Therapeutic Radiation for Lymphoma

Risk of Malignant Mesothelioma

M. Jane Teta, DrPH, MPH[1]
Edmund Lau, MS[2]
Bonnielin K. Sceurman, BS[3]
Meghan E. Wagner, MPH[1]

[1] Exponent, Inc., Health Sciences Practice, New York, New York.

[2] Exponent, Inc., Health Sciences Practice, Menlo Park, California.

[3] Exponent, Inc., Health Sciences Practice, Washington, DC.

M. Jane Teta has served as an expert witness in litigation regarding the potential health hazards of asbestos to mechanics historically involved in brake repair.

Supported by funding from

Address for reprints: Jane Teta, DrPH, MPH, Exponent, Inc., Health Sciences Practice, 234 Old Woodbury Road, Southbury, CT 06488; Fax: (203) 262-6443; E-mail: jteta@exponent.com

Received August 7, 2006; revision received October 24, 2006; accepted December 12, 2006.

BACKGROUND. Ionizing radiation has been used since the 1950s to treat a variety of cancers. Cancer patients who are treated with radiotherapy have shown increased risks for a variety of second malignancies, including mesothelioma, in several recent reports. The only existing study of Hodgkin lymphoma (HL) and subsequent mesothelioma had a short observation period.

METHODS. The authors used Surveillance, Epidemiology, and End Results data over a 30-year period to identify patients with HL and non-Hodgkin lymphoma (NHL) who also were diagnosed with mesothelioma. Standardized incidence ratios (SIR) and absolute excess risks were calculated by sex and treatment modality for both types of lymphoma.

RESULTS. Twenty-six patients were identified who had mesothelioma as second primaries based on 21,881 diagnoses of HL and 101,001 diagnoses of NHL. There was a statistically significant increase in mesothelioma (4 diagnoses; SIR, 6.59; 95% confidence interval [95% CI], 1.79–16.87) among men with HL who received radiation, but no women survivors were identified who had a diagnosis of mesothelioma. For NHL survivors, there was a nonsignificant excess of mesothelioma among men (SIR, 1.91; 95% CI, 0.77–3.93) and women (SIR, 3.75; 95% CI, 0.77–10.95) who had received radiation treatment. There were no increases among patients who were unirradiated.

CONCLUSIONS. Mesothelioma rates for patients who had received radiotherapy were increased for survivors of HL and NHL. No increases were observed among the unirradiated. These findings and the existing body of supporting studies confirmed that radiotherapy is a cause of mesothelioma. ***Cancer* 2007;109:1432–8.**

KEYWORDS: non-Hodgkin lymphoma, Hodgkin lymphoma, mesothelioma, radiotherapy, Surveillance, Epidemiology, and End Results.

Ionizing radiation is an undisputed human carcinogen and an established risk factor for several types of cancers, including leukemia (except chronic lymphocytic leukemia), thyroid cancer, and female breast cancer.[1] Radiotherapy for cancer presents a risk for second cancers. For example, several studies have reported elevated rates of leukemia in radiation-treated survivors of Hodgkin (HL) and non-Hodgkin lymphoma (NHL).[2–5] Second primaries develop in the field of radiation for cancers at the rate of 1% per annum.[6] The most common cause of death among long-term survivors of HL is second cancers.[7]

The treatment strategy for HL and NHL varies considerably, depending on the disease stage, histologic type, and prognosis.[8] In the past, radiotherapy for HL and NHL included extended-field radiation, that is, radiation to the areas of disease and surrounding lymph nodes. Radiation was preferred to chemotherapy, which was believed to be associated with more serious side effects. More recent approaches

DOI 10.1002/cncr.22526
Published online 21 February 2007 in Wiley InterScience (www.interscience.wiley.com).

include involved-field radiation (only to known areas of disease) combined with chemotherapy.[9,10] Patients with HL typically present with lymphadenopathy in the thorax region, whereas NHL includes many different subtypes that occur in various regions in the body.[8,11]

Interest has developed more recently in therapeutic radiation as a risk factor for solid tumors that are known to have longer latencies.[1] The rates of breast cancer and lung cancer have been reported as elevated in numerous investigations of patients with HL after radiotherapy.[2,12–18] Studies of radiation effects for both HL and NHL reported that the greatest increase in breast cancer risk occurred among women who were irradiated at a young age.[18,19]

Malignant pleural mesothelioma is a rare, fatal solid tumor that typically has a long latency after asbestos exposure. It is estimated that ≥85% of mesothelioma diagnoses are attributed to past asbestos exposure, which, until recently, was the only established cause of this disease in the United States.[20] A variety of other causes of mesothelioma have been suggested based on case reports and animal studies, including therapeutic radiation.[21–31] There have been many case reports of mesothelioma after radiotherapy for various diseases, and the most numerous have been related to HL.[32–39]

To our knowledge, the only epidemiology study to date that examined whether radiation increased mesothelioma rates in HL survivors followed 13,743 patients from 1973 to 1993 and reported no cases of mesothelioma.[40] The authors of that report recognized the limitation of their study, in that the maximum follow-up was only 20 years and was based on the available data at that time from the National Cancer Institute (NCI) Surveillance, Epidemiology, and End Results (SEER) database. However, 2 more recent studies that used updated SEER data through 2001 have reported statistically significant increases in malignant mesothelioma associated with radiotherapy for testicular cancer and NHL.[7,19]

Given the existing reports of increased risks of mesothelioma associated with radiotherapy for testicular cancer and NHL and using more recent SEER data, in this report, we provide a 10-year update to the study by Neugut et al.[40] for HL survivors who were treated with radiation. We also added 2 more years of SEER data to the database of survivors of NHL recently analyzed by Tward et al.[19]

MATERIALS AND METHODS

Data Source

Incidents of mesothelioma after a diagnosis of HL and NHL were identified from data collected by the SEER Program, which began reporting diagnosed malignancies in 1973. The most recent SEER database update includes diagnoses through 2003 (public-use data released as of November 2005). Data for the years 1973 through 2003 are available from 9 SEER registries in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and in the regional registries in Atlanta, Detroit, San Francisco-Oakland, and Seattle-Puget Sound. Cancer data from Alaskan Natives and from 3 regional registries (Los Angeles County, San Jose-Monterey, and rural Georgia) are available for the years from 1992 to 2003. For the current study, public-use cancer incidence data from 13 SEER registries[41] were used along with the corresponding population data.

Data Analysis

Incidents of HL and NHL were identified by using the SEER cancer site codes (HL, 33011 and 33012; NHL, 33041 and 33042). Similarly, patients with mesothelioma were identified by using the site code 36010. Each cancer patient is assigned a unique identification number in the SEER database. By using this number, any subsequent diagnosis of mesothelioma among patients with HL or NHL was identified, including any malignancies after a second malignancy. Similar to the study by Tward et al.[19] patients with <2 months of follow-up were excluded, including those who had 2 malignancies diagnosed within a 2-month period. The month and year of diagnosis were extracted along with age at diagnosis, vital status, radiation treatment, surgical treatment, and duration of follow-up. Data on chemotherapy treatment and on the radiation dose or treatment field are not available from the SEER database.

Person-years of follow-up were calculated from the time of the initial lymphoma diagnosis until the date of death, the date a patient was last known to be alive, or the follow-up cut-off date (December 31, 2003), whichever came first. Person-years were stratified by the patient's sex and according to whether or not the patient received beam-radiation treatment for their lymphoma. Mesothelioma incidence rates were calculated by sex, race (classified into 3 categories: white/unknown, black, and others), age (5-year groups), and calendar year (5-year groups). The expected number of mesothelioma cases was estimated by indirect standardization applying the number of person-years in each category to the corresponding mesothelioma incidence rate. Standardized incidence ratios (SIRs), that is, the number of observed mesothelioma cases divided by the expected number of such cases, and 95% confidence limits are presented by sex and treatment modality. The number of observed cases was assumed to be a

random variable that followed a Poisson distribution, and 95% confidence limits were calculated according to the procedure described by Breslow and Day.[42] Absolute excess risk (AER) was calculated as the number of observed mesothelioma cases minus the number of expected mesothelioma cases divided by the person-years at risk (PYR) in the strata under consideration. AER is reported as the number of excess cases per 10,000 PYR.

RESULTS

We identified 21,881 patients with HL and 101,001 patients with NHL: Among them, there were 26 patients who had mesothelioma second primaries (Table 1). Approximately 2% of those patients had received unknown or other forms of radiation (eg, radioisotope) and were not included in the current analysis. No patient with mesothelioma was excluded because of unknown radiation information. Patients were divided almost evenly between men and women. Approximately 50% of HL survivors received radiation compared with approximately 25% of NHL survivors. Because of this difference and the younger age at diagnosis of HL survivors, although there were many more NHL survivors, the numbers of PYR in the radiation treatment groups were similar for the 2 types of lymphoma. The average length of follow-up for men and women who received radiation was similar for HL (≈11 years) and NHL (≈5 years).

Among survivors of HL and NHL who received radiation treatment, the number of observed and expected mesothelioma cases and the corresponding SIR and 95% confidence intervals (95% CIs) are summarized in Table 2. There was a statistically significant increase in mesothelioma (4 cases; SIR, 6.59; 95% CI, 1.79–16.87) among men who were survivors of HL but not among women survivors, none of whom had a mesothelioma diagnosis. For NHL, there was a nonsignificant excess of mesothelioma among men (SIR, 1.91; 95% CI, 0.77–3.93) and women (SIR, 3.75; 95% CI, 0.77–10.95). For men and women who were NHL survivors combined, the larger dataset resulted in a statistically significant overall SIR (2.24; 95% CI, 1.07–4.12). Table 2 also summarizes the AER of mesothelioma among survivors of HL and NHL. Among the subgroups that had an elevated risk of second primary mesothelioma, the AER was <1 excess case per 10,000 PYR.

Details related to the 26 patients with mesothelioma are presented in Table 3. All but 2 patients have died since their diagnosis of mesothelioma. For patients who received treatment with radiation, the average time from the diagnosis of lymphoma to the diagnosis of mesothelioma was 16 years for HL and 7 years for NHL. The younger age at diagnosis for HL survivors who developed mesothelioma also was apparent (average, 32 years vs 67 years for NHL survivors). For lymphoma patients who did not develop subsequent mesothelioma, the average age when lymphoma was diagnosed was 38 years for HL and

TABLE 1
Demographic Characteristics of the Surveillance, Epidemiology, and End Results Lymphoma Cohort

	Diagnosis and no. of patients					
	HL		NHL		All Lymphomas	
Characteristic	NL	Mesothelioma	NHL	Mesothelioma	Lymphoma	Mesothelioma
Total	21,881	5	101,001	21	122,882	26
Men						
No radiation	6566	1	40,548	9	47,114	10
Radiation	5610	4	14,220	7	19,830	11
Women						
No radiation	4557	0	34,187	2	38,744	2
Radiation	5148	0	12,046	3	17,194	3
Men and women						
No radiation	11,123	1	74,735	11	85,858	12
Radiation	10,758	4	26,266	10	37,024	14
Average age at diagnosis, y						
Men	38	32.2	57.8	67.7	54.2	59.2
Women	37.2		63.5	64.2	58.9	64.2
Vital status						
Alive	14,390	0	40,567	2	54,957	2
Dead	7491	5	60,434	19	67,925	24

HL indicates Hodgkin lymphoma; NHL, non-Hodgkin lymphoma.

TABLE 2
Standardized Incidence Ratios and Absolute Excess Risks for Mesothelioma by Sex and Radiation Therapy

Radiation	Mesothelioma patients	Exp	AER	SIR	SIR 95% CI	Cases	Person years (1000s)
Hodgkin lymphoma							
Men							
No radiation	1	0.79	0.04	1.27	0.03–7.06	6566	47.8
Radiation	4	0.61	0.56	6.59*	1.79–16.87	5610	60.2
Women							
No radiation	0	0.13	− 0.04	0	0–27.88	4557	33.4
Radiation	0	0.14	− 0.03	0	0–25.65	5148	57.1
Non-Hodgkin lymphoma							
Men							
No radiation	9	10.26	− 0.07	0.88	0.40–1.67	40,548	185.5
Radiation	7	3.67	0.44	1.91	0.76–3.93	14,220	75.4
Women							
No radiation	2	2.15	− 0.01	0.93	0.11–3.36	34,187	172.8
Radiation	3	0.8	0.32	3.75	0.77–10.94	12,046	69.3
Men and women							
No radiation	11	12.41	− 0.04	0.89	0.44–1.59	74,735	358.3
Radiation	10	4.47	0.38	2.24*	1.07–4.12	26,266	144.8

Exp indicates expected number of mesothelioma cases; AER, absolute excess risk; SIR, standardized incidence ratio; 95% CI, 95% confidence interval. *$P < .05$.

60 years for NHL. Because the number of mesothelioma cases is relatively small, these average ages for patients who did not develop mesothelioma are not unlike the ages at diagnosis in the general population of patients with HL and NHL.

DISCUSSION

Radiotherapy was first used widely during the 1950s and has led to major improvements in survival for patients with lymphoma.[43] The HL 5-year survival rate in the United States has improved from 73% (1975–1977) to 86% (1996–2002):[44] For NHL, the 5-year survival rate in the United States was 48% during the former period and increased to 63% during the latter period.[44] Reductions in radiotherapy field sizes and treatment doses for HL and NHL have been made to address the known increased risks for second cancers and cardiac complications caused by radiotherapy.[45–47]

It is only very recently, however, that epidemiology studies have shown associations between mesothelioma and radiation treatment for NHL and testicular cancer.[7,19] Travis et al.[7] used SEER data through 2001, enhanced by data from other population-based registries in Canada and Europe, to identify 40,576 survivors of testicular cancer who were followed for second cancers. A statistically significant increased risk of pleural mesothelioma was reported among men who received supradiaphragmatic radiation (relative risk [RR], 4.0: 95%CI, 2.0–8.1). Tward et al.[19] used the SEER Program to identify 77,876 patients with NHL who were diagnosed from 1973 to 2001. Second primary malignancies were identified among these patients from the same database stratified by radiation treatment. There was a statistically significant excess of mesothelioma for patients who received radiotherapy (SIR, 2.26; 95%CI, 1.03–4.28), but no increase was observed among the unirradiated patients (SIR, 0.86; 95%CI, 0.39–1.63). Our results from 2 more years of data and 1 additional patient with mesothelioma are very similar.

The findings of the current study indicate a 6-fold excess of mesothelioma among men who were HL survivors who received radiation but only a 2-fold excess among men who were NHL survivors. There are several possible explanations for the difference in the magnitude of the SIRs: 1) HL survivors are diagnosed at younger ages, and a greater risk of second primaries caused by radiation have been reported among younger patients[7,14,16,18,19]; 2) imprecision in SIRs because of small numbers; and 3) the chest is a more common site of radiation among patients with HL. We were unable to assess the last explanation, because the SEER database does not contain information on the site of radiation. Thus, although we are unable to conclude that radiation to the thoracic region is associated specifically with an increased risk of second primary mesothelioma, it is plausible, because radiation-induced cancers typically arise within the field of radiation.

Where the SIR of second primary mesothelioma was elevated, the AER was small, ie, <1 excess case

TABLE 3
Characteristics of Patients With Mesothelioma

	Hodgkin lymphoma diagnosis		Mesothelioma diagnosis*		
Radiation	Age, y	Year	Age, y	Year	Surgery
Men					
No radiation	51	1989	53	1991	No
Radiation†	18	1973	47	2002	Yes
Radiation	56	1995	63	2002	No
Radiation	12	1977	28	1994	No
Radiation‡	24	1992	34	2002	No
Radiation	**Non-Hodgkin Lymphoma Diagnosis**		**Mesothelioma Diagnosis***		**Surgery**
	Age, y	**Year**	**Age, y**	**Year**	
Men					
No radiation	64	1981	68	1985	No
No radiation	78	1996	82	2000	Yes
No radiation	59	1988	66	1994	Yes
No radiation	69	1988	73	1993	No
No radiation	63	1981	64	1982	No
No radiation	75	1982	84	1991	No
No radiation	76	1997	77	1998	No
No radiation‡	70	1995	71	1995	No
No radiation	78	1998	84	2003	Yes
Radiation	69	1988	72	1991	No
Radiation	74	1996	79	2001	No
Radiation	67	1996	71	2000	Yes
Radiation	74	1995	79	2001	Yes
Radiation	60	1995	65	2001	No
Radiation	56	1976	70	1990	No
Radiation	51	1999	51	1999	Yes
Women					
No radiation	62	1987	71	1996	No
No radiation	79	1997	82	2000	No
Radiation	40	1977	58	1994	No
Radiation	66	1979	69	1982	No
Radiation	74	1984	86	1997	No

* All but 3 patients with mesothelioma had disease sites coded as pleura mesothelioma.
† One of 3 patients with "nonpleura" mesothelioma had an unknown disease site.
‡ Two of 3 patients with "nonpleura" disease had peritoneal mesothelioma.

per 10,000 PYR. This finding was expected, because mesothelioma is a rare disease, and it is estimated that ≥85% of mesothelioma diagnoses are attributed to past asbestos exposure.[20] Therefore, therapeutic radiation would not be expected to account for a large proportion of mesothelioma diagnoses. Given the strong elevations in RR, however, the attributable risk percent in the exposed patient ([RR − 1]/RR) with HL or NHL who is diagnosed with mesothelioma after radiotherapy would be large (85% for men with HL and 55% for NHL).

An additional complicating factor is possible misclassification among the unirradiated patients, some of whom may have received radiotherapy later, thereby creating a possible negative bias. This could occur because SEER treatment data are limited to a short period postdiagnosis. Furthermore, because of the lack of cross-registry linkage, patients who no longer reside in the same registry when a second primary is diagnosed cannot be linked with their initial diagnosis. Thus, the number of patients with postlymphoma mesothelioma who we identified by using the SEER data may be fewer than the true number of such patients who could be identified if nationwide tracking were feasible. In addition, the 4 registries that joined the SEER Program in 1992 had only 11 years of follow-up (through 2003). Thus, these shortcomings in the available SEER database suggest that increased risks may be underestimated.

No increase was observed among women who were HL survivors. A possible explanation is the small number of expected mesothelioma cases among women who survive HL (ie, 0.14 cases) and inadequate length of follow-up. The average latency for mesothelioma among patients who receive radiation is 16 years, whereas the average length of observation was only 11 years among women survivors of HL who received radiation treatment.

Because the administration of chemotherapy has moved away from hospitals and into physicians' offices, data on chemotherapeutic treatment are not complete for states that participate in the SEER Program. Therefore, SEER no longer includes information on this treatment modality. Although some investigators have reported an increased risk of solid tumors after chemotherapy treatment for lymphoma, it is believed that radiotherapy is the main carcinogenic agent in the development of second solid cancers.[48] More complete information was available to Travis et al.[7] who reported an increased risk of pleural cancer for testicular cancer survivors who had been treated with radiation alone (RR, 4.0; 95%CI, 2.0–8.1). The vast majority of patients who did not receive radiation treatment most likely received chemotherapy alone or in combination with surgery, because other forms of therapy were less common. No increased risk of second primary mesothelioma was reported among unirradiated lymphoma survivors. The data from that study indicated that chemotherapy treatment is not an independent risk factor for mesothelioma.

Mesothelioma caused by asbestos exposure is characterized by a very long latency period (average, 30–35 years from first exposure).[49] The relatively

short latency periods associated with high-dose radiotherapy, particularly for NHL survivors, suggest a different mechanism for the development of mesothelioma. Other possible explanations include higher radiation doses for aggressive forms of NHL; more frequent medical surveillance for the survivors; and, in some patients, a result of a combined-modality treatment with radiation and chemotherapy. Tward et al.[19] described the absence of a latency effect for the association of radiation treatment and second malignancies for NHL survivors.

Confounding by earlier asbestos exposure also must be considered. Pappo et al.[36] reported on 3 patients who developed mesothelioma after radiation treatment for childhood malignancies, including HL, diagnosed at ages 3 years, 7 years, and 11 years. Mesothelioma was diagnosed at ages 16 years, 18 years, and 20 years, and none of those patients had a history of asbestos exposure.[36] Significant increases in second tumors in the first 9 years after radiotherapy treatment alone for HL have been reported.[16]

Work history data are not available from SEER and have not been collected as part of the existing published radiation studies. Asbestos can be ruled out with confidence, however, as a confounder of the association between radiation and mesothelioma based on a number of considerations: 1) the association has been observed in studies of 3 different types of cancer, 2) the association is limited to those who were irradiated and was not observed among those who were unirradiated, 3) 2 diseases (HL and testicular cancer), which occur most frequently at young ages, would have had little postdiagnosis (1973–2003) opportunity for asbestos exposure, certainly not enough to result in a RR greater than that associated with radiation. Although asbestos exposure may explain some patients who ultimately develop mesothelioma and have received radiation treatment, the existing studies and data confirm an independent effect of therapeutic radiation in the development of mesothelioma.

The current study was not of sufficient size to conduct more detailed analyses by age and mesothelioma diagnoses, histology within these cancers, or other subgroup analyses. In addition, radiation doses and treatment fields were unavailable, which precluded the ability to conduct dose-response analyses and an evaluation of the specific treatment field(s) that may result in an increased risk of mesothelioma. However, the findings of these epidemiologic studies confirmed the hypotheses generated by the large number of case reports that therapeutic radiation can cause mesothelioma.

REFERENCES

1. Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention*. 2nd ed. New York: Oxford University Press; 1996.
2. Tucker MA, Coleman CN, Cox RS, Varghese A, Rosenberg SA. Risk of second cancers after treatment for Hodgkin's disease. *N Engl J Med*. 1988;318:76–81.
3. Kaldor JM, Day NE, Clarke EA, et al. Leukemia following Hodgkin's disease. *N Engl J Med*. 1990;322:7–13.
4. Travis LB, Curtis RE, Boice JD Jr, Hankey BF, Fraumeni JF Jr. Second cancers following non-Hodgkin's lymphoma. *Cancer*. 1991;67:2002–2009.
5. Travis LB, Curtis RE, Stovall M, et al. Risk of leukemia following treatment for non-Hodgkin's lymphoma. *J Natl Cancer Inst*. 1994;86:1450–1457.
6. American Cancer Society (ACS). Detailed Guide: Hodgkin's Disease: Radiation Therapy (last updated April 20, 2006). Atlanta, Ga: American Cancer Society; 2006. Available from: http://www.cancer.org/docroot/CRI/content/CRI_2_4_4x_Radiation_Therapy_84.asp?sitearea Accessed on July 28, 2006.
7. Travis LB, Fossa SD, Schonfeld SJ, et al. Second cancers among 40,576 testicular cancer patients: focus on long-term survivors. *J Natl Cancer Inst*. 2005;97:1354–1365.
8. Lee CK. Evolving role of radiation therapy for hematologic malignancies. *Hematol Oncol Clin North Am*. 2006;20:471–503.
9. Klimm B, Engert A, Diehl V. First-line treatment of Hodgkin's lymphoma. *Curr Hematol Rep*. 2005;4:15–22.
10. Briggs JH, Miller TP. Combined chemotherapy plus radiotherapy for treatment of early-stage intermediate- and high-grade non-Hodgkin's lymphoma. *Curr Oncol Rep*. 2000;2:176–181.
11. Ansell SM, Armitage JO. Management of Hodgkin lymphoma. *Mayo Clin Proc*. 2006;81:419–26.
12. van Leeuwen FE, Somers R, Taal BG, et al. Increased risk of lung cancer, non-Hodgkin's lymphoma, and leukemia following Hodgkin's disease. *J Clin Oncol*. 1989;7:1046–1058.
13. van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. *J Natl Cancer Inst*. 1995;87:1530–1537.
14. Swerdlow AJ, Douglas AJ, Hudson GV, Hudson BV, Bennett MH, MacLennan KA. Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. *BMJ*. 1992;304:1137–1143.
15. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. *J Natl Cancer Inst*. 1993; 85:25–31.
16. Dores GM, Metayer C, Curtis RE, et al. Second malignant neoplasms among long-term survivors of Hodgkin's disease: a population-based evaluation over 25 years. *J Clin Oncol*. 2002;20:3484–3494.
17. Travis LB, Curtis RE, Bennett WP, Hankey BF, Travis WD, Boice JD. Lung cancer after Hodgkin's disease. *J Natl Cancer Inst*. 1995;87:1324–1327.
18. Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. *JAMA*. 2006;290:465–475.
19. Tward JD, Wendland MM, Shrieve DC, Szabo A, Gaffney DK. The risk of secondary malignancies over 30 years after the treatment of non-Hodgkin lymphoma. *Cancer*. 2006; 107:108–115.

20. Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Asbestos. Atlanta, Ga: ATSDR; 2001.
21. Babcock TL, Powell DH, Bothwell RS. Radiation-induced peritoneal mesothelioma. *J Surg Oncol.* 1976;8:369–372.
22. Stock RJ, Fu YS, Carter JR. Malignant peritoneal mesothelioma following radiotherapy for seminoma of the testis. *Cancer.* 1979;44:914–919.
23. Peterson JT, Greenberg SD, Buffler PA. Non-asbestos-related malignant mesothelioma. *Cancer.* 1984;54:951–960.
24. Anderson KA, Hurley WC, Hurley BT, Ohrt DW. Malignant pleural mesothelioma following radiotherapy in a 16-year-old boy. *Cancer.* 1985;56:273–276.
25. Austin MB, Fechner RE, Roggli VL. Pleural malignant mesothelioma following Wilms' tumor. *Am J Clin Pathol.* 1986;86:227–230.
26. Pelnar PV. Further evidence of nonasbestos-related mesothelioma. *Scand J Work Environ Health.* 1988;14:141–144.
27. Kawashima A, Libshitz HI, Lukeman JM. Radiation-induced malignant pleural mesothelioma. *Can Assoc Radiol J.* 1990;41:384–386.
28. Brenner J, Sordillo P, Magill GB, Golbey RB. Malignant mesothelioma of the pleura: review of 123 patients. *Cancer.* 1982;49:2431–2435.
29. Tassile D, Roth AD, Kurt AM, Rohner A, Morel P. Colon cancers and peritoneal mesothelioma occurring 29 years after abdominal radiation for testicular seminoma. A case report and review of the literature. *Oncology.* 1998;55:289–292.
30. Sato F, Yamazaki H, Ataka K, et al. Malignant peritoneal mesothelioma associated with deep vein thrombosis following radiotherapy for seminoma of the testis. *Intern Med.* 2000;39:920–924.
31. Huncharek M. Non-asbestos related diffuse malignant mesothelioma. *Tumori.* 2002;88:1–9.
32. Lerman Y, Schachter P, Herceg E, Lieberman Y, Yellin A. Radiation associated malignant pleural mesothelioma, *Thorax.* 1991;46:403–404.
33. Hofmann J, Mintzer D, Warhol MJ. Malignant mesothelioma following radiation therapy. *Am J Med.* 1994;97:379–382.
34. Cavazza A, Travis LB, Travis WD, et al. Post-irradiation malignant mesothelioma. *Cancer.* 1996;77:1379–1385.
35. Weissmann LB, Corson JM, Neugut AI, Antman KH. Malignant mesothelioma following treatment for Hodgkin's disease. *J Clin Oncol.* 1996;14:2098–2100.
36. Pappo AS, Santana VM, Furman WL, et al. Post-irradiation malignant mesothelioma. *Cancer.* 1997;79:192–193.
37. Kramer G, Gans S, Rijnders A, Leer JW. Long term survival of a patient with malignant pleural mesothelioma as a late complication of radiotherapy for Hodgkin's disease treated with yttrium-silicate. *Lung Cancer.* 2000;27:205–208.
38. Velissaris TJ, Tang ATM, Millward-Sadler GH, Morgan JM, Tsang GM. Pericardial mesothelioma following mantle field radiotherapy. *J Cardiovasc Surg.* 2001;42:425–427.
39. Henley JD, Loehrer PJ, Ulbright TM. Deciduoid mesothelioma of the pleura after radiation therapy for Hodgkin's disease presenting as a mediastinal mass. *Am J Surg Pathol.* 2001;25:547–548.
40. Neugut AI, Ahsan H, Antman KH. Incidence of malignant pleural mesothelioma after thoracic radiotherapy. *Cancer.* 1997;80:948–950.
41. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov). SEER*Stat Database: Incidence—SEER 13 Regs Public-Use, Nov 2004 Sub for Expanded Races (1992–2002). Released April 2005, based on the November 2004 submission. Bethesda, Md: National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; 2005.
42. Breslow NE, Day NE.Statistical Methods in Cancer Research. Vol II: The Design and Analysis of Cohort Studies. IARC Pub No 82. Lyon, France: International Agency for Research on Cancer; 1987.
43. Aisenberg AC. Problems in Hodgkin's disease management. *Blood.* 1999;93:761–779.
44. The Leukemia and Lymphoma Society. Facts 2006–2007. White Plains, NY: The Leukemia and Lymphoma Society; 2006. Available at: http://www.leukemia-lymphoma.org/attachments/National/br_1152629053.pdf Accessed July 31, 2006.
45. Engert A, Schiller P, Josting A, et al. Involved-field radiotherapy is equally effective and less toxic compared with extended-field radiotherapy after four cycles of chemotherapy in patients with early-stage unfavorable Hodgkin's lymphoma: results of the HD8 trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol.* 2003;21:3601–3608.
46. Gustavsson A, Osterman B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in non-Hodgkin's lymphoma. *Acta Oncol.* 2003;42:605–619.
47. Gustavsson A, Osterman B, Cavallin-Stahl E. A systematic overview of radiation therapy effects in Hodgkin's lymphoma. *Acta Oncol.* 2003;42:589–604.
48. Travis LB. Therapy-associated solid tumors. *Acta Oncol.* 2002;41:323–333.
49. Lanphear BP, Buncher CR. Latent period for malignant mesothelioma of occupational origin. *J Occup Med.* 1992;34:718–721.