies in the broader context of the epidemiology and biology of radiation carcinogenesis may lead to useful generalizations about what to expect after radiotherapy for other types of first primary cancer. Information on the relative susceptibility of different organs to radiation-induced carcinogenesis suggests that one should be particularly alert to possible increases in acute leukemia and chronic

myelocytic leukemia relatively soon after radiotherapy, and to possible increases in cancers of the lung, female breast, thyroid gland, stomach, and skin beginning approximately ten years after treatment. Again, however, cancers that rarely are induced at doses of the order of several grays or less might assume greater importance at the extremely high doses characteristic of radiotherapy. With the preceding as background, I now consider risks of radiation-associated second primary tumors, separately by type of first primary tumor.

### Childhood Cancers

Although childhood cancer is rare, advances in treatment have created a large and growing population of long-term survivors, and it has become clear that this population is at elevated risk of developing second primary cancers relative to the general population (57-59). The long-term study of such patients is important both in terms of understanding the full magnitude and spectrum of treatment effects and because of the potential insights to be gained into cancer biology (60). Inherited predisposition appears to be an important factor for many childhood cancers, and the study of second cancers in such patients can be informative about shared genetic mechanisms (1,61-65). Because children have had lesser opportunity than adults to have experienced confounding environmental exposures, effects of genetic susceptibility and treatment can be evaluated more clearly (57,58). Furthermore, if subsets of patients who are especially susceptible (or resistant) to the carcinogenic effects of particular types of treatment can be identified, this knowledge could be used in treatment planning.

The most common childhood cancers are ALL and tumors of the brain and central nervous system (CNS), both of which now can be treated with considerable success (2,66,67). Notwithstanding the good survival, neither type is among the most common first primary cancers among children who go on to develop a second primary cancer over the ensuing 20 years. In a large, international study of late effects of treatment for childhood cancer, the most common *first* cancers among 353 *second* cancer patients were, in descending order, retinoblastoma, Hodgkin's disease, soft tissue sarcoma (mostly rhabdomyosarcoma), Wilms' tumor, brain tumors, and neuroblastoma (68). The exact order and percentages vary in different series, depending on cancer survival rates during the time periods covered, duration of follow-up, and referral patterns to participating study clinics (58,69-71); however, a consistent finding is that retinoblastoma and Hodgkin's disease as first primary cancers among patients with second cancers are considerably overrepresented relative to their incidence in the general population.

Based on follow-up through adolescence and into early adulthood, the most common types of *second* primary cancer are bone and connective (soft) tissue sarcoma, leukemia, and carcinoma of the thyroid and skin (57-59,68). Most of the leukemias are of the myeloid rather than lymphoid type (68). It has become clear that the different types of first primary cancer are associated with very high risks of specific, and often different, types of second cancers and that latency intervals for the different second cancers vary widely (57, 58). These patterns are revealing about the etiology of second primary cancers and suggest the influence of both genetic susceptibility and cancer therapy.

### *Retinoblastoma*

Retinoblastoma patients with bilateral or familial disease are at extremely high risk of developing osteosarcoma and soft tissue sarcoma, with RRs in the hundreds having

been reported (57,72-74). The osteosarcomas appeared after a very short latency period (75), and the cumulative incidence after 20 years was 7.2% (76). Mortality rates attributable to melanoma and brain tumors also were markedly elevated (73). Incidence of second cancers was not elevated among persons with unilateral retinoblastoma (74), most of whom would have had sporadic rather than familial disease (77).

The high rate of osteosarcoma and other second cancers among patients with nonirradiated bilateral retinoblastoma attests to the importance of genetic susceptibility, independent of any effect of radiotherapy (57,72). However, among patients with bilateral disease, the cumulative mortality attributable to second cancer after 40 years was 30% among those who were irradiated and 6.4% among those who were not irradiated (73). Positive associations were observed between radiation dose and the incidence of soft tissue sarcomas and all sarcomas combined over a dose range spanning tens of grays (74). Among patients with bilateral retinoblastoma, the risk attributable to irradiation appeared to be considerably greater if the radiation was administered during the first year of life than if it were given later (78). This pertained only to tumors of bone and soft tissue in the skull and face.

The molecular basis of the markedly increased susceptibility to second tumors among retinoblastoma patients with bilateral disease is related to a germline mutation in the retinoblastoma gene on chromosome 13 (79-82). It is possible that radiotherapy causes osteosarcoma and other second cancers by causing loss or inactivation of the wild-type allele inherited from the other parent.

### *Hodgkin's Disease*

Evidence points to a substantially greater role of therapy, as compared to shared genetic susceptibility, in the etiology of second cancers following treatment for Hodgkin's disease in childhood. Second cancers occurring among Hodgkin's disease patients of all ages are considered in greater detail in the following section. Briefly, large relative excesses of ANLL appear to be due primarily to treatment with alkylating agents, whereas a variety of solid cancers are associated with radiotherapy.

### *Rhabdomyosarcoma and Other Soft Tissue Sarcomas*

There is little information about treatment-specific risks of second cancer after soft tissue sarcoma in childhood. Obviously, potential radiation effects would depend on the part of the body irradiated. Five cases of AML, one case of myelodysplastic syndrome (MDS), and one case of osteogenic sarcoma were observed among 1,062 patients with rhabdomyosarcoma followed for a median interval of 3.7 years (83). Treatments included surgery followed by combination chemotherapy (cyclophosphamide, etoposide) and radiotherapy in different combinations. The highest RR for leukemia (RR = 51.6) was observed among patients who received cyclophosphamide and etoposide (83).

### *Wilms' Tumor*

In a study of 487 patients with Wilms' tumor treated between 1927 and 1981, 30 developed second primary tumors, 11 of which were malignant (84). Nearly 90% of the patients with Wilms' tumor were diagnosed before their fifth birthday, and 85% were treated with irradiation. All of the irradiated patients were given abdominal

radiotherapy, and nearly half of them also received thoracic radiotherapy as adjuvant therapy or because of metastases to the lung (84). All 11 second cancers occurred among irradiated patients. A variety of types of second cancer were observed, including one case of AML, two carcinomas of the thyroid gland, one carcinoma of the breast, three other carcinomas, and four sarcomas. Nine of the 10 solid cancers occurred within irradiated fields (mean doses, 6–40 Gy), as did 9 of 16 benign tumors, including 4 osteomas, 2 thyroid adenomas, and 2 uterine leiomyomas. The second cancers developed 7 to 34 years after treatment. Excluding the one observed case of nonmelanoma skin cancer, 10 cases of second cancer were observed among irradiated patients, versus 0.71 expected based on general population incidence rates ( $RR = 14$ ). Among nonirradiated patients, no cases of second cancer were observed ( $RR = 0$ ), but only 0.30 were expected.

Two more recent studies involved larger sample sizes. In a cohort of 1,248 patients with Wilms' tumor, the highest RRs were observed for cancers of the thyroid gland ( $RR = 136$ ; four cases), bone ( $RR = 127$ ; six cases), and connective tissue ( $RR = 84$ ; five cases) (57). The absolute excess risk of secondary thyroid cancer following treatment for Wilms' tumor was estimated as 4.8 excess cases per 10,000 persons per year (85). A total of 43 second cancers were observed among 5,278 patients in the National Wilms' Tumor Study who were followed for an average of 7.5 years (86). The RR was 8.4 for all second cancers, 7.0 for leukemia, and 8.9 for solid cancers, including lymphoma. A strong positive dose-response was observed between the RR for all second cancers combined and abdominal radiation dose, and there was an indication that treatment with doxorubicin increased risk associated with high-dose radiotherapy. The nine observed leukemias (six AML, one ALL, two CML) occurred between 1.2 and 6.4 years after diagnosis of Wilms' tumor. The other second cancers included 3 brain tumors, 13 sarcomas, 2 thyroid carcinomas, 3 hepatocellular carcinomas, 8 other carcinomas, and 1 retinoblastoma.

The occasional simultaneous diagnosis of Wilms' tumor with sarcoma, hepatoma, and AL points to possible shared host susceptibility factors (61,84). However, only one patient with a second cancer in the study of Li et al. (84) was known to have a genetic susceptibility syndrome [neurofibromatosis (NF) type 1]. It seems clear that radiotherapy played a major etiologic role for most of the observed second cancers among patients with Wilms' tumor. With the introduction of effective chemotherapeutic agents, radiotherapy now is used much less commonly to treat Wilms' tumor than in the past (40,87).

In the study of Li et al. (84), a second cancer caused the death of 7 patients, whereas Wilms' tumor caused the death of 241 patients. The survival rate for Wilms' tumor is far higher today than during most of the years covered by that study; nonetheless, the example illustrates the importance of keeping second cancer risks in their proper perspective.

### *Neuroblastoma*

Neuroblastoma can occur anywhere in the sympathetic nervous system, but most commonly arises in the abdomen (adrenal medulla) and, less often, in the chest or pelvis (88,89). Metastases to regional lymph nodes are common (89). Most cases occur among children younger than 5 years of age (89). The usual method of treatment today is surgery and combination chemotherapy, but neuroblastoma is a radiosensitive tumor, and radiotherapy historically has been used in its management (87,89).

Higher than expected numbers of cancers of the thyroid gland (RR = 349; seven cases), bone (RR = 150; four cases), and connective tissue (RR = 73; three cases) were observed among 790 2-year survivors of neuroblastoma who had been diagnosed at an average age of 2.4 years and followed for an average of 6.3 years (57). de Vathaire et al. (65) observed positive dose-response for malignant and benign thyroid tumors combined after radiotherapy for neuroblastoma. Estimated doses to the thyroid gland varied between 0 and approximately 25 Gy. For any given dose category, the RR among neuroblastoma patients was several-fold greater than for patients irradiated for other types of childhood cancer. If confirmed, this would indicate the existence of host susceptibility factors associated with increased risk of neuroblastoma and thyroid carcinoma or adenoma (65). The absolute excess risk of thyroid cancer following treatment for neuroblastoma was estimated as 14 excess cases per 10,000 2-year survivors per year (85).

### *Ewing's Sarcoma*

Ewing's sarcomas most often arise in the long bones of the limbs but also occur occasionally in bones of the trunk or head (90-93). Unlike osteosarcoma, which usually occurs at the ends of bones, Ewing's sarcoma generally occurs in midshaft (93). Reported ages at diagnosis range from 1 to 29 years with a mean of approximately 11 years (57,90,91).

Few patients with Ewing's sarcoma survive for more than a couple of years if not treated with irradiation, or radiotherapy and chemotherapy, but long-term survival is possible for patients given combined modality therapy (90,91). Radiotherapy has been part of the standard treatment for Ewing's sarcoma for decades and has included irradiation of the entire affected bone (with a boost to the tumor site) and, occasionally, prophylactic cranial irradiation as well (90,91). Doses to the affected bone typically have been 41 to 60 Gy (94,95). Before 1960, orthovoltage radiation was used, but megavoltage radiation has been used subsequently (90,96). Combination chemotherapy has been used along with radiation since the mid-1960s, whereas, in earlier years, chemotherapy either involved low doses of a single agent (amethopterin or cyclophosphamide) or was not given at all (90,94).

The rarity of Ewing's sarcoma has made it difficult to assemble large series of survivors for studies of second cancers. Although numbers of second cancers are small, a large relative excess of osteosarcoma has emerged as a consistent finding (57,90,96,97). Comparisons of observed numbers of cases with expected numbers based on population incidence rates have yielded RR estimates of 649 (based on seven cases) (57) and 2,400 (based on three cases) (90). These studies were restricted to patients who survived for more than 2 years after diagnosis of Ewing's sarcoma, and the osteosarcomas are unlikely to have been misdiagnosed recurrent first primary cancers. Most of the osteosarcomas developed within irradiated fields. The cumulative incidence of second primary sarcoma (osteoblastoma, fibrosarcoma, and malignant fibrous histiocytoma) was positively associated with radiation dose, and no sarcoma was associated with a dose of less than 48 Gy (95).

The mean latent period of the cases reported by Strong et al. (90) was less than 10 years, which is less than the usual latency period for radiogenic solid cancers following exposure to external low-LET radiation (16). One case, with a latency of 18.8 years, had been treated with irradiation only. The other two, with latencies of 4.3 and 6.2 years respectively, also had been treated with combination chemotherapy. The authors

suggested that the chemotherapy may have enhanced or accelerated the effects of radiotherapy in these patients.

Most patients who developed secondary osteosarcoma were between the ages of 10 and 15 years at the time of diagnosis of Ewing's sarcoma, an age that coincides with the adolescent growth spurt (90,92). Rapidly growing bone seems to be particularly susceptible to the carcinogenic effects of ionizing radiation (92).

The link between Ewing's sarcoma and osteosarcoma appears to be attributable more to treatment, primarily radiotherapy, than to a shared genetic predisposition (90,91,93). Kuttesch et al. (97) recommended against using doses in excess of 60 Gy to treat Ewing's sarcoma. Physicians caring for Ewing's sarcoma patients should be particularly attentive to the possibility of second primary osteosarcomas developing within or near the bone in which the Ewing's sarcoma occurred.

It is difficult to draw inferences about risks of other types of second cancer following Ewing's sarcoma, because of the small numbers of second cancers. Tucker et al. (57) observed two cases of leukemia (RR = 62) among 213 Ewing's sarcoma patients diagnosed at an average age of 10.9 years and followed for an average of 5.5 years, and Smith et al. (96) observed one case of AML among 25 patients with median follow-up of 7.6 years.

### *Acute Lymphoblastic Leukemia*

Until recently, ALL often was treated with high doses (18 to 24 Gy) of cranial or craniospinal radiation to prevent CNS involvement (87,98). This treatment was associated with a 22-fold RR of tumors of the CNS, and children less than 5 years of age at the time of treatment for ALL appeared to be at particularly high risk (98). Sixteen of the 24 CNS neoplasms were astrocytic tumors, 4 were embryonal tumors, and 2 were meningiomas. The increased incidence rate of CNS tumors persisted over the next 15 years following diagnosis of ALL (98). In another study, the incidence of CNS tumors following childhood ALL was 60-fold higher than expected based on population incidence rates, and all nine second cancer patients had received cranial radiotherapy (99).

Leukemia and CNS tumors may occur together as parts of certain genetic or familial syndromes (61,69,100-102), and part of the excess of CNS tumors might be explained by a shared predisposition. However, the 10-year cumulative incidence of second cancers among irradiated patients (1.6%) was higher than for a small series of nonirradiated patients (0.3%) (98). It is possible, though unproven, that radiotherapy interacts with genetic susceptibility to increase the incidence of CNS tumors (98).

Today, intrathecal chemotherapy is used more often than craniospinal radiotherapy to treat childhood ALL without evidence of CNS involvement, but many persons who received the radiation treatments are still alive and should continue to be followed (98). Cranial irradiation for childhood ALL or brain tumors causes other serious late effects, in addition to cancer; these include disorders of growth and development and impaired mental function (103-106).

### *Tumors of the Brain and Nervous System*

Radiotherapy continues to be widely used in the treatment of brain tumors (40). An increased risk of second primaries of the nervous system following radiotherapy of brain tumors would be expected based on results from studies of patients given

cranial radiotherapy for ALL (98) or for nonneoplastic conditions (108,109), and from studies of survivors of the atomic bomb explosions in Japan (20). A significantly increased incidence of cancers of the brain and CNS was observed in a population-based study of 1,262 patients with medulloblastoma from the United States and Sweden (107). Excesses also were observed for ALL and cancers of the thyroid and salivary glands. Nearly half of the total number of second cancers occurred within or near the radiation field.

Meningiomas and neurilemmomas appear to be particularly prone to being induced by radiotherapy during childhood (108,109). Both of these tumor types also occur in association with NF type 2 (110), whereas astrocytomas occur in association with NF type 1 (von Recklinghausen's disease) (111). In a series of 161 childhood cancer patients who developed a second tumor, 12 developed multiple tumors of the CNS (69). Five of the second tumors were meningiomas and four were astrocytomas, and three of the four astrocytoma patients appeared to have NF type 1 (69). Whether patients with NF type 1 or 2 also are at increased risk of radiation-induced second primary tumors is not known.

A small minority of children diagnosed with medulloblastoma have it in association with the nevoid basal cell carcinoma syndrome, also known as Gorlin's syndrome (75). This genetic syndrome is characterized by the occurrence of multiple basal cell carcinomas of the skin, increased susceptibility to medulloblastoma and ovarian fibromas and fibrosarcomas, and other abnormalities (75). In such patients, cranial and spinal radiotherapy for the medulloblastoma is followed within 3 years by the appearance of multiple basal cell carcinomas of the skin in or near the irradiated areas, that is, on the scalp, neck, spine, shoulders, and axillae (75). This anatomic distribution of lesions is very different from that seen in patients with Gorlin's syndrome who do not receive cranial or spinal irradiation. Patients with Gorlin's syndrome thus are a (small) subgroup with inherited susceptibility to basal cell carcinomas, and it appears that radiation can cause the additional mutation needed for tumor development (75). One would expect that persons affected by this syndrome who were irradiated for reasons other than medulloblastoma also would exhibit an early and increased incidence of basal cell carcinomas in the irradiated regions. Whether exposure to ultraviolet radiation might modify the interaction between genetic susceptibility and ionizing radiation, including the anatomic distribution of skin cancers, is not known.

### *Skin Hemangioma*

Whether hemangiomas of infancy and childhood are better regarded as neoplasms or as malformations is controversial (112). In either case, they are histologically benign and often regress spontaneously (112). Radiotherapy no longer is used to treat these lesions but was used commonly before 1960 (113). The median age at irradiation was 6 months, and the usual treatment modality was  $^{226}\text{Ra}$  (113,114). Most of the lesions were in the head or neck area, with lesser numbers in the trunk or extremities (114). Estimated average radiation doses were 0.5 Gy to the breast, 0.3 Gy to the thyroid gland, 0.2 Gy to the bone, and 0.1 Gy to the brain (114,115). Incidence rates of subsequent thyroid cancer and tumors of bone and soft tissue were positively associated with radiation dose, whereas the incidences of secondary breast and brain tumors were not (114,116). However, an indication of dose-response for intracranial tumors

was seen for infants treated during the first 7 months of life (116). In another study of patients with hemangioma (117), a positive association was observed between the prevalence of thyroid nodules and radiation dose to the thyroid gland.

### *Childhood Cancer of Mixed Types*

Because it is difficult to assemble large enough series to evaluate risk of second cancers in relation to radiation dose for specific types of first childhood cancer with any degree of precision, several studies have addressed risk of leukemia and cancers of bone and thyroid following radiotherapy for any of a variety of first primary cancers (118–120). In such case-control evaluations, controls generally are matched to cases by histologic type of first primary cancer and duration of survival before diagnosis of second cancer.

The incidence of leukemia showed a significant positive association with dose of alkylating agents among 9,170 2-year survivors of childhood cancer, but incidence was not associated with radiation dose (118). The year of diagnosis of the first primary cancer ranged from 1936 to 1979. The largest relative risks were observed following treatment for Hodgkin's disease or Ewing's sarcoma. There was no indication of a synergistic effect of radiotherapy and chemotherapy. The most common drugs used were procarbazine and nitrogen mustard, but chlorambucil and cyclophosphamide also were used (118). The authors acknowledged the possibility of a small radiation effect having been obscured by the strong effect of alkylating agents (118).

In a more recent study of leukemia risk among children diagnosed with cancer between 1962 and 1983, the relative risk of secondary leukemia was elevated among those treated with irradiation only (RR = 8.4), cytotoxic drugs only (RR = 33.6), or both irradiation and drugs (RR = 62.9) (120). Most patients who had chemotherapy were given more than one drug, but the RR was most strongly associated with doses of epipodophyllotoxins. The largest RR was observed following treatment for NHL. Possible reasons for the difference between these results and those of Tucker et al. (118) include the greater use of epipodophyllotoxins and less intensive radiotherapy to more extensive fields (120).

Among children diagnosed and treated for a first primary cancer of any type between 1936 and 1979, absolute and relative risks for subsequent bone cancer increased with time since diagnosis (119). The absolute excess risk was 10.7 excess cases per 10,000 persons per year during the second 5 years following diagnosis of the first cancer, and 36.1 excess cases per 10,000 persons per year among 20-year survivors (119). This time-response pattern differs from the wavelike excess seen among patients with tuberculosis and ankylosing spondylitis treated with  $^{224}\text{Ra}$  (37, 38). The RR also increased with radiation dose to the site of the tumor up to doses of 60 to 80 Gy (RR = 38); however, no increase was seen for doses less than 10 Gy (76,119). This supports the view that bone sarcomas are predominantly a high-dose effect of irradiation. There was an indication of a downturn in risk at the highest doses (76). Contrary to the suggestion that cancer risks associated with megavoltage radiation might be lower than those associated with orthovoltage radiation (45,46), the dose-response relation for bone sarcoma did not appear to depend on the energy of the radiation (119). Most bone sarcomas arising in nonirradiated sites were osteoblastic, whereas tumors in irradiated fields were of mixed histologic types, including fibroblastic, telangiectatic, osteoblastic, and chondroblastic morphologic types (121). Chemotherapy with alkylat-

ing agents (including cyclophosphamide) also was associated with increased incidence of bone sarcomas (76,119).

The RR of thyroid cancer among persons irradiated for childhood cancer was 53, and the RR was not significantly higher among patients with thyroid doses in excess of 30 Gy than among those with lower doses (85). The RR increased with time since treatment, as one would expect for radiation-induced solid cancers, and the cumulative incidence after 26 years was approximately 4% (85). The most common types of first primary cancer were Wilms' tumor and Hodgkin's disease, but the highest RR was observed among patients with neuroblastoma. Susceptibility appeared to be greatest among those exposed at the youngest ages (<5 years). Although the observed RR was high, the excess RR per unit radiation dose was considerably lower than has been reported for childhood exposures to much lower doses (16,35), possibly because of radiation-induced cell killing at high doses.

The RR of second cancers of all types was evaluated with respect to radiation dose to the affected site in a cohort of 634 children treated for a first cancer between 1942 and 1969 (122). Two of the second cancers were leukemias and the other 30 were solid cancers, including six each of bone and thyroid cancer and five each of soft tissue sarcoma and skin cancer. Twenty-eight of the second cancer cases had been treated with irradiation, and 18 of these 28 cancers developed within irradiated areas. With patients treated by surgery only as the reference group, the RR was 2.0 for radiotherapy only (local radiation dose >25 Gy), 4.4 for chemotherapy only, and 21.4 for combined modality treatment (122). Although these results are compatible with a synergistic effect of combined modality treatment, interpretation is complicated by the pooling of both first and second cancers, and the small number of second malignancies. There was no significant difference in the incidence of second cancers between patients treated with megavoltage radiation and those given orthovoltage radiation, but the study was too small to be discriminatory.

### *General Comments*

To date, most of the second cancers that can be attributed to radiotherapy for childhood cancers have been bone and soft tissue sarcomas; carcinomas of the thyroid gland, breast, and skin; and tumors of the nervous system, with a lesser risk of leukemia. Radiation is much less widely used to treat pediatric cancers today than it was in the past (40, 87).

Comparatively little information exists about treatment-related second cancer risks among long-term survivors of childhood cancer. Continued follow-up of the large study cohorts that have been assembled is critical to determine whether the enormous RRs seen through adolescence and early adulthood carry through into middle and older ages, when incidence rates of carcinomas increase dramatically (68,123).

Olsen et al. (66) described the occurrence of second cancers following childhood cancer in the five Nordic countries. The childhood cancers were diagnosed between 1943 and 1987, and the cohort was followed through 1987. An RR of 3.6 was observed, based on comparisons with general population incidence rates. Whereas the absolute difference between observed and expected incidence rates continued to increase with increasing duration of follow-up, the relative excess was highest during the first 10 years following diagnosis of first primary cancer, and then declined. This probably reflects the increasing relative importance of cancers caused by environmental factors

other than radiotherapy or chemotherapy (66). Treatment information was not included, so long-term effects of treatment cannot be evaluated separately.

### Hodgkin's Disease

Hodgkin's disease is unusual among cancers in having an incidence rate that varies relatively little with age after childhood (124). Because Hodgkin's disease often strikes at a young age and is curable, even very late complications of treatment are of concern. Historically, treatments have been similar for different ages at diagnosis, so age-at-exposure effects can be addressed (57,85).

The dramatic gains in survival of patients with Hodgkin's disease are largely attributable to the introduction of combined chemotherapy regimens, including MOPP (mechlorethamine, vincristine, procarbazine, and prednisone), in the 1960s and 1970s (5). However, radiotherapy also is commonly used and is especially effective in treating localized disease (125). In the past, radiation exposures often were extensive, as multiple fields were employed. Treatments ranged from local radiotherapy only, to subtotal lymph node irradiation on one side of the diaphragm, to total nodal irradiation (6,56,126,127). Total nodal irradiation involved mantle, paraaortic, and pelvic fields, with the radiation typically administered in dose fractions of 1.50 to 2.75 Gy per day over a period of weeks and resulting in a cumulative dose in the tens of grays to the target volume(s) (49,54). Mantle fields included cervical, supraclavicular, axillary, mediastinal, and pulmonary hilar nodal regions (49). The bone marrow, breast, lung, thyroid gland, stomach, and skin, all of which are radiosensitive sites, were exposed to varying degrees.

Numerous studies have shown the risk of ANLL and MDS to be markedly elevated during the first 10 years after diagnosis of Hodgkin's disease, but most of the excess is attributable to alkylating agents rather than to radiotherapy (6,56,118,127-132). After the first 10 to 15 years, the risk of ANLL and MDS appeared to plateau, at a cumulative risk of between 2.0% and 3.5% (6,126,130,133-135). Relative risks for ANLL associated with treatment with alkylating agents are substantial, with some estimates indicating 100-fold increases in risk (6,56,130). However, there has been little, if any, excess of leukemia among patients treated exclusively with radiation (56,118,128,130-132). It is possible that a large fraction of marrow stem cells within irradiated fields were sterilized by locally very high doses. Radiotherapy given in combination with chemotherapy has not been associated with greater risk than chemotherapy alone in most studies (56,129-132). Exceptions include several studies in which the risk of ANLL was positively associated with extent of radiotherapy when radiation was administered in combination with MOPP or other chemotherapy (56,126,130,135,136). Higher incidence was seen among patients who received total or subtotal nodal irradiation than among those irradiated on one side of the diaphragm only. The influences of extent of radiotherapy, total dose, and dose per fraction merit further study, particularly among patients receiving combined modality therapy.

High-dose splenic irradiation did not appear to influence leukemia risk (130). This was of interest because of reports of an increased incidence of leukemia among persons who had a splenectomy performed as part of their staging for Hodgkin's disease (6,56,127,128,135,137,138). It was hypothesized that high-dose splenic irradiation, of the order of 40 Gy, might induce functional hyposplenism with effects similar to those of splenectomy (139,140). In addressing this hypothesis, care must be taken to distinguish effects associated with irradiating the spleen from those associated with simultaneous

irradiation of the bone marrow. Even the findings for splenectomy have been inconsistent (126,130,141). Persons who underwent splenectomy because of external trauma did not experience increased rates of leukemia or other cancers relative to the general population (142,143).

Although radiotherapy for Hodgkin's disease appears to have been relatively ineffective at causing leukemia, it caused detectable increases in the incidence of several solid cancers, including those of the breast, lung, thyroid gland, stomach, bone and connective (soft) tissue, skin and, perhaps, colon and pancreas (6,56,119,127,131,132,144,145). In most cases, these excesses were delayed, first appearing 5 to 10 years after initial treatment and, unlike for leukemia, were still increasing after 15 years of follow-up.

The increase in breast cancer incidence is especially striking among women who received mantle-field irradiation at a young age (49,56,131,144,146-148). Hancock et al. (49) reported RRs of 136 for women irradiated before age 15 years, 19 for ages 15 to 24 years, and 7.3 for ages 25 to 29 years. The RR for breast cancer increased with time since radiotherapy for all age-at-exposure groups and was much higher after 15 years than before 15 years (49). Overall, breast cancer incidence was not increased among women irradiated for Hodgkin's disease after age 30, although a nonsignificant excess was observed among those followed for 15 years or more (49). Other investigators have reported similar results; that is, high RRs of breast cancer following radiotherapy for Hodgkin's disease, delayed onset of increased risk, and a higher risk among women who had been irradiated at younger ages (56,131,144,147). The long-term risk of radiogenic breast cancer would have been missed, or grossly underestimated, had evaluations been based on short-term (<10 to 15 years) follow-up.

Women given mantle-field radiotherapy for Hodgkin's disease at a young age should be monitored very closely for the later occurrence of breast cancer (49,56,144,148,149). Given the long latency of radiogenic breast cancer, more frequent than usual mammography might not be indicated after radiotherapy until 8 to 10 years had elapsed (56,150).

Radiotherapy for Hodgkin's disease delivered substantial doses to the lungs when mantle, supraclavicular, inverted-Y, splenic, or paraaortic fields were used (151), and lung cancer incidence consistently has been observed to be increased among patients with Hodgkin's disease (6,56,131,132,145,151-154). Risk of second lung cancer appeared to increase with increasing dose to the lungs for doses up to about 10 Gy (RR  $\approx$  14), after which the dose-response curve appeared to flatten or turn down (151,153). The absolute excess risk of lung cancer following Hodgkin's disease was estimated as 20 cases per 10,000 10-year survivors per year (151).

The excess of lung cancer appeared sooner after irradiation than is the norm for radiation-exposed populations. Whereas radiogenic lung cancer typically does not begin to appear until at least 10 to 15 years following exposure (16), excess lung cancer was apparent within 5 to 10 years of first diagnosis of Hodgkin's disease (6,153). Possible explanations include the high doses to the lung, immunosuppression associated with Hodgkin's disease, or a modifying effect of exposure to alkylating agents (153). At this time, it is unclear whether chemotherapy influences the risk of secondary lung cancer, either alone or when administered in combination with radiotherapy (131,132,151,153). Most populations given chemotherapy have been followed for a relatively short period, possibly too short for an effect to be detected.

Radiotherapy is a far less important cause of lung cancer than is cigarette smoking, both in terms of the magnitude of effect and the prevalence of exposure. An obvious question is whether carcinogenic effects of the two exposures are independent; that is, does the effect of radiotherapy add to that of smoking, or are the effects multiplicative? It is important that studies of this question collect information about smoking that was recorded before the diagnosis of lung cancer to avoid biased ascertainment of smoking history for lung cancer cases and controls. van Leeuwen et al. (151) did so and reported evidence of a positive interaction between irradiation and smoking. The risk associated with radiotherapy was greater among smokers than nonsmokers and among heavier smokers than lighter smokers. This was apparent only for the amount of smoking subsequent to the diagnosis of Hodgkin's disease, possibly indicating that smoking acted as a promoter of radiation-induced damage. However, data in the lowest dose strata are sparse, and data in the other strata are compatible with an additive relationship (155). A study of atomic bomb survivors indicated an additive relationship between the effects of irradiation and smoking (156), whereas studies of uranium miners indicated a multiplicative, or at least supraadditive, relationship (157). Thus, the issue is still unresolved and may depend on the nature of the radiation exposure. The stronger associations observed for smoking after the diagnosis of Hodgkin's disease than before the diagnosis also might be due to the availability of more accurate and detailed information about smoking history for more recent time periods (155). In either case, smokers who develop Hodgkin's disease would benefit from quitting smoking. In the future, chemoprevention also might be a possibility (158). Modification of radiotherapy regimens based on smoking history is not indicated.

It would be easier to attribute secondary lung cancers to particular causes—such as smoking, radiotherapy, or chemotherapy—if cancers caused by different exposures or combinations of exposures were distinguishable on morphologic examination. Analysis of the mutational spectrum for the p53 gene from tumor tissue removed from 11 lung cancer patients lends provisional support to the view that radiotherapy may cause distinctive types of mutations (159). Evidence of possible characteristic mutations associated with exposure to radon among uranium miners also has been reported, though results are somewhat inconsistent among studies (160–163).

As with lung cancer, an excess incidence of stomach cancer appeared after 5 to 10 years had elapsed since diagnosis and first treatment for Hodgkin's disease and then continued to increase with time (6,56). The stomach cancers were associated with having received radiotherapy for Hodgkin's disease and occurred within irradiated fields (6). Radiation-induced stomach cancer would be expected, based on findings for atomic bomb survivors (20) and patients treated with radiation for stomach ulcers (164).

Susceptibility to radiogenic thyroid cancer among Hodgkin's disease patients appeared to be greatest among those exposed at the youngest ages (<5 years), and radiotherapy during adulthood was not significantly associated with increased risk of thyroid cancer, even though the average thyroid dose was very high (6,85). This conforms with results for atomic bomb survivors and other medically irradiated populations, which also show inverse associations between radiation risks and age at exposure (20,35). The unique feature of the radiotherapy patients is the much higher thyroid doses. The absolute excess risk of thyroid cancer among 2-year survivors of Hodgkin's disease diagnosed during childhood was 9.4 excess cases per 10,000 persons per year (85).

Susceptibility to radiation-induced bone sarcoma appears to be greatest for exposures occurring during adolescence, a period of rapid bone growth (57,96). Radiother-

apy for Hodgkin's disease during adulthood is not associated with anywhere near the excess risk of bone cancer as that seen among patients diagnosed in childhood (57,136,165,166).

Excesses of NHL and melanoma of the skin also have been observed among patients with Hodgkin's disease, but neither has been shown to be treatment related (6,56,131), and neither is generally regarded as being a radiogenic cancer. Both NHL and melanoma occur at increased rates in immunocompromised populations (167,168). Radiation might influence second cancer risk through its effect on the immune system (25). Radiotherapy for Hodgkin's disease was reported to cause a prolonged reduction in levels of circulating lymphocytes (169), and patients with Hodgkin's disease may have compromised immune systems independent of therapy (5). As an alternative, the increased risks may reflect an underlying predisposition associated with Hodgkin's disease. Misclassification of Hodgkin's disease and NHL also might play a role, as the two lymphomas often were confused in earlier years (56). Because of the apparently heightened susceptibility of patients with Hodgkin's disease to malignant melanoma, they should be advised to limit their exposure to ultraviolet radiation, and dysplastic nevi should be closely monitored (6).

Given the high incidence rates of secondary breast cancer associated with radiotherapy for Hodgkin's disease at a young age, some authors have questioned whether radiation has a role in the treatment of Hodgkin's disease (170). However, balancing different treatment options involves trade-offs (171). Comparisons of potential adverse effects of alternative treatment regimens in terms of second cancer incidence versus mortality might not lead to the same conclusion. Secondary leukemias are almost invariably fatal, whereas solid cancers are not. Therapy-induced secondary leukemias usually occur within a few years of first treatment for Hodgkin's disease. Most radiation-induced solid cancers, including breast cancer, appear only after a latency period of at least 10 to 15 years. A 15-year survivor of Hodgkin's disease probably has benefited from his or her treatment, and this benefit should not be compromised in an attempt to minimize possible late effects. Concerns about dropping radiotherapy altogether include not only a possible increase in mortality rate attributable to Hodgkin's disease, but also a possible need for more cycles of chemotherapy, which might increase the incidence of secondary ANLL (56,131,132).

Nonetheless, it always is desirable to minimize any unnecessary exposure to ionizing radiation. At some oncology centers, the use of extended-field, high-dose, and high-dose-per-fraction radiotherapy has been curtailed in favor of combined modality therapy (171). Hancock et al. (49) reported that radiation fractions decreased from 2.20 to 2.75 Gy per day before 1971 to 1.50 to 2.00 Gy per day in more recent years. The general trend is toward the use of limited-duration chemotherapy and limited-field radiotherapy (125,154,171). Nonalkylating cytotoxic drugs also are used more often today than in the past (87). The use of disease stage or other prognostic indicators to distinguish patients in need of more aggressive therapy from those who would fare well even if treated less aggressively offers one means of maximizing the potential benefits relative to potential risks (171,172).

The large early excess of ANLL following treatment for Hodgkin's disease is due primarily to alkylating agents, and any leukemogenic effect of radiotherapy is very small by comparison. Alkylating agents and radiotherapy do not appear to act synergistically to increase leukemia risk, although some question remains concerning MOPP chemotherapy and extended-field irradiation. After 15 years of follow-up, the risk of second solid cancers exceeds that of secondary leukemia, and the excess of solid

cancers continues to increase. Solid cancers that have been linked to radiotherapy include cancers of the breast, lung, stomach, thyroid gland, bone, connective tissue, and skin. The excesses of breast, thyroid, and bone cancer following irradiation at young ages are particularly noteworthy. Treatment practices have been modified, in part out of concern regarding neoplastic and nonneoplastic sequelae (49,145,173-175).

### Non-Hodgkin's Lymphoma

Unlike Hodgkin's disease, the incidence rate of NHL increases dramatically with age, from less than 1 case per 100,000 persons per year among children age 0 to 4 years to nearly 120 per 100,000 among adults over age 85 (176). The incidence rate has been increasing over the last several decades, for reasons that are not well understood (177).

As with Hodgkin's disease, both radiotherapy and chemotherapy commonly are employed in the treatment of NHL (175). Depending on the radiation fields used, substantial portions of the bone marrow and many other organs may be exposed. The array of treatments used has ranged from high-intensity, partial-body exposures given in large fractions over a period of weeks to total-body exposures administered in small fractions over many months or even years (51,54,178). Cytotoxic drugs used have included cyclophosphamide, chlorambucil, prednimustine, and mechlorethamine together with procarbazine (178).

The incidence of ANLL was evaluated in a cohort of 11,386 2-year survivors of NHL from the United States, Canada, Sweden, and the Netherlands (178). The majority of patients were diagnosed with NHL between 1973 and 1980 and were over age 50 years at the time of diagnosis. Radiotherapy usually involved megavoltage sources and was administered to fields in the abdomen or pelvis or both (34% of irradiated patients), chest only (16%), chest plus abdomen or pelvis (24%), and head and neck only (20%). A small minority of patients received total-body irradiation. The median radiation dose to the active bone marrow was 5.1 Gy among persons given radiotherapy only and 8.6 Gy among those who also were treated with alkylating agents. Among patients who received radiotherapy only, the RR contrasting higher dose ( $\geq 6.35$  Gy) and lower dose ( $< 6.35$  Gy) groups was 3.1, which was not significantly different from 1.0 (178). When analysis was adjusted for average radiation dose to the bone marrow, the risk of ANLL was not associated with the proportion of the marrow within irradiated fields. Larger RRs (of 12 to 13) were obtained for the alkylating agents mechlorethamine/procarbazine and prednimustine. With adjustment for type and dose of alkylating agents, radiotherapy plus chemotherapy did not appear to be more leukemogenic than chemotherapy without radiotherapy, but the sample size was small. Similar results were obtained in a smaller Danish study; that is, a substantial excess incidence of ANLL was seen among NHL patients treated with alkylating agents, but megavoltage radiotherapy was not associated with the incidence of secondary ANLL, whether given alone or in combination with chemotherapy (179).

In a third study, the highest rate of ANLL following NHL was observed among patients who received intensive combined modality therapy (54). Patients were treated under experimental protocols that included total-body, hemi-body, and total-nodal irradiation in far higher percentages than was customary in standard practice. A positive association between the incidence of ANLL and radiation dose to the bone marrow was observed, and the association persisted when the analysis controlled for duration of chemotherapy. Eight of the nine cases of ANLL received multiple courses

of treatment for NHL, a reflection of the tendency of some types of NHL to remit and relapse (180). Repeated exposure of the bone marrow to cytotoxic agents may carry an especially high risk of leukemia (132,180).

The incidence of ANLL associated with total-body irradiation followed by salvage therapy with alkylating agents or alkylating agents plus irradiation was higher than that associated with other treatments for NHL (51). Four cases of ANLL, plus one case of MDS, were observed among 61 NHL patients who received low-dose total-body irradiation as their initial treatment and were followed for an average of 9.7 years (51). The RR, based on comparison with general population incidence rates, was 117. Megavoltage sources were used to administer a total dose of approximately 1.5 Gy in fractions of about 0.15 Gy twice per week. Most patients later also received partial-body radiotherapy. Salvage therapy with alkylating agents usually included cyclophosphamide and/or chlorambucil. The RR of ANLL was not significantly associated with radiation dose in this small sample.

Thus, although radiotherapy for NHL appears to increase the risk of leukemia, the effect is small relative to that associated with alkylating agents, and radiogenic leukemia is a rare complication. An unresolved question is whether the risk of ANLL associated with combined modality treatment depends on whether involved-field or extended-field radiotherapy is used (54,178). As noted above, radiotherapy for Hodgkin's disease appeared to have, at most, a small effect on the the risk of ANLL, whether or not chemotherapy was given. Standard radiotherapy regimens differ between NHL and Hodgkin's disease patients (54). Radiotherapy for NHL generally is given in small fractions (~0.1 Gy per day) over an extended period lasting for months, and resulting in a total dose on the order of grays. Total-body or hemi-body radiotherapy rarely is used for Hodgkin's disease. Total-nodal radiotherapy for Hodgkin's disease is (was) given in large fractions (~2 Gy per day) over an interval of weeks, resulting in a total dose on the order of tens of grays or higher (54). The net leukemogenic effect of the competing processes of marrow stem cell-killing and transformation may be very different for the different types of treatment (120,180).

Radiotherapy for NHL also was associated with an increased risk of bladder cancer (RR ~ 3), and the effect of radiotherapy appeared to add to that associated with treatment with cyclophosphamide (181). The bladder received an average dose of about 20 Gy. Using low doses of radiation (<0.5 Gy) and cyclophosphamide (<20 g) as the reference category, the RR associated with higher doses of radiation was 3.3, of cyclophosphamide was 4.3, and of both agents was 8.1. The median interval between treatment for NHL and diagnosis of bladder cancer was 8.5 years (range, 3 to 21 years), and risk estimates may increase with longer-term follow-up. Excess kidney cancer also was observed among long-term survivors of NHL, but the excess was not associated with radiotherapy (181,182).

Thyroid cancer occurred more often than expected (2 cases observed, 0.02 expected, SIR = 81) among persons treated for NHL during childhood (85). Although the number of cases is very small, a radiation effect seems likely. The absolute excess risk was 7.2 excess cases per 10,000 2-year survivors of NHL per year (85). Radiation rarely is used to treat children with NHL today (40,87).

### **Testicular Cancer**

The last 20 years have seen dramatic advances in the treatment of testicular cancer, primarily because of the introduction of platinum-based combination chemotherapy

(183,184). The majority of patients now can be cured, even those with widespread disease (185,186). Because most patients with testicular cancer are between the ages of 20 and 44 years at the time of diagnosis (186), survivors are at risk of second cancers over a period of decades.

Chemotherapy now is used in most cases of advanced testicular cancer, but orchiectomy plus adjuvant radiotherapy has long been an integral part of treatment plans for early-stage testicular cancer, particularly for the radiosensitive seminomas (183,187,188). Patients with early-stage disease were given abdominal radiotherapy only, but men with supradiaphragmatic involvement received more extensive radiotherapy (187,189,190). Among persons irradiated for seminomas, average organ doses were estimated to be approximately 22 Gy to the bladder and prostate gland, 17 Gy to the pancreas, 13 Gy to the stomach, and 8 Gy to the active bone marrow and kidney (188). Average doses among patients with nonseminomas were estimated to be about twofold higher (188).

In a series of 29,000 patients with testicular cancer that included 3,306 20-year survivors, the incidence of both ANLL and ALL was increased (188). Excess leukemia was observed among men treated with irradiation alone and among those treated with chemotherapy (with or without radiotherapy). A limitation of this study is that assignment to treatment categories was based on initial treatment only, as ascertained from cancer registry records, and did not take possible subsequent salvage therapy into account.

Excesses of cancers of the stomach, bladder, bone, connective tissue and, possibly, hepatobiliary tract and pancreas among testicular cancer patients appear to be attributable to radiotherapy (187,188,191,192). Each of these sites typically received a large dose of radiation, and relative risks increased with time after treatment among men whose initial treatment included radiotherapy only. The stomach and bladder are well known to be susceptible to radiation carcinogenesis, whereas bone and soft tissue sarcoma appear to be caused only by very high doses of radiation (16,18). Radiotherapy to the paraaortic field, in particular, results in a substantial dose to the stomach (187). Most sarcomas that occurred *after* the diagnosis of testicular cancer occurred in the trunk, within irradiated fields, whereas sarcomas diagnosed *before* the testicular cancer occurred on the limbs (191). This supports a radiation etiology, but radiation-induced sarcoma appears to be a rare complication of radiotherapy for testicular cancer (191). The pancreas is not generally regarded as a radiosensitive site (18), and pancreatic cancer can be difficult to diagnose, so the excess of pancreatic cancer should be interpreted with caution. Nonetheless, it might represent a high-dose effect. Other second cancers possibly attributable to radiotherapy for testicular cancer include cancers of colon, rectum, and lung, as well as nonmelanoma skin cancer (189,190,192). Chemotherapy for testicular cancer was not associated with increased risk of secondary solid cancers (187). Radiotherapy appears to play a considerably greater role than chemotherapy in the induction of treatment-related solid cancers among testicular cancer patients, at least for the first 20 years after treatment.

Abdominal irradiation remains the preferred treatment for early-stage seminomas (189). In general, however, less extensive fields are used and doses to the bone marrow and gastrointestinal tract are lower than in years past; furthermore, radiotherapy no longer is routinely used to treat teratomas (187,193). The risk of radiation-induced gastrointestinal tract cancer probably is lower among testicular cancer patients treated with the modern methods. However, survivors treated with higher doses and more extensive fields should continue to be monitored (187,188).

### Ovarian Cancer

Ovarian cancer contrasts with testicular cancer in having an older mean age at diagnosis and much less favorable prognosis (5-year relative survival, 39%) (194,195). The poor overall survival is due to the fact that many patients present with advanced disease. However, many persons with early-stage disease and some with advanced disease can be treated effectively, and there are substantial numbers of long-term survivors (54).

External-beam therapy has been administered as an adjuvant to surgery, as treatment for inoperable disease, and for palliation (196,197). The radiotherapy sometimes included only pelvic or whole abdominal fields but, for other patients, it was extended to above the diaphragm (195,197). Radioactive gold ( $^{198}\text{Au}$ ) and phosphorus ( $^{32}\text{P}$ ) also have been used in the treatment of minimal disease (196,197).

Increased rates of secondary ANLL and ALL have been reported among patients with ovarian cancer treated with radiotherapy in the absence of chemotherapy, but the increases have been small and not statistically significant and incidence did not increase with increasing radiation dose to the bone marrow (194,195,198). With a surgery-only group as the reference group, the RR actually was lower among women with estimated doses of 10 Gy or more (RR = 1.2) than for women with estimated doses less than 10 Gy (RR = 1.9) (194). This could easily be a chance finding but also might reflect high-dose cell killing (54,194). Alkylating agents appear to be responsible for most of the elevated risk of leukemia following ovarian cancer (54,194,195). The most commonly used alkylating agents included chlorambucil, cyclophosphamide, melphalan, thiotepa, and treosulfan, and all five were judged to be leukemogenic (54,194). For the treatment regimens used, the combined effects of radiotherapy and chemotherapy did not appear to exceed the effects of chemotherapy alone (54,194). Again, however, caution in interpretation is indicated, as these studies did not include detailed information about doses and it was not unusual for women treated with radiotherapy and chemotherapy to be given lower doses of the alkylating agents (194).

Among 32,251 women diagnosed with ovarian cancer, 4,402 of whom were followed for at least 10 years, radiotherapy was associated with increased risks of cancers of the bladder and connective tissue, particularly 10 or more years after treatment (195). The RR for bladder cancer was 6.4 (based on 16 cases) among 10-year survivors treated with radiotherapy (195). Dose to the bladder was estimated to be 20 to 60 Gy (198). The RR for cancer of connective tissue was 16.5 among 15-year survivors, but this was based on just three cases (195). Significant excesses of pancreatic and rectal cancers also were observed among 15-year survivors treated with radiotherapy (195). These may be high-dose effects not seen at the much lower doses experienced by atomic bomb survivors (20). Excesses of breast, colon, and uterine corpus cancer also were observed but probably are due to shared etiologic factors with ovarian cancer, rather than to its treatment (195,198).

Unless detected early, ovarian cancer still is difficult to treat, and efforts continue to find more effective therapy (197). Current treatments emphasize combination chemotherapy, which is associated with an increased risk of secondary leukemia (194).

### Breast Cancer

Before the advent of breast-conserving surgery and localized radiotherapy to treat node-negative disease during the 1980s, the primary method for local control of breast

cancer was radical mastectomy followed by regional radiotherapy to the chest wall and the draining lymph nodes (199,200). Radiation usually was administered to a combination of anterior and posterior supraclavicular fields, lateral and medial tangential breast fields, and a mediastinal field, sometimes with a boost to the axilla (201,202). Thoracic bone, bone marrow, lungs, and the contralateral breast received high doses of radiation from such treatments. Not surprisingly, women irradiated for breast cancer before 1980 are at increased risk of leukemia and cancers of the lung and contralateral breast (201–204). Incidence of cancers of the esophagus, bone, connective tissue, and thyroid gland also may have been increased by radiotherapy, but the available data are limited (205,206). The magnitude of second-cancer risk depends not only on the type of treatment, but also on the age at which treatment occurred.

The risk of secondary leukemia after breast cancer was associated with both radiotherapy and chemotherapy (202). With adjustment for level of exposure to alkylating agents, a positive dose-response relation was observed between the incidence of ANLL and MDS and mean radiation dose to the total active bone marrow. The RR increased from 1.6 for doses less than 5 Gy to 7.0 for doses greater than or equal to 9 Gy. Overall, the mean dose among irradiated women was 7.5 Gy, and the RR associated with radiotherapy in the absence of alkylating agents was 2.4. In contrast, the overall RR associated with alkylating agents alone was 10.0. The highest RRs were observed for melphalan, but dose-response relationships were apparent for both melphalan and cyclophosphamide. The RR associated with treatment with both irradiation and alkylating agents was 17.4. This suggests that the risk of secondary ANLL among women given both modalities of treatment may be more than additive; that is, radiotherapy and chemotherapy regimens in use before the 1980s may have acted synergistically to increase the risk of ANLL following breast cancer (202).

Notwithstanding the high RRs observed in certain subgroups, the overall absolute risk of therapy-induced leukemia among breast cancer patients was small (202). Furthermore, changes in breast cancer treatment practices over the past 20 years give reason to believe that leukemia risks associated with contemporary treatments are substantially lower than those described above. Today, adjuvant chemotherapy for breast cancer rarely includes melphalan; cyclophosphamide is the most commonly used alkylating agent, but in generally lower doses than in the study described above (202). Among patients with localized breast cancer, breast-conserving surgery with high-dose localized radiotherapy often is used instead of radical mastectomy and regional radiotherapy (200). The use of more limited fields entails less extensive exposure of the bone marrow. The study of Curtis et al. (202) indicated that risk of radiation-induced leukemia is low for mean marrow doses from thoracic irradiation of less than 5 Gy. Concern about radiotherapy-induced secondary leukemia is not a leading concern in the modern management of breast cancer, but possible synergistic effects with cytotoxic drugs should be evaluated further.

Interestingly, no cases of CML or ALL among breast cancer patients had been treated with alkylating agents, whereas there were 14 cases of erythroleukemia (202). Both CML and ALL are known to be caused by radiation (16), whereas erythroleukemia is uncommon in irradiated populations (202,207). These observations point to possible differences in mechanisms by which ionizing radiation and alkylating agents cause leukemia and indicate that different subtypes of leukemia may be more prone to induction by one or the other modality of therapy (202).

Incidental dose to the contralateral breast associated with regional radiotherapy for a primary breast cancer can be of the order of a few grays (201), doses known to be

able to cause breast cancer in some populations (16). Boice et al. (201) evaluated the incidence of cancer of the contralateral breast among 41,109 Connecticut women diagnosed with invasive breast cancer between 1935 and 1982. Among irradiated women, the average radiation dose to the contralateral breast was 2.7 Gy. Overall, radiotherapy for breast cancer was associated with a nonsignificant 20% higher incidence of cancer in the contralateral breast. Further stratification showed the excess to be concentrated among women who were irradiated before age 45 years and who survived for at least 10 years (RR ~ 1.6) (201). Women irradiated at older ages also were at high risk of a new breast cancer relative to women not previously diagnosed with breast cancer, but the added risk was not attributable to radiotherapy. A similar, large study in Denmark also indicated that the risk of contralateral breast cancer associated with radiotherapy for primary breast cancer is low, possibly nonexistent, for radiotherapy given past the age of 45 years (208). Insofar as modern radiotherapy techniques tend to deliver even lower doses to the contralateral breast, one can infer that this general conclusion still holds today. This does not obviate the need for close surveillance, as such patients remain at risk, not only of recurrent breast cancer, but also of a second primary breast cancer unrelated to radiotherapy. Furthermore, results from the Connecticut study (201) add to those for Hodgkin's disease patients described earlier (49,56,144,147), in demonstrating a strong age-dependence in the risk of radiotherapy-induced breast cancer. Women irradiated at a young age, before age 30 to 35 years, should be followed especially closely (150).

The lungs received substantial, though extremely variable, doses of radiation from adjuvant radiotherapy regimens that targeted the chest wall and regional lymph nodes, and radiogenic lung cancer appears to be a late effect of radiotherapy for breast cancer as administered in previous decades. However, risks appear to be relatively small. In a study of secondary lung cancer among women treated for breast cancer in Connecticut between 1935 and 1971, the average dose was estimated to be 15.2 Gy to the ipsilateral lung and 4.6 Gy to the contralateral lung, with doses varying over orders of magnitude within each lung (204). Women given radiotherapy who survived for at least 10 years had approximately twice the incidence of lung cancer as those who were not irradiated (203,204,209). The relative risk increased with time, with an RR of 5.5 among 20-year survivors (204). Approximately nine cases of radiation-induced lung cancer would be expected to occur per year among 10,000 women who received an average lung dose of 10 Gy and survival for at least 10 years (204). These risks are very small when compared to mortality risks associated with the primary breast cancer and the risk of lung cancer attributable to cigarette smoking (210). Modern treatments are likely to deliver lower incidental doses to the lung. The limited available data about lung cancer risks associated with breast-conserving surgery and adjuvant radiotherapy are compatible with the view that risks are low, but additional follow-up is needed to characterize long-term risks (209).

There is some evidence that the risk of radiotherapy-induced lung cancer is greater among patients with breast cancer who smoke than among those who do not (211). However, this alone does not warrant modification of radiotherapy protocols. Effective treatment of the primary breast cancer remains the overriding issue. Women with breast cancer who smoke should be counseled to quit, not only to avoid secondary lung cancers, but for other health reasons as well (210).

As always, it is desirable to limit unnecessary radiation exposure to the lungs, but concern about the risk of radiogenic lung cancer should not play a major role in

decisions about the clinical management of breast cancer. Nonneoplastic pulmonary and cardiac effects of thoracic radiotherapy for breast cancer pose greater risks (212–215).

Less information is available about the occurrence of other second cancers following treatment for breast cancer. Based on cancer registry data, radiotherapy for breast cancer was associated with an approximately fivefold increase in the risk of esophageal cancer among 10-year survivors (206). Among 10-year survivors of breast cancer in Connecticut, the RR of thyroid cancer was 3.5 among women who were given radiotherapy as part of their initial treatment and 1.0 among those who were not; however, these estimates were based on small numbers (205). Also among 10-year survivors of breast cancer, the RR for cancer of connective tissue was 7.6 for women given radiotherapy as their first course of therapy and 1.2 for those not given radiotherapy, but, again, these estimates were based on small numbers (four and three cases, respectively) and incomplete treatment information (205). Soft tissue sarcomas occurred more than twice as often as expected among women treated for breast cancer; more than two thirds of the cases occurred within the treated area, and a positive dose-response was observed (216).

In case series of second primary cancers of bone and connective tissue, the breast is a common site of the first primary cancer, and a high percentage of the second primary cancers occurred within or near the irradiated fields (217–220). Although osteosarcoma can occur in any bone of the body, it tends to occur in the appendicular skeleton among nonirradiated persons (221), whereas sarcomas of bone in the axial skeleton are more common among irradiated breast cancer patients (219). Common histologic types of sarcoma in irradiated patients include osteosarcoma, malignant fibrous histiocytoma, and fibrosarcoma (219,220). Bone and soft-tissue sarcoma are rare among adults, and the *absolute* risks attributable to radiotherapy are small (216,219). Nonetheless, physicians should pay close attention to lumps, swelling, or pain arising within irradiated fields beginning 5 to 10 years after radiotherapy (218).

### Cancers of Uterine Cervix and Uterine Corpus

Adjuvant radiotherapy has long been a key part of treatments for invasive cancers of the uterine cervix and corpus. Because patients with uterine cancer have been treated with irradiation since the early part of this century, and survival is relatively good, possible late effects can be addressed (222,223). Chemotherapy rarely was used, and radiation effects can be assessed directly (223). The incidence of secondary leukemia and solid cancers in relation to radiation dose and type has been described for a cohort of more than 150,000 women treated for cervical cancer between 1940 and 1970 (222–226), and secondary leukemia was evaluated in a cohort of 110,000 women with invasive cancer of the uterine corpus who were diagnosed between 1935 and 1985 (227).

For both types of uterine cancer, treatment modalities have included external-beam radiation and brachytherapy, alone or in combination. Organs in the pelvic region, including bone marrow, received very large doses, in the tens of grays, with doses dropping off sharply outside this region. However, even organs in the abdomen and chest received appreciable doses, as a result of leakage and scatter from external beam sources. Radiation doses from cervical cancer treatments were of the order of 165 Gy to the uterus; 65 Gy to the vagina; 30 to 60 Gy to the

bladder and rectum; 32 Gy to the ovary; 10 to 20 Gy to bone; 7 Gy to bone marrow; 2 Gy to the stomach, pancreas, kidney and liver; 0.3 Gy to the breast; and 0.1 Gy to the thyroid gland (223).

The mean marrow dose, averaged over the entire bone marrow, was 7.1 Gy among irradiated patients with cervical cancer and 5.2 Gy among irradiated patients with uterine corpus cancer (224,227). As expected, no excess of CLL associated with radiation was observed in either cohort (RR = 0.9 to 1.0). Linear extrapolation of risk estimates based on data from the atomic bomb survivors (16,19) would have led one to predict a large relative excess of acute and chronic myelocytic leukemia among patients with uterine cancer. However, the observed excess of AL and CML was relatively small, with an overall RR of 1.9 to 2.0 (224,227). Among cervical cancer patients the RR of AL+CML increased with mean dose to the active bone marrow up to a dose of about 4 Gy, and then declined (224). All of the excess leukemia occurred within the first 5 years after irradiation. Among women with cancer of the uterine corpus, results were compatible with a nearly flat dose-response, with RRs varying only between about 2 and 3 over a range of mean marrow dose from 1 to 15 Gy (227). The excess appeared within the first 5 years after treatment, but, unlike for cervical cancer patients, risk remained elevated even after 15 or more years. Notwithstanding the twofold elevation in relative risk of leukemia associated with radiotherapy in this cohort, the estimated absolute risk of leukemia attributable to radiotherapy was small, approximately 14 cases of radiation-induced leukemia per 10,000 women over a 10-year follow-up period (227).

Several factors probably were responsible for the low incidence of radiogenic leukemia in such highly exposed populations (32,224). First, dose to the active bone marrow was extremely inhomogenous. A large proportion of marrow stem cells in the pelvis, lumbar vertebrae, and upper femur probably received sterilizing doses. Although cell killing would occur less frequently for cells outside the pelvic region that were exposed to lower doses, doses dropped off so sharply with distance outside the irradiated field that relatively small volumes of marrow were exposed to strongly leukemogenic doses (32). Dose protraction and fractionation could influence the observed dose-response patterns in a number of ways, for example, by allowing time for repair of subtransformational and sublethal damage, for stem cells to move in and out of heavily irradiated marrow compartments, and for repopulation of depleted stem cell populations due to mitosis (224, 228). The net effect of these multiple processes probably is extremely complex (224).

Among other types of hematologic cancers, only NHL occurred more often among the more heavily irradiated cervical cancer patients than among those with lower doses (RR = 2.5 for dose  $\geq 2$  Gy vs. dose  $< 2$  Gy) (223). This cancer has not been found to be associated with exposure to radiation in studies of populations exposed to substantially lower doses, but it is associated with immunosuppression (25,168). It is possible that high-dose radiotherapy influences NHL risk indirectly, by compromising immune function (25,223). Lymphocytes are highly sensitive to the cell-killing effects of ionizing radiation (16,26). Neither multiple myeloma nor Hodgkin's disease were associated with radiotherapy for cervical cancer.

Positive associations between cancer incidence and radiation dose were observed for several solid cancers (223), though, again, in light of the magnitude of doses to many of these organs, the excesses were not large. Analyses focused on experience 10 or more years after exposure to accommodate the typical minimum latent period for radiogenic solid cancers. Among the most heavily exposed organs, dose-related

excesses were observed for cancers of the rectum (overall RR = 1.8), bladder (RR = 4.0), vagina (RR = 2.7), ovary (RR = 1.4), and bone (RR = 1.3). Although bone cancers were uncommon, a disproportionate percentage (relative to the total skeleton) occurred in bone that received the highest doses (10 to 30 Gy). Doses to organs in the abdomen were on the order of a couple of grays. Cancer of the stomach (RR = 2.1) and kidney (RR = 1.2) appeared to be increased by radiotherapy, but cancer of the pancreas did not. Incidental doses to the thyroid gland were low, less than 0.2 Gy, yet a nonsignificant twofold RR was observed, and the RR increased with dose among 5-year survivors (223). This is noteworthy insofar as analyses of the atomic bomb data do not demonstrate a radiation effect among women exposed over the age of 20 years (20).

Colon cancer did not appear to be increased among patients with cervical cancer, even though parts of the colon received very high doses (223). Among atomic bomb survivors and other medically irradiated populations with lower doses to the colon and rectum, the occurrence of colon cancer was positively associated with dose, whereas rectal cancer incidence (or mortality) was not (20,229,230). It may be that colon cancer is caused by low to moderate radiation doses (on the order of grays or less), whereas radiogenic rectal cancer is more likely to occur following doses on the order of tens of grays (223). Such differences might be related to the higher proliferative activity of epithelial cells in the colon and possible increased susceptibility to radiation-induced cell killing, but this is speculative (223). The small intestine, another organ with a high rate of cell turnover, received a dose of 10 to 20 Gy, but radiotherapy was not associated with an increased rate of cancer. The small intestine does not appear to be very susceptible to radiation-induced cancer (16).

Radiotherapy for cervical cancer delivered incidental doses to the breast of between 0.1 and 0.6 Gy, but no overall excess of breast cancer was seen (223,225). This is not surprising, as the mean age at treatment was 52 years, and women over the age of 40 are not believed to be very susceptible to radiation-induced breast cancer (16,18). However, the dose-response pattern differed, depending on whether a woman's ovaries were present at the time of irradiation (225). Among women without ovaries, a nonsignificant positive association was observed between breast cancer incidence and dose to the breasts. Among women with ovaries, radiotherapy was associated with a 35% *reduced* risk of breast cancer. This probably was due to the inactivation of ovarian cells that produce steroid sex hormones involved in the pathogenesis of breast cancer (225). The observed protective effect of ovarian irradiation appears to involve more than just the induction of an early menopause, which is well known to protect against breast cancer (231-233). Evidence of a protective effect was seen even among women irradiated past the age of 50 years (225,230,234).

Although radiotherapy for uterine cancer increases the risk of leukemia and several solid cancers of pelvic and abdominal organs, the increases are not large. It was estimated that a maximum of 5% of second cancers occurring among cervical cancer patients were due to radiotherapy (223). For second cancers of heavily irradiated organs, those with a mean dose of 1 Gy or greater, the RR for all sites combined was 1.3 among 10-year survivors, that is, a 30% increased incidence associated with irradiation (223). The RR increased to 2.1 for 30-year survivors. Most 30-year survivors of invasive cervical cancer would be regarded as having had a favorable outcome of treatment. Furthermore, technological improvements have reduced incidental exposures to organs outside of the target volume (41,42).

### Other Primary Cancers

#### *Lung*

In a series of 611 2-year survivors of small cell lung cancer, the incidence of second lung cancer was associated with radiotherapy for the first cancer (158). Most of the second lung cancers were squamous cell carcinomas or adenocarcinomas. There was a suggestion of an interaction with continued smoking (158), which is similar to findings for patients with Hodgkin's disease (151) and consistent with smoking acting as a promoter of radiation-induced damage. In a small series of 158 patients intensively treated for small cell carcinoma of the lung with both chemotherapy and radiotherapy (cranial irradiation with or without thoracic irradiation), three cases of ANLL were observed 2.3 to 3.0 years after diagnosis of lung cancer (235). Fewer than 0.01 cases would have been expected based on population incidence rates, so the associated RR was very large. However, it is not possible to draw any conclusions about effects of specific treatments based on this small sample. The Finnish Cancer Registry was used to identify patients diagnosed with a first primary lung cancer between 1953 and 1989 ( $n = 36,528$ ) and then follow this cohort for the incidence of second cancers (236). There was an indication of an excess of cancer of the esophagus associated with radiotherapy. Interpretation of findings concerning second cancers after lung cancer can be complicated, because smoking, the major risk factor for lung cancer, also is a risk factor for many other cancers (237).

#### *Gastrointestinal Tract*

In the past, radiotherapy was not routinely used in the treatment of most gastrointestinal tract cancers, and 5-year survival rates for cancers of the pancreas, liver, stomach, and esophagus are poor (Table 6-1); thus, there is comparatively little information about radiotherapy and second cancers. Among 3,633 patients treated for cancers of the colon, rectum, or stomach and followed for an average of 3 years, the subsequent incidence of ANLL was associated with treatment with nitrosoureas [methyl-N-(2-chloroethyl)-N'-cyclohexyl-N-nitrosourea (methyl-CCNU)], but no cases of ANLL were observed among the 254 patients treated with radiation (239).

#### *Prostate*

Based on data from the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (SEER), the incidence of bladder cancer was approximately 50% higher among irradiated patients with prostate cancer than among nonirradiated patients followed for at least 8 years, but neither leukemia nor rectal cancer was associated with radiotherapy (239).

#### *Brain and Nervous System Tumors (in Adults)*

Cranial irradiation during childhood has been shown to be associated with increased risk of developing tumors of the nervous system, but risks associated with radiotherapy during adulthood are not well described in part because of the generally poor survival

of adult patients with glioma. Studies of atomic bomb survivors indicate that second cancer risks probably are considerably lower than for exposure during childhood (20).

### *Thyroid Cancer*

The administration of high doses of  $^{131}\text{I}$  to treat thyroid cancer has been reported to be associated with the later occurrence of several cancers, but results have not been consistent among different studies. Edmonds and Smith (240) observed four cases of leukemia among 258 persons given  $^{131}\text{I}$  for thyroid cancer, whereas only 0.08 would have been expected based on general population rates. Greater than expected numbers of bladder and breast cancer cases also were seen. A nonsignificant excess of leukemia (4 cases versus 1.6 expected) and significant excesses of tumors of the salivary glands, genital organs, kidney, and adrenal gland were observed among 834 patients treated with  $^{131}\text{I}$  in Sweden, but the RR for solid cancers did not increase with time following treatment, and excesses were not seen for either bladder or breast cancer (241). In a third study of 1,771 patients treated with radioiodine for thyroid cancer, no cases of leukemia were observed, but the incidence of colorectal cancer was positively associated with the administered activity of  $^{131}\text{I}$  (242). It is difficult to draw any generalizations from these varied findings.

### *Polycythemia Vera*

The radionuclide  $^{32}\text{P}$  has been used to treat patients with the myeloproliferative disease polycythemia vera, sometimes in conjunction with irradiation (243). Leukemia incidence appeared to be higher among irradiated than among nonirradiated subjects (243), but a number of methodological issues cloud interpretation of the findings, including the role of the underlying disease being treated (18). Patients with polycythemia may be at high risk of leukemia progression even in the absence of radiotherapy (244). However, results of a randomized clinical trial also showed a higher cumulative incidence of AL among patients with polycythemia vera treated with  $^{32}\text{P}$  (6%) than among patients treated by phlebotomy alone (1%); the median follow-up was 6.1 years for the  $^{32}\text{P}$ -treated patients and 5.5 years for the phlebotomy group (245).

## **CLINICAL CHARACTERISTICS OF RADIATION-INDUCED SECOND PRIMARY TUMORS**

In general, individual radiotherapy-induced cancers cannot be distinguished from nonradiotherapy-induced cancers, either on morphologic or clinical examination (28). Second cancers sometimes are labeled as "radiation-related" based on their occurrence within or adjacent to irradiated fields, and, when the attributable risk is high, one can assign a high probability to a particular tumor's having been caused by radiation, but the individual tumors are not distinctive on histopathologic examination.

Radiation-induced sarcomas often occur in the trunk near the site of the first primary tumor, in places where complete resection is not possible (7,218). Such tumors often also are associated with lung metastases (7). They have a poorer prognosis compared with tumors in the arms or legs (221). However, this does not imply that such tumors differ clinically from nonradiation-induced tumors occurring at the same site (246).

Secondary leukemia has long been recognized as a distinct entity from leukemia occurring among persons with no known genotoxic exposures (9,247). Chemotherapy-related leukemia differs morphologically, cytogenetically, and clinically from so-called *de novo* leukemia (8). It typically develops within 5 years after treatment, is more likely than *de novo* leukemia to be preceded by MDS, and is almost uniformly fatal within 1 year (8,247). Radiotherapy is weakly leukemogenic relative to alkylating agents, and secondary leukemia as a distinct entity has been linked much more closely with chemotherapy than with radiotherapy (8,248). A review of CML and AL cases among atomic bomb survivors and irradiated patients with cervical cancer showed them to resemble *de novo* cases, but AL cases that occurred among patients with ankylosing spondylitis resembled those seen following treatment with alkylating agents (207). Patients with spondylitis sometimes were treated with drugs, such as phenylbutazone, as well as with radiation (249).

### GENERAL DISCUSSION

The second primary cancers that have been associated with radiotherapy for a first primary cancer are, for the most part, the ones one would expect based on the experience of atomic bomb survivors and other populations exposed at low to moderate doses (16-18). Acute leukemia, CML, and breast, lung, thyroid, and nonmelanoma skin cancer all emerged repeatedly as radiotherapy-related second cancers following treatment for different first cancers (Table 6-2). Second cancers of the stomach, bladder, nervous system, ovary, colon, and liver also were linked to radiotherapy, though less consistently. High-dose effects seen among patients given radiotherapy, but rarely among populations exposed to lower doses, include sarcomas of bone and connective (soft) tissues and cancers of the rectum and, possibly, uterus (250) and pancreas. To this point, bone sarcomas are the most commonly reported second cancer following a first primary cancer during childhood (76). These tumors typically arise within or adjacent to irradiated fields, in areas receiving doses in excess of 10 Gy. Genetic susceptibility, radiotherapy, and alkylating agents all appear to play a role in the etiology of secondary bone cancers. Radiotherapy has the potential for inducing both high- and low-dose effects, because of the sharp gradient in dose with increasing distance from irradiated fields or an implanted radiation source.

Another recurrent observation is the strong dependence of second cancer risk on age at diagnosis and treatment of the first cancer. The risk of radiation-induced breast cancer is very high if thoracic radiotherapy occurs before age 30 years and low or nonexistent if radiotherapy occurs after age 45. The risk of radiogenic osteosarcoma is highest for radiotherapy given during the time of the adolescent growth spurt. Radiogenic thyroid cancer and cancer of the nervous system are most likely after radiotherapy in early childhood, before age 5 years. These patterns serve as a guide about the types of radiotherapy-induced second cancers one might expect, depending on the parts of the body irradiated, the doses received, and the age at which irradiation occurs.

Radiotherapy for several types of cancer is associated with an increased risk of AL and CML, but not CLL. Excess incidence of leukemia is apparent within the first 5 years after radiotherapy. In general, however, the increase is small, particularly for localized radiotherapy. Relative risks associated with radiotherapy typically have been of the order of 2 to 3. In no instance have RRs for the association between secondary leukemia and radiotherapy in the absence of chemotherapy remotely approached

**TABLE 6-2.** Summary of radiotherapy-related second (multiple) cancers for selected types of first primary cancer

Type of first primary cancer	Type/site of second cancers associated with radiotherapy	Comments
Childhood cancers <sup>a</sup>		
Retinoblastoma	Bone and connective (soft) <sup>b</sup> tissue, brain (?)	Strong genetic component to susceptibility.
Wilm's tumor	Bone and connective tissue, thyroid, leukemia, liver (?)	Radiotherapy used less often now than previously.
Neuroblastoma	Bone and connective tissue, thyroid	Possible shared etiologic factors between thyroid cancer and neuroblastoma (?).
Ewing's sarcoma	Bone, leukemia	
ALL	Brain and nervous system	Prophylactic craniospinal radiotherapy used less often today.
Medulloblastoma	Brain and nervous system, skin	High skin cancer risk among patients with Gorlin's syndrome (rare).
Hodgkin's disease (adults)	Breast, lung, bone and connective tissue, thyroid (?), leukemia (?)	High RR for breast, thyroid, and bone cancer associated with irradiation at a young age. Leukemia risk much greater for alkylating agents.
Non-Hodgkin's lymphoma	Leukemia, bladder, thyroid, kidney (?)	Thyroid risk associated with young age at irradiation.
Testicular	Stomach, bladder, leukemia (?), bone and connective tissue, pancreas (?)	
Ovarian	Leukemia, bladder, connective tissue, rectum (?), pancreas (?)	Leukemia risk much greater for alkylating agents.
Breast	Leukemia, contralateral breast, lung, thyroid (?), bone and connective tissue, esophagus (?)	Possible interaction with alkylating agents for leukemia; little or no radiation-induced cancer of contralateral breast following exposure past age 45 years.
Uterine	Leukemia, bladder, stomach, kidney (?), rectum, vagina, ovary, bone and connective tissue, thyroid (?), breast (?)	Low risk of leukemia despite high dose to bone marrow; protective effect against breast cancer among women with ovaries.

See text for details and references.

<sup>a</sup>Based on follow-up through early adulthood.

<sup>b</sup>Connective tissue and soft tissue are used interchangeably here.

those associated with certain of the alkylating agents, for which RRs greater than 100 have been observed (54). Among patients with Hodgkin's disease and ovarian cancer, the highest relative risks for leukemia were seen among persons first diagnosed and treated during the 1970s, the period in which the most intensive combination chemotherapy regimens were used (56,120,130).

Leukemia is a rare disease and remains so, even with a doubling or trebling of risk. Overall, the risk of radiation-induced leukemia does not appear to be an issue of overriding importance in the planning of cancer therapy, unless a synergistic effect with chemotherapy is indicated (*vide infra*). There is some evidence that the risk of radiation-induced leukemia is greater when large volumes of bone marrow are irradiated with lower doses, or dose fractions, than when small volumes are irradiated with large doses (and dose fractions). Reasons for the low risk of secondary leukemia associated with high partial-body exposures probably include the ability of ionizing radiation to sterilize, as well as transform, marrow stem cells.

Whereas most radiogenic leukemia occurs within the first 10 to 15 years after irradiation, radiogenic solid cancers are just starting to appear at this time. The excess of breast cancer among patients with Hodgkin's disease irradiated before age 30 years is a noteworthy example, but the generalization holds for most other radiation-induced solid cancers as well. Exceptions include osteosarcoma after radiotherapy for retinoblastoma or Ewing's sarcoma and lung and stomach cancer after radiotherapy for Hodgkin's disease. In these instances, increased second cancer incidence is apparent 5 to 10 years after irradiation. In the case of retinoblastoma, this likely reflects genetic susceptibility among familial cases. In the case of patients with Ewing's sarcoma and Hodgkin's disease patients, it may reflect effects of concomitant chemotherapy or immunosuppression.

Radiotherapy appears to be more important than chemotherapy as a cause of second primary solid cancers. This generalization is tempered by the absence of information about possible long-term risks of chemotherapy agents. Some drugs have not been in use long enough for late effects to appear or to have been documented. This highlights the need for case-control studies of second cancers in long-term survivors of their first primary cancer (151).

Apparent differences in the ability of ionizing radiation and alkylating agents to cause leukemia and solid cancers, respectively, raise questions about the respective mechanisms of carcinogenesis. Ionizing radiation is relatively effective at inducing DNA strand breaks, and most mutations caused by radiation are associated with large-scale chromosomal changes, such as translocations and deletions (251,252). Such chromosomal mutations can result in carcinogenic transformation through loss of tumor suppressor genes or activation of protooncogenes (44). However, double strand breaks also are potentially lethal to cells. Alkylating agents are more likely to result in point mutations than in chromosomal mutations (251). Point mutations also can result in oncogene activation, but are less likely to result in cell death. Thus the balance between cell transformation and cell inactivation differs between radiotherapy and chemotherapy (251). This might explain, in part, the greater leukemogenicity of alkylating agents relative to radiation. The anatomic distribution of exposure probably also is important. Systemically administered drugs expose marrow stem cells throughout the body, whereas partial-body radiotherapy exposes lesser volumes of marrow (54). Low-dose total-body radiotherapy for NHL irradiates the marrow more evenly and at a lower dose rate, possibly with less cell killing. There is some evidence to suggest that this type of radiotherapy carries a higher risk of leukemia (51, 180).

It has been suggested that the development of leukemia and lymphoma is closely tied to the activation of protooncogenes, whereas the development of carcinomas and other solid cancers also depends strongly on the loss or inactivation of tumor suppressor genes (44,253). Ionizing radiation is more effective than alkylating agents in producing DNA double strand breaks, and such breaks can result in loss of heterozygosity at tumor suppressor loci at which one allele already includes a germline or somatic mutation (251,252). This might be one reason for the stronger association between radiotherapy and second solid cancers than between chemotherapy and second solid cancers.

Given the differences by which radiation and alkylating agents (or other cytotoxic drugs) interact with cells and with DNA, it is reasonable to ask whether the two modalities of treatment might act in a complementary fashion to induce second primary cancers. Is the carcinogenic effect of one agent contingent on the presence or dose

of the other? The appropriate criterion for assessing interaction in this context is departure from additivity of effect. Although possible interaction between treatment modalities is an important issue in oncology, it also is one that has proven difficult to address. To do so requires not only a large sample size, but also comprehensive and detailed knowledge of specific agents and doses administered, of their sequencing and timing, and of possible modifying effects of host susceptibility factors associated with the first primary cancer (30).

The evidence concerning cancer risks associated with combined modality therapy is mixed. Most studies of secondary leukemia among patients with Hodgkin's disease do not indicate that radiotherapy given together with chemotherapy increases risk beyond that associated with chemotherapy alone, with the possible exception of extended-field radiotherapy given together with MOPP. Extended-field radiotherapy is used less often to treat Hodgkin's disease now than in the past. Involved-field radiotherapy for NHL also did not appear to increase the risk of leukemia beyond that associated with chemotherapy alone, but low-dose total-body or hemi-body radiotherapy might be associated with higher risk. Most of the excess leukemia among patients with ovarian cancer appeared to be due to alkylating agents. Perhaps the strongest evidence of a greater-than-additive effect of combined modality therapy comes from a study of leukemia among patients with breast cancer (202). However, the types of breast cancer treatment used during the years covered by that study are not representative of contemporary practice. A finding of a *reduced* incidence of radiotherapy-induced second cancers among irradiated patients treated with actinomycin-D (dactinomycin) relative to patients treated with radiation only (254) has not been seen in most other studies (84,119,122).

Very limited data exist concerning possible modification of radiation effects by specific agents or host characteristics other than cytotoxic drugs, age at exposure, or gender. The issue of possible interaction between smoking and radiotherapy in the etiology of lung cancer has been addressed in the context of persons treated for Hodgkin's disease, breast cancer, and lung cancer (151,158,211). In each instance, results are suggestive of a supraadditive relation but are not definitive (155,210). A greater-than-additive relation reinforces already strong reasons for smokers undergoing radiotherapy to quit the habit, but is not adequate reason for modifying radiotherapy regimens of proven effectiveness.

The anatomic distribution of basal cell carcinomas of the skin among persons irradiated during childhood for tinea capitis (ringworm of the scalp) suggests that effects of ionizing radiation *might* be potentiated by exposure to ultraviolet radiation (22,255). The highest radiation doses (orthovoltage, 100 kVp) were delivered to the scalp (mean dose, 4.5 Gy), but most of the excess skin cancers occurred near the edges of the scalp or other exposed parts of the head or neck. If there is an interaction between ionizing and ultraviolet radiation, it would be expected to be particularly evident among fair-skinned persons, and the limited available data do indicate higher radiation risks among persons with light complexions (22,23).

Among the Japanese atomic bomb survivors, some of the same factors that protect against breast cancer in general—namely, early age at first full-term pregnancy, multiple births, and long periods of lactation—also appeared to protect against *radiation-induced* breast cancer (256). These associates should be evaluated among cancer patients given thoracic radiotherapy as children or young adults. A further observation from studies of breast cancer among atomic bomb survivors was that, among women younger than 20 years of age at the time of the explosions,

the excess RR per unit dose equivalent was greatest among women with early-onset breast cancer, defined as breast cancer diagnosed before age 35 (257). The authors raised the possibility that a subgroup of the population was genetically susceptible to radiation-induced breast cancer. Whether the risk of radiation-induced breast cancer is higher among women with a genetic predisposition to breast cancer, such as due to inherited mutations in the BRCA1, BRCA2 or p53 genes, is not known. Future studies of radiotherapy-induced breast cancer should consider radiation risks not only in terms of radiation dose and age at exposure, but also in terms of age at breast cancer diagnosis and family history of breast cancer.

Although the risk of radiogenic second primary cancer in the total population of irradiated patients with first primary cancer does not appear to be large, concern remains that certain subgroups of the population are at considerably higher risk. Examples include persons irradiated at a young age in the chest or neck regions and their associated high risks of second breast or thyroid cancer. Close surveillance of these groups is indicated. Possible interactions with environmental carcinogens such as tobacco smoke or ultraviolet radiation also could multiply radiation-attributable risks for cancers of the respiratory tract, skin, or other sites. If further research substantiates such interactions, behavioral modifications could be recommended to avoid or minimize exposure to the relevant environmental carcinogens. In the case of smoking, of course, sufficient understanding of health risks already exists to discourage the behavior.

Whereas environmental exposures cause mutations in particular genes in a very small percentage of somatic cells, germline mutations are carried in every somatic cell in the body. In some cases, just one additional mutation in the corresponding normal allele inherited from the other parent can be sufficient to cause cancer (75). Extremely high RRs for specific types of second cancer have been reported among patients identified as belonging to any of several familial cancer syndromes (62,102). Even nonirradiated patients are at high risk of cancer, but evidence discussed above concerning patients with familial retinoblastoma or nevoid basal cell syndrome (Gorlin's syndrome) indicates that radiotherapy can further increase this risk.

The genes associated with retinoblastoma and Gorlin's syndrome are located on chromosomes 13 and 9, respectively, and both appear to function as tumor suppressors (252). Persons with inherited mutations in the p53 gene, a tumor suppressor that is linked to the Li-Fraumeni syndrome, also may have increased susceptibility to radiation-induced cancer (102). Mechanisms by which tumor suppressor genes act include causing a delay at the G<sub>1</sub>/S checkpoint in the cell cycle (thereby allowing repair enzymes more time to repair DNA damage) and inducing cells with damaged DNA to undergo apoptosis (252). In either case, the effect is prevention of fixation and propagation of DNA damage. It is easy to see why loss of either function might be associated with increased incidence of both spontaneous and radiation-induced cancer.

Ataxia telangiectasia (AT) is an autosomal recessive disorder associated with a variety of neurologic, immunologic, and developmental defects, high sensitivity to acute effects of radiation, and high risk of lymphoid malignancies [reviewed by Lavin and Shiloh (258) and Morgan and Kastan (259)]. Although precise mechanisms await elucidation, it is apparent that the affected gene plays a central role in processes by which cells detect and respond to DNA damage, including cell cycle arrest, induction of DNA repair, and apoptosis (258-260). AT is rare, but approximately 1% of the population carries a single copy of the mutated gene (261). Female heterozygotes were reported to be at an elevated risk of radiogenic breast cancer relative to noncarri-

ers, even at very low doses of radiation (262). This finding has been questioned on methodological grounds (263), and further study is required.

Persons with the disease xeroderma pigmentosum (XP) have an inherited defect in excision repair genes which compromises their ability to repair DNA damaged by ultraviolet radiation [reviewed by Sarasin and Sary (264)]. They are extremely sensitive to the carcinogenic effects of ultraviolet radiation and develop multiple skin cancers at an early age (264).

The known familial cancer syndromes are rare and, while more prevalent among childhood cancer cases, do not pertain to the overwhelming majority of cancer patients. There may, however, be a much larger number of susceptibility genes of low penetrance awaiting identification (252). Further search for subsets of the population who are hypersusceptible to the carcinogenic effects of ionizing radiation is important to the understanding of carcinogenic mechanisms and could have important implications for the use of radiation in cancer treatment (251).

Cancer is widely regarded as a disease of the genes, and interest in radiation as a carcinogen has focused on its genotoxic effects. However, ionizing radiation also can influence cancer development indirectly, by altering the environment of a cell or nascent tumor (265). Possible examples of such effects include radiation-induced immune suppression or changes in serum levels of sex hormones, as discussed in the preceding sections on radiotherapy for Hodgkin's disease and cervical cancer. High-dose ovarian irradiation actually appears to protect against breast cancer, by killing cells that produce steroid sex hormones. There also are indications that bone marrow stromal cells that have been damaged by radiation can influence selection and proliferation of a leukemic clone (266, 267).

Improvements in the ability to treat many cancers have forced a redefinition of the meaning of "late" effects of treatment (268). The concern now is with lifelong effects, not just with possible complications occurring during the first few years after diagnosis. Radiotherapy-induced cancers are examples of important late effects. Prevention of such complications calls for continued vigilance in radiologic technique and modifications of treatments when indicated. However, overall, second cancer risks due to radiotherapy for the majority of the population appear to be relatively small, and treatments of demonstrated effectiveness should not be readily compromised in the interests of reducing such late effects. As Hellman (42) observed, "often the worst complication of treatment is tumor recurrence."

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