Lung Cancer After Hodgkin's Disease

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Patients with Hodgkin's disease develop lung cancer at a rate two to eight times that of the general population *(1-5)*. A portion of this increase might be related to thoracic radiotherapy *(6,7)* and, possibly, to chemotherapy *(6)*. To provide additional quantitative data on the risk of lung cancer after Hodgkin's disease, we conducted a survey of more than 13000 patients reported to selected population-based cancer registries within the United States.

We included all patients diagnosed with Hodgkin's disease as a first primary cancer who survived 2 or more months and were reported to the Surveillance, Epidemiology, and End Results[1] (SEER) Program (1973-1991) or to the earlier years of the Connecticut Tumor Registry (1935-1972). Information rou-

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tinely collected by participating registries includes patient demographic data, tumor histology, and initial course of cancer-directed therapy, according to one of several broad designations. Patients were grouped into categories of radiotherapy only, chemotherapy only, radiotherapy and chemotherapy, or other/no treatment. Information on tobacco use was not available. SEER files were examined for all invasive second primary lung cancers *(8,9)*. Standard methods,[2] described previously *(10)*, were utilized to quantify the risk of subsequent lung cancer.

We evaluated 13 886 patients with Hodgkin's disease, including more than 3000 10-year survivors (Table 1). Secondary lung malignancies developed in 121 patients (119 cases histologically confirmed), representing a significant excess (observed-to-expected [O/E] ratio 2.69; 95% confidence interval [CI] = 2.23-3.21). Risk was elevated in the intervals 1-4 years, 5-9 years, and >=10 years after Hodgkin's disease (*P* for trend = .014). Significant excesses of lung cancer were evident among patients whose primary therapy included radiation only, chemotherapy only, or both. Long-term survivors treated initially with radiotherapy alone had a fivefold risk of secondary lung cancer (*P* for trend= .0004).

Large significant risks of small-cell lung carcinoma (SCLC) (O/E 7.12; 95% CI = 4.29-1 1.12) occurred after radiotherapy alone but not after other types of treatment (Table 2). In contrast, notable excesses of squamous cell carcinoma and adenocarcinoma occurred within most therapy groups. List et al. *(11)* previously observed that more than 50% of lung cancers after Hodgkin's disease may be small cell in type, although risk could not be quantified. Significant associations between radiation and SCLC have been previously found for high-dose atomic bomb survivors and uranium miners *(12)*. SCLC accounted for approximately 20% of the cases within our series, similar to its representation (16.8%) among primary lung cancers within the SEER database *(13)*.

Patients who develop lung cancer after Hodgkin's disease typically smoke *(2,4,7,22)*. Although this lymphoma is generally not considered tobacco-related *(14-16)*, a recent analysis *(17)* of mortality data among cigarette smokers suggested an excess risk of Hodgkin's disease. Tobacco and radiation may interact in the development of secondary pulmonary neoplasia *(7,18,19)*, but the pathogenic mechanisms are not clear. In one small investigation *(20)*, the spectrum of mutations in TP53 in lung cancers after radiotherapy for Hodgkin's disease did not resemble smoking-related patterns, although all patients had a history of heavy tobacco use.

The significant risk of lung cancer after initial chemotherapy in our series is noteworthy, given that several of the drugs used to treat Hodgkin's disease may cause lung tumors in laboratory animals *(21)*. Although a role of subsequent radiotherapy to account for our findings cannot be excluded, other investigators have reported associations between chemotherapy for Hodgkin's disease and either secondary lung cancer *(6)* or all subsequent solid tumors taken together *(3)*.

Because of the lack of detailed information on initial and subsequent therapy and the absence of data on radiation dose to lung and on tobacco use, a causal link between treatment for Hodgkin's disease and lung cancer cannot be conclusively made on the basis of our results. Furthermore, the significant excesses observed within 5 years after therapy are not consistent with current understanding of latency periods for radiation-induced lung cancer *(22)* and suggest the action of etiologic co-factors that remain to be identified. Significantly increased risks of lung cancer also appear within 5 years after treatment of non-Hodg-

Table 1. Lung cancer following Hodgkin's disease by initial therapy and time since diagnosis of first malignancy*

	Time since diagnosis of Hodgkin's disease									
	2 mo- <1y		1-4 y		5-9 y		≥10 y		All intervals	
No. of persons entering interval	13 886		11 571		6460		3186		13 886	
No. of person-years within interval	10 442		34 391		23 299		14 448		82 580	
	No. of patients with lung cancer following Hodgkin's disease†									
Treatment group‡ (No. of patients with Hodgkin's disease)	O	O/E	O	O/E	O	O/E	O	O/E	O	O/E
All patients (n = 13 886)	7	1.16	44	2.48§	39	3.25§	31	3.35§,‖	121¶	2.69§
Radiation only (n = 5801)	3	1.53	9	1.35	23	4.49§	21	4.80§,#	56	3.09§
Chemotherapy only (n = 4390)	2	0.74	27	3.80§	7	1.70	7	3.27§,**	43	2.68§
Radiation and chemotherapy (n = 2244)	1	1.69	4	2.60	6	5.35§	1	1.41††	12	3.03§
Other‡‡/no therapy (n = 1451)	1	1.29	4	1.65	3	1.81	2	0.98	10	1.45

*Patients were diagnosed with Hodgkin's disease as a first primary cancer from 1935-1972 (Connecticut Tumor Registry, n = 2159) or 1973-1991 (Surveillance, Epidemiology, and End Results [SEER] Program, n = 11 727) and survived 2 or more months. Follow-up ended December 31, 1988, and December 31, 1991, respectively, for the two cohorts.

†O = observed number of lung cancers. O/E = observed-to-expected ratio of lung cancer.

‡Treatment group represents only the first course of therapy reported to the SEER Program. Data on subsequent therapy are not available.

§*P*<.05.

‖*P* for trend = .014.

¶119 cases (98%) were histologically confirmed.

#*P* for trend = .0004.

**P* for trend = .79.

††*P* for trend = .85.

‡‡Includes surgical, hormonal, immunologic, unspecified, or unknown therapies.

Table 2. Histopathologic type of secondary lung cancer by initial therapy for Hodgkin's disease*

Treatment group¶ (No. patients with Hodgkin's disease)	Squamous cell lung cancer†		Adenocarcinoma‡		Small cell lung cancer§		Other types‖	
	O	O/E	O	O/E	O	O/E	O	O/E
All patients (n = 13 886)	42	3.29#	33	2.65#	24	3.54#	22	1.69#
Radiation only (n = 5801)	17	3.41#	12	2.36#	19	7.12#	8	1.49
Chemotherapy only (n = 4390)	19	4.02#	13	2.94#	4	1.57	7	1.60
Radiation and chemotherapy (n = 2244)	3	2.74	4	3.46	0	(E 0.6)	5	4.56#
Other**/no therapy (n = 1451)	3	1.52	4	2.25	1	1.04	2	0.92

*Patients were diagnosed with Hodgkin's disease as a first primary cancer from 1935-1972 (Connecticut Tumor Registry, n = 2159) or 1973-1991 (Surveillance, Epidemiology, and End Results [SEER] Program, n = 11 727) and survived 2 or more months. Follow-up ended December 31, 1988, and December 31, 1991, respectively, for the two cohorts. O = observed number of lung cancers. E = expected number of lung cancers. O/E = observed-to-expected ratio of lung cancers.

†ICD-O morphology codes (*25*): M-8051, M-8052, M-8070-76.

‡ICD-O morphology codes (*25*): M-8050, M-8140-43, M-8200, M-8250-51, M-8260, M-8290, M-8300, M-8310, M-8320, M-8430, M-8470-71, M-8480-81, M-8490, M-8550, M-8560, and M-8571.

§ICD-O morphology codes (*25*): M-8041-45.

‖ICD-O morphology codes (*25*): M-8001, M-8010-12, M-8020-22, M-8030-33, M-8082, M-8123, M-8240-46, and M-8980-81.

¶Treatment group represents only the first course of therapy reported to the SEER Program. Data on subsequent therapy are not available.

#$P<.05$.

**Includes surgical, hormonal, immunologic, unspecified, or unknown therapies.

kin's lymphoma *(10)* but not breast cancer *(23)*.

Nonetheless, results from the population-based SEER Program clearly indicate that patients with Hodgkin's disease are at significantly increased risk of pulmonary neoplasia. Given possible underreporting of second malignancies among survivors migrating from SEER areas, our estimates may be conservative. On the basis of these data, however, it can be estimated that approximately 138 excess lung cancers might be expected to occur among 10000 Hodgkin's disease patients followed for 15 years after therapy. Our results underscore the need for additional epidemiologic and molecular studies to clarify the relationship between smoking, radiation, chemotherapy, immunologic factors, and other influences in the occurrence of lung cancer among these patients. In the interim, clinicians should be informed that the risk of lung cancer increases significantly with time since diagnosis of Hodgkin's disease, and patients who smoke would be well advised to quit (7).

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Notes

'Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

'Person-years of observation were compiled according to age, sex, and calendar periods from 2 months after Hodgkin's disease diagnosis to one of the following dates: last follow-up, death, diagnosis of second lung cancer, or end of study, whichever occurred first. Lung cancerincidence rates specific for age, sex, and calendar-year intervals were multiplied by the accumulated person-years at risk to estimate the number of cancer cases expected. Statistical tests and 95% confidence limits were based on the assumption that the observed numbers of second lung cancers were distributed as a Poisson variable. Teats for homogeneity and linear trend were conducted according to the methods of Breslow et al: *(24).* All *P* values are two-sided.

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