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Second Malignancies After Radiation Treatment and Chemotherapy for Primary Cancers

Lydia B. Zablotska, Matthew J. Matasar, and Alfred I. Neugut

Cancer survivors have been shown to have an increased risk for second malignant neoplasms (SMN). These increased risks result from genetic predisposition, harmful environmental exposures, or cancer treatment therapies. Regardless of their cause, SMNs now comprise the sixth most common group of malignancies after skin, prostate, breast, lung, and colorectal cancers.[1] It is important to emphasize that the fear of SMN related to the treatment of the first cancer diagnosis should not outweigh the positive effects of curative therapy for the first cancer. Both physicians and patients should, however, be aware of the consequences of the cancer treatment regimens, specifically radiation therapy (RT) and chemotherapy, and consider them while devising follow-up plans.

Radiation Therapy

The following are general criteria for attributing a malignancy to the effects of radiation, defined by Goolden in 1951: (a) a history of prior irradiation; (b) malignancy occurring within the prior irradiation field; (c) gross or microscopic pathologic evidence of radiation damage to the surrounding tissues; and (d) a long, latent interval between the prior irradiation and the development of the malignancy.[2–5] Only the first two criteria are considered essential.

External-beam radiation therapy has the potential for the induction of mutations in normal cells because of the harmful effects of the radiation used to kill cancer cells. Years or decades later, such mutated cells may give rise to new primary cancers.

Although ionizing radiation has been shown to cause most types of cancer, some organs and tissues appear to be more susceptible than others. Based on radiation epidemiologic studies, the most radiation-sensitive solid tissues and organs are the bone marrow, thyroid, and female breast. Bone and soft tissue sarcomas also can occur following radiation therapy.[6] In addition, cancers of the lung, stomach, colon, bladder, and esophagus have been conclusively associated with ionizing radiation exposure. Possible links have been described for cancers of the kidney, ovary, brain, and central nervous system (CNS). Cancers of other sites have not been correlated with radiation exposure.[7]

In addition to individual susceptibility, the risk of second cancers after radiation therapy depends on the total dose of radiation delivered during the course of treatment, as well as on the type and energy of the radiation. Megavoltage treatments currently in use deliver concentrated high energy to tumors, with low scatter of the radiation to areas outside of the treatment field (low peripheral doses). Orthovoltage treatments, which were used in previous decades, on the other hand, frequently injured the skin and delivered higher doses of radiation to the bone than to the surrounding tissues, and in the process produced substantial peripheral doses.

The type of dose delivery (protracted or instantaneous) also plays a role in the carcinogenesis of second malignancies. It is generally recognized that, as the exposure time for a given total dose is extended, the biologic effect is reduced. Protracted delivery of a dose over hours or days, in general, will result in less severe consequences because of reduced tumorigenic effectiveness as compared to the instantaneous delivery of the total dose.

Finally, the risks of second cancers depend on the volume of irradiated tissues and organs. Current treatment guidelines recommend that smaller fractions should be used when larger volumes need to be irradiated to decrease the acute side effects of radiation treatment. The late effects of radiotherapy could be lessened by "hyperfractionation" of radiation therapy (smaller doses twice per day over the same treatment period).[6]

Recent technologic advances (shielding, collimation of the radiation beam, use of multivoltage beams, more precise localization of tumors) have significantly reduced the irradiation of normal tissues and the risk of posttherapy new cancers. However, because radiation-associated cancers tend to appear at the same age as spontaneous cancers, patients who were exposed many years ago at young ages may, potentially, be at risk of developing SMN cancers due to radiation exposure.

Individual risks for patients are modified by such factors as their age at the time of exposure, time since exposure/survival time, gender, exposure to other carcinogens (including chemotherapy), as well as by immune and hormonal status. Although the risks associated with radiation exposure are substantially less than the risks posed by the initial tumor, it is important to know them before the start of the radiation therapy to make informed decisions about treatment regimens that might minimize the side effects of radiation therapy. This information is also important for counseling patients who are at increased risk of developing second malignancies due to other risk factors, as well as for continuing surveillance of those treated. Our knowledge of the possible adverse effects associated with radiation therapy should be used for the development of surveillance programs aimed at the early detection of cancers and campaigns to decrease negative behaviors and exposures that have been shown to promote the development of second cancers after radiation therapy.

Individual Cancers

In our review, we look at the subjects who received irradiation for treatment of nine specific primary malignant diseases and summarize the evidence from the descriptive (case reports and case series) and analytical (case-control, cohort, and randomized controlled trials) epidemiologic studies to show the current state of knowledge on the consequences of the treatment for each of the nine diseases.

After reviewing epidemiologic studies for the nine primary cancers, we compare and contrast their findings. We show that they add to our knowledge of the effects of high-dose exposures and can be used for risk estimation purposes as well as to provide both physicians and patients with the necessary information to make informed decisions regarding radiation therapy for primary cancer.

Pediatric Cancers

Various epidemiologic studies have shown that the incidence of the majority of cancers increases with age. Based on data from the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki, the effect of radiation exposure is to multiply age-specific solid cancer rates by a constant radiation dose-dependent factor through lifetime. Thus, those with absorbed dose of 0.20 Sv experience a 10% increase in the risk of solid cancer above background rates. Estimates of risk also depend on age at exposure (increase by 10 years decreases relative risk for solid cancers by 130%).[8] Based on the same data, most organizations have adopted a multiplicative risk model for most solid cancers, which states that after a specified latency period, "the excess cancer risk is given by a constant factor applied to the age-dependent incidence of natural cancers in the population"[9] (p. 108) (in other words, the relative risk remains constant as subjects are followed over time).

The majority of cancers that are associated with radiation exposure, thus, will appear at the same time when spontaneous cancers of the same organ appear. The difference between exposed and unexposed populations, then, will be in the number of new incident cases. Researchers, therefore, have combined subjects with specific types of first childhood cancers and studied them as a group named "pediatric cancers."

The significance of the problem of second malignancies after pediatric cancers is underscored by the fact that survival following childhood cancer has improved markedly and now approaches 70%.[1] Thus, it is important to compare the carcinogenic potential of different treatments for primary pediatric cancers. Some pediatric cancers are more likely to be treated with radiation than others and, as a consequence, they are associated with second malignancies within the radiation field. First reports about second cancers following primary pediatric cancers started appearing in the late 1970s with the advent of new radiation treatment regimens. A large study of pediatric patients who were followed for at least 2 years after initial treatment of the primary tumor showed no association between RT and the subsequent development of leukemia.[10] Although large, this study had a very small proportion of subjects who received only RT; the majority of subjects also received chemotherapy. Thus, the effects of RT could have been obscured by the effects of treatment by various alkylating agents. In a more-recent study of childhood cancer survivors, the risk of second leukemia after RT was significantly increased eightfold.[11] The difference between the two studies could be explained by the size of the irradiation field. Patients with HD usually receive more targeted radiation treatment, whereas the cumulative doses for radiotherapy for NHL are usually smaller than the doses delivered for treatment of HD. Nevertheless, in the process of treatment, larger areas of radiosensitive tissues, such as bone marrow, are exposed to radiation.

Other second cancers that have been associated with RT for primary childhood cancers include cancers of the bone,[12] skin,[13] nervous system,[14] and thyroid gland.[15] As one would expect with solid cancer, in these studies the incidence increased with time since treatment. For example, in The Late Effects Study Group, which followed 9,000 survivors of childhood cancer, a lifetime risk of thyroid gland cancer after RT for primary childhood cancer was almost 4% after 26 years of follow-up.[15] To avoid problems associated with low power of individual studies, Ron et al. pooled data from seven individual studies to evaluate the risk of thyroid cancer following exposure to external radiation. Individual estimates of increased risk of thyroid cancer varied from 1.4 to 33.5 per Gy[16]; that is, those who were exposed to 1 Gy of radiation during RT for primary cancer had a much higher risk of developing second primary thyroid cancer compared to those who did not receive RT. This study provided strong evidence that, along with the breast and bone marrow, the thyroid gland is one of the most radiosensitive organs.

Population-based study of the occurrence of second cancers following primary childhood cancer in the five Nordic countries showed that childhood cancer survivors have a fourfold-higher risk of second cancers compared to the

general population.[17] The largest increase was observed during the first 10 years following RT; however, risks remained increased throughout their lifetimes and the absolute excess of second cancers increased with time. This result probably reflects the promotional effect of radiation on the carcinogenic effects of environmental exposures.

Several publications from the large Childhood Cancer Survivor Study cohort show an increased risk of second malignant neoplasms more than 20 years after RT for primary childhood cancer. In comparison with the general population, their risk of bone second cancers, in particular bone sarcomas and breast cancer, was increased sixfold.[18]

In summary, the effects of radiation treatment for childhood cancers start to increase in early adolescence and early adulthood and continue to be increased later in life. Bone marrow, bone and soft tissues, and breast and thyroid gland appear to be the most radiosensitive. Risk of second tumors depends on the age at exposure (the risk is greatest among those exposed at the youngest ages) and on the time since exposure. Current knowledge of the effects of ionizing radiation had an important influence on RT practices. Specifically, lead aprons and shields are currently being used to protect the most radiation-sensitive organs and tissues. In addition, advances in technology, such as utilization of wedge compensators or half-beam blocks, minimize scattering of radiation to adjacent tissues. Finally, because of the greater awareness of the effects of radiation, survivors of childhood cancers are being constantly monitored and screened for second cancers during follow-up.

Bone Marrow Transplantation

High-dose total-body irradiation (TBI) is part of the conditioning regimen for bone marrow transplantation used for treatment of leukemia and other diseases (see also Chapter 15). One of the mechanisms of development of second cancers following TBI is thought to be due to radiation-induced immunosuppression.[19] In addition to radiation-associated effects, it is also necessary to consider the effects of immunosuppressive drugs that are used concomitantly with radiation. Curtis et al. showed that patients who received TBI had an increased risk of subsequent new solid cancers compared to those who did not receive radiation treatment.[20] High doses of TBI were associated with increased risks of melanoma and cancers of the brain and thyroid. The risk was higher for recipients who were younger at the time of transplantation than for those who were older (P for trend less than 0.001).

Another registry-based study found that high-dose TBI increased the risk of subsequent solid tumors threefold [95% confidence interval (CI), 1.1, 10.3].[21] Younger age at the time of treatment increased the risk of brain and thyroid tumors. In addition, cancers of the salivary gland, bone, and connective tissues were also increased.

In summary, various studies show the trend toward an increased risk over time after transplantation and the greater risk among younger patients. Second cancers could be related to both transplant therapy and to chemotherapy treatments given before it. All these factors indicate the need for lifelong surveillance of the patients who received irradiation as part of the bone marrow transplantation.

Hodgkin's Disease

Introduction of intensive radiotherapy and chemotherapy to treat Hodgkin's disease (HD) three decades ago dramatically changed survival times and prognosis for patients with this disorder (see also Chapter 8). Long-term sequelae of treatment have become increasingly important as patients now survive for several decades. HD is a systemic cancer and radiation treatment frequently consists of irradiation of mantle fields, including all lymph node regions ('total lymphoid irradiation' with cumulative doses 20–40 Gy) or only some regions ('subtotal lymphoid irradiation' with doses less than 20 Gy), by external-radiation beams.[22] Dose–response analysis of the effects of radiation is frequently confounded by the concurrent chemotherapy in the majority of patients.

Several studies looked at breast cancer incidence and mortality, the most frequently seen second malignancy following treatment for HD. Table 17.1 summarizes the results of the most influential studies. In general, risk of breast cancer was increased and ranged from 2 to 75 times compared to the risk in the general population. Most cancers appeared within or at the margin of the radiation field, and the risk increased with dose. Investigators from the Late Effects Study Group estimated that the cumulative probability of breast cancer at age 40 following radiation exposure for HD in childhood is close to 35% (following a median dose of radiotherapy of 40 Gy).[23]

Clemons et al.[22] reviewed 18 epidemiologic studies on the risk of breast cancer in patients treated with radiation for HD. They concluded that women between the ages of puberty and 30 years are at the highest risk. Data on the use of exogenous estrogen hormones, age at first pregnancy, and prevalence of early menopause were not available to control for possible

TABLE 17.1. Studies of breast cancer risk among patients treated for primary Hodgkin's disease.

Reference	*Year*	*RT and follow-up*	*Age at the time of first treatment*	*SIR and 95% CI*
Hancock et al.[114]	1993	1961–1989	Mean age 25 years	SIR = 4.1 (2.5, 5.7)
Bhatia et al.[23]	1996	1955–1986, follow-up till 1996	Younger than 16 years old	SIR = 75.3 (44.9, 118.4)
Tinger et al.[115]	1997	1966–1974 treatment era	Mean age 30 years	4.7
Tinger et al.[115]	1997	1974–1985 treatment era	Mean age 28 years	2.2
Hudson et al.[116]	1998	1968–1990	—	SIR = 1.33 (1.12, 1.72)
Wolden et al.[117]	1998	1960–1995	Younger than 21 years	SIR = 1.26 (1.15, 1.42)
Swerdlow et al.[27]	2000	1963–1993	60% younger than 35 years old	SIR = 2.5 (1.4, 4.0)
Van Leeuwen et al.[70]	2000	1966–1986	Younger than 40 years old	SIR = 7.7 (4.3, 12.7)

RT, radiotherapy; SIR, standardized incidence ratio; CI, confidence interval.

confounding effects of these variables. Breast cancers due to irradiation tend to appear after a 15-year latency period at the age from 30 to 40. Breast cancer risk is highly dependent on age at irradiation, time since irradiation, dose, and concurrent chemotherapy. These findings, along with the finding that no cases of breast cancer after radiation therapy for HD have been reported in men, suggest that the actively growing and differentiating cells of female breast tissue are particularly vulnerable to radiation exposure.

A nested case-control study of lung cancer among patients previously treated for HD found that radiation doses greater than 5 Gy increased the risk sixfold (95% CI, 2.7, 13.5).[24] Smoking acted in a multiplicative way with radiation exposure [relative risk (RR) comparing moderate-heavy smokers to nonsmokers and light smokers among those without radiation treatment was 6.0; RR comparing those with radiation treatment to those without among nonsmokers and light smokers was 7.2; RR comparing those with radiation treatment to those without among all subjects adjusting for smoking was 20.2]. Treatment with alkylating agents, on the other hand, acted additively with radiation therapy (individual risks added up to perfect additivity). Similar to other studies, increased age at diagnosis of HD was associated with an increased risk of lung cancer.

Birdwell et al.[25] noticed that high doses to the abdomen from radiation for HD cause multiple gastrointestinal (GI) cancers, including stomach, pancreas, and small intestine (RR for all GI cancers, 2.0, 95% CI, 1.0, 3.4). Risks started to increase after a latency period of 10 years and were highest among younger patients. GI cancers were similarly increased in the large study based on the International Database on HD (more than 12,000 cases)[25] and in the study of atomic bomb survivors (53% of all incident cancers in the atomic bomb study were due to cancers of the digestive system).[26]

Findings of increased risk of second cancers are further supported by the largest current study of 5,519 British patients with HD who were followed for more than 30 years.[27] Irradiated patients had a 1.7 fold (95% CI, 1.0, 2.5) higher incidence of GI cancers, 2.5 fold (95% CI, 1.4, 4.0) higher incidence of breast cancer, and 2.9 fold (95% CI, 1.9, 4.1) higher incidence of lung cancer than the general population. Risk of leukemia was increased in patients who received combined modality treatment (chemotherapy with radiotherapy) or chemotherapy alone compared to those who received RT alone. Similar to previous studies, relative risks tended to increase 5 to 10 years after treatment and decreased with increasing age at first treatment. Women older than 25 years were not at risk of increased breast cancer [$RR_{<25\ years}$, 14.4 (95% CI, 5.7, 29.3) and $RR_{25–44\ years}$, 1.6 (95% CI, 0.5, 3.7)]. A combined study of 16 population-based cancer registries in Europe and North America, which included HD patients diagnosed before the age of 21 years, also found that the risk of second malignancy decreased with increasing age at HD diagnosis and treatment on a relative scale.[28] High estimates of relative risks of second cancers in this cohort were due to low background rates in the relatively young cohort.

In summary, it appears that radiation treatment for HD increases the risk of second malignancies. Long-term risks depend on age at exposure and time since exposure. Latency periods differ from study to study, but a major increase in risks appears at 10 to 14 years of follow-up. Second cancers sometimes appear at a much younger age than similar cancers. Radiation treatment for HD is linked to cancers of the GI tract, breast, lung, bone, and soft tissue, melanoma, and thyroid gland (Table 17.2).

Breast Cancer

Standard treatment for invasive breast cancer includes high, concentrated doses of radiation to the chest and to the lymph nodes (about 40–60 Gy total).[29] Initially, localized radiotherapy was combined with radical mastectomy, but since the mid-1980s treatment consists of breast-conserving surgery and radiotherapy. Women irradiated before the mid-1980s received higher doses of radiation to the lungs, contralateral breast, thoracic bone, and bone marrow. A small increase in risk of leukemia was shown in a cohort of women from the Connecticut Tumor Registry irradiated between 1935 and 1972.[29] Following an average dose of 5.3 Gy to the bone marrow, the risk was 16% higher in irradiated women than in nonirradiated women (90% CI, 0.6, 2.1). A larger study based on five population-based cancer registries in the United States (1973–1985)[30] found a 2.4 times increased risk (95% CI, 1.0, 5.8) of acute nonlymphocytic leukemia after radiation treatment with an average dose of 7.5 Gy over the total active bone marrow. They observed a positive dose–response relation in the data (those exposed to doses higher than 9 Gy had a 7-fold-higher risk). Increase in risk was first seen 2 years after initial treatment, and it persisted, albeit at a much lower level, 7 years after treatment. The authors described a statistical multiplicative interaction effect of radiotherapy and treatment with alkylating agents on the development of ANLL (RR for radiotherapy alone, 2.4; RR for alkylating agents therapy, 10.0; RR for combined therapy, 17.4).

Boice et al.[31] described an increase in the risk of cancer in the contralateral breast in patients from the Connecticut Tumor Registry diagnosed between 1935 and 1982. An average dose of 2.8 Gy was associated with a twofold increase in risk in 10-year survivors. Risk was significantly higher among women who were younger than 45 years at the time of radiation treatment. The investigators estimated that the absolute excess risk of contralateral breast cancer was 4.4 cases per 10,000 person-years per Gy (compared to 6.7 cases per 10,000 person-years per Gy for atomic bomb survivors).[26]

Several studies have shown a significantly increased risk of lung cancer following radiation therapy (RT) after total mastectomy. Ten-year survivors from the Connecticut Tumor Registry who were diagnosed with histologically confirmed primary invasive breast cancer between 1935 and 1971 had an 80% higher risk (95% CI, 0.8, 3.8) of developing lung cancer if they received radiotherapy as part of their initial treatment regimen compared to those not receiving initial RT (mean dose to both lungs, 9.8 Gy).[32] Risk continued to increase with time and after 15 years reached 2.8 (95% CI, 1.0, 8.2). The excess relative rate was 0.20 per Gy (95% CI, –0.62, 1.03) compared to an estimate of 0.95 per Gy (95% CI, 0.60, 1.4) for trachea, bronchus, and lung in the atomic bomb study.[26] In a case-control study from this cohort, Neugut et al.[33] assessed risk of lung cancer in relation to radiation treatment and smoking in 10-year survivors. They observed a multiplicative interaction effect if both exposures were present (OR for RT alone, 3.2; OR for smoking and no RT, 17.7; OR for both RT and smoking, 32.7).

TABLE 17.2. Studies of risks of second malignant neoplasms (SMNs) among patients treated for primary Hodgkin's disease.

Reference	*Year*	*Design*	*Median follow-up, years*	*Site(s) of SMN*	*Primary treatment modalities*	*Estimates of risk and 95% CI*
Swerdlow et al.[27]	2000	Cohort	8.5	Gastrointestinal	ChT	SIR = 1.5 (0.8, 2.5; $P > 0.05$)*
					ChT + RT	SIR = 3.3 (2.1, 4.8; $P < 0.001$)
				Lung	ChT	SIR = 3.3 (2.2, 4.7; $P < 0.001$)
					ChT + RT	SIR = 4.3 (2.9, 6.2; $P < 0.001$)
				NHL	ChT	SIR = 14.8 (8.7, 23.3; $P < 0.001$)
Swerdlow et al.[71]	2001	Nested case-control	8.5	Lung	MOPP + RT (vs. RT)	OR = 2.41 (1.33, 4.51; $P = 0.004$)
Dores et al.[18]	2002	Cohort	25	Cumulative solid tumor	ChT	RR = 2.1 (n/a; $P < 0.05$)
					ChT + RT	RR = 2.0 (1.9, 2.0; $P < 0.05$)
				Acute nonlymphcytic leukemia	ChT	RR = 36.1 (25.6, 49.3; $P < 0.05$)
van Leeuwen et al.[70]	2000	Cohort	14.1	Breast	RT	RR = 7.7 (4.3, 12.7)
					ChT + RT	RR = 7.5 (2.7, 16.3)
					ChT + RT + salvage	RR = 1.4 (0.2, 5.1)
				Nonbreast solid tumor	RT	RR = 4.9 (3.0, 7.4)
					ChT + RT	RR = 4.4 (2.0, 8.3)
					ChT + RT + salvage	RR = 10.0 (6.8, 14.3)
				Gastrointestinal	RT	RR = 3.7 (1.0, 9.5)
					ChT + RT	RR = 7.8 (2.1, 20.0)
					ChT + RT + salvage	RR = 13 (6.2, 23.9)
Neglia et al.[18]	2001	Cohort	5	Cumulative SMN	Not specified	RR = 2.34 (1.44, 3.81)
				Breast		RR = 4.89 (0.95, 25.24)
				Leukemia		RR = 3.99 (0.84, 18.88)
				Soft tissue sarcoma		RR = 10.32 (1.18, 90.18)
				Thyroid		RR = 1.74 (0.50, 6.01)
Bhatia et al.[23]	1996	Cohort	11.4	Cumulative SMN	Not specified	SIR 18.1 (14.3, 22.3)
				Breast		SIR 75.3 (44.9, 118.4)
				Leukemia		SIR 78.8 (56.6, 123.2)
				Leukemia	ChT	RR = 1,091 (344, 2256)
					ChT + RT	RR = 439 (270, 645)
				Non-Hodgkin's lymphoma	ChT	RR = 60 (0.02, 235)
					ChT + RT	RR = 23 (6, 50)
Metayer et al.[28]	2000	Cohort	10.5	Cumulative SMN	Not specified	RR = 7.7 (6.6, 8.8)
				Breast		RR = 14.1 ($P < 0.05$)
				Thyroid		RR = 13.7 (8.6, 20.7)
				Leukemia		RR = 20.9 (13.9, 30.3)
				Non-Hodgkin's lymphoma		RR = 27.4 (17.9, 40.2)
Green et al.[69]	2000	Cohort	17.1	*Cumulative SMN (male)	Not specified	RR = 9.39 (4.05, 18.49, $P < 0.00001$)
					RT	RR = 12.32 (2.54, 36.01, $P < 0.005$)
					ChT + RT	RR = 8.64 (2.81, 20.16, $P < 0.001$)
				Cumulative SMN (female)	Not specified	RR = 10.16 (5.56, 17.05, $P < 0.00001$)
					RT	RR = 4.46 (0.92, 13.02, $P = 0.062$)
					ChT + RT	RR = 15.93 (7.95, 28.51, $P < 0.00001$)

OR, odds ratio; NHL, non-Hodgkin's lymphoma; RR, relative risk; ChT, chemotherapy; RT, radiation therapy; SMN, second malignant neoplasm.

*P value of significance.

As was noted earlier, radiation treatment regimens have changed over the past two decades, lowering radiation doses to the lungs.[34] In a large population-based study from the SEER (Surveillance, Epidemiology, and End Results) database of subjects diagnosed and followed up from 1973 till the end of 1998, the risk of cancer in the ipsilateral lung 10 to 14 years after RT and radical mastectomy was increased by 2.06 (95% CI, 1.53, 2.78), whereas the risk of ipsilateral lung cancer 10 to 14 years after conservative surgery (lumpectomy) and adjuvant RT was not increased (RR, 0.80; 95% CI, 0.23, 2.84).[35]

Studies of other cohorts also showed increased risk of second cancers following breast cancer.[36] Another SEER-based study showed that the standardized incidence ratio (SIR) of esophageal cancer after RT for primary breast cancer was 54% higher than in the general population (95% CI, 1.27, 1.84).[37] Risk increased with time, reaching 5.42 (95% CI, 2.33, 10.68) for esophageal squamous cell carcinoma 10 years after radiotherapy. No information on smoking or alcohol consumption was available.

Gynecologic Cancers

Hormones, in general, in these cancers could play an important role in the timing of late effects of radiation treatment,

their dependence on the age at exposure, and time since exposure. Some studies do not have data on the use of exogenous estrogen hormones, age at first pregnancy, time of menopause, and other factors related to hormonal status. Therefore, possible confounding effects of these variables could not be evaluated.

Cancer of the Uterus

Curtis et al. examined the relationship of leukemia risk to radiation dose following radiotherapy of the uterine corpus in a nested case-control study based on a cohort of women drawn from nine population-based registries in the United States and Europe.[38] After external-beam therapy (mean dose, 9.88 Gy), cases were two times more likely to develop leukemia (excluding chronic lymphocytic leukemia) than matched controls (ERR, 0.13 per Gy; 95% CI, 0.04, 0.27).

Based primarily on data from the cohort of atomic bomb survivors, the association between radiation exposure and development of leukemia appears to depend on total dose to the bone marrow, total percent of the person's bone marrow exposed to radiation, and the dose rate at which radiation was delivered. As was mentioned earlier, the dose response for atomic bomb survivors is linear-quadratic for doses below 4 Gy (ERR, 4.8 per Sv).[39] The difference between the estimates from the Curtis et al. study and the estimate from the LSS cohort can be partly explained by the killing of stem cells of the bone marrow at high doses. Treatment regimens with low-dose-rate radiation (e.g., brachytherapy) were more leukemogenic per unit dose than external-beam therapy, perhaps due to the repair of radiation damage in protracted exposure regimens.

As a result of a wide field of radiation encompassed by the partial-body radiation treatment (only parts of the body are irradiated as opposed to the total-body irradiation as in bone marrow transplantation) of cancer of the corpus uteri, patients are also at risk of developing second solid cancers. Subjects with primary cancer of the uterine cervix from a Swedish cancer registry had a 20% higher risk of developing a second malignancy compared to the population rates.[40] Organs situated in the immediate proximity to the radiation field had the highest risk of second cancer (colon, vulva, and bladder) 9 years after initial treatment. A fourfold increase in leukemia was observed 3 to 9 years after exposure, but it was based on a small number of cases (95% CI, 1.68, 8.59).

Ovarian Cancer

A SEER-based study of long-term survivors of ovarian cancer found a twofold-increased risk of leukemia 5 to 9 years after radiotherapy,[41] although several case-control studies did not.[42,43] A twofold increase in risk was also observed for all solid cancers 10 to 14 years after exposure (P less than 0.05).[41] Significant associations were seen for cancers of connective tissue, bladder, and pancreas. A case-control study of ovarian cancer survivors who later developed bladder tumor showed that those treated with radiotherapy alone had a twofold-higher risk (95% CI, 0.77, 4.9).[44]

In summary, RT for gynecologic cancers has been linked to the development of various second primary malignancies. They mainly experience increased risks of second malignancies of the organs situated in immediate proximity to the radiation field as well as leukemia.

Testicular Cancer

Testicular cancer is the most common cancer in men in the age group 20 to 44 years.[1] Early reports showed that these patients are at increased risk of second cancers following 10 to 15 years after radiotherapy.[45] Significant increases were observed for all solid cancers (RR, 1.6; 95% CI, 1.3, 2.1), gastrointestinal cancers (RR, 2.6; 95% CI, 1.7, 3.9), and leukemia (RR, 5.1; 95% CI, 1.4, 13.0).

A large population-based study of testicular cancer survivors in 1997 confirmed an increased risk of stomach, bladder, and pancreatic cancers by twofold. Overall risk was similar after seminomas (SIR, 1.42) or nonseminomatous tumors (SIR, 1.50). The largest investigation to date of leukemia following testicular cancer was done in the follow-up of the same cohort.[46] Those treated with radiotherapy had a three times higher risk of developing leukemia (95% CI, 0.7, 22.0). This risk is similar to the risks estimated after radiation therapy for cancers of the cervix,[47] breast,[30] or Hodgkin's disease.[48] Although atomic bomb survivors received lower doses of radiation, they experienced higher risks than medically irradiated subjects mainly because the dose was delivered to the entire body without dose fractionation.[49]

In summary, because testicular cancer is a disease of men under the age of 40 years, they are at increased risk of developing second malignancies later in life. In particular, both physicians and patients should be aware of increased risks of second cancers located in the bladder, lungs, connective tissue, and stomach. These patients should be under continuous surveillance for possible second cancer. In addition, because of the high risks of lung cancer, patients should be advised to quit smoking.

Prostate Cancer

In a large population-based retrospective cohort study of survivors of first primary prostate cancer in the Detroit metropolitan area who were diagnosed between 1973 and 1982, the overall risk of second malignancies was similar to the rates of cancer in the general population.[50] Subanalyses, however, showed that prostate cancer survivors were at increased risk of bladder cancer (SIR, 1.49; 95% CI, 1.07–2.02) when compared to the Detroit-area male population. Researchers concluded that the magnitude of relative and absolute risks did not suggest the presence of large risks associated with radiation treatment. In another large population-based study from the database of the Connecticut Tumor Registry, comparison of the risk of developing a SMN cancer following prostate irradiation compared to the underlying risk in patients with prostate cancer showed that the risks were not significantly different, at any time period and in all age groups, between the two groups of patients.[51] Short follow-up (mean follow-up under 4 years) could have contributed to these negative findings. However, more careful investigation of the cases who survived more than 10 years again showed no significantly

increased risk of second malignancy following radiation therapy for primary prostate cancer.[52]

In the largest to date epidemiologic study of second cancers after prostate cancer based on the SEER database, a cohort of patients who received radiation treatment sometime between 1973 and 1990 showed a significant 50% increase in risk of second primary bladder cancer.[53] Risk remained increased for at least 8 years after initial radiation treatment. There was no increased risk of rectal carcinoma or leukemia after this type of radiation exposure.

In summary, prostate cancer is the most common male cancer in the United States, with nearly 200,000 men diagnosed annually.[1] Findings regarding the effect of RT for prostate cancer have been conflicting. If present, risks are probably significantly lower than risks described for other first cancers. This fact could be explained by smaller doses and less-aggressive treatments.

Lung Cancer

In a large retrospective cohort study of 2-year survivors of primary small cell lung cancer, patients who received RT experienced a 13-fold increase in the risk of second primaries among those who received chest irradiation, whereas non-irradiated patients experienced only a 7-fold increase compared to that of the general population.[54] The highest risk was observed among those who continued smoking, with evidence of an interaction between chest irradiation and continued smoking (RR, 21). Risks continued to increase with time after radiation treatment.

In a large population-based study based on the Finnish Tumor Registry lung cancer patients treated with RT between 1953 and 1989, there was a significant increase in the risk of esophageal cancer and leukemia among lung cancer patients subject to radiotherapy.[55] The risk of a second cancer among lung cancer patients increased with the length of follow-up.

Colorectal Cancer

In the past, radiotherapy was not widely used to treat colorectal cancer. There are, consequently, only a few epidemiologic studies of the effects of radiation in colorectal cancers. These studies have shown that patients with primary cancers of the colon and rectum have small increases in risks of SMN cancers as a result of radiation therapies. In particular, irradiation increases the risk of second primaries of the breast, uterus, ovaries, and other pelvic organs in the radiation field.[1,56]

Chemotherapy

That only a small percentage of individuals receiving a given chemotherapeutic regimen will go on to develop a SMN suggests that individual variations play a role in this process. Indeed, it has become apparent that a number of individual factors contribute in part to this risk. Germ-line mutations have long been recognized to predispose to primary malignancies; indeed, more than 40 genes have been cloned that, when mutated from the wild-type, are known to increase the susceptibility to malignancy.[57] Although the mechanisms of this increased susceptibility are variable, it has become apparent that many individuals with these germ-line mutations are at heightened risk of SMN and, specifically, treatment-associated malignancies.

Next we explore the various factors that contribute to the risk of SMN among patients treated with systemic chemotherapy, including the organ affected by the primary cancer, the chemotherapeutic agents employed, and host factors such as environmental exposures and immune status.

Individual Cancers

Although the use of chemotherapeutic alkylating agents imparts a risk of secondary malignancy, particularly secondary leukemia, the concern regarding SMNs is not restricted to their use alone. Indeed, for many of the hematologic and solid malignancies, there are concerns about the potential for patients to experience treatment-related neoplasms. Evidence for such an association is stronger for some malignancies, weaker for others; in some malignancies, there are as yet no convincing data regarding an elevated risk of SMN as a result of treatment. Whether this lack of effect is due to an inability of cancer chemotherapy to significantly prolong life, or whether it reflects a truly low oncogenic potential of the agents employed, is difficult to determine; what is clear, however, is that as chemotherapeutic regimens continue to become both more complex and more effective, the challenge of treatment-related SMN will require ongoing vigilance.

Pediatric Cancers

Acute Lymphocytic Leukemia

A number of reports have been published regarding the risk of treatment-associated malignancies following treatment of childhood acute lymphocytic leukemia (ALL). Children treated with all the most common protocols in ALL therapy, including the Berlin–Frankfurt–Munster (BFM) protocol, Children's Cancer Group protocol, and the Dana–Farber protocol, experience an estimated risk of SMN within 15 years of treatment ranging from 2.5% to 3.3%, although children receiving weekly or twice-weekly epipodophyllotoxin have been found to have a 12% cumulative incidence of secondary myelogenous leukemia.[14,58–60] Despite these concerning statistics, the BFM study failed to find an association between a specific chemotherapeutic agent and subsequent acute myeloid leukemia (AML); 12 of the 16 cases of secondary AML they report had not received epipodophyllotoxin.[60] Patients in these groups who also received craniospinal radiation were found to be at an increased risk of a number of radiation-induced SMNs, including primary CNS malignancy, thyroid cancer, and skin cancers; more-recent ALL protocols have rejected craniospinal radiotherapy in favor of intrathecal chemotherapy for younger patients without evidence of CNS involvement at initiation of therapy.

An additional risk of SMN among patients treated during childhood for ALL is that of malignant melanoma. It had been reported that patients receiving monthly maintenance therapy of vincristine and prednisone, weekly methotrexate, and daily 6-mercaptopurine (6-MP) were found to have an increased number of melanocytic nevi and dysplastic nevi; on this basis, concern was raised that these patients may be at

higher risk of subsequent malignant melanoma than the general population.[61] Whether such an effect will be seen with more modern maintenance regimens has not yet been determined.

Sarcoma

In contrast to the specific case of RB-associated sarcoma, the treatment and sequelae from therapy of primary pediatric sarcoma have been well studied. Among these patients, a consistent and long-lasting rate of SMN following intensive chemotherapy of sarcoma has been identified. The reported cumulative incidence of solid SMN among patients treated for Ewing's sarcoma ranges from 5% at 15 years of follow-up to more than 20% at 20 years, whereas the risk of leukemia has been estimated in the range of 2%.[62–64] These patients went on to develop a variety of hematologic complications, including myelodysplasia (MDS) as well as AML and ALL, between 1 and 8 years after therapy for Ewing's sarcoma. Secondary sarcomas within the field of radiotherapy have been described as well; no clear association with systemic chemotherapy has yet been established for these SMNs.

Treatment of pediatric rhabdomyosarcoma has also been associated with the development of SMNs. The latency period for these patients appears to be slightly longer, with a median time to diagnosis of between 5 and 11 years following initial treatment.[65,66] The cumulative incidence of SMN following rhabdomyosarcoma appears to be similar to that found in Ewing's sarcoma, but unlike the case of Ewing's sarcoma, this risk seems to be at least in part attributable to a potentiating effect of systemic chemotherapy.[62,67] Although solid tumor SMNs appear to be salvageable with multimodal therapy, hematologic SMNs following treatment for pediatric sarcoma appear to share the generally poor prognosis of secondary leukemias more commonly seen with epipodophyllotoxins and alkylating agents.[64,66]

Wilm's Tumor

Long-term follow-up data gathered by the National Wilms Tumor Study Group (NWTSG) demonstrated that, between 1969 and 1991, patients treated in childhood for Wilm's tumor went on to develop an eightfold-greater risk of SMN.[68] These malignancies consisted of both solid tumors, largely within the field of irradiation, and hematologic malignancies, including both lymphomas and leukemias. The NWTSG reported that their cohort had developed carcinomas of the breast, thyroid, colon, and parotid gland, hepatocellular carcinoma, and primary CNS malignancies. The study group concluded that it appeared that treatment of these patients with doxorubicin increased the risk of SMN, potentiating the oncogenic effect of the administered ionizing radiation.

Hodgkin's Disease

Patients treated for Hodgkin's disease with chemotherapy, ionizing radiation, or both have a risk of developing a variety of SMNs that, cumulatively, is 2 to 4 times greater than unaffected individuals.[23,27,28,48,69–71] The relative risk of developing specific solid tumors as SMNs shows a great variability, ranging from 2 to more than 50 times greater, depending upon the tissue of origin as well as the chemotherapeutic agents used and whether ionizing radiation was administered concomitantly. The cumulative incidence of SMN following the treatment of Hodgkin's disease thus shows a great variability as well, from as low as 2% to as high as 27% within 30 years of treatment.

Specific tissues of origin for these secondary SMNs include thyroid, breast, and skin (melanoma and nonmelanoma). Thyroid cancer remains the most common SMN following the treatment of Hodgkin's and is affected by both chemotherapeutic agents as well as the dose of ionizing radiation.[18] And, although the risks associated with ionizing radiation have already been discussed, the risks associated with alkylating agents apply to patients treated for Hodgkin's disease as well. Indeed, up to 25% of SMNs among these patients are either lymphomas or leukemias.[27,28,48,69,70] The risk of hematologic malignancy as an SMN is, in large part, attributable to the chemotherapeutic agents included in the management of the disease, that is, alkylators versus others. Risks of leukemia, demonstrating the dose–response relationship as discussed, continue to rise with additional chemotherapy, and thus patients requiring retreatment for recurrence of Hodgkin's disease are at higher risk yet of SMN. Given the significant concerns regarding long-term risk of SMNs from therapy, pediatric oncologists have begun modifying treatment regimens, with boys receiving fewer alkylating agents and girls receiving less chest wall irradiation.

Breast Cancer

Women with breast cancer are known to be at higher risk for SMN malignancies within the contralateral breast, as well as at least a slightly elevated risk of primary malignancies of many other organs, including the ovaries, endometrium, and lower gastrointestinal tract; this risk elevation, however, appears to be independent of the treatment modalities used in the primary malignancy.[72–74] These associations suggest that these organs share one or more common risk factors for malignancy with the breast, including hormonal status, diet, and adiposity. A subset of patients with breast cancer carries a heritable risk due to mutations in *BRCA1* and *BRCA2*; these patients are also at greatly increased risk for ovarian neoplasms and second primary breast cancer. Among patients with a history of breast cancer, rigorous screening for SMN within the breast is universally advocated, and many experts argue for screening for both ovarian and endometrial neoplasms as well.[31,74]

The modalities employed in the treatment of breast cancer have the ability to impact the frequency of SMNs within and beyond the breast. However, unlike each of the organs discussed so far, treatments of breast cancer can either raise or lower this risk. There appears to be an increased risk among patients receiving radiotherapy administered for breast cancer of ipsilateral lung cancer, particularly among smokers.[33,75] When alkylating agents or anthracyclines are used in the adjuvant setting, an increased risk of treatment-associated leukemia has been seen, an effect that appears to be augmented by concomitant radiotherapy.[30,76]

Antiestrogenic therapy has been well documented in its ability to both decrease the mortality from primary breast cancer as well as diminish the frequency of second breast cancers.[77–79] This chemoprotective effect has been observed in the high-risk subgroup of patients with *BRCA1* and *BRCA2* mutation-associated primary malignancies, with odds ratios

of between 0.4 and 0.6, odds that approach those seen with prophylactic oophorectomy.[80] Data from the largest randomized clinical trial, however, have to date been unable to confirm this observation. Although limited by an extremely small number of incident cancers among *BRCA* mutation carriers in the trial, the investigators were unable to show a protective effect among *BRCA1*-positive patients (RR, 1.67; 95% CI, 0.32, 10.7) and only found a trend toward efficacy among *BRCA2*-positive patients (RR, 0.38; 95% CI, 0.06, 1.56).[81] Newly emerging data suggest that the protective benefit of tamoxifen's antiestrogenic effect on breast tissue can be further prolonged by the use of aromatase inhibitors after the discontinuation of tamoxifen. Tamoxifen, however, acts in certain tissues, such as breast tissue, as an estrogen receptor antagonist, whereas in others as an estrogen receptor agonist, tissues that include the ovaries and endometrium.[82] Research has consistently found that women who undergo long-term tamoxifen therapy are at approximately twice the risk of endometrial cancer, or about 80 excess cases per 10,000 tamoxifen-treated individuals.[83–85] Early suggestions that tamoxifen may confer an additional risk of ovarian, colorectal, and stomach cancers as SMNs have not been borne out by additional investigation.[82,85] Although there is some debate concerning the potential value of screening for endometrial cancer via transvaginal ultrasonography or endometrial biopsy among breast cancer patients taking tamoxifen, experts agree on the value of annual visits to an experienced gynecologist for these patients and on the importance of an expeditious evaluation of abnormal vaginal bleeding.[1,86]

Testicular Cancer

Etoposide is a mainstay of chemotherapy in testicular malignancies, often at high doses, and it comes as little surprise that long-term survivors demonstrate an elevated risk of hematologic malignancy. Estimates have placed the cumulative incidence of AML or non-Hodgkin's lymphoma as SMNs following treatment of testicular cancer at between 1.3% and 2%.[46,87–89] Although the development of metachronous contralateral testicular cancer remains a concern for patients cured of a primary unilateral cancer, the incidence of contralateral testicular cancer as an SMN does not appear to be influenced by the treatments chosen for the first primary malignancy.[90]

Survivors of primary testicular cancer have also been described as having an increased incidence of solid tumors involving the stomach, colon, rectum, pancreas, prostate, kidney, bladder, and thyroid, as well as soft tissue sarcomas and cutaneous malignancies. All of these, with the possible exception of cutaneous malignancies, have been found to be solely associated with the dose of ionizing radiation administered.[91] The association of both melanoma and nonmelanoma skin cancers with chemotherapy of testicular cancer has been reported but remains incompletely elucidated.[92]

Lung Cancer

Both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) have been clearly associated with an increased risk of developing SMNs. However, the elevated risk of second upper aerodigestive tract tumors, including head and neck tumors, esophageal cancers, and second primary lung cancers, has been clearly and closely linked to smoking status[93,94] and the field cancerization that can ensue following continuous exposure to the carcinogens present in cigarette smoke.[95,96] No association has been identified to link the treatment of a primary NSCLC with an increased risk of SMN. This stands in contrast to the case of SCLC, for which such an association does appear to exist.

Although long-term survival in SCLC patients with extensive disease (ED) rarely exceeds 5 years, more-favorable results have been reported in patients with limited disease (LD); disease-free survival at 2 years in some reports has approached or exceeded 50%.[97–99] Among SCLC survivors, there has been noted a markedly greater risk of subsequent development of an SMN, as has been noted. However, this risk is not limited to those patients undergoing therapeutic irradiation. An early retrospective analysis of long-term SCLC survivors had found a markedly elevated risk of SMN, with an overall risk of 10.3% per person-year and an 8-year actuarial risk of 50.3%.[100] Although all SCLC patients have an increased rate of second lung cancers (typically NSCLC in histology), this risk rises from approximately 7 times that of unaffected patients to approximately 13 times among patients treated with any of a number of combination chemotherapy protocols.[54]

Prostate Cancer

Although some reports concerning the risk of therapy-associated SMN with radiotherapy of prostate cancer have emerged, far less attention has been either merited or received from the risk of SMN from chemotherapy for prostate cancer. While systemic chemotherapy has a limited role in the treatment of prostate cancer, there is some use of nitrogen mustard, which has been associated with increased risk of myelodysplastic syndrome in patients receiving it for the treatment of prostate cancer.[92] The use of antiandrogenic therapy in controlling this malignancy is far more common than traditional chemotherapeutic agents, and the theoretical possibility exists that such agents could predispose to tumors that are suppressed by the androgenic state. Suggestion of such a possible phenomenon can be found in a recent report of an increased risk of male breast cancer among patients treated for prostate cancer.[101]

Gastrointestinal Cancers

It is interesting to note that among the most prevalent gastrointestinal cancers—colorectal cancer, gastric cancer, and pancreatic cancer—there are no convincing data suggesting linkage between chemotherapy and SMN. The reasons underlying this lack of convincing connections undoubtedly vary by malignancy.

Gynecologic Cancers

Analyses of the common gynecologic malignancies—cervical, uterine, and ovarian—have established some patterns of increased risk of SMNs. However, there lacks a robust literature addressing the attributable risk of systemic chemotherapy in patients with cancer of either the uterine cervix or the

corpus uteri; that chemotherapy has at this time a limited role in the treatment of these malignancies both makes the identification of such an association difficult and renders any findings clinically unimportant.

Ovarian cancer presents a different scenario altogether, as it is often treated with a multimodal regimen that includes systemic chemotherapy. Historically, associations had been seen between melphalan-based chemotherapeutic regimens that would now be considered outdated and risk of secondary leukemia in patients treated for ovarian cancer.[43,102] A Swedish record-linkage study from 1995 found a relative risk of 7 for leukemia among patients with ovarian cancer, likely reflecting the common use of melphalan during the time period under investigation, 1958–1992.[40] Although an elevated risk of acute nonlymphocytic leukemia has been suggested to exist for patients treated for ovarian cancer with cyclophosphamide, chlorambucil, or regimens containing doxorubicin and cisplatin,[102–105] a retrospective analysis stratified by decade demonstrated that the risk of leukemia following treatment of ovarian cancer has decreased from 40 during the 1970s to 17 from 1980 to 1992.[41] While this suggests that more modern regimens, largely cisplatin based, may be less leukemogenic, clearly more data are needed to more thoroughly clarify this risk relationship more thoroughly.

Transplantation and Oncogenesis

An additional predisposing factor toward treatment-induced SMN that has recently emerged is immunosuppression (see Chapter 15). Over the past two decades we have seen a dramatic improvement in the ability to suppress immunologic transplant rejection thanks to new, potent immunosuppressive agents, including cyclophosphamide, cyclosporine A, tacrolimus, and mycophenolate mofetil, but it has become apparent that the long-term administration of such medications can dramatically increase the risk of developing late neoplasia, both hematologic and solid malignancies.[106,107]

Risk of hematologic malignancy has been noted to be dramatically elevated among transplant recipients, both allogeneic bone marrow transplant (BMT) recipients as well as patients receiving solid organ donation. Indeed, the name posttransplantation lymphoproliferative disorder (PTLD) has emerged in the literature to report and describe such patients. PTLD as a diagnostic category includes a spectrum of pathology ranging from atypical marrow hyperplasia to frank non-Hodgkin's lymphoma; what the constituent diagnoses share is a common association with Epstein–Barr virus infection, either acute seroconversion or reactivation of latent infection.[107] Rates of lymphoma are dramatically increased by bone marrow ablation and hematopoietic stem cell transplant in the treatment of malignancy; these rates are higher yet when the stem cell transplant was given for an indication of an underlying immunocompromised condition, such as Hodgkin's disease or chronic myelogenous leukemia (CML).[108] These PTLDs can occur quite rapidly following BMT, with a median time to onset of 2.5 months, whereas secondary leukemias have an almost equally rapid arrival, with a median time to onset of 6.7 months.[109,110] PTLD complicates solid organ transplant as well; while most studies place the cumulative "de novo" tumor incidence among recipients of solid organs at between 5% and 15%, PTLD accounts for 15% to 25% of these malignancies, a marked elevation of risk as compared to the general population.[111,112]

Although the rise in risk of lymphoproliferative disorders among transplant recipients is striking, there have been noted elevated risks of a number of solid tumors as well in this population. Kaposi's sarcoma, another malignancy with a viral pathogenesis (human herpesvirus 8), is seen among transplant recipients, as are hepatomas among patients with chronic infection by hepatitis B or C virus. And while some solid tumors (renal carcinoma in renal transplant patients, for example) are largely attributable to the underlying conditions necessitating transplantation (e.g., analgesic nephropathy), it is clear that others are strongly associated with the induction of an immunocompromised state. This connection is most clear in the case of squamous cell skin cancer: the cumulative incidence of this malignancy 10 years after transplant is 10% and 20 years after transplant rises to 40%. In Australia, where the baseline incidence is higher than that in the United States because of more-intense solar UV exposure, these numbers rise to 45% and 70%, respectively.[113]

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