Second Malignancy Risk After Treatment of Hodgkin Lymphoma

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26.1 Introduction

In view of the excellent cure rates that are currently achieved in the relatively young population of patients with Hodgkin lymphoma (HL) [1], it has become increasingly important to evaluate and limit the long-term complications of treatment. Research conducted over the last three decades has clearly demonstrated that, paradoxically, some treatments used to treat cancer have the potential to induce new (second) primary malignancies. Of all late complications of treat-

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ment, second malignant neoplasms (SMNs) are considered to be among the most serious because they cause not only substantial morbidity but also considerable mortality. Among long-term survivors of HL, second cancer deaths have been reported to be the largest contributor to the substantial excess mortality that these patients experience [2–4].

Increased risk of SMNs has been observed both after radiotherapy (RT) and chemotherapy (CT). In 1972, Arseneau and colleagues [5] were the first to report an increased risk of second cancer after HL treatment. Based on 12 second malignancies in 425 patients treated at the US National Institutes of Health from 1953 to 1971, they estimated a 3.5-fold risk increase compared to the general population. MOPP combination chemotherapy (mechlorethamine, vincristine, procarbazine, and prednisone) for HL was introduced in 1967; the leukemogenic potential of this regimen and similar ones became evident in reports published in 1973 [6], 1975 [7], and 1977 [8]. In the 1980s several studies showed that, after an induction period of 5–10 years, radiotherapy for HL increased the risk of solid malignancies, especially lung cancer [9–12].

It is important to recognize that not all SMNs are caused by treatment. The occurrence of two primary malignancies in the same individual may have several causes. It may represent a chance occurrence (in which case the two cancers developed as a result of unrelated factors); it may result from host susceptibility factors (e.g., genetic predisposition or immunodeficiency); it may be linked to carcinogenic influences in common, or a clustering of different risk factors in the same individual; or it may represent an effect of treatment for the first tumor [13, 14]. In view of the high prevalence of cancer in the general population and the increasing incidence of most cancers with age, background etiological factors other than treatment are likely to be responsible for a substantial proportion of second cancer, especially in older populations. Therefore, whenever a clinical impression arises that a specific combination of two distinct primary malignancies occurs more frequently than expected, comparison with cancer risk in the general population is imperative. If a SMN has been demonstrated to occur in excess, the contributions of other risk factors and the role of host susceptibility factors should be ruled out convincingly before the risk increase can be attributed to treatment. Even then, host factors may modify treatment effects, so that the risk associated with a given treatment will vary among individuals. The evaluation of the carcinogenic effects of therapy is further complicated by the fact that therapeutic agents are frequently given in combination. Appropriate epidemiologic and statistical methods are required to quantify the excess risk and to unravel treatment factors responsible for it.

In this chapter we address major aspects of SMN risk following treatment for HL. After an overview of the methods used for assessing second cancer risk, we discuss major contributors to second risk, i.e., radiation therapy and chemotherapy. Subsequently, a review is given of the risks of leukemia, non-Hodgkin lymphoma (NHL), and selected solid tumors in patients treated for HL. Emphasis is on large studies that were published recently. Finally, clinical implications of the most important findings are discussed.

26.2 Methods of Assessing Second Cancer Risk

Estimates of second cancer risk after treatment for HL derive from several sources, including population-based cancer registries, hospital-based cancer registries, or clinical trial series. The cohort study and the nested case-control study are the most common epidemiologic study designs used in second cancer research [15, 16]. Case reports have an important role in the early recognition of potential associations between different malignancies. However, because of lack of information on the underlying population at risk, they are not useful in quantifying risks.

In a *cohort study*, a large group of patients (the cohort) with a specified first malignancy is fol-

lowed for a number of years to determine the incidence of second (and subsequent) malignancies. Because most patient cohorts in which second cancer risk has been assessed were identified retrospectively, follow-up of all patients in such studies is completed up to some point in the recent past. To evaluate whether second cancer risk in the cohort is increased compared with cancer risk in the general population, the observed number of SMNs in the cohort is compared with the number expected on the basis of age-, gender-, and calendar year-specific cancer incidence rates in the general population. This can be done in a so-called "person-years" type of analysis. In this approach, adjustment is made for the distribution of the cohort according to age, sex, and calendar period, while the observation period of individual patients (person-years at risk) is also taken into account. The *relative risk* (RR) of developing a SMN is estimated by the ratio of the observed number of SMNs in the cohort to the number expected. In epidemiologic terminology, the *observed-to-expected ratio* is often called the *standardized incidence ratio* (SIR). For cancer deaths, the equivalent measure is the *standardized mortality ratio* (SMR), in which observed second malignancy deaths are compared with expected numbers of deaths.

A disadvantage of the person-years method as applied in its simplest form is that it assumes the risk of SMN development to be constant over time; that is, it assumes the second cancer experience of 1000 patients followed for 1 year to be comparable to that of 100 patients followed for 10 years. When this assumption is inappropriate (as with treatment-related cancers developing after an induction period), it is more informative to calculate SIRs within specified posttreatment intervals (usually 5-year periods) [17, 18]. A temporal trend of excess SMN risk may in itself provide an important initial clue to treatment-related causes; for example, the SIR of solid malignancy following RT for HL generally increases with time since exposure.

When the observed-to-expected ratio is increased, the question arises whether the risk increase is caused by the treatment. This can be evaluated by comparing SIRs between treatment groups, preferably with a reference group of patients not treated with RT or CT. Such a comparison group is unfortunately not available for patients with HL. When the observation period (or survival rate) differs between treatments, their overall observed-to-expected ratios cannot be validly compared without accounting for the difference in length of follow-up. This adjustment for treatment-associated differences in follow-up time (or age) is often done using Poisson regression (see below).

Second cancer risk in the cohort (and in different treatment groups) can also be expressed by the *cumulative* (actuarial estimated) *risk* [19], which gives the proportion of patients expected to develop a SMN by time t (e.g., 5 years from diagnosis) if they do not die before then. When the cohort's death rate from causes other than SMNs is high, the assumption of "non-informative censoring" underlying the actuarial method is often not valid. In particular, the assumption that patients who died due to other causes would have the same temporal pattern of SMN risk as those who survived is incorrect. In such cases actuarial risk tends to overestimate the true risk and *competing-risk techniques* should be used to estimate cumulative risk [15, 20–23]. In comparing estimates of cumulative risk across studies, it is important to keep in mind that this measure of risk depends strongly on the age distribution of a specific cohort; because of the low background incidence of cancer at young ages, cohorts of HL patients including childhood HL will report much lower cumulative risks than cohorts including adults only.

Most studies reporting cumulative risks make no comparison with cancer risk in the general population, yet population-expected cumulative risks over time can be easily calculated on the basis of cancer incidence rates from a population-based registry [24]. Because certain treatment-related cancers are rare in the general population (e.g., leukemia, sarcoma), a high SIR (compared to the population) may still translate into a rather low cumulative risk. *Absolute excess risk* (AER),

which estimates the excess number of SMNs occurring per 10,000 patients per year (beyond those expected to occur based on cancer rates in the general population), best reflects the clinical burden of SMN in a cohort. Consequently, this risk measure is also the most appropriate one to judge which second malignancies contribute most to the excess morbidity or mortality.

The calculation of observed-to-expected ratios on the basis of person-years analysis, and the calculation of cumulative risks using life table analysis, involves rather simple statistical methods, which have a strong intuitive appeal. Besides these elementary methods, statistical modeling with Cox proportional hazards model and Poisson regression techniques is increasingly being used to refine the quantification of second cancer RRs (e.g., by estimating dose- and time-response relationships) and to examine the interplay between treatment variables and other factors [25–27].

Each of the data sources that are commonly used to constitute cohorts has specific advantages and disadvantages. *Population-based cancer registries* have large numbers of patients available, which allows the detection of even small excess risks of second cancers [27–30]. An additional advantage is that the observed and expected numbers of cancers come from the same reference population. Disadvantages include limited availability of treatment data and underreporting of SMNs [13, 30, 31] (in particular hematologic malignancies). Population-based registries differ greatly in these aspects and hence in their usefulness for second cancer studies. If treatment data are not available, it is impossible to know whether excess risk for a SMN is related to treatment or to shared etiology with the first cancer. Underreporting of SMNs clearly leads to an underestimation of second cancer risk. Far higher risks of second leukemia following HL have been found in hospital series [11, 32] than in population-based studies [29]. Part of this difference, however, may be attributable to the more intensive treatments administered in large treatment centers [33]. Despite their disadvantages, population-based registries are well suited to evaluate broadly which SMNs occur in excess following a wide spectrum of different first primary malignancies. They are also a valuable starting point for case-control studies that evaluate treatment effects in detail (see below).

A major advantage of *clinical trial databases* is that detailed treatment data on all patients are available. Comparison of SMN risk between the treatment arms of the trial controls for any intrinsic risk of SMNs associated with the first cancer. However, a limitation of most trials is the small number of patients involved. Although this problem can be overcome by combining data from a number of trials [34], multicenter trial series pose other problems. For example, the main end points of interest in most clinical trials are treatment response and survival, and many trials neither collect information on treatment for recurrences nor on long-term occurrence of SMNs, so that follow-up data to a fixed end date may be very incomplete (and biased). Ideally, routine reporting and assessment of SMN risk should become an integral part of clinical trial research [15, 35, 36].

Most *hospital-based tumor* registries have been in existence for decades and collect extensive data on treatment and follow-up. They share the advantages of clinical trial databases and sometimes have better opportunities to obtain long-term follow-up data. Investigators using hospital tumor registries have ready access to the medical records; often a review of the histologic slides of the first and the second malignancy can also be arranged easily. An additional advantage is that, compared with trial data, hospital registries provide a wider range of treatments and dose levels, which may yield important information on drug and radiation carcinogenesis. Most studies of second cancer risk following HL have been based on hospital registries [8, 32, 37, 38]. As with trial data, however, loss to follow-up and surveillance bias compared to population-based studies can be problematic.

The cohort study is not an efficient study design for detailed examination of the association of treatment factors (e.g., cumulative dose of alkylating agents) with second cancer risk.

Large cohorts are required to yield reliable estimates of second cancer risk, rendering the collection of detailed treatment data for all patients prohibitively expensive and time consuming. In such instances, the so-called nested case-control study within an existing cohort is the preferred approach [15]. The case group consists of all patients identified with the SMN of interest, and the controls are a random sample of all patients in the cohort who did not develop the cancer concerned, although they experienced the same amount of follow-up time. To achieve maximum statistical power, most case-control studies of second cancer risk use a design in which more than one control is individually matched to each second cancer "case." Matching factors employed in most studies include sex, year of birth, and year at diagnosis of the first primary cancer. The most important criterion for control selection is that each control must have survived, without developing the SMN of interest, for at least as long as the interval between the diagnosis of the first and the second malignancy of the corresponding case. Even if the control group is three times as large as the case group, detailed treatment data need to be collected for only a small proportion of the total cohort. It is critical to the validity of the study results that the controls are truly representative of all patients who did not develop the second cancer of interest. In the analysis of a case-control study of second cancer risk, treatment factors are compared between cases and controls. Treatments that have been administered more often, for a longer duration, or with a higher dose to the case group than to the controls are associated with increased risk of developing the SMN of interest. It is important to understand that in a nested case-control study, the risk associated with specific treatments is estimated relative to the risk in patients receiving other treatment and *not* relative to the risk in the general population. The cumulative risk of developing a SMN cannot be derived using data from a case-control study alone. Estimates of the AERs associated with specific treatments can be derived, however, if the case-control study follows a cohort analysis in which observed-to-expected ratios were calculated for broad treatment groups. Although case-control methodology has only come into widespread use for the investigation of SMN risk in recent decades, several landmark studies have already demonstrated its strengths [33, 39–42].

26.3 Magnitude of the Risk Increase of Second Malignancy, Temporal Patterns, and Age Effects

The largest overall SIR (10- to 15-fold increase) compared to the general population is observed for leukemia (with the greatest risk seen for AML (22-fold), followed by a 6- to 14-fold increased risk for non-Hodgkin lymphoma (NHL), and 4- to 12-fold excesses for connective tissue, bone, and thyroid cancer) (Table 26.1). Moderately increased risks (two- to ninefold) are observed for a number of solid tumors, such as cancer of the lung, stomach, esophagus, colon, rectum, breast, cervix, and mouth and pharynx and melanoma (Table 26.1) [27, 43–48]. Because leukemia and NHL are diseases with a low incidence in the population, even a high relative risk compared to the population translates into a relatively low cumulative risk.

Many studies show that, over the long term, the cumulative risk of solid tumors far exceeds that of leukemia and NHL (e.g., 30-year cumulative risks of 28.5% for solid tumors compared to a 25-year cumulative risk of 3% for leukemia, respectively) (Tables 26.2 and 26.3) [32, 45]. Several studies [32, 44–47] show that, compared with the general population, HL patients experience an excess of about 45–80 malignancies per 10,000 person-years of observation (Tables 26.2 and 26.3). Solid tumors account for the majority of excess cancers (approximately 30–60 per 10,000 patients per year), with lung cancer contributing 10–12 excess cases per 10,000 person-years. Leukemia and NHL each account for about 8–9 cases per 10,000 person-years.

Table 26.1 Relative risks of second malignancy after HL for selected sites in large[a] cohort studies published since 2003

	Bhatia et al. [43]	Hodgson et al. [27]	Swerdlow et al. [44]		Schaapveld et al. [45]	Sud et al [46]
	USA	International	Britain		Netherlands	Sweden
	$N = 1380$[b]	$N = 18862$[b]	$N = 5798$[b]		$N = 3905$[b]	$N = 9522$
	Ages ≤ 16 years	All ages	All ages		Ages <51 years	All ages
	Med. fup 17 years	Med. fup 12.2 years			Med. fup 19.1 years	Mean fup 12.6 years
	Years of dx 1955–1986	Years of dx 1970–1997	Years of dx 1963–2001		Years of dx 1965–2000	Years of dx 1965–2012
		RR[c] (*n* observed)	SIR (*n* observed)			SIR (*n* observed)
Site	SIR (*n* observed)		Chemo[d]	Ch + RT[d]	SIR (*n* observed)	
All sites	18.5[e] (143)	–[f]	2.0[e] (157)	3.9[e] (302)	4.6[e] (884)	2.4[e] (1121)
All solid	18.5[e] (109)	–[f] (1490)	–[f]	–[f]	4.2[e] (757)	–
Leukemia	174.8[e] (27)	– (–)[f]	18.4[e] (33)	22.7[e] (42)	9.5[e] (41)	6.5[e] (79)
NHL	11.7[e] (7)	– (–)[f]	11.5[e] (31)	17.1[e] (51)	13.4[e] (104)	8.0[e] (125)
Female breast	55.5[e] (39)	6.1[g] (–)	0.5 (5)	2.4[e] (30)	4.7[e] (183)	2.5[e] (146)
Lung	27.3[e] (4)	6.7[c] (–)	2.9[e] (40)	5.1[e] (60)	6.4[e] (176)	3.6[e] (138)
Stomach	63.9[e] (3)	9.5[c] (–)	1.1 (4)	2.7[e] (8)	7.4[e] (39)	1.8[e] (31)
Colon	36.4[e] (8)	4.3[c] (–)	1.1 (10)	2.0[e] (17)	2.9[e] (42)	2.2[e] (83)
Pancreas	–[f]	4.7[c] (–)	1.0 (2)	2.9 (5)	5.7[e] (23)	2.1[e] (28)
Bone	37.1[e] (8)	– (–)[f]	0	9.0[e] (2)	–[f]	–[f]
Soft tissue	–[f]	– (–)[f]	0	8.9[e] (5)	12.0[e] (22)	5.7[e] (20)
Bone and soft tissue	–[f]	11.7[c] (–)	–[f]	–[f]	–[f]	
Melanoma	–[f]	1.6[c] (–)	0.5 (1)	2.7[e] (7)	2.8[e] (34)	2.1[e] (42)
Cervix	–[f]	2.2[h] (–)	1.4 (2)	2.7 (6)	–[f]	–[f]
Thyroid	36.4[e] (19)	3.1[i] (–)	2.3 (1)	5.7[e] (3)	14.0[e] (23)	5.1[e] (20)

NHL non-Hodgkin lymphoma, *Med. Fup* median follow-up, *Years of dx*, years of diagnosis; *RR*, relative risk; *n*, number of second malignancies

[a]Only includes studies with ≥100 second malignancies; for cohorts included in several reports, only the paper with the longest follow-up is included

[b]Number of Hodgkin disease patients included in the study

[c]RRs are for males and females combined and for individuals diagnosed with HL at age 30 years and attained age range 40–60 years

[d]Chemo refers to patients treated with chemotherapy only; Ch + RT refers to patients treated with chemotherapy plus radiotherapy

[e]Significantly raised ($P < 0.05$)

[f]Data not published

[g]RR is for women diagnosed with HL at age 30 years and attained age 40 years

[h]RR is for all female genital second cancers

[i]RR is for individuals diagnosed with HL at age 30 years and all attained ages

Although SMN risks are often summarized as a single relative risk (SIR) or AER value for the sake of simplicity, it is important to recognize that variation over time is one of the fundamental features of second cancer risk. Further, the nature of this variation is different for different second malignancy sites, and ages at treatment, and additionally relative risks vary over time differently than AERs (Figs. 26.1 and 26.2). Consequently, no single risk value fully describes the SMN risk that patients experience at different times after treatment. Leukemia risk increases approximately 2–4 years following alkylator-based chemotherapy, with the SIR peaking 5–9 years after treatment and decreasing thereafter [32, 33, 44, 45, 47, 52–54]. The SIR of NHL is increased in the first 5 years after treatment, and study findings disagree regarding whether NHL risk

Table 26.2 SIR, AER, and cumulative incidence of second malignancy among HL survivors in selected studies

	Hodgson et al. [27]	Swerdlow et al. [44]		Schaapveld et al. [45]	Sud et al [46]
	International	Britain		Netherlands	Sweden
	N = 18,862[b]	*N* = 5798[b]		*N* = 3905	N=9522
	All ages	All ages		15–50 years	All Ages
	Med. fup 12.2 years	Dx yrs 1963–2001		Med. fup 19.1 years	Mean fup 12.6 years
	Dx yrs 1970–1997			Dx yrs 1965–2000	Dx yrs 1965–2012
		Chemo	Ch+RT		
All cancers					
SIR	(–)	2.0	4.6	3.9	2.4
AER	(–)	32.9	121.8	65.3	71.2
CI	(–)	20 year = 13%	30 years = 32.5%	20 year = 18%	
All solid					
SIR	4.6[b], 3.7[c]	(–)	4.2	2.0	(–)
AER	(–)	(–)	100.5	33.1	(–)
CI	30 years = 18.3% (M)[d] and 26.1% (F)[d]	(–)	30 years = 28.5%	25 years = 21.9%	(–)
Breast cancer					
SIR	6.1	0.5	4.7	2.4	2.5
AER	61[f]	−1.8	54.3	5.1	9.2
CI	(–)		30 years = 16.6%		
(Acute) leukemia					
SIR	(–)	18.4	(–)	22.7	6.5
AER	(–)	12.8	(–)	11.7	6.9
CI	(–)		(–)		

SIR standardized incidence ratio, *AER* absolute excess risk, *CI* cumulative incidence
[b]Supradiaphragmatic sites
[c]Infradiaphragmatic sites
[d]Diagnosed at age 30
[f]AER predicted for a 30-year-old female attained age 50

increases [11, 54] or remains constant over time [37, 44, 47, 53].

Most studies report that the overall SIR of solid tumors is minimally elevated in the 1–4-year follow-up period and increases thereafter [11, 32, 37, 45, 47, 53–55]. In studies that include data on HL patients who survived 20 years or more, the RR of solid tumors continued to increase through the 15- to 20-year follow-up period and stabilized thereafter [32, 37, 38, 43–45, 47, 49–56]. A recent Dutch study of patients diagnosed with HL before age 50 reported that the SIRs of solid tumors remained very stable up to 35 years after HL, without much evidence of a decrease in very long-term survivors [45]. Reports from the Late Effects Study Group on survivors of pediatric HL and the US Childhood Cancer Survivor Study reported a stable 20- to 24-fold increased relative risk from 15 to over 30 years after diagnosis [43, 49]. An international registry-based study of 5-year HL survivors employed Poisson

Table 26.3 SIR, AER, and cumulative incidence of second malignancy among pediatric HL survivors

	Castellino et al. [49]	Bhatia et al. [43]	Basu et al. and Constine et al. [50, 51]
	USA	USA	USA
	1675	*N* = 1380	*N* = 930
	Ages <21 years	Ages ≤16 years	Ages <19 years
	Med. fup 23.8 years	Med. fup 17 years	Med. fup 16.8 years
	Years of dx 1970–1986	Dx years 1955–1986	Dx years 1960–1990
All cancers			
SIR	8.7	18.5	14.2
AER	69.2	65[a]	62.6
CI	30 years = 10.9% (M) and 26.1% (F)	30 years = 26.3%	20 year = 8% (M) and 23% (F)
All solid			
SIR	(–)	18.5	(–)
AER	(–)	51[a]	(–)
CI	(–)	30 years = 23.5%	(–)
Breast (females)			
SIR	17.0	55.5	37.3
AER	29.0	53[a]	18.6
CI	30 years = 18.3%	30 years = 16.9%	30 years = 24%
Acute leukemia			
SIR	12.7	174.8	21.5
AER	3.4	1.3	5.7
CI	(–)	20 years = 2.1%	(–)

SIR standardized incidence ratio, *EAR* excess absolute risk, *CI* cumulative incidence
[a]Results were published per 1000 person-years. For consistency these have been multiplied by 10 (i.e., 10,000 P-Y)

regression methods comparable to those used to evaluate the temporal trends of cancer risk among atomic bomb survivors [27]. Variation in the risk of solid cancer was found to depend strongly on age at exposure, and attained age, with distinctly different patterns for female breast cancer, thyroid cancer, and other solid tumors (Fig. 26.3). With increasing attained age, the relative risk of breast cancer declined among females diagnosed at a young age (modeled age 20 years), whereas this decline was much less pronounced among women treated at older ages (30 or 40 years at HL diagnosis) (Fig. 26.2). In contrast, the relative risk of other solid cancers remained stable with advancing attained age, with a small decline after attained age of 60 years (Fig. 26.1). The AER of breast cancer and non-breast solid cancers increased with increasing attained age for all age groups [27] (Figs. 26.1 and 26.2). These findings demonstrate the importance of considering both age at exposure and attained age in the evaluation of SMN risk, as well as the potential importance of considering different solid cancers separately. Combining different age-at-treatment groups or all solid tumor types together may obscure significant variation in risks over time that can occur among different age groups or different SMN types. Also, the AER of SMNs changes over time differently than the SIR (Figs. 26.1 and 26.2). With increasing time since treatment, the major influence on the AER is the increasing background (i.e., "expected") rate of cancer, which rises rapidly with increasing age. As these baseline risks increase with advancing age, even stable elevations in SIRs translate into rising AER over time (Fig. 26.1).

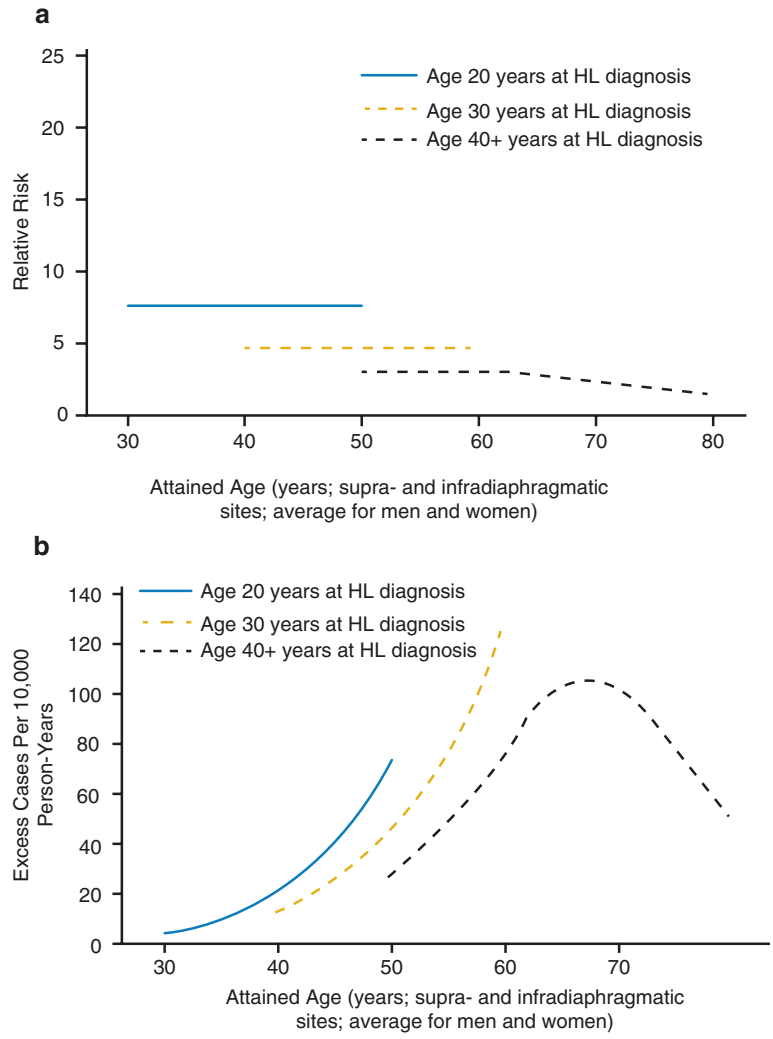


Fig. 26.1 Relative risk (*RR*) and absolute excess risk of supra- and infradiaphragmatic solid cancers according to age at HL diagnosis and attained age. (**a**) RR of supra- and infradiaphragmatic solid cancers. (**b**) AER of supra- and infradiaphragmatic solid cancers (From: Hodgson et al. [27])

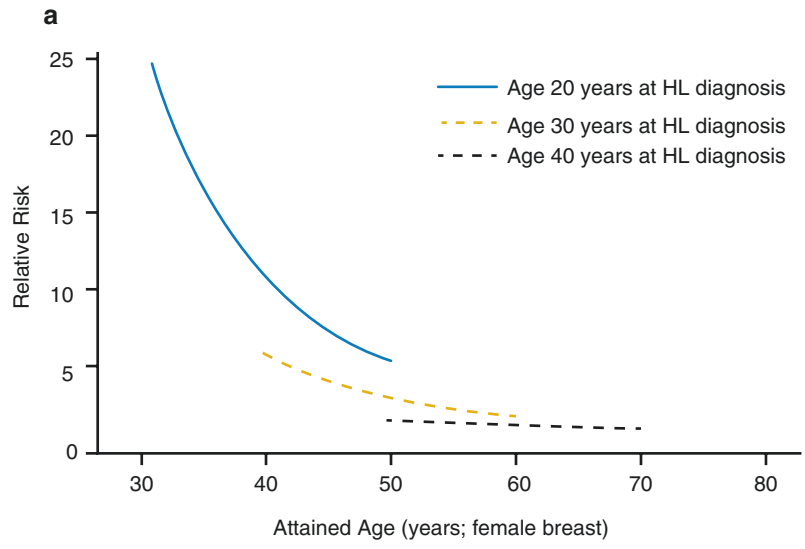


Fig. 26.2 Relative risk (*RR*) and absolute excess of female breast cancer according to age at HL diagnosis and attained age. (**a**) RR of female breast cancer. (**b**) AER of female breast cancer (From: Hodgson et al. [27])

Fig. 26.2 (continued)

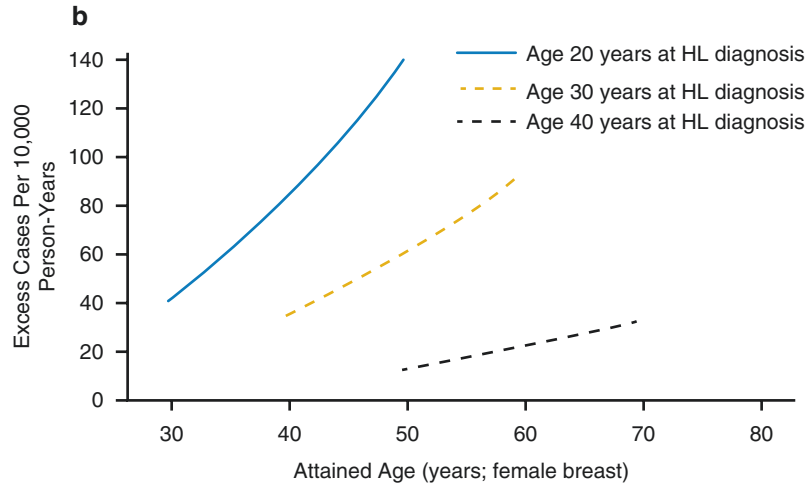
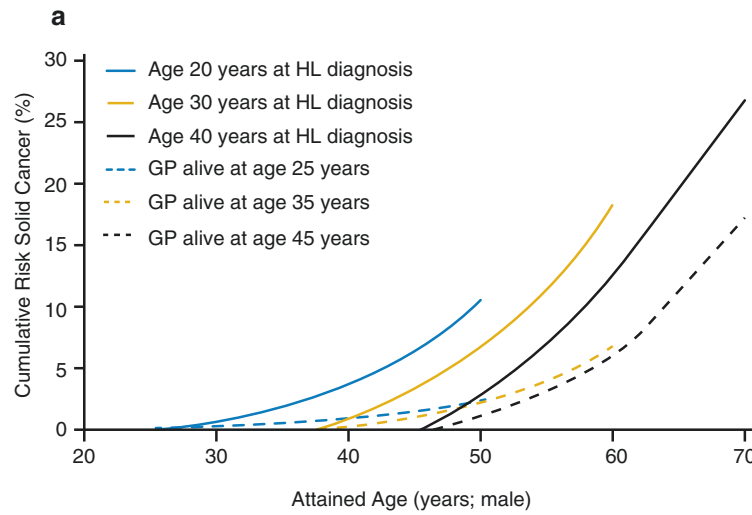
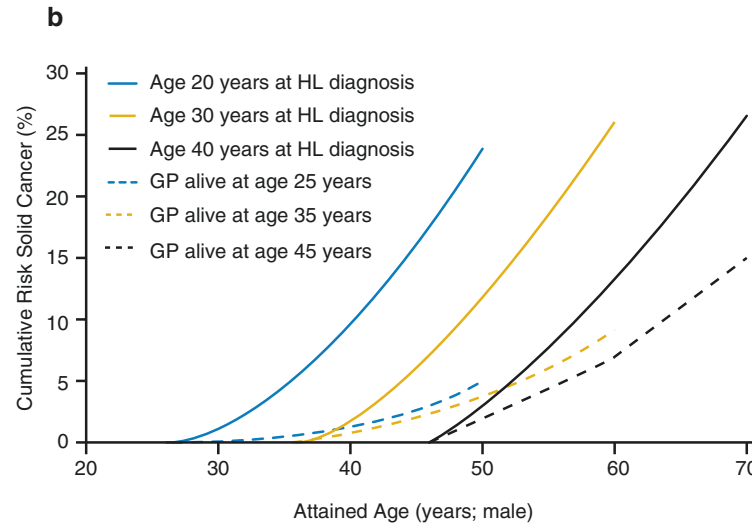


Fig. 26.3 (**a**) Cumulative incidence of all solid cancers among 10,619 male 5-year survivors of Hodgkin lymphoma (HL) compared with men of the same age in the general population (GP). (**b**) Cumulative incidence for 8243 female 5-year survivors compared with women of the same age in the GP (From: Hodgson et al. [27])





26.4 Contributors to Second Cancer Risk

26.4.1 Radiation Therapy

Increased risks of second cancers following RT for HL have been reported for over two decades [29]. These reports add to a substantial body of evidence demonstrating that radiation is carcinogenic over a broad range of doses and can increase the risk of a variety of different tumor types [57–61]. Certain tissues, such as the female breast, and thyroid appear to be particularly susceptible to radiation-induced malignancy.

Among HL patients, treatment with mantle RT (involving the axillary, mediastinal, and neck nodes) to doses of 35–45 Gy is associated with a 2- to 20-fold increased relative risk of breast cancer, with a strong influence of age at exposure, as discussed in detail below [24, 27, 32, 37, 43, 45, 60, 62]. Mantle RT is also associated with an increased relative risk of lung cancer, although the absolute excess risk is in fact small in the first 10–20 years after exposure, particularly among those treated at young ages (e.g., ≤0.2 per 10,000 person-years among those treated before age 20 years) [43, 52]. The risks of other solid cancers, especially stomach cancer, have also been shown to be elevated after RT [40].

Much of our current understanding of the relationship between radiation dose and cancer risk has been derived from cohort studies of individuals exposed to low levels of radiation, such as atomic bomb survivors [60, 63–65]. However, extrapolation of the dose-risk relationships seen at low total body doses into the 15–40 Gy ranges used for HL RT cannot be done with certainty, due to differences relating to dose rate, neutron exposure, and the possibility of cell killing at high doses. More recently, studies of SMN risk have evaluated the dose-risk relationship in the radiation dose range commonly used in the treatment of HL.

There appears to be an approximately linear increase in the risk of leukemia with increasing radiation dose to the bone marrow, up to approximately 2–4 Gy [66–68]. At doses above this, the risk of leukemia per unit radiation dose to the bone marrow appears to decline [66–68], a finding generally attributed to killing or inactivation of preleukemic cells at the higher radiation doses [66, 69]. One study of leukemia risk in survivors of uterine cancer, however, showed little evidence for such a clear downturn in risk [67].

The "bell-shaped" dose-risk curve for leukemia, with a peak at 2–4 Gy, does not seem to apply to the risk of most solid tumors. Most studies examining the dose-risk relationship for solid tumors suggest a continued increase in risk with doses up to approximately 40 Gy [41, 42, 70, 71]. Three studies have evaluated the relationship between radiation dose and breast cancer risk among adult females treated for HL with mantle RT [41, 42, 72]. The RT dose to the area of the breast where the case's tumor had developed was estimated for each case-control set based on simulation films of the original HL radiotherapy and mammograms indicating the position of the breast tumor. All studies showed increasing risk of breast cancer over the dose range commonly used in the treatment of HL. For example, in a large international collaborative case-control study of women treated for HL at age 30 years or less [42] (105 patients with breast cancer after HL and 266 controls without breast cancer), the risk was eightfold increased (95% CI, 2.6–26.4) for the highest dose category (median dose of 42 Gy) compared to the lowest one (<4 Gy) (P trend <0.001, Table 26.4) [42]. Similarly, a recent Dutch case-control study estimated radiation dose to the site of breast cancer for 174 breast cancer cases and 466 controls [72]. The investigators reported a linear increase in breast cancer risk with increasing dose, with an excess odds ratio (EOR) of 6.1%/Gy (adjusted for duration of post-RT ovarian function). Compared to those with <3 Gy to the breast, the odds ratio of breast cancer was 4.7-fold higher among those with breast exposures of ≥36 Gy (Fig. 26.4).

The risk of lung cancer also rises with increasing radiation dose up to 40 Gy and with an increasing volume of lung irradiated (Table 26.4) [73, 74]. Similarly, an international case-control study (32 cases and 71 matched controls) showed that risk of esophageal cancer in HL survivors increased with higher radiation doses with a radi-

Table 26.4 Relative risks of breast, lung, and stomach cancers after Hodgkin lymphoma, according to radiation dose to affected site in breast/lung/stomach and number of cycles of alkylating chemotherapy[a,b]

Breast cancer[a]			Lung cancer[b]			Stomach cancer[c]		
Radiation dose to affected site in breast	Relative risk	95% CI	Radiation dose to affected site in lung	Relative risk	95% CI	Radiation dose to affected site in stomach	Relative risk	95% CI
0–3.9 Gy	1.0	(Referent)	0	1.0	(Referent)	0	1.0	(Referent)
4.0–6.9 Gy	1.8	0.7–4.5	>0–4.9 Gy	1.6	0.5–5.2	>0.1–0.9 Gy	1.3	0.4–4.1
7.0–23.1 Gy	4.1	1.4–12.3	5–14.9 Gy	4.2	0.7–21	1.0–4.9 Gy	1.0	0.3–3.5
23.2–27.9 Gy	2.0	0.7–5.9	15.0–29.9 Gy	2.7	0.2–15	5.0–24.9 Gy	0.5	0.1–2.7
28.0–37.1 Gy	6.8	2.3–22.3	30.0–39.9 Gy	8.5	3.3–24	25.0–34.9 Gy	4.6	1.2–20.5
37.2–40.4 Gy	4.0	1.3–13.4	≥40.0 Gy	6.3	2.2–19	35.0–39.9 Gy	8.2	2.6–29.7
40.5–61.3 Gy	8.0	2.6–26.4				≥40.0 Gy	4.2	1.2–15.6
No. of cycles of alkylating agents								
0	1.0	(Referent)	0	1.0	(Referent)	0	1.0	(Referent)
1–4	0.7	0.3–1.7	1–4	4.0	1.3–12.5	1–5	1.0	0.5–2.4
5–8	0.6	0.3–1.1	5–8	6.2	2.6–17.1	6	1.7	0.7–4.4
≥9	0.2	0.1–0.7	≥9	13.0	4.3–45	7–10	1.9	0.7–4.9
						≥11	3.0	1.2–7.7

[a]Adapted from results by Travis et al. [42]
[b]Adapted from results by Gilbert et al. [72]
[c]Adapted from results by Morton et al. [40]

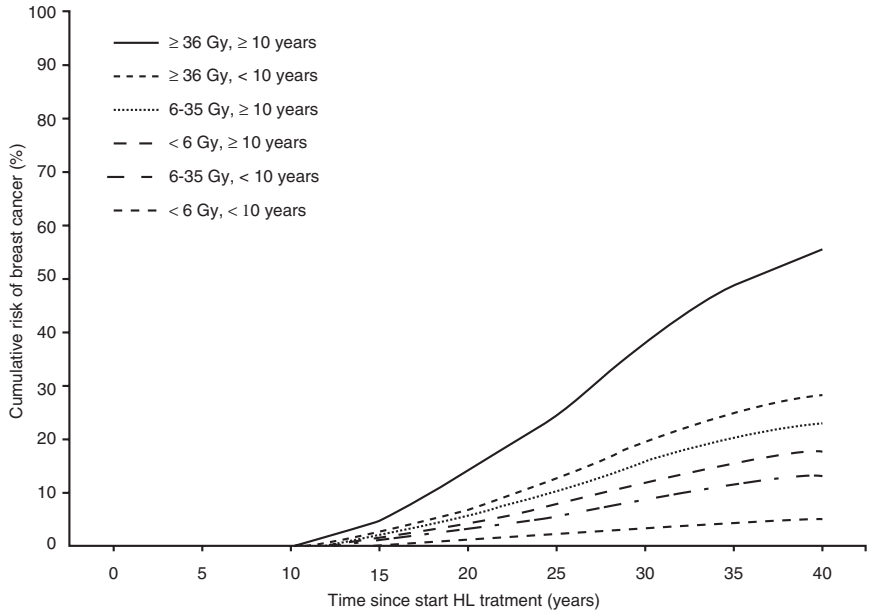


Fig. 26.4 Estimated cumulative incidence of breast cancer in female Hodgkin lymphoma survivors for tertiles of radiation dose to breast tumor location and duration of post-RT intact ovarian function (greater or less than 10 years intact). Cumulative risks among 10-year survivors treated with death as competing risk, estimated form ORs derived from case-control data relative to the cumulative breast cancer risk for the entire cohort, assuming that the distribution of all individuals in the cohort across dose categories was equal to that for the controls (From: Krul et al. [72])

ation dose response compatible with a linear increase in risk (EOR/Gy = 0.38) [75]. Furthermore, two studies in survivors of childhood cancer [76, 77] suggest that the risk of bone sarcoma increases rapidly with increasing dose above 10 Gy [78]. An international case-control study of stomach cancer nested in a cohort of 19,882 HL survivors found that stomach doses ≥25 Gy were associated with a significantly elevated risk of gastric cancer particularly when also given procarbazine-containing chemotherapy [40]. Risk increased with larger radiation doses to stomach up to 40–44 Gy (Table 26.4). Similarly, van den Belt et al. reported that the risk of stomach cancer increases linearly with radiation dose to the stomach, with tenfold increased risk for mean stomach doses of >20 Gy compared to less than 11 Gy [79]. A case-control study, evaluating risk of pancreatic cancer after HL treatment, again found an increased risk with higher radiation dose to the pancreas, with an odds ratio of 9.1 at doses ≥40 Gy compared to patients who received a pancreatic dose <0.5 Gy (adjusted for number of alkylating agent containing cycles of chemotherapy) [80]. Radiation-induced thyroid cancer may be an exception to these general findings for other solid cancers: dose-risk studies have suggested a leveling or decrease in thyroid cancer risk with doses above 10–30 Gy [61, 81, 82] although one study reported increasing risk of thyroid cancer with increasing dose up to 60 Gy [83].

Although no studies have evaluated the association of radiation dose to the colon and subsequent colon cancer risk, several studies observed increased cancer risk after subdiaphragmatic irradiation. In the study by van Eggermond et al. the risk of rectal cancer was 6.3-fold increased and the risk of colon cancer 6.0-fold and the risk among patients treated with inverted-Y irradiation compared to general population rates, with highest risk observed for transverse colon cancer (SIR 15.0; 95% CI, 4.3–40.8) [52]. Compared to patients not treated with infradiaphragmatic radiation therapy and a procarbazine dose ≤4200 mg/m^2, CRC risk was 6.8-fold higher for patients who had infradiaphragmatic radiation therapy and had received a procarbazine dose >4200 mg/m^2.

The treatment of large volumes of normal tissues in pediatric patients, even with lower prescribed doses of 15–36 Gy, was still associated with substantially increased risks of second malignancy in one study [84], illustrating the importance of not only limiting the prescribed dose but also reducing the volume of normal tissue irradiated (and hence the normal tissue dose) compared to historic mantle or extended-field RT.

These dose-risk studies provide a critical component to understanding the potential risk of second cancers associated with contemporary involved field RT (IFRT) or involved node/site RT (INRT/ISRT for HL). Specifically, they suggest that reduction in normal tissue dose associated with reducing the prescribed dose from 36–40 to 20–30 Gy and reducing the volume of irradiated normal tissue by omitting uninvolved nodal regions from the RT volume should produce a lower risk of most solid SMN, perhaps with the exception of thyroid cancer. Data are emerging that this is the case. One study found that for patients with mediastinal disease, the transition from mantle fields to mediastinal IFRT resulted in an approximately 65% reduction in breast tissue exposure, largely due to the exclusion of the axillae [85], and clinical studies provide evidence that this volume-related reduction in breast exposure appears to translate into a reduced risk of subsequent breast cancer. A large Dutch study, including 1122 female 5-year survivors of HL, examined the effect of radiation fields (volume) on the risk of breast cancer up to more than 30 years after treatment of HL [24]. Mantle field irradiation was associated with a 2.7-fold (95% CI, 1.1–6.9) increased risk of breast cancer compared to similarly dosed (36–44 Gy) radiation to the mediastinum alone (Fig. 26.5) [24]. This finding, which was recently confirmed in a much larger Dutch cohort, with updated follow-up, is reassuring since present-day radiotherapy for HL employs smaller radiation volumes which have been shown to reduce normal tissue doses [24, 45, 86, 87].

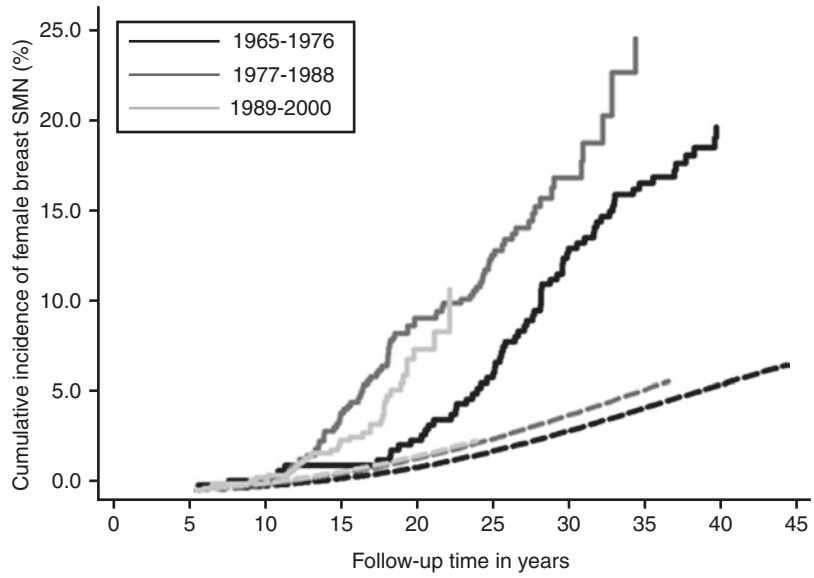


Fig. 26.5 The cumulative incidence of breast cancer after HL according to period treatment among 1698 female 5-year survivors of Hodgkin lymphoma age 15–50 years at first Hodgkin lymphoma treatment. Solid lines represent the observed incidence, dashed lines the expected incidence (From: Schaapveld et al. [45])

26.4.2 Chemotherapy

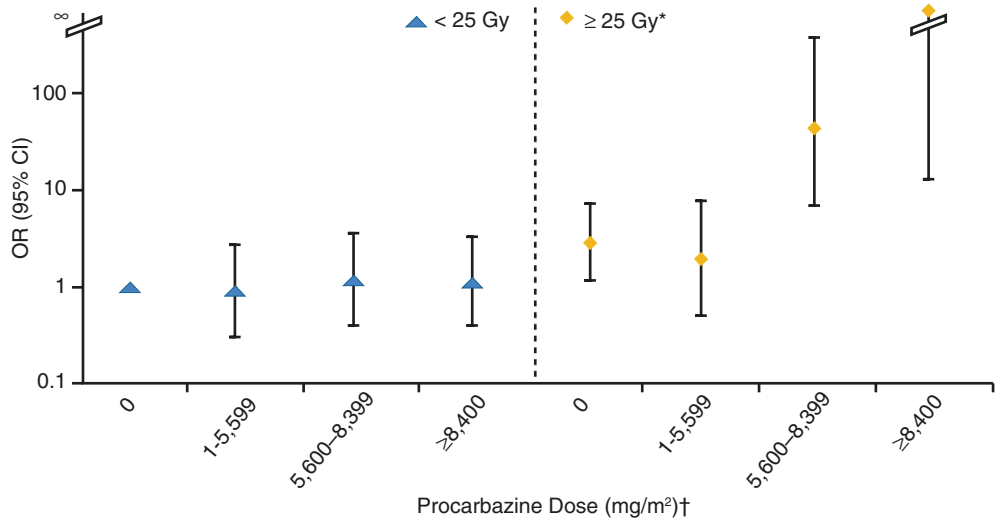
There is a well-established association between exposure to alkylating chemotherapy agents and an increased risk of acute myeloid leukemia (AML) in HL survivors. The MOPP chemotherapy regimen (mechlorethamine, vincristine, procarbazine, and prednisone) was widely employed in the 1970s, as it became evident that it was superior to RT alone in curing high-risk HL. However, it was associated with an increased relative risk of AML of 20- to 50-fold [11, 54, 88–92]. The cumulative dose of alkylating agents appears to be the strongest determinant of risk [14, 88, 93, 94]. Most cases of alkylating agent-induced AML are preceded by myelodysplasia (MDS), which generally progresses to AML within a year [54, 94–96]. Cytogenetic studies of alkylator-induced AML/MDS have shown unbalanced chromosome aberrations, primarily with loss of whole chromosomes 5 and/or 7 or various parts of the long arms of these chromosomes [94, 96, 97].

Several more recent studies suggest that topoisomerase II inhibitors, such as doxorubicin and 4-epidoxorubicin (epirubicin), may also be associated with increased risks of AML [33, 97, 98], but this association is not nearly as well established as it is for alkylating agents and requires further study. Certainly, ABVD chemotherapy (doxorubicin, bleomycin, vinblastine, dacarbazine) is associated with a much lower risk of AML than MOPP chemotherapy, although it is not clear that this risk is eliminated altogether [44, 54, 99]. Etoposide, used in HL chemotherapy regimens such as BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) and OEPA (vincristine, etoposide, prednisolone, doxorubicin), is also leukemogenic [100, 101]. As compared with "classical" alkylating agent-induced AML, etoposide-related AML typically occurs sooner after exposure, generally lacks a preceding myelodysplastic phase, and is characterized by balanced translocations involving chromosome bands 11q23 and 21q22 [14, 94, 102–104].

Evidence increasingly suggests that chemotherapy also may play a role in the development of non-hematologic SMNs, which typically occur >10 years after exposure [14, 105]. Alkylating agents have been reported to increase risks for lung, thyroid, gastrointestinal, and bladder cancers as well as sarcoma. For example, lung cancer risk after HL is increased 2- to 4-fold with increasing number of cycles of alkylating agent-containing chemotherapy, particularly MOPP [39, 43, 44, 74, 106, 107]. Among childhood cancer survivors, receipt of any alkylating agent has been associated with 2.4-fold increased risk for

thyroid cancer; receipt of procarbazine and platinum has been associated with 3.2- and 8.6-fold increased risk, respectively, of gastrointestinal cancer, and both alkylating agents and anthracyclines have been associated with sarcoma risk [52, 75, 108–110].

The causal link between cyclophosphamide and bladder cancer represents one of the few established relationships between a specific alkylating agent and carcinogenesis at a specific site, likely as a result of direct genotoxic exposure of bladder epithelium from cyclophosphamide metabolites [111, 112]. Procarbazine-related risks for the gastrointestinal tract also may be related to direct exposure [40, 52, 80, 109, 113]. For procarbazine and risks of cancers of the stomach and pancreas, dose-dependent effects have recently been found in survivors of HL [40, 79]. Furthermore, patients who received both radiation to the stomach ≥25 Gy and high-dose procarbazine (≥5600 mg/m^2) had strikingly elevated stomach cancer risk (RR, 77.5; 95% CI, 14.7–1452) compared with those who received radiation <25 Gy and procarbazine <5600 mg/m^2. Risk was also elevated (RR, 2.8; 95% CI, 1.3–6.4) among patients who received radiation to the stomach ≥25 Gy but procarbazine <5600 mg/m^2; however, no procarbazine-related risk was evident with radiation <25 Gy (Fig. 26.6). Treatment with dacarbazine also increased stomach cancer risk (RR, 8.8; 95% CI, 2.1–46.6), after adjustment for radiation and procarbazine doses [40]. In a recent study, risk of colorectal cancer was 3.8-fold (95% CI, 2.2–6.1) after >4200 mg/m^2 procarbazine, adjusted for infradiaphragmatic radiation field. Patients who received both >4200 mg/m^2 procarbazine and infradiaphragmatic radiation therapy had a very high colorectal cancer risk (RR, 6.8; 95% CI, 3.0–15.6), compared to patients receiving none of these treatments [52]. Similarly, pancreatic cancer risk increased with an increase in number of alkylating agent-containing chemotherapy



Patients	n	18	7	6	8	18	5	15	10
	%	21	8	7	9	21	6	17	11
Patients	n	70	24	25	19	28	13	2	0
	%	39	13	14	10	15	7	1	0
	OR‡	1.0	0.9	1.2	1.1	1.9	2.0	43.8	∞
	95% CI	reterent	0.3 to 2.7	0.4 to 3.6	0.4 to 3.2	1.2 to 7.6	0.5 to 8.0	7.4 to 861.9	12.9 to ∞

Fig. 26.6 Risk of stomach cancer after Hodgkin lymphoma in relation to radiation dose to stomach and procarbazine dose (From: Morton et al. [40])

cycles. The odds ratio was 17.9 (95% confidence interval 3.5–158) increased for patients treated with both subdiaphragmatic radiation (≥10 Gy) and ≥6 alkylating agent-containing chemotherapy cycles compared with patients receiving neither of these treatments, with a significantly greater than additive joint effect for these two treatments combined (subdiaphragmatic radiation ≥10 Gy and <6 alkylating agents, OR 3.0 (95% CI, 0.7–17), and subdiaphragmatic radiation <10 Gy and ≥6 alkylating agents, OR 1.8 (95% CI, 0.4–9.7)) [80].

26.4.3 Genetic Factors

There is increasing interest in identifying the molecular and cellular basis underlying the development of SMNs in HL survivors and other cancer survivors. Germline mutations in the RB1 tumor suppressor gene, associated with hereditary retinoblastoma, constitute a well-described example of a rare mutation with high penetrance that confers a large risk of developing radiation-related second cancer [114–116]. Although there is evidence that patients with a family history of cancer are more likely to develop radiation-related SMNs [48, 117–122], it is unlikely that a single candidate gene abnormality will account for a significant component of the SMN risk following HL treatment. Currently, there is no uniform evidence that BRCA1 or BRCA2 gene mutations mediate the development of radiation-related breast cancers. Two studies have reported that mammographic radiation exposure does not significantly contribute to the risk seen in BRCA1/2 mutation carriers [123, 124], though three other studies found that young BRCA1/2 mutation carriers had an increased risk of breast cancer if exposed to a significant number of chest X-rays [125–127]. There have been no studies examining whether carriers of BRCA mutations with HL have an increased risk of RT-associated cancers. Homozygous mutations in the ataxia-telangiectasia (ATM) gene are associated with significant radiation toxicity, although two studies have reported that no ATM mutations were found in women who had developed breast cancer after RT for HL [121, 128]. Moreover, while P53 gene mutations are associated with an increased risk of primary malignancy [129], and increased radiation sensitivity in vitro [130, 131], there is currently no evidence that P53 mutations modify the risk of treatment-related SMN in HL patients.

Outside of the context of cancer predisposition syndromes, most studies have investigated SMN risks in relation to specific genes, selected based on understanding the biologic pathways of drug metabolism and carcinogenesis. These studies have reported associations for variants in oxidative stress, DNA detoxification, and DNA repair genes with treatment-related leukemia [132–138] and *FGFR2* with breast cancer after supradiaphragmatic radiotherapy for HL [139].

Methylating agents (e.g., dacarbazine) produce DNA damage, the repair of which is mediated in part by the MLH1 gene. Worrillow et al. examined the frequency of a common MLH1-93 polymorphism among patients who developed cancer following chemotherapy and/or radiotherapy, or were diagnosed with de novo myeloid leukemia or HL, and healthy controls [134]. Carrier frequency of the MLH1-93 variant was higher in patients who developed therapy-related AML or breast cancer after methylating chemotherapy for HL compared to patients without previous methylating exposure.

More recently, genome-wide association studies (GWAS), which agnostically interrogate hundreds of thousands to millions of variants across the genome [140], have revealed genomic regions associated with treatment-related leukemia [141] and with SMNs occurring among HL survivors initially treated with radiotherapy [142–144], supporting the idea of genetic susceptibility to treatment-related SMNs. A recent Dutch study used a GWAS approach to investigate the modifying effects of SNPs on the risk of radiation-induced breast cancer in an international case-case analysis including 327 breast cancer patients after chest RT for HL and 4671 first primary breast cancer patients from the international cohort [143]. Nine SNPs showed statistically significant interaction with RT on breast cancer risk. A polygenic risk score (PRS) composed of these SNPs (RT-interaction-PRS) and a previously

published breast cancer PRS derived in the general population were evaluated in a case-control analysis comprising the 327 HL patients with breast cancer and 491 chest-irradiated HL patients without breast cancer. Patients in the highest tertile of the RT-interaction-PRS had a 1.6-fold higher breast cancer risk than those in the lowest tertile. After external validation this RT-interaction-PRS can be incorporated in risk prediction models for HL patients. Remarkably, the authors observed a 4-fold increased RT-induced risk in the highest compared with the lowest decile of the breast cancer PRS, similar to the effect size found in the general population. Morton et al. also recently reported results of a GWAS study, investigating modification of radiation-induced BC risk by SNPs. Pooling data from the US Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort, comprising 207 survivors (136 with Hodgkin lymphoma) who developed breast cancer and 2774 (246 with Hodgkin lymphoma) without any subsequent neoplasm, this study found a locus on 1q41 (rs4342822) which was associated with a, per allele, 1.9-fold (95% CI, 1.5–2.4) increased subsequent breast cancer risk among survivors who received 10 or higher gray breast radiation exposure [144]. They also reported two suggestive associations for low-frequency variants at 11q23 and 1q32.3 with breast cancer risk after childhood cancer, suggesting a potential role for low-frequency SNPs in RT-induced breast cancer.

Because of the large sample sizes required for such studies, international collaboration will be essential to validate these findings and move this field forward. Lending further support to the importance of this research area, several GWAS have identified genomic regions associated with toxicity after radiotherapy [145, 146].

26.5 Risk of Selected Second Malignancies

26.5.1 Risk Factors for Leukemia

Leukemia following HL is certainly the most studied treatment-induced malignancy, and thus, extensive knowledge of its risk factors has emerged [14, 147, 148]. Leukemia was the first malignancy for which elevated risk after treatment for HL was observed, probably because of the relatively short latency period, the rarity of acute leukemia in the general population, and the high SIR [149].

Overall, in patients treated in the 1960s–1980s, risks compared with the general population have been reported to be 10- to over 80-fold increased (Table 26.1). Nearly all studies show that the SIR of leukemia is higher than that of NHL and much greater than that of solid tumors overall (Table 26.1). Because the background risk of leukemia in the population is low, however, this strongly increased SIR translates into a relatively low cumulative risk, ranging between 1.4% and 4.1% at 15 years [11, 32, 44, 45, 52, 55, 88, 99]. Overall, the AER has varied between 8 and 30 excess cases per 10,000 patients per year (Tables 26.2 and 26.3) [43, 44, 47, 150].

Radiotherapy alone is associated with a small, or no, increased risk of leukemia compared with the risk in the general population [11, 32, 43, 55, 85], while alkylating agent CT, as widely used up to the 1990s, is linked with greatly elevated risk. In cohort analysis of CT-treated patients, the SIRs of leukemia overall tend to be over 20-fold increase compared to the general population, while for AML over 50-fold risk increases are reported [11, 44, 45, 54, 88, 90–92].

Several studies have compared the leukemogenicity of different CT regimens. Where exposure has been quantified, risk appears to be most related to total dose of alkylating agents or nitrosoureas [11, 33, 77, 88, 92, 149]. Risk of AML rises sharply with an increasing number of MOPP (mechlorethamine, vincristine, procarbazine, prednisone) (or MOPP-like) cycles [33, 88]. The risk associated with 10–12 MOPP cycles appears to be approximately 3–5 times higher than the risk following six MOPP cycles [33, 88]. Total dose of alkylators and nitrosoureas is likely the explanation of the higher risk associated with salvage CT or maintenance CT [55, 88, 151], but there is evidence that retreatment may be itself a factor in risk [51, 88, 148, 152]. Among those treated with variations of MOPP that substitute

cyclophosphamide for mechlorethamine, the risks are lower [11, 88, 92, 153, 154]. It has never been clarified whether mechlorethamine or procarbazine has the strongest effect on AML risk.

From the 1980s, MOPP-only CT has been gradually replaced by ABV(D) (doxorubicin, bleomycin, vinblastine, and dacarbazine)-containing regimens in many centers. There are only a few reports on AML occurrence following ABV(D) alone. Patients treated with ABVD in the Milan Cancer Institute, where this regimen was designed, were shown to have a significantly lower risk of AML than MOPP-treated patients (15-year cumulative risks of 0.7% and 9.5%, respectively) [99]. Another study showed that HL patients treated with MOPP/ABV(D)-containing regimens in the 1980s had substantially lower risk of AML/MDS than patients treated in the 1970s with MOPP alone (10-year cumulative risks of 2.1% and 6.4%, respectively, $P = 0.07$) [54]. An international collaborative study showed that the AER of AML declined significantly after 1984, from 7.0 to 4.2 per 10,000 patients per year in those diagnosed before age 35 years and from 16.4 to 9.9 per 10,000 patient-years in the ≥35 age group [155]. Also, AML risk was recently assessed in three generations of Stanford clinical trials for HL patients. The incidence of AML/MDS was significantly lower in patients treated in the period 1989–2003, especially with the Stanford V regimens (0.3% at 10 years) [45, 156].

A large Dutch cohort study also found an almost fourfold lower cumulative incidence of leukemia and myelodysplasia among patients treated in 1989–2000 than among patients treated in 1965–1976 [45].

There is, however, concern about the role of anthracyclines and epipodophyllotoxins (both of which are topoisomerase II inhibitors) in the risk of leukemia. Limited evidence suggests that doxorubicin in combination with higher doses of alkylating agents and/or epipodophyllotoxins may have a synergistic effect on the risk of AML. Analyses of the German Hodgkin Lymphoma Study Group (GHSG) also show low risks of AML after COPP-ABVD (mechlorethamine replaced by cyclophosphamide) and standard BEACOPP (bleomycin, etoposide, doxorubicin combined with COPP), while substantially increased risk of AML was observed for the escalated BEACOPP regimen [34, 150]. A GHSG analysis showed that 6 years after HL treatment patients who received ≥4 cycles of escalated BEACOPP had an increased risk to develop t-AML/MDS compared with patients treated <4 cycles of escalated BEACOPP (1.7% vs. 0.7%, respectively; $P < 0.0001$); for patients not treated with BEACOPP the 6-year risk was only 0.3% [101].

Some studies suggest that RT adds to the leukemia risk associated with CT [147, 157], whereas other large series indicate that the risk of AML after combined treatment is comparable to that after CT alone [33, 43, 44, 88]. The interaction between RT and CT could be evaluated most rigorously in the large case-control study by Kaldor et al. [33] which included 163 cases of leukemia following HL. For each category of radiation dose (<10, 10–20, >20 Gy to the active bone marrow), leukemia risk clearly increased with the number of CT cycles. In contrast, among patients with a given number of CT cycles, risk of leukemia did not consistently increase with higher radiation dose. Taken together, the preponderance of available data does not support the hypothesis that the combination of CT and RT confers a higher risk of leukemia than CT alone.

Therapeutic intensification with autologous stem cell transplantation (ASCT) is commonly used for lymphoma patients who relapse. In some series relatively high actuarial risks (4–15% at 5 years) of AML and myelodysplasia (MDS) have been observed after ASCT for HL [147]. Evidence suggests that much of the risk is related to intensive pretransplant CT. Forrest and colleagues compared the risk of AML/MDS between 202 patients who had undergone ASCT and 1530 patients who underwent conventional therapy for HL [158]. The 15-year cumulative incidence of developing AML/MDS was 1.1% (95% confidence interval (CI), 0.6–1.8) for those treated with conventional therapy alone and 3.6% (95% CI, 0.9–9.6) for those undergoing ASCT ($P = 0.22$). In multivariate analysis, leukemia risk was also not influenced by ASCT [158].

The risk of AML in relation to treatment-associated acute and chronic bone marrow toxicity has been examined in only two studies to date [88, 159]. Significantly increased risks of leukemia were found among patients who developed thrombocytopenia, either in response to initial therapy or during follow-up. After adjustment for type and amount of CT, patients who showed a ≥70% decrease in platelet counts after initial treatment had an approximately fivefold higher risk of developing leukemia than patients who showed a decrease of 50% or less [88]. Severe acute thrombocytopenia may indicate greater bioavailability of cytotoxic drugs, which would likely contribute to the development of leukemia. In support of these findings, a study of leukemia risk after autologous bone marrow transplantation found that low platelet counts at the time of transplant were predictive for MDS/AML development in NHL patients who had received intensive pretransplant CT [159].

The prognosis of AML/MDS after HL treatment is poor, with only 15% of patients surviving more than 1 year without apparent survival benefit from allogenic stem cell transplantation in most studies [147, 156, 160]. However, in a recent GHSG study, treatment-related AML/MDS patients who underwent ASCT did have a significantly better outcome with median OS not reached after a median follow-up of 41 months ($P < 0.001$) [101].

26.5.2 Risk Factors of Non-Hodgkin Lymphoma (NHL)

Krikorian and colleagues were the first to demonstrate a clearly elevated cumulative risk of NHL after HL, which amounted to 4.4% at 10 years in patients given both irradiation and CT [161]. Other investigators have confirmed the increased risk of NHL in HL survivors [11, 32, 37, 43–45, 47, 52, 53, 55, 88]. In most studies the SIR for NHL ranges between 6 and 36 compared to the risk in the general population (Table 26.1). Because the background risk of NHL in the general population is low, this rather high SIR translates into a relatively low cumulative risk, ranging between 2% and 4% at 20 years [32, 45, 52, 162] in the larger studies. AER in these studies has varied between 5 and 13 excess NHL cases per 10,000 patients per year [43, 44, 47]. The majority of cases of second NHL diagnosed after HL are intermediate or aggressive histology B-cell lymphomas [162–164] and more often arise in extranodal sites than primary NHL [163, 165] (79% of cases [164]).

The causes of the excess risk are not well understood. The results of older studies may in part reflect misclassification of the primary lymphoma in the absence of modern lymphoma immunophenotyping protocols (i.e., NHL misdiagnosed as HL) [163]. Rueffer et al. [163] reported that an expert panel of pathologists reviewing the histology of 4104 HL patients (GHSG) rejected 114 cases (2.1%) initially diagnosed as HL and rediagnosed them as primary NHL. Only very few studies included a review of diagnostic pathology slides of the second NHL and original HL in order to avoid such misclassification [53, 88, 163].

Other investigators argued that the clinical, histologic, and immunophenotypic findings of NHL among HL survivors were analogous to those of NHL arising in immunosuppressed patients, suggesting that immunodeficiency plays a role in the pathogenesis of second NHL in these patients [164]. This view is supported by several studies in which risk did not vary appreciably between treatments [11, 52, 90]. However, in other studies, the risk of NHL was found to be lowest among patients treated with RT alone and highest among patients who received intensive combined modality treatment, both initially and for relapse [55, 88, 161, 163, 166]. In the study by Schaapveld et al. HL patients who received a cumulative dose of procarbazine >8400 mg/m^2, as compared with no chemotherapy, had 2.7-fold higher risk of subsequent NHL [45]. Also, patients who had undergone splenectomy had a (1.8-fold) higher risk of NHL than did those who had not undergone splenectomy.

There exists some evidence indicating that transformation to NHL may be part of the natural history of the lymphocyte predominant subtype of HL [165, 167], which might explain the asso-

ciation between lymphocyte predominant HL and NHL risk observed in the International Database on HL [55] and the British National Lymphoma Investigation [168]. It may be that more than one of the above mechanisms operates in the development of NHL following treatment for HL. Although transformation to NHL may be part of the natural history of some types of HL, the role of intensive combined modality treatment and its associated immunosuppression should be explored further. Future studies should incorporate a review of all slides of the second NHL and the original HL diagnosis by an expert pathologist.

26.5.3 Risk Factors for Breast Cancer

For female HL survivors, the strongly elevated risk of breast cancer following radiotherapy is a major concern [24, 32, 45, 47, 169–173]. In several studies breast cancer is the largest contributor to the AER of second malignancy in female survivors [27, 32, 37, 43, 45, 174]. The magnitude of the risk of breast cancer after HL and risk factors for its development have been discussed in several review papers [59, 175–177]. The risk of breast cancer after HL greatly depends on age at treatment, time since treatment, therapies given for HL, and hormonal factors.

The overall SIR of breast cancer in female HL survivors has been only modestly elevated in studies which included all age groups (about 1.5- to 2.5-fold risk increases compared to the general population) (Table 26.1) [27, 29, 43, 47, 54, 55, 154]. Larger SIRs (four- to sevenfold) were observed in studies with predominantly young adults or a large proportion of long-term survivors [24, 32, 37, 38, 45, 178]. AERs for all ages have been around 2–10 per 10,000 HL patients per year (Table 26.3) [47, 52, 54], again with a greater risk (20–60 per 10,000 per year) in studies with predominantly young adults and/or a large proportion of long-term survivors [24, 32, 37, 45, 178]. Several studies covering the whole age range have shown that the SIR of developing breast cancer increases dramatically with younger age at first irradiation (or start of treatment) (Fig. 26.2) [24, 27, 32, 37, 47, 52, 178, 179]. A strong trend of increasing SIR of breast cancer with decreasing age at exposure has also been observed in other radiation-exposed cohorts [65, 180–182]. In a Dutch study, survivors who had radiation treatment before 21 years of age had an 18-fold increased risk of breast cancer compared with the general female population of the same age; women irradiated at ages 21–30 had a sevenfold increased risk, women irradiated at ages 31–40 had a 3.2-fold increased risk, and a small, nonsignificant increase was observed for women irradiated at ages 41 or older (SIR, 1.4) [24]. Similar trends have been reported by others [37, 45, 47, 52, 178, 183]. Most studies confirm that breast cancer risk is not elevated compared with the general population in women treated after age 35–40; a recent analysis however showed a SIR of 1.7 (95% CI, 1.1–2.5) even for women treated at ages 35–50 [45]. In most studies the AER of breast cancer is also highest after treatment before age 20 (Fig. 26.2) [24, 27, 32, 37, 45, 47, 178], but shows little variation between exposure at ages 20–35.

The SIR of breast cancer after HL treatment at ages under 16 has ranged from 17 to 458 [90, 91], with most studies showing SIRs around 50–100 [32, 37, 38, 43, 179, 184–186]. Three studies with long-term follow-up reported that, among women treated before age 20, the SIR compared with age-matched peers from the general population did not consistently vary by age at treatment [43, 70, 184]. This would imply that prepubertal radiation exposure increases the risk to the same extent as exposure during puberty. In the atomic bomb survivors and other radiation-exposed cohorts, the RR also did not vary by exposure age for ages under 20 [187]. However, a recent British study reported greatest SIRs for female HL survivors irradiated around age 14 [178] and a subsequent case-control study observed especially high risk when women were irradiated within 6 months of menarche [188] possibly associated with pubertal breast development. A recent report from the US Childhood Cancer Survivor Study in women treated with chest (60% of whom were treated for Hodgkin lymphoma) corroborated this finding. Women who began chest radiotherapy within 1

year of menarche had a 1.7-fold increased breast cancer compared to women who began chest radiotherapy further from menarche (excluding women who never experienced menarche) [189]. However, in a recent Dutch case-control study, menarche age close to start of radiation therapy did not modify breast cancer risk [72].

The large variation in breast cancer risks across studies, especially in young patients, is not surprising in view of the large differences between series in important variables such as the proportion of patients irradiated, duration of follow-up, and completeness of follow-up. Studies with more complete follow-up have generally found lower risks of breast cancer [32, 43, 47, 91, 178, 186] than those in which follow-up was less complete or not addressed [89, 90, 179].

Incomplete follow-up may lead to overestimation of second malignancy risk if patients who remain well lose contact with clinical follow-up, while those with second cancer come to attention because of this. In a Dutch study, with (nearly) complete follow-up, the 30-year cumulative incidence of breast cancer (accounting for death as a competing risk) amounted to 26% for women first treated before age 21% and 19% for those treated at ages 20–30 [24]. In pediatric HL survivors, Bhatia and colleagues estimated a cumulative incidence of breast cancer of 13.9% at age 40 years, reaching 20.1% at age 45 years [43]. Castellino and colleagues [158] recently reported a cumulative incidence of breast cancer of 18.3% at 30 years after treatment in the US Childhood Cancer Survivor Study. Travis and collaborators estimated treatment-specific cumulative risks of breast cancer: for an HL survivor who was treated at age 25 with a chest radiation dose of at least 40 Gy without alkylating agents, the cumulative absolute risks of breast cancer by age 35, 45, and 55 years were 1.4% (95% CI, 0.9–2.1), 11.1% (95% CI, 7.4–16.3), and 29.0% (95% CI, 20.2–40.1), respectively [190]. Based on 373 breast cancer patients in a very large HL cohort (n = 5002 women), Swerdlow and colleagues [178] recently reported modeled cumulative risks by follow-up time, age at treatment, and treatment modalities. For women who received 40 Gy under age 20, and no alkylating chemotherapy (see below), the cumulative incidence of breast cancer at 40 years was 48%. The case-control study by Krul et al. predicted cumulative incidence of breast cancer based on radiation field and dose and duration of post-RT ovarian function [72]. The predicted 35-year cumulative incidence of breast cancer was highest (27.6%) for women with high-dose mantle field RT (≥35 Gy) and long duration of ovarian function (≥20 years). Women with lower-dose (in)complete mantle field RT (≤35 Gy) and long duration of ovarian function had a lower cumulative incidence (22.4%), followed by women with high-dose (in)complete mantle field RT and medium and short durations of ovarian function (19.6% when 10–19% and 13.8% when <10 years, respectively).

The high risk of breast cancer after HL is largely attributable to chest radiotherapy. Since, in many cohort studies, 80% to over 90% of patients received supradiaphragmatic RT, few studies could estimate RRs associated with such RT compared with no RT [24, 32, 37, 43]. In the British cohort reported by Swerdlow and colleagues, a large proportion of patients had been treated with CT alone, and no increased risk of breast cancer was observed among them [44].

Elevated risk of breast cancer develops late and is typically observed from 15 years after first treatment (Fig. 26.7) [24, 32, 37, 45, 47, 52, 178]. This strong trend in breast cancer risk by time since treatment strongly indicates a radiogenic effect. Furthermore, in several cohort studies, almost all cases of breast cancer after HL have been in or at the margin of the radiation field, for instance, 16 of 16 cases [90], 22 of 26 [38], and all of 42 cases [43] in three publications. In the large, population-based study by Travis and colleagues [42], 49% of 105 breast cancers occurred in the unblocked chest treatment field, 24% under the lung blocks, 15% at the blocked edge, 8% in the field edge, and 3% out of beam, with relative location not known for one patient.

Four case-control studies investigated the effects of RT dose and other treatment factors on breast cancer risk [41, 42, 70, 72]. In all studies, the risk of breast cancer increased significantly with higher RT dose up to the highest dose levels

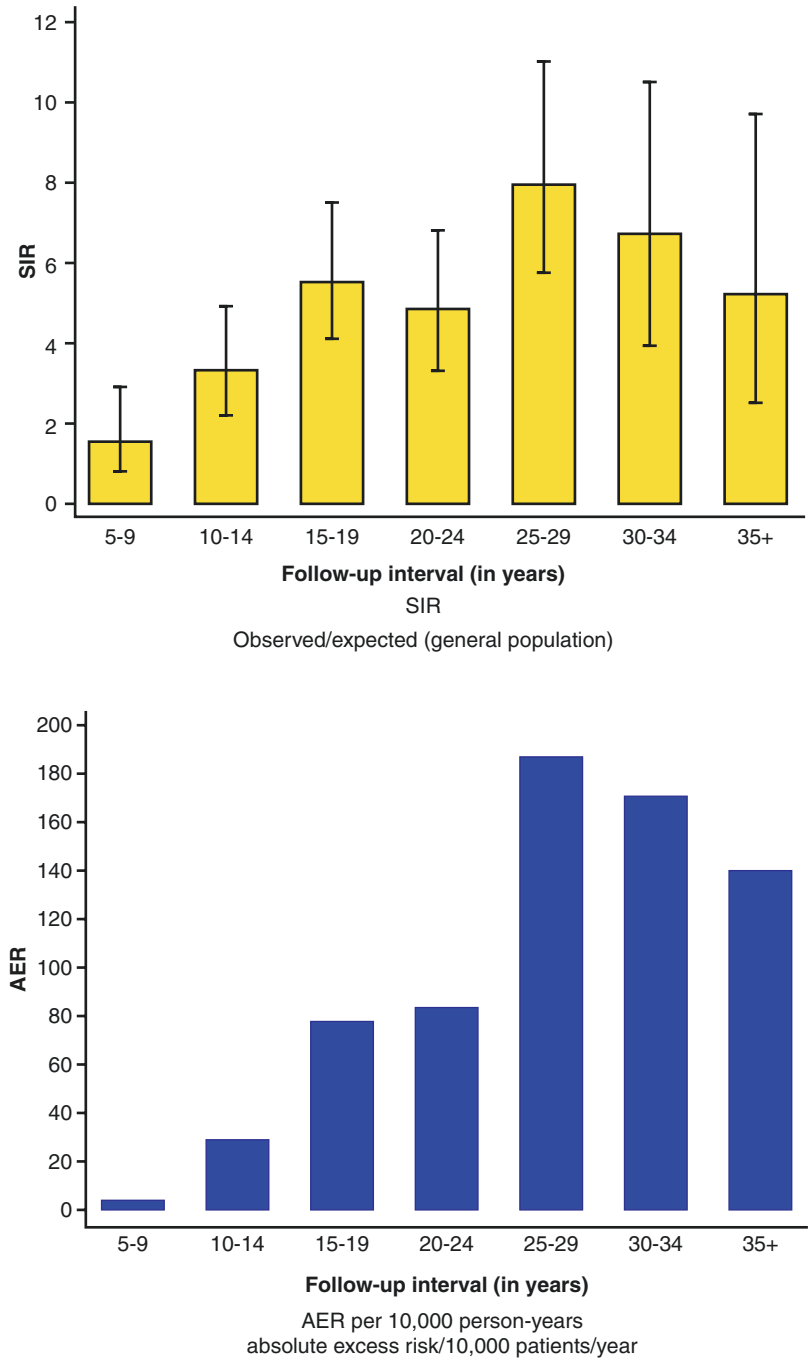


Fig. 26.7 Risk of breast cancer after Hodgkin lymphoma by follow-up time (1698 female Dutch Hodgkin Lymphoma patients; From: Schaapveld et al. [45])

(Table 26.4; see for details: Sect. 26.4.1). A recent large Dutch study examined the effect of radiation fields (volume) on the risk of breast cancer up to more than 30 years after treatment of HL [45]. Among 1698 female 5-year survivors, treated for HL between ages 15 and 50 years (median follow-up time of 19.1 years), 183 cases of breast cancer were identified (overall SIR, 4.7; AER, 54.3 per 10,000 per year). Importantly, a complete mantle field RT (involving the axillary, mediastinal, and neck nodes) was associated with a 2.7-fold (95% CI, 1.4–5.3) increased risk of

breast cancer compared to a similarly dosed (36–44 Gy) supradiaphragmatic field which excluded the axilla.

In six studies, patients who received both CT and RT had significantly decreased risk (about halved) compared to those treated with RT alone, and the RT-related risks were attenuated by treatment with alkylating agents [24, 41, 42, 45, 60, 189]. Risk of breast cancer decreased with increasing number of alkylating agent cycles ($P = 0.003$ for trend); the RR associated with nine or more cycles of alkylating CT compared with no alkylating CT was 0.2 (95% CI, 0.1–0.7) (Table 26.4) [42]. In the large Dutch cohort study, chemotherapy regimens with higher cumulative procarbazine doses seemed to be associated with a greater reduction of breast cancer risk, with 30% and 70% risk reductions for regimens with less than 8.4 g/m^2 procarbazine and more than 8.4 g/m^2 procarbazine, respectively [45]. The substantial risk reduction associated with CT appears to be due to the high frequency of premature menopause in CT-treated patients [24, 41, 72, 188] and the resulting reduction in the exposure to ovarian hormones. De Bruin et al. [24] reported that 30% of all women reached menopause before age 41; such an early menopause was associated with a 60% (95% CI, 20–80%) reduced risk of breast cancer (Table 26.5). A strong decrease in breast cancer risk (about 60%) has also been observed among women who received a castrating dose of 5 Gy or more to the ovaries, compared with those who received lower doses (Fig. 26.4) [24, 41, 42, 70, 72, 189]. These results indicate that ovarian hormones are a crucial factor to promote tumorigenesis once RT has produced an initiating event.

In the Dutch study a long versus short duration of intact ovarian function after radiation was a strong predictor of subsequent breast cancer risk. Women with less than 10 years of intact ovarian function after radiotherapy had a 70% (95% CI, 40–80%) decreased risk of breast cancer compared with women with 10–20 years of ovarian function after irradiation, while those with more than 20 years of intact ovarian function after radiotherapy had 5.3-fold (95% CI, 2.9–9.9) increased risk of breast cancer (Table 26.5). These risk reductions were observed both among women treated before age 21 and among those treated between ages 21 and 30. Among women treated between ages 31 and 40, cumulative exposure to endogenous estrogens was not associated with risk for breast cancer, possibly because these women were closer to natural menopause at time of treatment [24]. These findings were subsequently confirmed in a British case-control study, which reported a 3.6-fold risk increase for women having 25 or more premenopausal years after start of RT [188], and a recent Dutch case-control study which found a 3.8-fold risk increase for women who had an

Table 26.5 Effects of fertile lifespan after irradiation to the breast on breast cancer risk (invasive and DCIS) according to age at first treatment[a]

	All ages <41	Age <21	Age 21–30	Age 31–40
No. of patients	715	201	323	191
No. of events	98	36	40	22
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Model 3[b]				
Premature menopause[c]				
Menopause at age 41 or later	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Menopause before age 41	0.4 (0.2–0.8)	0.2 (0.0–0.8)	0.1 (0.0–0.5)	1.3 (0.4–3.6)
Model 4[b]				
Years intact ovarian function[c]				
<10 years	0.3 (0.2–0.6)	0.1 (0.0–0.6)	0.1 (0.0–0.3)	1.2 (0.4–3.5)
10–20 years	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
>20 years	5.3 (2.9–9.9)	11.9 (3.7–37.9)	6.0 (2.3–15.4)	3.2 (0.3–30.7)

BC breast cancer, *IBC* invasive breast cancer, *DCIS* ductal carcinoma in situ, *HR* hazard ratio, *Ref* referent, *RT* radiation therapy

[a]Adapted from de Bruin et al. [24]

[b]Adjusted for each other, radiation field size, age at first RT to the breast and time since first RT to the breast, smoking, obesity, nulliparity, oral contraceptive use; calendar time was used as the time scale

[c]Unknown age at menopause was modeled as a separate category

intact ovarian function for 25 years or more post-chest RT [72].

It is not yet known whether current less gonadotoxic CT, such as ABVD, is also associated with reduced risk of RT-associated breast cancer risk. Furthermore, it is important to know whether hormone replacement therapy (HRT) for CT-induced premature menopause affects RT-associated breast cancer risk. HRT is an established risk factor for breast cancer [191, 192] and might counteract the protective effect of CT. The recent Dutch case-control study found that use of HRT ≥2 years did not increase breast cancer risk (OR, 0.9; 95% CI, 0.3–2.3) in women with an early menopause (menopause <45 years) whereas breast cancer risk was nonsignificantly increased among women without early menopause (OR, 3.7; 95% CI, 0.97–14.0; *P* for interaction 0.06) [72]. A limitation of this study was that few women used HRT for long durations. Another recent study of breast cancer risk after chest RT in childhood did not find a clear association of HRT use and breast cancer risk [189].

Individual genetic susceptibility may also modify the risk of treatment-related BC. Recently, a Dutch case-control study showed, using a GWAS approach, that radiation-induced BC risk may indeed be modified by individual genomic variation. Individuals in the highest tertile of a polygenic risk score (RT-interaction-PRS), composed of nine SNPs that showed statistically significant interaction with RT on BC risk, had a 1.6-fold higher BC risk than those in the lowest tertile (see Sect. 26.4.3) [143].

A few recent studies investigated whether the clinicopathological characteristics of radiation-induced breast cancers differ from those of sporadic breast cancers [193–196]. Remarkably, one study found that breast cancers following RT for HL have a molecular profile distinct from idiopathic breast cancers from age-matched women. Another study reported more estrogen-negative breast cancers after RT for HL [195]. However, two other studies did not find much difference in breast cancer-specific survival between women with breast cancer after HL and other age-matched breast cancer patients [194, 196].

In summary, from 10 to 15 years after treatment chest RT at young ages is associated with a very high dose-dependent risk of breast cancer that persists for at least 40 years. This hazard needs to be borne in mind both when selecting treatment for girls and young women with HL and when following up patients treated in this way. Gonadotoxic chemotherapy such as the MOPP regimen reduced the increased risk of breast cancer from RT through the induction of premature menopause. Reductions of radiation dose and field size (replacement of mantle RT by involved field/involved node/site RT) in current treatment protocols are expected to result in lower breast cancer risk. Nonetheless, although in the recently published Dutch cohort study a large proportion of the female survivors treated in 1990–2000 had received less extensive supradiaphragmatic irradiation fields, there was little evidence that these women had a lower risk of breast cancer than those who were treated in earlier periods [45]. One possible explanation for this finding is that the concomitant change towards less gonadotoxic chemotherapy may have partly counterbalanced the effects of lower radiation exposure of the breasts.

26.5.4 Risk Factors for Lung Cancer

Next to breast cancer, lung cancer accounts in many studies for the largest absolute excess of solid malignancy after HL [45, 47, 52]. An excellent review of risk factors for lung cancer after HL has been published [197]. The risk of lung cancer after HL depends on time since treatment, age at treatment, treatments administered for HL, and smoking.

The SIR of lung cancer is hardly increased in the first 5 years after treatment, with larger SIRs (five or greater), thereafter until at least 25 years [32, 37, 39, 45, 47, 52, 198].

A meta-analysis of 21 observational studies reported that the relative risk of lung cancer varied little with age at HL treatment and was highest among those aged 15–24 years (RR = 8.6) and lowest among those aged >55 years at first treat-

ment (RR = 2.9) [190]. Dores et al. [47] reported that the SIR of lung cancer decreased from a 5.5-fold increase (compared with the general population) for patients diagnosed before age 21 to a 1.5-fold excess for patients diagnosed at age 61 or above. In the UK study [52], the SIRs for lung cancer decreased from 20-fold among those diagnosed before age 25 to a 2.2-fold excess for patients diagnosed at age 55 or above.

A large international collaborative case-control study examined lung cancer risk in relation to the radiation dose to the specific location in the lung in which cancer later developed [39]. This study included 222 lung cancer patients and 444 matched controls (patients with HL in whom lung cancer had not been diagnosed) [39, 73]. Case patients developed lung cancer after an average of 10.8 years. The risk increased with increasing radiation dose to the area of the lung in which cancer later developed (*P* for trend <0.001; see also Table 26.4). The risk estimates for the highest dose categories of 30.0–39.9 Gy and ≥40 Gy compared with no RT were 8.5 (95% CI, 3.3–24) and 6.3 (95% CI, 2.2–19), respectively, suggesting that the risk might level off at very high doses [73]. This study also addressed the modifying effects of the patient's smoking habits on RT-associated risks. The increased RRs from smoking appeared to multiply the elevated risks from radiation (Table 26.6). This implies that there are very large AERs for lung cancer among irradiated patients who smoke.

Chemotherapy for HL can also increase the risk of lung cancer [39, 44, 52, 53, 197, 199]. The British National Lymphoma Investigation cohort study of 5519 patients [44, 52] showed a significantly elevated risk of lung cancer following CT alone, with the SIR (3.3; 95% CI, 2.2–4.7) compared with the general population being of similar magnitude to that observed in patients treated with either RT (SIR = 2.9; 95% CI, 1.9–4.1) or mixed modality treatment (SIR = 4.3; 95% CI, 2.9–6.2).

Two large case-control studies have investigated the separate and joint roles of CT, radiation, and smoking in detail [39, 74]. In both reports, there was a clear trend of increasing lung cancer risk with greater number of cycles of alkylating CT (*P* trend <0.001 (Table 26.4) [39]) or MOPP-CT (*P* trend = 0.07 [74]). In the study by Travis and colleagues [39], data were also collected on cumulative dose of individual cytotoxic drugs. Among patients treated with MOPP, increasing total dose of mechlorethamine or procarbazine was strongly associated with increasing lung cancer risk when evaluated separately (*P* trend for dose for each <0.001) [39]. Risk of lung cancer after treatment with alkylating agents and radiation together was as expected if individual excess RRs were summed: RRs of 4.2 (95% CI, 2.1–8.8) were observed for patients given alkylating agents alone, 5.9 (95% CI, 2.7–13.5) for patients treated with RT alone (>5 Gy), and 8.0 (95% CI, 3.6–18.5) for those who received combined modality treatment, compared with the reference group of patients who received no alkylating agents and had less than 5 Gy of radiation [39]. As was observed for the joint effects of smoking and RT, the risks from smoking appeared

Table 26.6 Risk of lung cancer in patients with HL according to type of treatment and smoking category

Treatment for Hodgkin lymphoma		RR (95% CI) by smoking category (no. of case patients; control patients)[a]	
Radiation ≥5 Gy	Alkylating agents	Nonsmoker, light, other[b]	Moderate–heavy[c]
No	No	1.0[d]	6.0 (1.9–20.4)
Yes	No	7.2 (2.9–21.2)	20.2 (6.8–68)
No	Yes	4.3 (1.8–11.7)	16.8 (6.2–53)
Yes	Yes	7.2 (2.8–21.6)	49.1 (15.1–187)

Adapted from Travis et al. and Swerdlow et al. [39, 44]
RR relative risk, *95% CI* 95% confidence interval
[a]Represents estimated tobacco smoking habit 5 years before diagnosis date of lung cancer and corresponding date in control patients, with the use of information recorded up to 1 year before these dates
[b]This group includes nonsmokers, light current cigarette smokers (less than one pack per day), former cigarette smokers, smokers of cigar and pipes only, and patients for whom tobacco smoking habit was not stated
[c]Moderate (one to two packs per day) and heavy (two or more packs per day) current cigarette smokers
[d]Reference group

to at least multiply risks from alkylating CT (Table 26.6) [39].

Smoking remains a major cause of lung cancer in patients treated for HL, as is evident from the observation that only 7 out of 222 cases included in the study by Travis and colleagues [39] occurred in patients who had never smoked. Further, it was estimated that 9.6% of all lung cancers were due to treatment, 24% were due to smoking, but 63% were due to treatment and smoking in combination; the remainder (3%) represented tumors in which neither smoking nor treatment played a role.

In summary, both supradiaphragmatic RT and CT contribute to the elevated risk of lung cancer after HL. In addition, the above data suggest that patients with HL who smoke will have a considerably greater risk of lung cancer after chest RT and/or CT than those who do not smoke, and this is in accord with experience in other radiation-exposed groups [200]. As a consequence, smokers who have received chest RT should be particularly strongly advised to refrain from smoking. The evidence implicating specific chemotherapeutic agents as carcinogenic to the lung is less clear. It is not yet known whether modern CT regimens other than MOPP also increase the risk of lung cancer. The role of lung cancer screening in HL patients has not yet been assessed; international collaboration is needed to study the efficacy of screening with low-dose spiral computer tomography [36, 197]. Of note, a cost-effectiveness simulation study, which also used data from low-dose spiral computer tomography screening in 53 HL survivors showed that screening may be cost-effective for smoking HL survivors treated with mantle field irradiation but likely was not for irradiated nonsmokers although a small life expectancy benefit of computer tomography screening was also noted for nonsmokers [201].

26.6 Clinical Implications

Hodgkin lymphoma survivors who are at high risk of developing second cancers can be identified largely based on their prior treatment exposures, current age, and latency since treatment. Expert opinion-based recommendations have been published advocating the early onset of breast cancer screening starting 8 years following mediastinal RT, for women who are age 25–30 [202]. However, a large proportion of irradiated females do not perceive their risk of breast cancer to be much higher than that of the general population [203–206]. As a consequence, a large proportion of HL survivors do currently not undergo appropriate breast surveillance at young ages, when their risk is already high and comparable to that of carriers of BRCA1/2 mutations. A study among irradiated female childhood cancer survivors in the USA showed that 64% of those aged 25–39 years and 24% of those 40–50 years old had not had a mammography in the past 2 years, despite a guideline recommending annual screening [206]. Although early breast surveillance starting is recommended following mediastinal RT, the optimal screening modalities have yet to be determined. However, because mammography is less sensitive in young women with dense breast tissue, magnetic resonance imaging (MRI) should be considered at younger ages. Ng et al. reported the outcome of 148 women screened with breast MRI ≥8 years after mediastinal RT (given prior to age 35 years) and a median age at enrollment of 43 years [207]. The sensitivity of mammogram alone, MRI alone, or both modalities was 68%, 67%, and 94%. Specificity for each modality alone or in combination was not significantly different. One of 18 cancer cases detected had lymph node involvement. A similar study of MRI breast screening among survivors of pediatric HL in which the median age at first screening was 30 years reported that the sensitivity for mammogram alone, MRI alone, and both modalities was 70%, 80%, and 100%, respectively, with all detected cases being node negative. In both studies, mammography was more likely to miss invasive cancers than MRI [208]. These studies suggest that the addition of MRI to mammography will detect breast cancers at earlier stages than mammography alone. However, the use of MRI will also likely increase the proportion of false-positive test results. In a simulation study Hodgson et al. predicted that using alter-

nating mammography/MRI-based screening 79% of all participating female adolescent Hodgkin lymphoma survivors treated with mediastinal radiotherapy would experience at least one false-positive test over the course of screening [209]. However, this study also showed that early initiation of BC screening could reduce BC mortality among these women with one breast cancer death prevented for every 80 women invited to MRI screening (when treated at age 15 years and starting screening at age 25 years).

Some have recommended that patients who received para-aortic RT and/or procarbazine should undergo colorectal cancer screening starting 10–15 years following treatment [49]. Two recent colonoscopy screening study showed a high prevalence of advanced colorectal neoplasia in patients previously treated with abdominal and/or pelvic RT and/or procarbazine-containing CT. In the study by Daly et al., in 54 survivors (mostly Hodgkin lymphoma patients) who underwent colonoscopy screening at a median age of 45% years, 44.4% had polyps detected, deemed precancerous in 15 patients [210]. Rigter et al. also found a high prevalence of advanced colorectal neoplasia (advanced adenomas 14%, advanced serrated lesions 12%) in 101 Hodgkin lymphoma survivors who underwent colonoscopy (median age at colonoscopy of 51 years) [211]. The prevalence of advanced adenomas was nonsignficantly increased among Hodgkin lymphoma survivors compared to 1426 population controls (9%; $P = 0.08$), but Hodgkin lymphoma survivors significantly more often had advanced serrated lesions (12% vs. 4% in controls) and serrated polyposis syndrome (6% vs. 0% in controls).

Screening for secondary lung cancer is more controversial. As noted above, older HL survivors treated with alkylating agents or mantle RT are at significantly increased risk of developing lung cancer, particularly if they are smokers. One important consideration is that the absolute risk of lung cancer is low among nonsmoking patients treated before age 30 with contemporary chemotherapy (e.g., ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine), and it is unlikely that they would benefit from screening. Risk is highest among those treated with chest RT and alkylator-based chemotherapy at ages >40 years, particularly if they are smokers. The results of studies evaluating the efficacy of screening with spiral computer tomography in other high-risk patients may illuminate the potential benefit to HL survivors, but it currently remains investigational.

Physicians should make a special effort to dissuade HL patients from smoking. While most survivors will be aware that smoking increases their risk of lung cancer, they may not understand that their smoking-related risk may be significantly greater than that of others with whom they share the activity, and they are often not aware of the poor prognosis associated with lung cancer. Advice on smoking cessation during an office visit can improve quit rates, and pharmacotherapy improves the probability of success [212].

While retrospective studies describing the RT-related risk of SMNs have been useful in identifying groups of survivors for whom the early utilization of cancer screening may be worthwhile, and have been instrumental in motivating the development of clinical trials which are now much less reliant on the use of RT, it is important to recognize that they often have limited value in counseling contemporary patients about the risks of modern therapy. For example, most of the widely cited cohort studies of SMN risk among HL survivors include patients treated in the 1960s [43, 45–48, 52, 54]. At that time, RT was often the sole primary treatment for early-stage HL, and the RT fields typically encompassed the whole neck, bilateral axillae, the entire length of the mediastinum, the spleen, and para-aortic nodes. Patients were often prescribed 40–45 Gy and treated without customized lung shielding [213, 214]. Since that time, several important improvements have occurred in the delivery of RT that reduce the normal tissue exposure: prescribed doses are typically 20–30 Gy for adults and 21 Gy for children. With the development of involved-field RT (IFRT), the omission of uninvolved axillary nodes from these historic fields significantly reduced the average breast tissue dose compared to historic mantle RT fields, and follow-up studies of more limited field RT suggest that the associated reduction in

irradiated breast volume translates into a clinically significant reduction in SMN risk [24, 34, 45]. More recently, utilization of modern image guidance and the further reduction in target volumes limited to only the initially involved lymph nodes, referred to as involved node RT (INRT) or involved site RT (ISRT), further reduce the dose to normal tissues, with early results demonstrating excellent disease control [86, 87]. As our understanding of the relationship between radiation dose and SMN risk develops, it should be possible to create predictive models of the SMN risk associated with modern HL treatments based on epidemiologic observations and radiobiologic principles.

Obviously the best means of limiting radiation-related SMN is to avoid using RT when it does not contribute meaningfully to HL cure. Data are emerging that may facilitate the selection of a greater proportion of patients for treatment with chemotherapy alone based on clinical or biologic factors. As an increasing proportion of patients are treated with chemotherapy alone, an emerging issue will be the extent to which contemporary chemotherapy regimens contribute to the risk of solid tumors. Many patients in second cancer studies received MOPP chemotherapy, and the increased SMN risks associated with alkylator-based chemotherapy do not apply to patients receiving, for example, ABVD chemotherapy. Patients treated initially with chemotherapy alone, even in more recent years, have increased risks of solid cancers [27, 44, 52], though it is unknown what regimens or specific agents might account for this risk. A British National Lymphoma Investigation (BNLI) study found that the relative risk of second cancer was raised among 2366 HL survivors treated with chemotherapy alone (RR = 2.0), although the risk was not increased among the 257 patients treated with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [44]. As noted above, genetic susceptibility likely plays a role in the development of treatment-related SMNs, but it is unlikely that an abnormal allele in a single candidate gene will account for a significant proportion of SMNs. New cohorts should be assembled to create a resource of biologic samples that would facilitate study of the molecular biology of second cancers.

Finally, when interpreting results of second cancer studies, it must be kept in mind that the problem of treatment-induced malignancies has arisen by virtue of the successes of HL treatment. The SMN risk of treatment must be balanced against the potential benefit in terms of curing patients' HL. For example, 10-year follow-up of patients treated with "dose-escalated" BEACOPP demonstrated that this regimen increased the risk of secondary AML compared to COPP/ABVD (0.4% vs. 3.0%), but produced a significant improvement in overall survival (75% vs. 86%) [215]. These outcomes highlight both the challenges of improving the cure rate for high-risk patients without adding clinically significant toxicity and the importance of considering SMN risk in the context of the beneficial effects that the exposures under study may have on curing the primary HL.

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